Development of a Pummerer–type cyclisation for the synthesis of analogues of the anti-tumour natural product ecteinascidin 597

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Engineering and Physical Sciences

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Laura H. S. Smith

School of Chemistry
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Abstract

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Development of a Pummerer–type cyclisation for the synthesis of analogues of the anti-tumour natural product ecteinascidin 597

A connective Pummerer reaction was developed with a view to its use in the synthesis of analogues of ecteinascidin 597, a member of a family of potent anti-tumour natural products.

A one-step synthesis of \( N \)-benzyl 2-hydroxyamides, involving the reaction of 2,2-dimethyl-1,3-dioxolan-4-one with amines, was investigated and the products were oxidised to give glyoxamides. Reaction conditions were optimised for the cyclisation of electron-rich \( N \)-benzyl glyoxamides in the presence of thiols and a Lewis acid (\( \text{ZnCl}_2 \) or \( \text{Sc(OTf)}_3 \)) to give 4-sulfanyl tetrahydroisoquinolinones, and mechanistic studies indicated the importance of hemithioacetal and thionium intermediates in these reactions.

The scope of the reaction was found to encompass electron-rich \( N \)-benzyl pyruvamide substrates, which gave 4-methyl-4-sulfanyl tetrahydroisoquinolinone products via what is believed to be a combination of thionium ion and cyclisation-substitution pathways.

Under more forcing conditions, connective Pummerer cyclisation of \( N \)-benzyl 2,2-diethoxyacetamides was successful.

Sharpless asymmetric aminohydroxylation and a Sharpless asymmetric dihydroxylation-Mitsunobu sequence were exploited in the synthesis of an enantioenriched 1,2-aminoalcohol. Subsequent conversion to branched, \( N \)-benzyl 2-hydroxyacetamides by PMB and silyl protection and \( N \)-acylation then oxidation and cyclisation furnished 1-silyloxyethyl-4-sulfanyl tetrahydroisoquinolinones. Modification of these tetrahydroisoquinolinones gave bridged macrolactones which map onto the A subunit of the ecteinascidins.

A one-pot macrolactone synthesis using a connective Pummerer reaction was unsuccessfully attempted on a substrate bearing 2,2-diethoxyacetamide and thiol moiety in addition to an electron-rich benzene ring.

A new protecting group strategy was necessary for continuation of the analogue synthesis and a variety of \( N,O \)-acetals were evaluated for the protection of the 1,2-aminoalcohol.
Declaration

No portion of the work referred to in the 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 a peer-reviewed journal:


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I am also grateful to my parents for their support; caffeine, fluoxetine and alcohol for helping me to function; and to Dirk, James, Kim and Patrick for keeping me sane.

“Stench and high reactivity make the thiol the most froward of common functional groups, beloved by misogynists, misanthropes and masochists alike.” P. J. Kocieński, Protecting Groups (3rd Edition), Georg Thieme Verlag KG, 2005.
List of abbreviations

AA       asymmetric aminohydroxylation
AD       asymmetric dihydroxylation
Alloc    allyloxycarbonyl
Ar       aryl
aq.      aqueous
atm      atmospheres
BHT      2,6-di-t-butyl-4-methylphenol
BINOL    1,1'-bi-2,2'-naphthol
Bn       benzyl
Boc      t-butoxycarbonyl
BOPCl    bis(2-oxo-3-oxazolidin-3-yl)phosphinic chloride
br.      broad (NMR or IR)
Bz       benzoyl
c.       concentrated
c-       cyclo
CAN      cerium (IV) ammonium nitrate
cat.     catalytic
Cbz      benzyloxycarbonyl
CDI      carbonyl diimidazole
CIP      2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate
COD      cycloocta-1,4-diene
COSY    CORrelation Spectroscopy
CSA      camphorsulfonic acid
d       doublet (NMR)
δ        chemical shift relative to tetramethylsilane (NMR)
Δ        reflux
dba      dibenzylideneacetone
DBU      1,8-diazabicyclo[6.4.0]undec-7-ene
DCC      1,1'-dicyclohexylcarbodiimide
DDQ      2,3-dichloro-5,6-dicyanobenzoquinone
DEAD     diethylazodicarboxylate
(DHQD)2PHAL    hydroquinidine 1,4-phthalazinediyl diether
(DHQ)2PHAL    hydroquinine 1,4-phthalazinediyl diether
DIAD     di-i-propylazodicarboxylate
DIBAL    di-i-butylaluminium hydride
DIPAMP   1,2-bis[(2-methoxyphenyl)(phenylphosphino)]ethane
DIPEA    di-i-propylethylamine
\(n\)CPBA 3-chloroperbenzoic acid
MIC minimum inhibitory concentration
\(\mu\)M micromolar
\(\mu\)wave microwave
mmol millimoles
MNBA 2-methyl-6-nitrobenzoic anhydride
MOM methoxymethyl
MS mass spectrometry or molecular sieves
Ms methylsulfonyl (mesyl)
nM nanomolar
NMM \(\Lambda\)-methylmorpholine
NOE nuclear Overhauser effect
Nu nucleophile
PDC pyridinium dichromate
pet. ether petroleum ether 40-60° fraction
pM picomolar
PMB 4-methoxybenzyl
PMP 4-methoxyphenyl
ppm parts per million
psi pounds per square inch (14.7 psi = 1 atm)
Py pyridine
PyBox 2,6-bis(4-phenyl-2-oxazolinyl)pyridine
q quartet (NMR)
quant. quantitative (yield)
quin quintet (NMR)
Red-Al™ sodium bis(2-methoxyethoxy)aluminumhydride
RF\(^{\circ}\) fluorous tag, -CH\(_2\)CH\(_2\)C\(_8\)F\(_{17}\)
RT room temperature
s singlet (NMR)
sat. saturated
SM starting material
STS soft tissue sarcoma
Su succinimidyl; pyrrolidin-2,5-dione-1-yl
t triplet (NMR)
T/C test/control organism comparison; percentage life-span ratio or tumour size ratio
TBAB tetra-\(n\)-butylammonium bromide
TBAF tetra-\(n\)-butylammonium fluoride
TBAI tetra-\(n\)-butylammonium iodide
TBS  

$t$-butyldimethylsilyl

TBDPS  

$t$-butyldiphenylsilyl

TCE  

2,2,2-trichloroethanol

THF  

tetrahydrofuran

Tf  

triflyl; trifluoromethylsulfonyl

TFE  

2,2,2-trifluoroethanol

TIPS  

tri-$t$-propylsilyl

TMTTr  

4,4',4``-trimethoxytrityl; tri(4-methoxyphenyl)methyl

TMEDA  

$\frac{N}{N',N'\prime}$-tetramethylethylenediamine

tol  

tolyl

Troc  

2,2,2-trichloroethoxycarbonyl

Trt  

triphenylmethyl (trityl)

Ts  

4-methylbenzenesulfonyl (tosyl)
1. Introduction

The ecteinascidins (Et) are a family of antitumour, antibiotic tetrahydroisoquinoline natural products. Their potent biological activity and complex structures have interested synthetic and medicinal chemists for over 20 years and Et 743 (Yondelis®/trabectedin) is a licensed drug for the treatment of soft tissue sarcoma. The atom, ring and subunit labelling used throughout is based on that of Et 743 1 (Scheme 1).

![Scheme 1 – Atom, ring and subunit labelling of Et 743 (1)](image)

1.1 Isolation and biological activity of the ecteinascidins

From 1960 to 1982, a program was carried out by the USA National Cancer Institute to collect and test the extracts of plant and marine species for biological activity, in particular against tumour cells. One of the species tested whose extracts displayed anti-cancer properties was Ecteinascidia turbinata, a colonial sea-squirt which grows in shallow water environments in the Caribbean and Mediterranean seas. The extracts were tested in vivo against P338 murine leukaemia and lifetime T/C values (comparison of lifetime of test organisms to untreated control organisms) ranged from 140-270 % at doses of 50-265 mg/kg (a value of >125 is desirable for potential anti-tumour drugs).1

In 1986, Rinehart isolated and characterised six compounds from E. turbinata: Et 729 2, 743 1, 745 3, 759A 4, 759B 5 and 770 6, which were numbered according to their apparent molecular weights. (729, 743 and 759B were later discovered to be molecular weights after dehydration when the actual molecular ions were detected using high resolution–fast atom bombardment mass spectrometry [HR-FABMS]; the names were kept to avoid confusion.) Et 743, the most abundant, was isolated in 1×10⁻⁴ % yield.2 The active compounds were unstable towards both normal and reverse-phase chromatography as well as light, acid and enzymes, but, following a series of solvent extraction processes, centrifugal countercurrent chromatography, MPLC and HPLC were successfully exploited (Scheme 2).3 Anti-microbial and in vitro cytotoxic activity (against Micrococcus luteus and CV-1 monkey kidney cells respectively) was monitored.
throughout the process in order to locate the phases and fractions containing biologically active compounds.

Scheme 2 – Isolation process for Et 729, 743, 754, 759A, 759B and 770. CCC = centrifugal countercurrent chromatography, MPLC = medium pressure liquid chromatography, HPLC = high performance liquid chromatography.

Moving belt liquid chromatography–FABMS was employed for initial characterisation and HR-FABMS was used in conjunction with $^{13}$C NMR to determine the molecular formulae. A single sulfur atom was detected in Et 743 by electron spectroscopy for chemical analysis (ESCA) and a number of functional groups and aromatic substituents could be identified by NMR and IR. The presence of three trioxygenated tetrahydroisoquinoline units in Et 743 was proposed due to the
aromatic peaks present in both the $^1$H and $^{13}$C NMR spectra, the strong UV spectrum and three fragments from the HR-FABMS spectrum; $C_{12}H_6NO_3$, $C_{15}H_{17}NO_5$ and $C_{13}H_4NO_2$ (a fourth fragment, SCH$_3$, was also observed).  

![Chemical Structures](image)

**Ecteinascidin**
- Et 729: $R^1 = OH$, $R^2 = R^3 = H$ 2
- Et 743: $R^1 = OH$, $R^2 = H$, $R^3 = Me$ 1
- Et 745: $R^1 = R^2 = H$, $R^3 = Me$ 3
- Et 759A: $R^1R^2 = O$, $R^3 = Me$ 4
- Et 759B: $R^1 = OH$, $R^2 = H$, $R^3 = Me$, S-oxide 5
- Et 770: $R^1 = CN$, $R^2 = H$, $R^3 = Me$ 6

**X-ray structures obtained for:**
- $R^1 = OMe$, $R^2 = H$, $R^3 = CHO$ 7
- Et 759C: $R^1 = OH$, $R^2 = H$, $R^3 = Me$, N-12-oxide 8

**Scheme 3** – The structure of Et 729, 743, 745, 759A, 759B and 770 and comparison with other tetrahydroisoquinoline natural products

In 1990 the structures of the six compounds were correctly elucidated by Rinehart and Wright. Extensive 2D NMR experiments including COSY, HMBC, HMQC and NOE were used to explore the connectivity and spatial relationships between the atoms and indicated a pentacyclic tetrahydroisoquinoline skeleton, similar to several known antibiotic, anti-tumour natural products including the safracins, saframycins and renieramycins. The ecteinascidins also contain a novel 10-membered sulfur-containing bridging lactone which forms a spiro linkage to a third tetrahydroisoquinoline unit. Et 729 2 and 743 1 differ by a methyl group at N-12, Et 745 3 is a reduced form of Et 743 which lacks the C-21 hemiaminal and Et 770 6 bears an aminonitrile.
moiety instead. Et 759A 4 and 759B 5 were originally thought to be Et 743 N-oxides,7 but Et 759A is actually a C-21 lactam and Et 759B is an S-oxide. Relative stereochemistry, particularly at C-4 and quaternary centre C-1’, was later confirmed by a single crystal X-ray structures of N-12 formyl, C-21 methoxy Et 729 7 and newly-isolated Et 759C 8, whilst absolute stereochemistry was assumed to match that of safracin A 9 at C-1 (Scheme 3).8

The ecteinsascidins did not exhibit anti-viral activity when tested against Herpes simplex and Vesicular stomatitis viruses, but the new compounds did show cytotoxicity towards both bacterial and mammalian cells. Anti-bacterial activity of the new compounds against M. luteus was quantified using a disc-diffusion assay. Et 729 and 743 were found to be the most active, inhibiting M. luteus at doses as low as 0.01 μg per 6.4 mm disc. Et 759A, 759B and 770 showed moderate activity whilst Et 745 required a much larger dose (40 μg) to cause any significant inhibition of bacterial growth (Table 1).2 Et 743 and 745 were tested further against 9 bacterial species in disc-diffusion assays; Et 745 only inhibited one species at a dose of 5 μg per 6.4 mm disc. Et 743 prevented growth of 8 of the species at a dose of 10 μg/disc as well as a species of fungus, Penicilium oxalicum.

<table>
<thead>
<tr>
<th>Dose/μg</th>
<th>Et 729</th>
<th>Et 743</th>
<th>Et 745</th>
<th>Et 759A</th>
<th>Et 759B</th>
<th>Et 770</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6</td>
<td>18</td>
<td>23</td>
<td>trace</td>
<td>10</td>
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<tr>
<td>0.8</td>
<td>16</td>
<td>20</td>
<td>–</td>
<td>8</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>0.4</td>
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<td>14</td>
<td>–</td>
<td>trace</td>
<td>10</td>
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<td>0.2</td>
<td>11</td>
<td>13</td>
<td>–</td>
<td>–</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>0.1</td>
<td>8</td>
<td>12</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>0.05</td>
<td>7</td>
<td>9</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 1 — Anti-bacterial activity of the eckteinsascidins in a disc-diffusion assay against M. luteus. Disc size = 6.4 mm.

A similar trend was noted when the eckteinsascidins were tested for in vitro cytotoxicity against CV-1 cells; Et 743 and 729 were again the most active, Et 770 and 759B showed moderate activity and Et 745 and 759A were the least potent (Table 2).2

In a tube dilution assay, Et 743 inhibited L1210 mouse leukaemia cell growth (ID50 = 0.5 ng/ml) at much lower concentrations than Et 745 (ID50 = 88 ng/ml). In an in vivo study against P388 murine leukaemia, Et 729 was the most active compound of the three tested, (T/C = 214 at a dose of 3.8 μg/kg), Et 743 also produced a positive outcome (T/C = 167 at 15 μg/kg) whilst Et 745 showed a minor effect at a much higher dose (T/C = 111 at 250 μg/kg). The low biological activity of Et 745 (and the relatively low activity of Et 759A) suggested that the C-21 hemiaminal (or aminonitrile) moiety present in the more potent eckteinsascidins was important for activity.
<table>
<thead>
<tr>
<th></th>
<th>Et 729</th>
<th>Et 743</th>
<th>Et 745</th>
<th>Et 759A</th>
<th>Et 759B</th>
<th>Et 770</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6</td>
<td>18</td>
<td>28</td>
<td>14</td>
<td>16</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td>0.8</td>
<td>16</td>
<td>23</td>
<td>9</td>
<td>16</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>0.4</td>
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<tr>
<td>0.05</td>
<td>9</td>
<td>14</td>
<td>–</td>
<td>–</td>
<td>trace</td>
<td>–</td>
</tr>
</tbody>
</table>

**Table 2 – In vitro cytotoxic activity against CV-1 cells.** Disc size = 6.4 mm.

Et 722 11 and 736 12 were reported a couple of years later and feature a very similar tetrahydroisoquinoline skeleton, but instead of a tetrahydroisoquinoline C subunit, they contain a spiro-linked tetrahydro-β-carboline moiety (Scheme 4).

![Scheme 4](image)

**Scheme 4 – The structure of Et 722 and Et 736.**

Both Et 722 11 and Et 736 12 are active against L1210 leukaemia cells *in vitro* with ID₉₀ values of 2.5 ng/ml and 5.0 ng/ml (around 3.4 and 6.7 μM) respectively. Et 736 is also effective against a range of cancer cell lines *in vivo*, although it is less potent than Et 743 (Table 3).

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Et 736 (dose in μg/kg per day)</th>
<th>Et 743</th>
</tr>
</thead>
<tbody>
<tr>
<td>P388</td>
<td>265 (25)</td>
<td>190 (12.5)</td>
</tr>
<tr>
<td>B16</td>
<td>200 (50)</td>
<td>253 (12.5)</td>
</tr>
<tr>
<td>M5076</td>
<td>slightly active</td>
<td>&gt;204 (12.5)</td>
</tr>
</tbody>
</table>

**Table 3 – In vivo activity of Et 736 compared to Et 743.** B16 = melanoma, M5076 = ovarian sarcoma.
Four further ecteinascidins, believed to be biosynthetic precursors of those already known, were later reported: Et 583 13, 597 14, 594 15 and 596 16. Although the bridged macro lactone was retained, they lacked the C-subunit and instead bore either an amine or ketone at C-1’. Et 597 15 was used to verify the absolute stereochemistry of the ecteinascidins: the conformation of the C-1’ amide in N-Ac Et 597 17 was revealed by NOE and a further NOE interaction was detected between the acetyl group and the E ring, thus determining the relative stereochemistry at C-1’. Successive treatment of Et 597 with HgCl2, NaBH4 then MeOH/H+ liberated cysteine methyl ester, then chiral GC analysis of its N,S-di(trifluoroacetyl) derivative ratified its L-stereochemistry. As Et 597 14 and Et 743 1 are thought to be formed in the same biological pathway and have similar circular dichroism (CD) spectra, they most likely have the same absolute stereochemistry (Scheme 5).9

![Structures of compounds](image)

**Scheme 5 – The structures of Et 583 (13), 594 (15), 596 (16) and 597 (14) and N-Ac Et 597 (17).**

Et 597 14 was 2.5–10 times less potent than Et 743 1 or 729 2 towards several tumour types in *in vitro* assays, whilst Et 583 13 and 594 15 required concentrations up to 2 orders of magnitude higher to cause the same inhibition as Et 743. This suggests that the C subunit may be important for anti-tumour activity (Table 4).

<table>
<thead>
<tr>
<th>Cell type</th>
<th>IC50 (ng/ml)</th>
</tr>
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<tbody>
<tr>
<td>P388</td>
<td>2.0</td>
</tr>
<tr>
<td>A549</td>
<td>2.0</td>
</tr>
<tr>
<td>HT29</td>
<td>2.0</td>
</tr>
<tr>
<td>MEL28</td>
<td>2.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Et 597</th>
<th>Et 583</th>
<th>Et 594</th>
<th>Et 743</th>
</tr>
</thead>
<tbody>
<tr>
<td>P388</td>
<td>2.0</td>
<td>10</td>
<td>10</td>
<td>0.2</td>
</tr>
<tr>
<td>A549</td>
<td>2.0</td>
<td>10</td>
<td>20</td>
<td>0.2</td>
</tr>
<tr>
<td>HT29</td>
<td>2.0</td>
<td>10</td>
<td>25</td>
<td>0.5</td>
</tr>
<tr>
<td>MEL28</td>
<td>2.0</td>
<td>5.0</td>
<td>25</td>
<td>5.0</td>
</tr>
</tbody>
</table>

**Table 4 – *In vitro* anti-tumour activity of Et 597, Et 583, Et 594 and Et 743.** A549 = human lung carcinoma, HT29 = human colon carcinoma, MEL28 = human melanoma.
Et 770 6 (previously reported alongside Et 743 1) and its S-oxide, Et 786 18, have been isolated in \( 6.0 \times 10^{-3} \) % and \( 1.6 \times 10^{-4} \) % yield respectively from a Thai tunicate, *E. thurstoni*, following pretreatment with KCN. Both compounds exhibited *in vitro* cytotoxicity towards breast cancer cells (IC\(_{50} = 2.5 \text{ and } 7.6 \text{ nM respectively} \) and nasopharynx carcinoma cells (KB) (IC\(_{50} = 34 \text{ and } 150 \text{ nM respectively})

\[ \text{Scheme 6} \quad \text{Et 786 (18), isolated from a Thai tunicate} \]

Other natural ecteinascidins include Et 815 19, a C-21 malonaldehyde analogue of Et 743. As may be expected for a compound lacking a C-21 hemiaminal or aminonitrile, Et 815 is less active than Et 743; its minimum inhibitory concentration (MIC) against *Bacillus subtilis* and IC\(_{50s}\) against several cancer cell lines were an order of magnitude higher.\(^\text{11}\) C-21 N-acetamides Et 788 20 and 802 21 displayed similar or weaker activity compared to Et 815.\(^\text{12}\) S-oxide Et 745B 22 and N-oxide 759C 8 also exhibited higher MIC and IC\(_{50}\) values than Et 729 and Et 743 (Scheme 7).

\[ \text{Scheme 7} \quad \text{Further natural ecteinascidins including Et 815 (19), 788 (20), 802 (21), 745B (22), 759C (8) and 637 (23).} \]
C-1’ amide Et 637 23 displayed very similar anticancer activity to Et 743 1, casting doubt on the necessity of the C subunit for anti-tumour activity (Scheme 7). In IGROV-1 (ovarian cancer) cells treated with Et 637 or Et 743, similar perturbation to the cell cycle was noted (transcription-dependent arrest at G2/M, eventually leading to apoptosis); an experiment with ALL/MIK (leukaemia) cells demonstrated that Et 637 caused a higher apoptosis rate than Et 743 and the two compounds showed comparable cytotoxicity towards a range of cancer cell lines, although Et 637 was more potent against leukaemia cells (Table 5).13,14

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Et 637</th>
<th>Et 743</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGROV-1</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>SKOV-3</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>A2780</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>HCT116</td>
<td>15</td>
<td>17.5</td>
</tr>
<tr>
<td>H460</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Reh</td>
<td>7.5</td>
<td>20</td>
</tr>
<tr>
<td>ALL-MIK</td>
<td>7.5</td>
<td>20</td>
</tr>
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</table>

Table 5 – *in vitro* activity (1 h treatment) of Et 637 and Et 743 against a range of cell lines. IGROV-1, SKOV-3, A2780 = human ovarian cancer; HCT116 = human colon cancer; H460 = large cell lung cancer; Reh, ALL-MIK = human leukaemic.

The biosynthesis of ecteinascidins is believed to occur via a tyrosine diketopiperazine intermediate 25; 14C-labelled tyrosine 24 is incorporated into the natural product by cell-free extract of *E. turbinata*, as are 14C-labelled tyrosine diketopiperazine 25, dopamine diketopiperazine 26 and 35S-cysteine 29. Conversion of diketopiperazine 25 to diketopiperazine 26 in the cell-free extract has been observed, thus 26 is believed to be the first committed intermediate of the biosynthesis. From 26, it is believed that further aromatic oxidation, partial reduction of the diketopiperazine ring, D ring formation and condensation with an aldehyde such as 27 would give pentacycle 28. Aldehyde 27 may be serine derived, although uptake of 14C-labelled serine has not been detected. B ring oxidation and addition of a cysteine residue would then furnish Et 597-like compound 30 which would undergo oxidation of the A-ring methoxy group and transamination to provide Et 596-like ketone 31 then reaction with dopamine derivative 32 or tryptophan 33 (isolated alongside Et 736 12) would lead to Et 743 and Et 736-type natural products (Scheme 8).15,16
A number of synthetic ecteinascidin analogues have been evaluated for biological activity, starting with several Et 743 derivatives which were tested by Rinehart alongside the first isolated ecteinascidins. Monoacetylated 35 and mono-O-methylated Et 743 34 showed similar cytotoxic activity towards CV-1 cells as Et 743; a di-O-methylated analogue 36 displayed a moderate effect whilst p-bromobenzoylated 38 and de-acetylated 37 derivatives exhibited a further drop in potency (Scheme 9).\textsuperscript{2,7}

Suwanborirux and Saito explored the effects of acylation of Et 770 36 at the 6'-O and 2'-N positions on anticancer activity. A variety of aromatic esters were tested against HCT116, QG56 (human lung carcinoma) and DU145 (human prostate carcinoma) cell lines. Benzoyl, methoxy- or 

**Scheme 8 – Putative biosynthesis of the ecteinascidins from diketopiperazine intermediates**

**Scheme 9 – Rinehart’s Et 743 analogues**
nitro- substituted benzoyl, pyridine-carboxyl, quinoline-carboxyl and isoquinoline-carboxyl esters generally gave IC$_{50}$ values below 2 nM. Bromobenzoyl and naphthoyl esters were significantly less cytotoxic. Additionally, a N-2’ indole-3-carboxamide was accidentally synthesised and showed excellent cytotoxicity when tested, prompting the investigation of a range of amides.$^{17}$ Formation of nitrobenzoyl and heterocyclic amides was carried out on a 18,6’-bis-O-allyl protected substrate and both the protected and unprotected amides were tested. The unprotected amides displayed IC$_{50}$ values of nM-magnitude for the same 3 cell lines, whilst the di-O-allyl protected intermediates were 100-1000 times less potent (Scheme 10).$^{18}$

![Scheme 10 - 6’-O acyl and 2’-N acyl analogues of Et 770](image)

Amide or imide groups at C-22 were found to be good bioisoters for the spiro-tetrahydroisoquinoline C subunit; Corey’s simplified analogues lack the F, G and H rings and have IC$_{50}$ values of around 0.2-4.0 nM against 4 solid cancer cell lines: A-549 lung carcinoma, HCT116, A375 malignant melanoma, and PC-3 prostate carcinoma. In particular, phthalascidin 39, which bears a phthalamido (NPhth) group at C-22, was found to display very similar in vitro activity to Et 743 1 across a range of cell lines and concentrations, suggesting the two compounds inhibit cancer cells via the same mechanism. Other phthalascidin-based analogues were also studied: modification to the C-5 acetate or E ring reduced activity slightly, substitution of the C-21 aminonitrile with a hemiaminal made little difference, but reduction at C-21 increased IC$_{50}$ by a factor of 1000 (Scheme 11).$^{19}$
Scheme 11 – Corey’s simplified amide and imide analogues

Et 743 interacts with several targets in tumour cells that inhibit growth or trigger apoptosis and the most important pathway is believed to be a novel form of minor groove DNA alkylation which triggers events leading to cell death. Other mechanisms have been reported but are of limited consequence as they require higher drug concentrations than can be achieved in the cell or are required for anti-tumour activity.

Scheme 12 – Proposed mechanism for DNA alkylation. B = DNA base adjacent to modified guanine involved in hydrogen bonding.

The C-21 hemiaminal of Et 743 reacts with the exocyclic nitrogen (N-2) of guanine 40 within specific triplet sequences (5'-CGG, 5'-TGG, 5'-AGC and 5'-GGC) to form a covalent adduct with DNA. Whilst the C subunit protrudes from the complex, the A and B subunits sit inside the minor groove and interact with neighbouring bases, thus determining sequence selectivity – Et 729, which lacks a N-12 methyl group, has been shown to bind to a triplet (5'-CGA) which Et 743 does not. Using electrophoresis to detect formation of DNA-Et 743 adducts, no alkylation was detected for homopolymeric duplex oligonucleotides dC/dI or dA/dT, nor a DNA fragment in which guanine had been replaced with inosine 41 (which lacks the exocyclic nitrogen), whilst a
significant reduction in the mobility of homopolymeric duplex oligonucleotide dC/dG after treatment with Et 743 indicated binding had occurred. NMR studies of binding suggest the mechanism involves a protonated species acting as a general acid in the formation of iminium ion, which then undergoes attack to form the Et 743-DNA adduct (Scheme 12).

This alkylation causes bending of the DNA double helix and widening of the minor groove. Eukaryotic cells have several types of machinery for the repair of DNA, including a mechanism called transcription coupled nucleotide excision repair (TC-NER) which operates only on transcribed DNA. A damaged, single strand of DNA is removed in response to distortion of the double helix then the gap is repaired using the other strand as a template. Once bound to DNA, Et 743's exposed C subunit interacts with proteins, such as XPG, which are involved in TC-NER. This stalls the repair process and results in formation of a cytotoxic adduct which can either disrupt the cell cycle or cause apoptosis. Many cancer drugs which target DNA require a NER-deficient system, Et 743 is most active in NER-proficient cells and XPG-defective colon cancer cell lines show some resistance to Et 743. As cancer cells undergo transcription and cell division faster than healthy cells, Et 743 is selective for tumour cells.

Et 743 may disrupt other DNA repair mechanisms as well as other processes and structures within cells. Microtubules have several purposes within cells, including forming mitotic spindles during cell division. Microtubule distribution is affected by Et 743 via an unknown mechanism, leading to disruption of mitosis. Et 743-DNA adducts have been shown to cross-link to topoisomerase I, an enzyme responsible for unfolding DNA for transcription or replication, resulting in strand cleavage. However, both of these effects require μM concentrations of Et 743 — higher than is required for cytotoxic activity — and are therefore thought to be auxiliary modes of action.

Cells deficient in proteins involved in homologous recombination (HR), which fixes double strand breaks, are ~10 times more sensitive to Et 743. Et 743-DNA complexes are thought to stall the DNA replication fork and HR-deficient cells cannot repair the ensuing double strand breaks. Over-expression of P-glycoprotein (P-gp), a cell membrane pump which actively removes a broad range of molecules including anti-tumour agents from cells, often causes cancer drug resistance. Et 743 down-regulates P-gp expression, is still cytotoxic in cell lines which over-express P-gp and improves the activity of other drugs in such cells when used in pre-treatment, meaning that Et 743 could be valuable in multidrug therapy.

In nude mice with human tumour xenografts, treatment with Et 743 resulted in significant reduction in tumour size (T/C % < 1) across several cancer types (MX-1 breast cancer, MEXF989 melanoma, LXFL529 non-small cell lung cancer and HOC22 ovarian cancer), and animals were tumour-free after ~1 month. Et 743 had less impact on MRIH121 renal and PC2 prostate cancers (tumour size T/C % ~ 40) with no cures occurring within the test group.
Et 743 was progressed into clinical trials due to its unique mode of action and novel structure, and its high activity against tumours, both in vitro and in vivo. Phase I clinical trials demonstrated the efficacy of the drug in human patients who had previously received treatment for cancer. Common side effects included reversible transaminitis (elevated levels of transaminase enzymes, which metabolise amino acids, often indicative of liver damage), neutropenia (decreased neutrophil count), and hyperbilirubinaemia (increased levels of bilirubin, associated with jaundice). Et 743 had a linear pharmacokinetic profile with a high volume of distribution, high clearance and a long terminal half-life. nM-order plasma concentrations of the drug were achieved using the recommended dose established by the studies, 1.5 mg/m², to be administered by 24 h intravenous infusion every 3-4 weeks. 

Several phase II studies involving different cancer types have been reported. Gastrointestinal stromal and colorectal cancers did not respond to the use of Et 743, but other trials were more successful, with response durations averaging around 6 months to 1 year.

Side effects, such as transaminitis and hyperbilirubinaemia, were found to be proportional to total drug exposure and could be prevented by dose-lowering. In pre-treated breast cancer patients, 17 % showed a partial response, 4 % showed a minor response and stabilisation of bone metastasis was observed. In women with relapsed or taxane-resistant ovarian cancer, a 25 % major response was recorded. In patients with advanced, pre-treated soft tissue sarcoma (STS), a major response was seen in 10 % of cases, whilst 8 % displayed a minor response and disease stabilisation was observed in 35 %. Pre-dosing of patients with an anti-emetic, dexamethasone, reduced hepatotoxicity. Further trials in previously-studied cancers as well as prostate cancer, mesothelioma, endometrial carcinoma, primary peritoneal cavity cancer and fallopian tube cancer have been carried out or are in progress. Et 743 has also been evaluated for combination therapy alongside drugs such as cisplatin.

Subsequent in vitro testing showed Et 743 exhibits activity in the pM range against several lines of STS cells, whilst activity against 4 types of carcinoma cells was found to be in the nM range, showing that Et 743 is more toxic towards STS cells.

Et 743 was approved, as Yondelis®/trabectedin, by the European Medicines Authority in 2007 for advanced STS where anthracycline and ifosfamide are unsuitable or have failed, and in 2009 in combination with DOXIL®/Caelyx® (pegylated liposomal doxorubin) for relapsed ovarian cancer. Due to the rarity of STS, trabectedin has orphan drug status, allowing its approval without full phase III clinical studies. Trabectedin is also licensed in 40 countries outside the EEA for STS and/or ovarian cancer.

Supply of Et 743 by farming of *E. turbinata* and isolation of the natural product was not economically feasible; aquaculture could produce ~100 tonnes of *E. turbinata* per year, but the expensive and complex extraction process gave variable yields of Et 743, and an alternative, synthetic method was sought to provide the drug.
1.2 Synthetic studies towards ecteinascidin natural products

A number of synthetic approaches to the ecteinascidins and other tetrahydroisoquinoline alkaloids have been published over the last few years and several reviews discussing this work have been produced.6,34,35 The current literature review will focus on synthetic approaches specifically towards ecteinascidin natural products, rather than approaches towards tetrahydroisoquinoline skeletons and natural products in general. The syntheses are described roughly in chronological order, but related approaches or those by the same author have been grouped together for ease of comparison.

The first total synthesis of Et 743 was reported by Corey in 1996.36 Corey's route relied on the synthesis of two optically-active α-amino acid derivatives 45 and 46 by asymmetric hydrogenation. Modification and joining of these two fragments gave the ABCDE ring system 47. Introduction of a cysteine residue 48 allowed formation of the H ring then the C subunit was formed in a Pictet-Spengler reaction by addition of a phenylethylamine 32.

The left-hand amine fragment 45 was synthesised from sesamol 49. MOM-protection of the phenol allowed the regioselective introduction of the methyl and formyl groups by directed ortho-lithiation and quenching with MeI and DMF respectively. After adjusting the phenol protecting group, Knoevenagel condensation of the aldehyde with 50 gave diester 51 as a mixture of isomers. Cleavage of the allyl ester of 51 was followed by a Curtius reaction using DPPA and BnOH to form dehydroaminoacid 52 as a single isomer. Asymmetric hydrogenation was carried out using Knowles’ [Rh(COD)-([R,R]-DIPAMP)]+BF$_4$– complex and gave the desired aminoester 53 in 96 % ee (chiral HPLC).37 Hydrolysis of the dimethyl acetal moiety and a Pictet-Spengler cyclisation on the resulting aldehyde formed the B ring stereospecifically, then the Bn and Cbz groups were cleaved by hydrogenolysis to give 45. Synthesis of the right-hand fragment 46 used a very similar route; methyl 3,5-dihydroxy-4-methoxybenzoate 54 was protected then the ester moiety was converted to an aldehyde. Knoevenagel condensation with malonate 55 gave 56 then a Curtius reaction gave dehydroaminoacid 57, again as a single isomer (the stereochemistry of both 52 and 57 was confirmed by NOE). Asymmetric hydrogenation of 57 with [Rh(COD)-([R,R]-DIPAMP)]+BF$_4$– afforded aminoester 58 in 96 % ee (chiral HPLC). 58 was converted to aldehyde 46 by changing the protecting group on nitrogen and ester reduction, then coupled to amine 45 in a Strecker reaction to give aminonitrile 59 (Scheme 13).
Scheme 13 – Corey’s synthetic route to Et 743: synthesis and coupling of aminoacid fragments

(a) NaH, DMF, Et₂O, 0 °C; MOMBr, 0 °C, 90 %
(b) n-ButLi, TMEDA, hexane, 0 °C; MeI, –78 °C, 87 %
(c) n-ButLi, THF, –30 °C; DMF, 0 °C, 64 %
(d) MsOH, CH₂Cl₂, 0 °C
(e) BnBr, NaH, DMF, 86 % (2 steps)
(f) 50, AcOH, PhH, 99 %, E/Z 4:1
(g) Pd(PPh₃)₄, Et₃N-HCO₂H, THF, 94 %
(h) DPPA, Et₃N, 4Å MS, PhMe, 70 °C; BnOH, 93 %
(i) [Rh(COD)-(R,R)-DIPAMP]+BF₄⁻, H₂ (45 psi), MeOH, 97 %, 96 % ee
(j) BF₃·OEt₂, H₂O, CH₂Cl₂, 0 °C
(k) BF₃·OEt₂, CH₂Cl₂, 4Å MS, 73 % (2 steps)
(l) H₂, Pd/C, EtOAc, quant.
(m) TBSCI, NEt₃, DMAP, CH₂Cl₂, quant.
(n) DIBAL, CH₂Cl₂, –78 °C
(o) PDC, 4Å MS, CH₂Cl₂, 99 % (2 steps)
(p) 55, piperidine, AcOH, PhMe, 92 %
(q) DPPA, Et₃N, 4Å MS, PhMe, 70 °C; BnOH, 89 %
(r) [Rh(COD)-(R,R)-DIPAMP]+BF₄⁻, H₂ (45 psi), MeOH, quant., 96 % ee
(s) AllocCl, Py, 93 %
(t) DIBAL, CH₂Cl₂, –78 °C
(u) KCN, AcOH, 61 %.
Scheme 14 – Completion of Corey’s synthesis of Et 743

(a) AllylBr, Cs₂CO₃, DMF, 87 %
(b) DIBAL, PhMe, –78 °C
(c) KF·2H₂O, MeOH
(d) MsOH, 3Å MS, 55 % (3 steps)
(e) Tf₂NPh, NEt₃, DMAP, CH₂Cl₂, 72 %
(f) TBDPSCI, DMAP, CH₂Cl₂, 89 %
(g) MOMBr, DIPEA, CH₂Cl₂, 89 %
(h) PdCl₂(PPh₃)₂, Bu₃SnH, AcOH, CH₂Cl₂, 92 %
(i) CH₂O, NaBH₃CN, AcOH, MeCN, 95 %
(j) PdCl₂(PPh₃)₂, SnMe₄, LiCl, DMF, 80 °C
(k) (PhSeO)₂O, CH₂Cl₂, 82 %
(l) TBAF, THF, 91 %
(m) N-Alloc-S-Fm-cysteine 48, EDCI, DMAP, CH₂Cl₂, 91 %
(n) Tf₂O, DMSO, –40 °C; DIPEA, 0 °C; t-BuOH; (Me₂N)₂C=N-t-Bu, 0 °C
(o) PdCl₂(PPh₃)₂, Bu₃SnH, AcOH, 84 %
(p) 65, DBU, DMF, CH₂Cl₂; oxalic acid
(q) 32, silica gel, EtOH, 82 %
(r) TFA, THF, H₂O
(s) AgNO₃, H₂O, 77 % (2 steps).
The free C-5 phenol in 59 was protected, then the bridging lactone opened reductively to give a hydroxyaldehyde which, after removal of the TBS groups from the E ring, underwent a Pictet-Spengler reaction to form 47, which bears the D and E rings of the natural product. The use of a symmetrical aromatic ring prevented the potential formation of regioisomers, but did necessitate the selective transformation of one hydroxyl group to a methyl group later in the synthesis. For this purpose, triflation of the least-hindered phenol was carried out with Tf₂NPh, then protecting group manipulation gave 60. N-methylation was achieved by reductive amination and a Stille cross-coupling was employed to exchange triflate for methyl on the E ring to furnish 61. Oxidation of the aromatic A ring with benzeneselenic anhydride was carried out to install a hydroxyl group at C-10 to allow subsequent functionalisation at C-4. Deprotection of the C-22 primary alcohol was followed by carbodiimide coupling with cysteine derivative 48 to afford 62. A one-pot reaction to form the bridging H-ring lactone was carried out in good yield: a Swern-type reagent was used to activate the tertiary alcohol at C-10, then base-promoted elimination gave quinone methide 63. N-t-butyl-N',N',N'',N'''-tetramethylguanidine was added to promote both cleavage of the Fm protecting group and addition of the resulting thiolate to the quinone methide and, finally, acylation of the C-5 phenol furnished 64. Removal of the Alloc group allowed conversion of the resulting C-1′ primary amine to a ketone using 65 to effect a transamination reaction. A Pictet-Spengler condensation with phenylethylamine derivative 32 created the C subunit stereospecifically. This was an improvement over model studies which employed (+)-tetrahydrocarvone as a chiral auxiliary in the condensation between amine 32 and methyl 3-mercaptopyruvate and had generated the FG ring system in moderate yield (~54 %) and dr (6.5:1). Removal of the remaining protecting groups then gave the natural product 1 (Scheme 14).

A route from amine 45 and amino acid 66 to pentacyclic intermediate 47 offering improved yields, reproducibility and operational simplicity was later published. Coupling of amine 45 to acid 66, allylation of the C-5 phenol and selective lactol reduction gave 67, then E ring silyl ether cleavage, an acid-catalysed Pictet-Spengler cyclisation, lactam reduction and addition of cyanide to the hemiaminal product gave intermediate 47 (Scheme 15).
Despite Corey's successful completion of a total synthesis of Et 743, a new route was necessary for industrial manufacture. Cyanosafracin B 10, a tetrahydroisoquinoline antibiotic which can be produced on a kilogram scale by bacterial fermentation, was chosen as the starting point for a semi-synthesis which could be used to synthesise Et 743 on a multi-gram scale. It has a very similar ABCDE ring system to Corey’s intermediate 47 and many of the steps used were adapted from Corey’s total synthesis. From 10, protection of the free amine and C-15 phenol, hydrolysis and reduction of the methoxyquinone A ring gave a catechol which was treated with BrCH₂Cl, and protecting group manipulation afforded 68. Treatment of 68 with phenyl isothiocyanate then HCl triggered an Edman degradation reaction which cleaved the alanine residue (and the phenolic MOM group) then adjustment of the protecting groups gave 69. The C-22 primary amine of 69 was oxidised with NaNO₂ and the resulting diazo salt hydrolysed to give a primary alcohol 70, an intermediate similar to 47 in Corey’s synthesis. Following Corey’s precedent, esterification with protected cysteine residue 71, oxidation at C-10 with benzeneselenenic anhydride and H ring formation were carried out to give 72, then removal of the protecting groups, oxidation of the primary amine to a ketone and reaction with 32 in a Pictet Spengler reaction furnished Et 743 1 (Scheme 16). This route has also been adapted for the synthesis of other ecteinascidin natural products: Et 729 2, Et 745 3, Et 759B 5, Et 736 12, Et 637 23 and Et 594 15, as well as analogues. 45
Scheme 16 – Semi-synthesis of Et 743 from cyanosafraclin B (a) Boc₂O, EtOH, 81% (b) MOMBr, DIPEA, DMAP, MeCN, 40 °C, 83% (c) NaOH, MeOH, 68% (d) H₂, 10% Pd/C; BrCH₂Cl, Cs₂CO₃, DMF, 110 °C (e) AllylBr, Cs₂CO₃, DMF, 56% (2 steps) (f) TFA, CH₂Cl₂, 95% (g) phenyl isothiocyanate, CH₂Cl₂, 87% (h) HCl/dioxane 82% (i) TrocCl, Py, CH₂Cl₂, 0 °C, 98% (j) MOMBr, DIPEA, DMAP, MeCN, 40 °C, 88% (k) Zn, aq. AcOH, 83% (l) NaNO₂, AcOH, THF, H₂O, 0 °C, 50% (m) 71, EDCI, DMAP, CH₂Cl₂, 95% (n) Bu₃SnH, PdCl₂(PPh₃)₂, AcOH, CH₂Cl₂, 90% (o) (PhSeO)₂O, CH₂Cl₂, −10 °C, 91% (p) DMSO, Tf₂O, CH₂Cl₂, −40 °C; DIPEA; t-BuOH, 0 °C; (Me₂N)₂C=N-t-Bu, 0 °C; Ac₂O, 58% (q) TMSCl, NaI, CH₂Cl₂, MeCN (r) Zn, aq. AcOH, 70 °C, 77% (2 steps) (s) 65, DBU, oxalic acid, 57% (t) 32, silica gel, EtOH, 90% (u) AgNO₃, MeCN, H₂O, 90%.

In his racemic synthetic studies on Et 743 CDE ring systems, Kubo has investigated the use of diketopiperazines to create substrates for Pictet-Spengler reactions.

Piperonal 73 was converted to A ring fragment 74 by Baeyer-Villiger oxidation of the aldehyde and hydrolysis of the resulting ester to afford a phenol, then MOM-protection, directed ortho-lithiation with a MeI quench, deprotection and Duff formylation using hexamethylenetetramine. Two CE ring fragments 75a and b, differing by their aromatic substituents (although neither maps exactly onto the Et 743 E ring), were synthesised using one route. Benzaldehydes 77a and b were condensed with 1,4-diethyl-2,5-piperazinedione 76 under basic conditions, and
regioselective cleavage of one acetamide group also occurred. Hydrogenation of the alkenes and replacement of the acetyl group furnished 75a and b. Condensation of 75a and b with 74 to give 78a and b was carried out in the same manner as used in the synthesis of 75a and b, then protecting group manipulation furnished 79a and b. Partial, regioselective reduction of the C-11 imide was accomplished using LiAlH(O-t-Bu)₃ then treatment with MsCl or Ms₂O depending on the aromatic substituents yielded 80a and b as single regioisomers in moderate yield (Scheme 17).

Scheme 17 – Kubo’s studies on Et 743 (a) mCPBA, CH₂Cl₂, Δ; 10% aq. KOH, MeOH, 70 % (b) NaH, DMF, 0 °C; MOMCl, DMF, 0 °C, 99 % (c) n-BuLi, THF, -17 °C; MeI, THF, -17 °C, 72 % (d) HCl, EtOH, Δ, 77 % (e) hexamethylenetetramine, AcOH, Δ, 73% (f) BnBr, NaH, DMF, 0 °C, 92 % (g) 76, t-BuOK, t-BuOH, DMF, 66 % (77a) 74 % (77b) (h) H₂, Pd/C, EtOH, DMF, 97 % (77a) 75 % (77b) (i) Ac₂O, 100-110 °C, 83 % (75a) 97 % (75b) (j) t-BuOK, t-BuOH, DMF, 80 % (78a) 78 % (78b) (k) BnBr, NaH, DMF (l) N₂H₄·H₂O, DMF, 61 % (78a, 2 steps) 95 % (78b, 2 steps) (m) ClCO₂-Pr, NET₃, DMAP, CH₂Cl₂, 93 % (79a) 87 % (79b) (n) LiAlH(O-t-Bu)₃, THF (o) MsCl, NET₃, CH₂Cl₂, 0 °C, 58 % (2 steps) (p) Ms₂O, CH₂Cl₂, 36 % (2 steps).
Kubo then investigated the regioselectivity of Pictet-Spengler reactions employing a correctly-substituted E ring\textsuperscript{46,47}. Diketopiperazine 81 was synthesised from 82, then protecting group chemistry, partial imide reduction and treatment with Ms\textsubscript{2}O furnished 83 and 84 as a 3:1 mixture in favour of the wrong regioisomer. Kubo then instituted a blocking group strategy to improve regioselectivity. Bromination of 81 and protection gave 85 then the same reduction and cyclisation conditions were used to generate 86 as a single isomer in excellent yield. Deprotection, Eschweiler-Clarke methylation and hydrogenolysis then gave 87 (Scheme 18).

\begin{center}
\includegraphics[width=\textwidth]{Scheme18.png}
\end{center}

**Scheme 18** – Kubo’s studies on Pictet-Spengler reactions in the synthesis of CDE ring systems

(a) Cl\textsubscript{2}CHOMe, TiCl\textsubscript{4}, CH\textsubscript{2}Cl\textsubscript{2}, 77 % (b) mCPBA, TFA, CH\textsubscript{2}Cl\textsubscript{2}, 75 % (c) BnBr, NaH, DMF (d) ClCO\textsubscript{2}-Pr, NEt\textsubscript{3}, DMAP, CH\textsubscript{2}Cl\textsubscript{2} (e) H\textsubscript{2}, Pd(OH)\textsubscript{2}/C, EtOH, 51 % (3 steps) (f) LiAlH(O-t-Bu)\textsubscript{3}, THF (g) Ms\textsubscript{2}O, 88 % (2 steps), regioisomeric ratio 1:3 (h) Br\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}, THF, 91 % (i) BnBr, NaH, DMF (j) ClCO\textsubscript{2}-Pr, NEt\textsubscript{3}, DMAP, CH\textsubscript{2}Cl\textsubscript{2} 87 % (2 steps) (k) 1,3-dimethoxybenzene, TFA, 72 % (l) LiAlH(O-t-Bu)\textsubscript{3}, THF (m) Ms\textsubscript{2}O, 96 % (2 steps) (n) TFA, H\textsubscript{2}SO\textsubscript{4} (o) CH\textsubscript{2}O-H\textsubscript{2}O HCO\textsubscript{2}H, 70 °C (p) H\textsubscript{2}, Pd(OH)\textsubscript{2}/C, EtOH, 90 % (3 steps)

In his model studies on the Et 743 ABFGH ring system 88, Danishefsky synthesised an optically-active intermediate by means of a Sharpless asymmetric dihydroxylation (AD) and developed a novel, S\textsubscript{N}1-type reaction between a C-4 silyl ether and a tethered thiol to form the H ring. The presence of functionality at C-4 was important to his strategy for C and D ring formation which he had exploited in the synthesis of several tetrahydroisoquinoline alkaloids.\textsuperscript{48}
Scheme 19 – Danishefsky’s model studies on the ABFGH ring system of Et 743.

(a) mCPBA, TsOH, CH₂Cl₂ then K₂CO₃, MeOH, CH₃Cl, 99 % (b) Br₂, K₂CO₃, CH₂Cl₂, −78 °C, 80% (c) AlCl₃, CH₂Cl₂, 99% (d) BrCH₂Cl, Cs₂CO₃, MeCN, Δ, 82% (e) vinylltributyltin, Pd(PPh₃)₄, PhMe, Δ, 90% (f) Sharpless AD-mix-α, t-BuOH, H₂O, 0 °C, 83 % (g) TsCl, Py, CH₂Cl₂, 72 % (h) K₂CO₃, MeOH, 0 °C (i) NaNO₂, LiClO₄, MeCN, 60 °C, 74 % (2 steps) (j) BnBr, NaH, THF, 80 % (k) H₂, Pd/C, EtOAc (l) BrCH₂CH(OEt)₂, K₂CO₃, MeCN, Δ, 54 % (2 steps) (m) 6 N HCl, dioxane, H₂O, 0 °C, 86% (n) Boc₂O, Et₃N, EtOAc (o) TBSCI, DMAP, imidazole, CH₂Cl₂, 95 % (2 steps) (p) H₂ (1 atm), 10% Pd/C, EtOAc, 99% (q) 94, EDCI, DMAP, CH₂Cl₂, 95 % (r) Hg(O₂CCF₂)₂, AcOH 80 % (s) TFA, 4Å MS, CH₂Cl₂, 95 % (t) Bu₂SnH, PdCl₂(PPh₃)₂, AcOH, 90% (u) 65, DBU, DMF, CH₂Cl₂, 85% (v) 32, silica gel, dry EtOH, 80% (w) TFA, CH₂Cl₂, 89%.

The A ring was derived from aldehyde 89; conversion of the aldehyde moiety to a hydroxyl group was accomplished by Baeyer-Villiger oxidation and hydrolysis of the ester intermediate. Bromination, protecting group manipulation and a Stille reaction with a vinyltin reagent gave olefin 90. Exposure of 90 to Sharpless AD conditions generated an diol (ee not given) which was converted to epoxide 91 then opened with azide. O-protection and reduction of the azide intermediate provided 92 (no ee given). This first stereocentre did not exert significant stereochemical control over the formation of the B ring: N-alkylation with BrCH₂CH(OEt)₂ gave an acetal which underwent a Pomeranz-Fritsch reaction then N- and O-protection furnished 93 as a
mixture of diastereoisomers. Replacement of the benzyl group with a protected cysteine residue 94 and unmasking of the thiol gave 95, the substrate for H ring formation. The diastereoisomers were separated and individually exposed to acidic reaction conditions to afford the same macrolactone 97 (via carbocation 96) in excellent yield in each case. Following Corey’s precedent, deprotection of the primary amine and reaction with 65 then 32 formed the C subunit system stereospecifically (even though 97 lacks some of the steric bias of Corey’s ABCDEH ring system 72), then removal of the Boc group gave 88 (Scheme 19). 99

Danishefsky later published a formal synthesis of Et 743 50 ending with an intermediate 98 first reported by Fukuyama. 51 Two fragments 99 and 100 were synthesised then coupled together to give a substrate for the key vinylogous Mannich cyclisation; the route to the AB ring fragment was similar to that of the model studies, although Sharpless AD was replaced with asymmetric hydrogenation to control the formation of the first stereocentre. The E ring fragment was synthesised from 3-methylcatechol 101 employing a similar strategy to Corey; synthesis and asymmetric transfer hydrogenation of a dehydroaminoacid.

To form the A ring fragment, catechol 102 was brominated, subjected to a Baeyer-Villiger-hydrolysis sequence and protected. Lithium-halogen exchange and addition of the resulting organometallic species to Weinreb amide 103 gave ketone 104. Asymmetric transfer hydrogenation of 104 using Noyori’s ruthenium-\((R,R)\)-TsDPEN complex\(^{52,53}\) 105 and HCO\(_2\)H-NEt\(_3\) gave enantioenriched alcohol 106. 106 was converted to an amine by treatment with DPPA and reduction of the resulting azide with no loss of ee, then reductive amination with a mono acetal-protected glyoxal derivative, substitution of the C-5 phenolic protecting group and cyclisation of the acetal gave 99. To synthesise the E-ring fragment 100, mono-tosylation of 101 gave the substrate for a regioselective iodination, then the required protecting group steps were performed to yield phenol 107. Hydroxymethylation was carried out using paraformaldehyde under Lewis acidic conditions and the free hydroxyl groups were orthogonally protected. A Jeffery-Heck reaction was used to install the dehydroaminoester moiety of 109 as a single stereoisomer, then asymmetric hydrogenation with Rh\([(COD)-\(S,S\)-Et-DuPHOS)]\(^+\)OTf\(^{-}\) 110 gave the corresponding aminoester in 99 % ee. \(N\)-methylation and ester hydrolysis gave acid 100 which was coupled to amine 99 using BOPCl to furnish 111 in good yield (Scheme 20).
Scheme 20 – Danishefsky’s formal synthesis of Et 743: synthesis and coupling of the AB and E ring fragments (a) $\text{Br}_2$, NaOAc, AcOH, 0 °C, Br$_2$ClH$_2$, Cs$_2$CO$_3$, DMF, 105 °C, 66% (b) $\text{mCPBA}$, 25 to 64 °C; HCl, 0 °C, 78% (c) TBDPSCI, NEt$_3$, DMAP, 89% (d) n-BuLi, PhMe, THF; 103, −78 °C, 80% (e) 105, HCO$_2$H, NEt$_3$, DMF, 0 to 40 °C, 78%, 95% ee (f) DPPA, DBU, PhMe, DMF, 50 °C, 89%, 95% ee (g) H$_2$ (1 atm), Pd/C, EtOAc, 80% (h) (MeO)$_2$CHCHO, AcOH, NaBH$_4$, CN, MgSO$_4$, MeOH, 0 to 65 °C then TBAF, THF, 0 °C, 94% (i) AllylBr, NaH, DMF, 0 °C, 84% (j) HCl, dioxane, 0 °C, 90% (k) TsCl, NEt$_3$, CH$_2$Cl$_2$, 84% (l) ICl, AcOH, 70 °C, 96% (m) MeI, K$_2$CO$_3$, acetone, $\Delta$, 95% (n) NaOH, EtOH, $\Delta$, 90% (o) (CH$_2$O)$_n$, Et$_2$AlCl, CH$_2$Cl$_2$, 0 °C, 86% (p) BrBr$_2$, K$_2$CO$_3$, acetone, $\Delta$, 85% (q) PMBCl, NaH, THF, DMF, 99% (r) 108, Pd(OAc)$_2$, P(o-tol)$_3$, NEt$_3$, TBAB, MeCN, 80 °C, 87% ($Z$ isomer only) (s) 110, H$_2$ (100 psi), CH$_2$Cl$_2$, MeOH, 93%, 99% ee (t) LiOH, MeOH, THF, H$_2$O, 93% (u) MeI, NaH, THF, 82% (v) BOPCI, NEt$_3$, CH$_2$Cl$_2$, 85%.
Danishefsky had originally envisioned carrying out the key Mannich-cyclisation step on a ketone such as 112 to form the C and D rings with simultaneous formation of the C-3 and C-11 stereocentres. Extensive studies were performed on the cyclisation of ketone 112 and related compounds which bore different aromatic substituents and/or were C-13 epimers. In each case, a single diastereoisomer of product 113 (or a compound with the corresponding aromatic substituents and/or C-13 stereochemistry to its starting ketone) was detected. Whilst the stereochemistry at C-11 was controlled successfully by that of C-13 to give a syn relationship between the two stereocentres, in all the examples described, an anti-relationship between C-3 and C-11 was obtained which was incorrect for Et 743 1 and could not be rectified by epimerisation (Scheme 21).55,50

![Scheme 21](image)

Scheme 21 – Danishefsky’s studies on the Mannich cyclisation of ketone 112

Revision of the synthetic route led to the development of a vinylogous Pictet-Spengler reaction in which only one stereocentre (C-11) was formed, and subsequent manipulation of the enamine product generated the C-3 stereocentre.

Amide 111 was converted to Pictet-Spengler substrate 114 by removal of the PMB and allyl protecting groups, elimination of the secondary alcohol at C-3 to form the necessary alkene and oxidation of the benzylic C-11 alcohol. Treatment of 114 under acidic conditions cleaved the Boc group, triggering formation of an iminium ion which underwent attack by the hydroxystyrene moiety to give pentacycle 115a in moderate yield. Conversion of the alkene to an alcohol was optimised on a similar, readily accessible compound 115b, which varied from the ‘actual’ substrate 115b by an A-ring alkoxy substituent. NBS-mediated dihydroxylation–hemiaminal reduction and hydroboration of enamine 115b were unsuccessful. To prevent potential N-oxide formation, thus allowing use of a wider range of oxidants, 115b was subjected to McCluskey reaction conditions (TrocCl, TBAI, PhMe, Δ), which replaced the N-12 methyl group with Troc to give 116b, but peracids also failed to give the desired epoxide. DMDO did effect the desired transformation and, following NaBH₃CN reduction, alcohol 117b with the correct stereochemistry at C-11 was obtained. With conditions in hand, 115a was subjected to protecting group modification, including a McCluskey reaction, to give epoxidation substrate 116a, then treatment with DMDO followed by a large excess of NaBH₃CN furnished 117a (use of a smaller excess of reducing agent gave a mixture of the desired product 117a and ketone 118 which was presumed to have been formed by rearrangement of the aminoeopoxide moiety). Protecting group
manipulation, C-21 lactam reduction using a $n$-BuLi–DIBAL complex and addition of cyanide to the resulting hemiaminal gave an intermediate $98$ identical to Fukuyama’s (Scheme 22):$^{50,51}$

Fukuyama’s initial work on the synthesis of Et 743 $1$ began with a chiral-pool strategy – a glucose derivative $119$ was exploited to provide the four carbon atoms of the C ring plus one extra carbon atom from each of the B and D rings. Incorporation of the aromatic A and E rings furnished pentacycle $120$ which Fukuyama proposed could be converted to the ABCDE skeleton via $121$.

Known epoxide $119$ (which can be derived from D-glucose $122$) was opened with TsNH$_2$. Mesylation of the resulting alcohol, protecting group manipulation and base-induced aziridination gave $123$. $124$ was synthesised from 3-methylcatechol $101$: regioselective tosylation,
bromination and methylation of 101 yielded 125, then tosylate hydrolysis, MOM protection and exposure to magnesium gave a Grignard reagent 124, which was used to open aziridine 123 to furnish 126.

**Scheme 23 – Fukuyama’s synthetic studies on Et 743.** (a) TsNH₂, Cs₂CO₃, DMF, 80 °C (b) MsCl, NEt₃, CH₂Cl₂, 0 °C, 96 % (2 steps) (c) HCl, MeOH, Δ, 99 % (d) SnCl₄, CH₂Cl₂, 88 % (e) NaOH, MeOH, 91 % (f) TBSCI, imidazole, DMF, 98 % (g) TsCl, NET₃, CH₂Cl₂, 0 °C, 83 % (h) Br₂, AcOH, CH₂Cl₂, 97 % (i) MeI, K₂CO₃, acetone, Δ, 96 % (j) NaOH, EtOH, H₂O, Δ, 97 % (k) MOMCl, DIPEA, CH₂Cl₂, 97 % (l) Mg, THF (m) CuI, THF, 0 °C, 91 % (n) Boc₂O, DMAP, MeCN, 96 % (o) TBAF, THF, 98 % (p) Tf₂O, Py, CH₂Cl₂, 0 °C (q) LiN₃, DMF, 80 °C, 90 % (2 steps) (r) TMSBr, CH₂Cl₂ (s) TFA, CH₂Cl₂, 97 % (2 steps), (t) PyHBr₃, CH₂Cl₂, 89 % (u) TFA, H₂O, 70 °C, 88 % (v) MeI, K₂CO₃, acetone, Δ, 89 % (w) BCl₃, CH₂Cl₂, −78 to 0 °C, 87 % (x) H₂, Rh/C, EtOAc, 82 % (y) BrCH₂CO₂Ph, 4Å MS, propylene oxide, MeCN, 80 °C, 92 % (z) Pb(OAc)₄, PhH, 80 °C, 80 % (aa) 130, TFA, CH₂Cl₂, 0 °C, 89 %.

Modification of the protecting groups gave a free alcohol at C-3 which was triflated and displaced with azide to give 127. After removal of the MOM and Boc groups, the phenol was
regioselectively brominated to create a blocking group to control the regioselectivity of the subsequent Pictet-Spengler reaction, which occurred in good yield to furnish 128 as a single isomer. The phenol moiety of 128 was methylated then the C-4 benzyl protecting group removal and azide reduction provided amine 129. Treatment of 129 with BrCH₂CO₂Ph gave a morpholinone which was oxidised with Pb(OAc)₄ to give an imine which underwent attack by phenol 130 to provide 120 in good yield. Fukuyama envisaged transformation of 120 to 121 by reductive morpholinone opening and oxidative cleavage of the resulting diol (Scheme 23). Although Fukuyama pursued a different approach in his total synthesis, addition of a phenol to an optically active imine is a common step to both approaches.

In his total synthesis, Fukuyama used two key fragments; an aminoalcohol 131 formed using a chiral template 132 derived from one enantiomer of phenylglycine in 7 steps⁵⁷ and an amino acid 133 which was synthesised by asymmetric hydrogenation. These were combined in an Ugi multi-component reaction to give a compound 134 that contained all the carbon atoms of the ABCDE skeleton. Heck and phenolic aldol reactions were used to close the A and D rings, whilst the H ring was constructed using a method similar to Danishefsky’s and the C subunit was installed using Corey’s methodology.⁵¹

Fukuyama’s left hand fragment 131 synthesis started with sesamol 49 which was hydroxylated to give phenol 135 in 2 steps. Nucleophilic attack of 135 on phenylglycine-derived chiral template imine 132⁵⁷ proceeded in good yield and stereoselectivity to give 136. Removal of the template to furnish 131 was accomplished in 4 steps: reductive ring opening to give a diol, selective silyl protection of the primary alcohol, oxidative cleavage of the 1,2-aminoalcohol moiety and cleavage of the resulting imine with hydroxylamine. Activation of the free phenol as a triflate and a Negishi-type cross-coupling installed a methyl group on the aromatic ring.

The right hand fragment 131 was synthesised from 3-methylcatechol 101. Selective monotosylation, bromination, methylation of the free phenol and replacement of Ts with MOM gave 137. Lithium-halogen exchange and a DMF quench introduced an aldehyde moiety which was protected as an acetal during installation of an iodide via directed ortho-lithiation. Cleavage of both the acetal and MOM groups under acidic conditions and benzyl protection of the free phenol gave aldehyde 138 which underwent a Horner-Wadsworth-Emmons reaction with phosphonate 139. The resulting olefin was subjected to asymmetric hydrogenation conditions using Rh[(COD)-(S,S)-Et-DuPHOS]+OTf⁻⁵⁴ to give an α-aminoester in 94 % ee (by chiral HPLC) without loss of the aromatic iodide, then basic hydrolysis furnished the corresponding α-aminoacid 133. The two fragments 131 and 133 were combined with isocyanide 140 and acetaldehyde in a 4-component Ugi reaction⁵⁸ to give 134 as an inconsequential mixture of diastereoisomers (Scheme 24).
Scheme 24 – Synthesis and coupling of Rukuyama’s left and right-hand fragments

(a) MOMCl, NaH, THF, DMF, 97 % (b) n-BuLi, B(OMe)_3, THF then H_2O_2, AcOH, 92 % (c) 132, TFA, CH_2Cl_2, –10 °C, 89 % (d) Tf_2O, Py, CH_2Cl_2, 0 °C, 90 % (e) NaBH_4, MeOH, 0 °C, 85 % (f) TBDPSCl, imidazole, DMF, 91 % (g) MeZnCl, PdCl_2(dppf), THF, Δ, 97 % (h) Pb(OAc)_4, MeCN, 0 °C (i) NH_2OH·HCl, NaOAc, EtOH, 89 % (2 steps) (j) TsCl, NEt_3, CH_2Cl_2, 83 % (k) Br_2, AcOH, CH_2Cl_2, 97 % (l) MeI, K_2CO_3, acetone, Δ, 96 % (m) NaOH, EtOH, H_2O, 97 % (n) MOMCl, DIPEA, CH_2Cl_2, 97 % (o) n-BuLi, THF, –60 °C; DMF, 79 % (p) HC(OMe)_3, CSA, MeOH, 94 % (q) n-BuLi, Et_2O, 0 °C; I_2 (r) c. HCl, THF, 72 % (2 steps) (s) BnBr, K_2CO_3, MeCN, Δ, 98 % (t) 139, 1,1,3,3-tetramethylguanidine, CH_2Cl_2, 93 % (u) Rh[(COD)-(S,S)-EtDuPHOS]^+OTf^−, H_2 (500 psi), ETOAc, 50 °C, 99 %, 94 % ee (v) LiOH, MeOH-THF-H_2O, quant. (w) 140, MeCHO, MeOH, Δ, 90 %.
Following protecting group manipulation (including removal of the Boc group), attack of the N-12 amine onto the anilide to give diketopiperazine 141 was effected by heating in EtOAc. Mesylation of the free C-5 phenol was carried out then Boc protection of N-12 secondary amide of the diketopiperazine ring facilitated partial reduction and dehydration to give enamine 142. An intramolecular Heck reaction on 142 formed the D ring and the protecting groups were changed to give 143. Epoxidation of the enamine moiety of 143 with DMO and in situ methanolysis followed by reduction gave an alcohol which was protected to give 144. Double acetate hydrolysis and phenol protection provided a lactam bearing a pendant alcohol then Red-Al™ reduction gave an oxazolidine which was opened with TMSCN to give 145 (Scheme 25).

Scheme 25 – Continuing Fukuyama’s synthesis of Et 743

<table>
<thead>
<tr>
<th>Step</th>
<th>Reagents</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>TBAF, THF</td>
<td>89 %</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>Ac₂O, Py, DMAP</td>
<td>93 %</td>
<td>2 steps</td>
</tr>
<tr>
<td>c</td>
<td>TFA, anisole, CH₂Cl₂</td>
<td>93 %</td>
<td>2 steps</td>
</tr>
<tr>
<td>d</td>
<td>EtOAc, Δ</td>
<td>87 %</td>
<td>2 steps</td>
</tr>
<tr>
<td>e</td>
<td>MsCl, Py, CH₂Cl₂, 0 °C</td>
<td>91 %</td>
<td>(f) Boc₂O, DMAP, MeCN, 97 %</td>
</tr>
<tr>
<td>f</td>
<td>CSA, quinoline, PhMe, Δ</td>
<td>88 % (2 steps)</td>
<td>(i) Pd₂dba₃, P(o-tol)₃, NEt₃, MeCN, Δ</td>
</tr>
</tbody>
</table>

Adjustment of the alcohol protecting groups revealed a C-4 primary alcohol which was oxidised to an aldehyde then attacked by the phenolic A ring following cleavage of the benzyl protecting
groups to give 146. Phenol allylation and exchange of the C-22 alcohol’s acetate protecting group for a protected cysteine residue 147 gave 148. Cleavage of the thioester was achieved with hydrazine, and the resulting thiol cyclised under highly-diluted acidic conditions to give 149. Completion of the synthesis then required deprotection of the amines, phenol and aminal; methylation of the secondary amine; oxidation of the primary amine and a Pictet-Spengler reaction on the resulting ketone with 32-HCl to form the C subunit (Scheme 26).

**Scheme 26 – Completion of Fukuyama’s synthesis of Et 743**  
(a) Ac₂O, Py, DMAP, 92 %  
(b) HF, MeCN, quant  
(c) DMP, CH₂Cl₂, 92 %  
(d) H₂, Pd/C, THF, 84 %  
(e) AllylBr, DIPEA, CH₂Cl₂, Δ, 89 %  
(f) K₂CO₃, MeOH, 99 %  
(g) 147, EDCI, DMAP, CH₂Cl₂, 94 %  
(h) NH₃·H₂O, MeCN, 98 %  
(i) TFA, TFE  
(j) Ac₂O, Py, DMAP, 71 % (2 steps)  
(k) Zn, AcOH, Et₂O, 92 %  
(l) CH₂O, AcOH, NaBH₃CN, MeOH, 96 %  
(m) PdCl₂(PPh₃)₂, AcOH, Bu₃SnH, CH₂Cl₂, 89 %  
(n) 150, DMF, CH₂Cl₂; DBU; citric acid (54 %)  
(o) 32·HCl, NaOAc, EtOAc, 96 %  
(p) AgNO₃, MeCN, H₂O, 93 %.

In his work on the ecteinascidins, Zhu has relied on the use of a chiral pool compound, Garner’s aldehyde 151, to introduce stereochemistry, as well as using asymmetric phase transfer catalysis in the synthesis of α-aminoacid derivatives.

Sesamol 49 was used as the starting material for model studies on the ABH ring system of Et 743. Following ring methylation, a magnesium phenolate was generated then employed in a
phenolic aldol reaction with \((R)\)-Garner’s aldehyde \((R)\)-151 to give alcohol 152 as a single, syn isomer.\(^{59}\) Modification of the protecting groups gave amine 153 which underwent a Pictet-Spengler reaction with ethyl glyoxylate under mild conditions to give 154 as a 2:1 mixture of diastereoisomers in favour of the desired all-cis compound 154a. Zhu later reported conditions which gave a higher yield for this transformation (LiCl, PhMe, HFIP, 85%), but furnished the trans-isomer 154b exclusively.\(^{60}\) The trans-diastereoisomer of amine 153 did not undergo Pictet-Spengler ring closure.\(^{61}\) Partial epimerisation of 154b to 154a could be accomplished by temporary Troc protection of the amine and treatment with DBU. Reduction of 154a’s C-22 ester moiety and condensation with 155 gave a sulfide which was treated with trifluoroacetic acid to trigger cleavage of the 1,3-dioxane and S-trityl groups and cyclisation of the resulting thiol to give 156 (Scheme 27).\(^{62}\)

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

**Scheme 27 – Zhu’s model studies on the Et 743 ABH ring system** (a) NaH, MOMCl, Et₂O, DMF, 0 °C, 90% (b) \(n\)-BuLi, TMEDA, hexane; MeI, Et₂O, 93% (c) TMSCl, NaI, MeCN; KOH, 85–90% (d) MeMgCl, THF; \((R)\)-151, CH₂Cl₂, 98% (e) AllylBr, Cs₂CO₃, NaI, DMF, (f) cat. TsOH, MeOH, 0 °C (g) 2,2-dimethoxypropane, cat. TsOH, 70% (3 steps) (h) TBDMSOTf, lutidine, –60 to 0 °C; KF, MeOH, 90%, (i) EtO₂CCHO, LiBr, PhMe, TFE, 80 °C, 48–55%, 75% based on conversion, dr 2:1 154a:154b, (j) TrocCl, CH₂Cl₂, aq. NaHCO₃ (k) DBU, THF, dr 10:1 (l) Zn, AcOH–Et₂O, 83% (3 steps), dr 2.5:1 154a:154b (m) LAIH₄, THF, –20 to 0 °C, 85% (n) 155, EDCI, DMAP, CH₂Cl₂, 83% (o) TFA, PhMe, 70%.
Scheme 28 – Zhu’s attempted Et 743 synthesis – (a) TsCl, NEt₃, CH₂Cl₂, –70 °C (b) MeI, K₂CO₃, acetone, Δ, 84 % (2 steps) (c) Cl₂CHOMe, TiCl₄, CH₂Cl₂, 0 °C, 85 % (d) NaBH₄, MeOH, THF, H₂O, 0 °C, quant. (e) PBr₃, PhMe, CH₂Cl₂, 0 °C, 96 % (f) 158, 159 (10 mol %), CsOH•H₂O, CH₂Cl₂, –78 °C; AcOH, THF, H₂O, 85 % (g) LiBH₄, MeOH, Et₂O (h) NaOH, H₂O, EtOH, Δ (i) AllocCl, aq. NaHCO₃, CH₂Cl₂ 78% (3 steps) (j) TBSCI, imidazole, DMF, then 2 N HCl, 91% (k) (COCl)₂, DMSO, CH₂Cl₂, –78 °C; NEt₃, 92% (l) PhMe, 3Å MS, 40 °C (m) TMSCN, BF₃•Et₂O, CH₂Cl₂, –30 °C, 56 % for the major isomer (2 steps) (n) 165, EDCI, DMAP, CH₂Cl₂, 74% (o) TFA, TFE, 0 °C to RT, 65% (p) (COCl)₂, DMSO, CH₂Cl₂, –78 °C; NEt₃, 74% (q) KF, AcOH, MeOH, 89% (r) 0.5% MsOH, MeCN, 0 °C, 78%.

This methodology was then applied to an attempted synthesis of the ABCEH ring system.⁶² To form the E ring, enantioenriched aminoaldehyde 163 was synthesised. 3-Methyl catechol 101 was converted to bromide 157 by protection, formylation, aldehyde reduction and bromination. 157 was used to alkylate glycine derivative 158 under asymmetric phase-transfer conditions using 159 as a catalyst to give 160 in good yield and ‘higher than 90 %’ ee (reaction of 160 with N-Boc-D-Ala was carried out to give a dipeptide in 87 % yield and 10:1 dr).⁶³ Protecting
group chemistry and reduction of the ester gave amine 161 which was converted to aldehyde 162 and condensed with aminoalcohol 163. The resulting oxazolidine was opened with cyanide to furnish 164. The C-22 alcohol was coupled with 165 and the product exposed to acidic conditions which cleaved the 1,3-dioxolane and the thiol’s TMTr protecting group (a more acid-labile group than in previous studies) and triggered macrocyclisation of the resulting thiol in one step. Oxidation of the C-11 alcohol and removal of the silyl protecting groups gave 166. 166 was treated with acid to promote a Pictet-Spengler cyclisation to form the D ring, but, disappointingly, the regiochemistry of the product was wrong for the natural product and elimination of the sulfide also occurred as a side reaction (this elimination was thought to be caused by decomposition of enamine 167) to afford 168 instead of the desired ABCDEH ring system (Scheme 28).60

Zhu then developed a new approach to Et 743. A combination of early stage D-ring and late stage H ring formation were employed to circumvent problems with sulfide elimination.

The DE ring system was synthesised by Pictet-Spengler reaction of amine 161 with (S)-Garner’s aldehyde (S)-151 to form tetrahydroisoquinoline 169 with the correct regiochemistry, then protection of the phenol, amine and alcohol gave 170.64 Acetonide 170 was treated with acid to remove the acetal and Boc protecting groups to give amine 171. 170 was also used in the synthesis of Et 597, and was converted to aldehyde 172 by chemoselective acetal hydrolysis and oxidation (Scheme 29).65

![Scheme 29 – Zhu’s synthesis of the DE ring fragments of Et 743 (1) and Et 597 (14) (a) (S)-151, 3Å MS, AcOH, CH₂Cl₂, TFE, 84% (b) AllocCl, CH₂Cl₂, sat. NaHCO₃, 88% (c) AllylBr, Cs₂CO₃, DMF, RT, 86% (d) Ac₂O, Py, DMAP, CH₂Cl₂, 92% (e) TFA, CH₂Cl₂, 72% (f) CeCl₃·7H₂O, oxalic acid, MeCN, 91 % (g) (COCl)₂, DMSO, CH₂Cl₂, –60 °C; NEt₃ (product was used crude).]
Scheme 30 – Zhu’s synthesis of Et 743 (a) MOMCl, NaH, DMF, Et₂O, 0 °C, 96 % (b) n-BuLi, THF, B(OMe)₃, H₂O₂, AcOH, 0 °C, 95 % (c) ethyl glyoxylate, LiCl, 3 Å MS, HFIP/PhMe, 97 % (d) 4-nitrophenyltriflate, K₂CO₃, DMF, 94% (e) trimethylboroxine, Pd(PPh₃)₄, K₃PO₄, dioxane, Δ, 93% (f) SOBr₂, benzotriazole, CH₂Cl₂, 91% (g) NEt₃, MeCN, 0 °C, 91%, dr 3:1 (h) TBSCI, imidazole, DMF, 97% (i) K₂CO₃, MeOH, 94% (j) DMP, CH₂Cl₂, then TMSCN, ZnCl₂, CH₂Cl₂, 78% (k) LiBH₄, MeOH, THF, 0 °C, 80% (l) Ac₂O, Py, DMAP, CH₂Cl₂, 92% (m) HF·H₂O, MeCN, 91% (n) DMP, CH₂Cl₂, 93% (o) TFA, CH₂Cl₂, 95% (p) K₂CO₃, MeOH, 96% (q) 165, EDCI, DMAP, CH₂Cl₂, RT, 95% (r) TFA, TFE, then Ac₂O, Py, DMAP, CH₂Cl₂, 77% (s) n-Bu₂SnH, PdCl₂(PPh₃)₂, AcOH, CH₂Cl₂, 87% (t) CH₂O, NaBH₄CN, AcOH, 96% (u) Zn, AcOH, 92% (v) 150, DBU, sat. aq. oxalic acid, DMF, CH₂Cl₂, 53% (w) 32, NaOAc, EtOH, 97% (x) AgNO₃, MeCN, H₂O, 92%.

The A-ring fragment 173 was derived from sesamol 49, MOM protection facilitated directed ortho-lithiation and introduction of a hydroxyl group which was necessary for the next step: a phenolic aldol reaction with ethyl glyoxylate. The C-6 phenol group was triflated then subjected...
to Suzuki-Miyaura conditions to install a methyl group, and bromination of the C-1 benzylic alcohol furnished 173. Reaction between amine 171 and benzyl bromide 173 was thought to occur via a $S_N1$ mechanism and furnished the product 174 in ~3:1 dr. Following protection of the C-4 primary alcohol, transformation of the C-21 acetoxy group to an aldehyde gave the substrate for a Strecker reaction to form the C ring. Reduction of the C-22 ester and protection of the resulting alcohol gave 175. The C-4 silyl ether was cleaved and the resulting alcohol oxidised to give an aldehyde which underwent nucleophilic attack by the A ring to close the B ring. The C-22 acetate was replaced with cysteine derivative 165 to furnish 176. Treatment of 176 with TFA cleaved the TMTr group and effected cyclisation in one step, then removal of the Alloc and allyl groups and $\text{N}$-methylation gave 177. The synthesis was completed by deprotection steps, conversion of the C-1' primary amine to a ketone and a Pictet-Spengler reaction with amine 32 (Scheme 30).\textsuperscript{64}

Zhu modified his strategy for his total synthesis of Et 597. Rather than introducing the A ring as an electrophilic fragment, it was instead used as a nucleophile to attack an electrophilic DE ring fragment.

The A ring 178 was synthesised from 3-methoxy-4-hydroxybenzaldehyde 179. Silyl ether protection was carried out, then Baeyer-Villiger oxidation-hydrolysis introduced a hydroxyl group which was MOM-protected. Treatment with $n$-BuLi and MeI installed a methyl group on the aromatic ring and also alkylated the silyl protecting group. MOM cleavage and deprotonation produced a magnesium phenoxide 178 which attacked aldehyde 172 to give 179. Protecting group manipulation gave primary N-2 amine 180 which condensed with aldehyde 181 to form the B ring with excellent diastereoselectivity (reaction was thought to occur via either a Pictet-Spengler mechanism or a phenolic aldol condensation and conjugate addition of the amine to the orthoquinone methide intermediate). Oxidation of the pendant C-21 primary alcohol and a Strecker reaction generated the D ring to give 182. Removal of the O-Troc group and protection of the free phenol allowed esterification with 165 to proceed smoothly to give 183. A one pot removal of the S-TMTr group and cyclisation was unsuccessful, so the transformation was performed in a step-wise manner: removal of the S-TMTr group was carried out in the presence of Et$_3$SiH, then exposure to TMSBr effected cyclisation of the free thiol to form the H ring and removal of the MOM groups. Acetylation of the newly revealed phenol and removal of the allyl and Alloc groups gave 184. $\text{N}$-methylation and deprotection furnished Et 597 14. Et 583 13 could also be accessed simply by deprotection of 184 (Scheme 31).
Scheme 31 – Zhu’s total synthesis of Et 597 (a) TBSCl, imidazole, DMF, 98 % (b) mCPBA, CHCl₃, 45 °C; Na₂CO₃, MeOH, 85 % (c) MOMCl, DIPEA, CH₂Cl₂, Δ, 96 % (d) n-BuLi, THF, –10 °C; MeI, –78 °C, 92 % (e) TMSBr, CH₂Cl₂, –20 to 0 °C, 90 % (f) MeMgCl, THF (g) CH₂Cl₂, 74 % (2 steps) (h) MOMCl, DIPEA, CHCl₃, Δ, 88 % (i) TBSOTf, 2,6-lutidine CH₂Cl₂, –78 °C to RT; KF, MeOH 86 % (j) K₂CO₃, MeOH, 94 % (k) 181, AcOH, 3Å MS, CH₂Cl₂, 90 % (l) (COCl)₂, DMSO, CH₂Cl₂, –60 °C; NEt₃; TMSCN, ZnCl₂, CH₂Cl₂, 87 % (m) Zn, AcOH, Et₂O, 90 % (n) AllylBr, K₂CO₃, MeCN, 94 % (o) 165, EDCI, DMAP, CH₂Cl₂ 93 % (p) Et₃SiH, TFA, CH₂Cl₂, 87 % (q) TMSBr, CH₂Cl₂, –20 to 10 °C (r) Ac₂O, Py, DMAP, CH₂Cl₂, 60 % (2 steps) (s) Pd(PPh₃)₄, Bu₃SnH, AcOH, CH₂Cl₂, 85 % (t) CH₃O, NaBH₄CN, AcOH, MeCN, MeOH, 95 % (u) Zn, AcOH, Et₂O, 89 % (v) AgNO₃, MeCN, H₂O, 92 %.

Williams has reported a formal synthesis of Et 743;⁶⁶ his route to the AB ring fragment bears some similarity to Zhu’s model studies, including his use of (R)-Garner’s aldehyde (R)-151 as a chiral pool building block, but he used a novel radical cyclisation onto a glyoximine to form the B ring. Synthesis of the E ring fragment exploited attack of a commercially available chiral template on a benzyl bromide derivative to generate an enantioenriched aminoacid 185. Unfortunately, poor regioselectivity in a Pictet-Spengler reaction to form the D ring later in the synthesis detracted from its overall utility.
Commencing from 2,3-dimethoxytoluene 186, formylation and deprotection of the catechol moiety were carried out according to literature precedent, then regioselective bromination, acetal formation and Baeyer-Villiger oxidation-hydrolysis provided phenol 187. The titanium phenolate of 187 underwent aldol condensation with (R)-Garner’s aldehyde (R)-151 to afford an anti-product which was converted to amine 188a by protecting group manipulation. Reaction of amine 188a with ethyl glyoxylate gave an imine, which was treated with Bu$_3$SnH to effect a 6-endo-trig radical cyclisation to furnish 189 as a single diastereoisomer in good overall yield. Treatment of syn-isomer 188b under the same conditions resulted in a 1:1 diastereoisomeric mixture at C-1. Ester 189 was reduced then protection of the resulting alcohol gave the AB ring fragment 190 (Scheme 32).

Scheme 32 – Williams’ synthesis of the AB ring fragment of Et 743 (a) Cl$_2$CHOMe, TiCl$_4$, CH$_2$Cl$_2$, 0 °C, 92 % (b) BBr$_3$, CH$_2$Cl$_2$, –78 °C, 97 % (c) Br$_2$, NaOAc, AcOH, CH$_2$Cl$_2$, 0 °C, 92 % (d) BrCH$_2$Cl, C$_2$H$_2$O$_2$, MeCN, sealed tube, 110 °C, 69 % (e) mCPBA, CHCl$_3$, Δ then 4M HCl, MeOH, 73 % (f) Ti(O-i-Pr)$_4$, PhMe then (R)-151, 0 °C (g) AllylBr, Cs$_2$CO$_3$, DMF, 65% (2 steps) (h) TsOH, MeOH, 0 °C (i) 2,2-dimethoxypropane, TsOH (cat), DMF, 84 % (2 steps) (j) TBSOTf, 2,3-lutidine, –78 °C, 76 % (k) ethyl glyoxylate, 4Å MS, PhMe then Bu$_3$SnH, AIBN, PhH, 90 °C, 58% (2 steps) (l) LiAlH$_4$, THF, –78 °C (m) NaH, BnBr, THF, DMF, 0 °C, 77 % (2 steps).

The E ring fragment 185 was synthesised from vanillin 191. A methyl group was installed by regioselective aminomethylation, conversion to a benzyl chloride and reduction. Cleavage of the O-methyl group then gave catechol 192. Orthogonal protection of the phenol moieties, aldehyde reduction and conversion of the resulting alcohol to a bromide under Appel conditions furnished 193. The sodium enolate of 194 was used to attack 193, then adjustment of the phenol protecting groups afforded 195. The synthesis of 185a has not been reported by Williams but that of 185b has, and presumably a similar sequence of steps was employed: removal of the Boc protecting group, high pressure hydrogenolysis of the template and Fmoc protection.

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Scheme 33 – Williams’ synthesis of the E ring fragment, coupling to the AB ring fragment and synthesis of Danishefsky’s intermediate. (a) CH₂O, Me₂NH, EtOH, Δ, 94 % (b) Ac₂O, Δ; c. HCl; SnCl₂, c. HCl, dioxane, Δ, 78 % (c) AlCl₃, Py, CH₂Cl₂, 90 % (d) TIPSCI, NET₃, DMF, 82 % (e) Me₂SO₄, K₂CO₃, acetone, 88 % (f) TBAF, THF, 82 % (g) BnBr, K₂CO₃, acetone, 86 % (h) LiAlH₄, Et₂O, quant. (i) CBr₄, PPh₃, THF, 94 % (j) 194, NaHMD5, THF, 79-92 % (k) H₂ (1 atm), Pd/C, EtOH, 95 % (l) TBSCI, DMAP, NET₃, CH₂Cl₂, 82 % (m) synthesis of an N-Me analogue 185b and not N-H compound 185a was reported by Williams, but presumably a similar sequence of steps was employed: TFA, CH₂Cl₂; H₂ (80 psi), PdCl₂, EtOH, THF; FmocOSu, NaHCO₃, DMF (n) 185a, (COCl)₂, DMF, CH₂Cl₂ then 190, 2,6-lutidine, CH₂Cl₂, 0 °C, 70 % (o) Et₂NH, CH₂Cl₂; Boc₂O, EtOH, CH₂Cl₂, 90 % (p) Dowex 50W-X8, MeOH, 90 % (q) TBAF, THF, 95 % (r) (COCl)₂, DMSO, CH₂Cl₂, −78 °C; NET₃ (s) TFA, anisole, CH₂Cl₂, 72 %, regioisomeric ratio 0.72:1 in favour of the one not shown (t) TrocCl, Py, CH₂Cl₂, 0 °C (u) BnBr, K₂CO₃, TBAI, acetone, 65 % (2 steps) (v) pyrrolidine, Pd(PPh₃)₄, CH₂Cl₂, 56 % (w) MOMBr, DIPEA, CH₂Cl₂, quant.
185a was then converted to the corresponding acid chloride and coupled to amine 190, providing 196 in good yield. Removal of the Fmoc, acetal and silyl protecting groups, Boc protection and oxidation of the C-11 alcohol gave hemiaminal 197. Treatment of 197 with acid triggered loss of the Boc group and a Pictet-Spengler condensation, along with elimination of the C-4 methoxy group to generate olefin 198. Despite extensive experimentation, in accordance with Kubo’s work, the regioselectivity of the Pictet-Spengler reaction was poor and favoured the undesired isomer. Modification of the protecting groups of 198 gave 117a, an intermediate previously synthesised by Danishefsky (Scheme 33).

In his synthetic studies, Takemoto employed a combination of Fukuyama’s chiral template methodology and a chiral pool starting material to generate fragments 199 and 200 respectively. These were combined in a one-pot Au(I) catalysed cyclisation-amide formation reaction; an amide-ketone condensation closed the C ring then enamide activation triggered D-ring formation and the B ring was closed via a Pomeranz-Fritsch cyclisation.

Amine 131, a compound previously reported by Fukuyama and prepared in the same manner, underwent protecting group manipulation to furnish 199. Following a synthetic route developed by Zhu, tyrosine 24 was converted to aminoester 201 by Friedel-Crafts acylation, amine protection, iodination, O-methylation, Suzuki-Miyaura cross coupling with trimethylboroxine and Baeyer-Villiger oxidation. Protecting group modification and bromination of the aromatic ring (to create a blocking group for a Pictet-Spengler cyclisation later on) afforded amine 202. Propargylation of the amine and further protecting group chemistry gave acid 200. In a one-pot reaction, 200 cyclised in a 6-exo-dig fashion on exposure to Au(PPh3)⁺ to afford vinyl ester 203 which was opened by amine 199 to give ketoamide 204. Intramolecular condensation of the amide and ketone moiety gave an enamide which was treated with PhNMe₂·Br₃ to trigger an oxidative Friedel-Crafts cyclisation to give 205 which contains both the C and D rings. 205 was benzyl-protected then treated with DMDO and NaBH₃CN to convert the enamine to a 1,2-hydroxyamine 206. Finally, oxidation of the primary alcohol, acetalisation, removal of the mesyl group to reveal a phenol (with concomitant loss of the Troc group) and a Pomeranz-Fritsch reaction furnished 207, which is very similar to Danishefsky’s intermediate 117a (Scheme 34).

The examples selected for this review encompass a wide range of methods for the synthesis of optically-active fragments including catalytic approaches and the use of chiral pool materials. In many cases, ring formation is carried out by addition of an aromatic nucleophile to an aldehyde or aldehyde equivalent (such as imines or acetics) and, for the D ring, several approaches have been used to control regioselectivity. As well as careful choice of protecting group strategy, these synthetic approaches all feature formation of the B ring first, with H ring formation involving installation of the C-4 sulfide much later.
Scheme 34 – Takemoto’s approach to Et 743
(a) AlCl₃, nitrobenzene, r.t., then AcCl, 100 °C
(b) CbzOSu, dioxane, aq. NaHCO₃, 79% (2 steps)
(c) I₂, Ag₂SO₄, MeOH (d) K₂CO₃, MeI, DMF, 91% (2 steps)
(e) trimethylboroxine, Pd(PPh₃)₄, K₂CO₃, BHT cat., dioxane, μwave, 100 °C, 85% (f) mCPBA, CH₂Cl₂, 86% (g) K₂CO₃, MeOH (h) H₂, Pd/C, Boc₂O, MeOH, 85% (2 steps)
(i) NBS, MeCN, 88% (j) BnBr, K₂CO₃, TBAI, DMF, 92% (k) AcCl, MeOH (3M HCl), CH₂Cl₂ (l) propargyl bromide, LiOH·H₂O, 4Å MS, DMF, 81% (2 steps)
(m) TrocCl, CH₂Cl₂, aq. NaHCO₃, 93% (n) AcBr, SnBr₂, CH₂Cl₂, 94% (o) LiOH, MeOH, H₂O, THF (p) AuCl(PPh₃) (1 mol %), AgNTf₂ (1 mol %), CH₂Cl₂; 202, CH₂Cl₂, 80% (3 steps)
(q) Boc₂O, THF; TBAF, THF, 75% (2 steps) (r) NaH, BnBr, TBAI, DMF, THF, 78% (s) aq 4M HCl, MeOH/dioxane; Boc₂O, CH₂Cl₂, sat. aq. NaHCO₃ (t) MsCl, DIPEA, CH₂Cl₂ (u) TFA, anisole, CH₂Cl₂, 99% (4 steps) (v) anhydrous TsOH, MgSO₄, PhMe, 90 °C, 75% (w) PhNMe₃·Br₃, 3Å MS, MeCN, RT then 60 °C, 70 % (x) BnBr, K₂CO₃, KI, DMF, 91% (y) DMDO, MeOH, acetone; CSA (z) NaBH₂CN, TFA, THF, 86% (3 steps) (aa) DMP, CH₂Cl₂ (bb) TsOH, (MeO)₂CH, MeOH, 60% (2 steps) (cc) TMSOK, MeCN, 75% (dd) 5 M HCl, dioxane/H₂O, 82%.
1.3 Proposed synthetic route to Et 597 analogues

Our proposed, asymmetric approach to Et 597 analogues employs a key connective Pummerer reaction between a branched, enantioenriched glyoxamide 208 (formed by Sharpless asymmetric aminohydroxylation [AA] of a styrene and modification of the resulting aminoalcohol) and a cysteine derivative 209. This would generate the B ring 210 with simultaneous formation of the C-S bond, then macrolactonisation would give ABH ring system 211. Lactam reduction, homologation and deprotection would give aminoaldehyde 212. Acylation at N-2 using protected α-aminoacid 213 and sequential phenolic aldol and C-N bond formation steps would furnish the Et 597 skeleton 214, hopefully avoiding fragmentation of the benzyl sulfide that was observed by Zhu.⁶⁰ Lactam reduction and deprotection would complete the synthesis to give an Et 597 analogue (Scheme 35).

Scheme 35 – Proposed synthetic route to Et 597 analogues using a key connective Pummerer cyclisation
We intended to extend this work to include a connective Pummerer cyclisation triggered by intramolecular addition of a thiol to a glyoxamide, thus forming the B and H rings in a single step (Scheme 36).

![Scheme 36 - Proposed intramolecular connective Pummerer cyclisation](image)

1.4 The connective Pummerer reaction

The traditional Pummerer reaction employs thionium ion intermediates 217, which are generated by reaction of sulfoxides with electrophilic reagents (E), and undergo attack by a range of nucleophiles (Nu) including aromatic rings, amides, carboxylates and allyl silanes.

![Scheme 37 - The traditional Pummerer reaction and more recent variants](image)

Vinylsulfoxides can undergo vinylogous or additive Pummerer-type reactions. The interrupted Pummerer reaction (in which direct attack of a nucleophile on the activated sulfoxide displaces ‘OE’ to give a sulfonium ion which may either be isolated or fragment to a sulfide) is also well...
documented. Pummerer reactions can also be performed directly on sulfides under oxidative conditions (Scheme 37).\(^{72}\)

In the Procter group’s connective Pummerer reaction, condensation of thiols with aldehydes gives hemithioacetal intermediates 218 which collapse on electrophilic activation to give a thionium ion 217. The advantages of this convergent approach are that sulfides and sulfoxides need not be synthesised, whilst many thiols are commercially available and the aldehyde substrate is easily prepared; the product retains all the functionality of the reaction partners and by-products arising from unwanted interrupted Pummerer reactions cannot form.\(^{73}\)

![Scheme 38 – Proposed mechanism of the connective Pummerer reaction](image)

To date, the aldehyde employed is a glyoxamide 219 and the nucleophile is a tethered benzene, thus the reaction affords a variety of \(N\)-heterocyclic products, privileged motifs in many pharmaceuticals and natural products. \(N\)-Phenyl glyoxamides (\(n = 0\)) and \(N\)-2-phenylethyl glyoxamides (\(n = 2\)) cyclise under connective Pummerer conditions to yield oxindoles 220 and benzazepinones 221 respectively. \(N\)-Benzyl glyoxamides (\(n = 1\)) can give a range of products depending on the aromatic ring substituents. Electronic activation ortho to the glyoxamide results in tetrahydroisoquinolinone products 222.\(^{74,75}\) 2,4-Dimethoxy, 2,3,4- and 2,4,6-trimethoxy substituted rings promote reaction at the ipso position, triggering the formation of azaspirocycles 223.\(^{76}\) In less activated and more sterically hindered ipso-directing systems (such as 2,6-dimethoxy and 2-fluoro-4-methoxy), \(\alpha\)-arylacetamides 224 are generated by formation and collapse of spiro-intermediate 225 and hydrolysis of the resulting iminium ion (Scheme 39).\(^{77}\)

![Scheme 39 – Products of the connective Pummerer reaction](image)
A range of functionalised thiols have been successfully used in the connective Pummerer reaction, including cysteine derivatives. A perfluorinated alkyl thiol (C₈F₁₇CH₂CH₂SH, R²SH) is often used to give fluorous-tagged products such as 226 which can be rapidly and simply purified by Fluorous Solid Phase Extraction (FSPE). The tag can be removed oxidatively via a cerium (IV) ammonium nitrate (CAN) mediated Pummerer rearrangement or reductively with SmI₂ following modification of the heterocyclic products, for example by alkylation or palladium-catalysed cross coupling (Scheme 40).

Scheme 40 – Modification of heterocycles and fluorous tag removal. (a) CAN, MeCN, H₂O, quant (b) mCPBA, CH₂Cl₂ (c) MeI, K₂CO₃, DMF, 40 °C (d) TMS-acetylene, CuI, Pd(Ph₃)₄, NEt₃, 60 °C, 60 % (3 steps) (e) SmI₂, THF, 88 %.

Experiments have been carried out to probe the mechanism of the connective Pummerer-type reaction and the results support the proposed reaction pathway. In the formation of oxindoles, omission of either TFAA or BF₃·OEt₂ gives only hemithioacetal or trifluoroactylated hemithioacetal, which suggests that both of these reagents are necessary to activate the hemithioacetal for thionium ion formation. A cross-over experiment has been performed, in which two hemithioacetals 227 and 228 were formed separately then combined before addition of TFAA and then BF₃·OEt₂. No cross-over products were observed, which shows that equilibria lie towards the hemithioacetal and that mechanisms involving breakdown of the hemithioacetal, cyclisation of the glyoxamide and addition of the thiol are unlikely (Scheme 41).

Scheme 41 – Cross-over experiment to probe the mechanism of the connective Pummerer reaction
2. Results and Discussion

2.1 Synthesis and cyclisation of simple glyoxamides

Although the synthesis of tetrahydroisoquinolinone systems 229, 230 and 231 under connective Pummerer conditions had previously been reported by the group, yields were typically lower than those of the corresponding oxindole and benzazepinone compounds even when highly activated substrates were employed (Scheme 42).74

![Scheme 42 – Previous examples of tetrahydroisoquinolinones formed under connective Pummerer conditions]

The first task, therefore, was to optimise reaction conditions for the connective Pummerer cyclisation of simple $N$-benzyl glyoxamides 232 and 233 (which exist as a mixture of aldehyde and hydrate) (Scheme 43). A 3,5-dimethoxyphenyl group was chosen as a model for the aromatic A ring of Et 597 as the corresponding aldehyde was commercially available, allowing rapid and facile synthesis of the substrates via reductive amination and acylation, and the two electron-donating groups would direct reaction with electrophiles (such as thionium ions) to the 2 and 6 positions, whilst the plane of symmetry would prevent any potential regioselectivity issues. As glyoxamides with a free NH tend to exist as the wrong rotamer for cyclisation, two different 'protecting' groups for nitrogen were initially selected. The $n$-Bu group was chosen as it would be inert to connective Pummerer reaction conditions and therefore no complications involving its participation in the reaction could arise. We planned to use PMB (4-methoxybenzyl) as a protecting group for our more complex model systems; although its aromatic ring is activated at the wrong place for a Pummerer cyclisation and is not sufficiently electron-rich for spirocyclisation,76 we could not say for sure whether the PMB group would be compatible with the connective Pummerer conditions.
Scheme 43 – Model substrates for optimisation of the connective Pummerer cyclisation to form tetrahydroisoquinolines

Glyoxamides are readily accessible by oxidation of 2-hydroxyacetamides 234 (usually DMSO-mediated), which are themselves often made by hydrolysis of 2-acetoxyacetamides.82 Other methods for the synthesis of glyoxamides include oxidative cleavage of 2,3-dihydroxypropanamides 235 or acrylamides 236 (Scheme 44).83,84,85

Scheme 44 – Synthesis of glyoxamides

Following precedent from within the group, amine 237 reacted with 2-acetoxyacetic acid in the presence of a carbodiimide coupling reagent, N'(3-dimethylaminopropyl)-N’-ethylcarbodiimide hydrochloride (EDCI), and the resulting 2-acetoxyacetamide was hydrolysed to give 2-hydroxyacetamide 238 in good overall yield (Table 6, entry 1). As we eventually hoped to carry out connective Pummerer cyclisations on a substrate containing a second ester moiety, a route to glyoxamides which avoided potential problems with regioselective ester hydrolysis was desirable. Despite some literature precedent for the reaction of secondary amines with glycolic acid (2-hydroxyacetic acid), reaction between amine 237 and glycolic acid with EDCI gave poor yields of 2-hydroxyacetamide 238, presumably due to competitive self-condensation of glycolic acid. Changing the reaction solvent or adding an amine base (N-methyl morpholine, NMM) gave no improvement (Table 6, entries 2, 3 and 4).86,87 For n-butyl amine 239, EDCI coupling with 2-acetoxyacetic acid then ester hydrolysis gave the corresponding 2-hydroxyacetamide 240 in 77
% yield, whilst direct reaction with glycolic acid and EDCI gave a much lower yield of 21 % (Table 6, entries 1 and 2).

We then turned our attention to changing the protecting group on the glycolic acid derivative. 2,2-Dimethyl-1,3-dioxolan-4-one 241 has been reported to react with dialkylamines to form 2-hydroxyacetamides. 88,89 2,2-Dimethyl-1,3-dioxolan-4-one is commercially available but is also readily prepared from dry acetone and glycolic acid in the presence of acid. 90 In amide formation, the reaction has a much higher atom efficiency than using a coupling reagent such as EDCI, and the by-product of the reaction is acetone, which is readily removed by distillation. A trial reaction using an excess of dibenzylamine 237 under literature conditions looked promising; although conversion was relatively low after 16 h, the reaction proceeded cleanly and optimisation appeared possible (Table 6, entry 5).

![Chemical structure](image)

Table 6 – 2-Hydroxyacetamide formation

As the reaction of dibenzylamine 237 with the acetonide 241 was slow using conventional, thermal heating, we hoped that the rate-acceleration afforded by microwave heating could improve the conversion of the reaction. 91 Optimisation reactions were carried out using 1 mmol of amine.

Using an excess of the acetonide, microwave heating at 150 °C in PhMe gave 2-hydroxyacetamide 238 in good yield. Although complete conversion was not achieved and starting material (15 %) was also recovered, microwave heating showed a clear improvement over thermal heating (Table 7, Entry 1).
On switching the solvent to DMF and increasing the temperature to 160 °C, a lower yield of product was isolated and the crude $^1$H NMR and discolouration of the crude reaction mixture indicated the presence of by-products. Reducing the temperature to 150 °C again gave a cleaner reaction mixture, but only a small increase in yield (only a trace of unreacted starting material was recovered) (Table 7, entries 2 and 3).

With dimethoxyethane (DME) as the solvent, the reaction was very clean and the yield obtained was comparable to that using PhMe. When the reaction was run in THF, conversion appeared to be much slower, with 35 % of the starting material isolated after 2 h at 150 °C (Table 7, entries 4 and 5).

Complete conversion was finally achieved in the absence of solvent, and 2-hydroxyacetamide 238 was isolated in good yield using either a 1.5- or 2-fold excess of the acetonide (Table 7, entries 6 and 7).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5 equiv 241, PhMe, 150 °C, 1 h</td>
<td>64 %&lt;sup&gt;a&lt;/sup&gt; 75 %&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>1.5 equiv 241, DMF, 160 °C, 1 h</td>
<td>44 %&lt;sup&gt;a&lt;/sup&gt; 54 %&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>1.5 equiv 241, DMF, 150 °C, 1 h</td>
<td>53 %&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>1.5 equiv 241, DME, 150 °C, 1 h</td>
<td>63 %&lt;sup&gt;a&lt;/sup&gt; quant&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>1.5 equiv 241, THF, 150 °C, 2 h</td>
<td>38 %&lt;sup&gt;a&lt;/sup&gt; 59 %&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>1.5 equiv 241, neat, 150 °C, 1 h</td>
<td>72 %&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>2.0 equiv 241, neat, 150 °C, 1 h</td>
<td>74 %&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Table 7 – Optimisation of reaction. <sup>a</sup>isolated yield; <sup>b</sup>yield based on recovered starting material

Reaction of $n$-Bu amine 239 with the acetonide 241 (2 equiv) on a 1 mmol scale gave the corresponding 2-hydroxyacetamide 240 in 68 % yield, although a slight decrease in yield was observed on increasing the scale of the reaction (Scheme 45).
With substrates in hand, we turned our attention to optimisation of the connective Pummerer reaction. We chose to use a fluorous thiol (HSCH₂CH₂C₈F₁₇) for optimisation studies as it would allow the use of FSPE to aid isolation of the tetrahydroisoquinolinone product. Disappointingly, following successful Swern oxidation of 2-hydroxyacetamide 240 to glyoxamide 232, treatment with typical connective Pummerer conditions (thiol, 16 h then TFAA 1 h then BF₃·OEt₂ 3.5 h) gave a complex reaction mixture from which only traces of the desired tetrahydroisoquinolinone 242 could be isolated after FSPE and flash chromatography (Scheme 46).

Attempts to effect a Friedel-Crafts cyclisation of the glyoxamide under literature conditions (TsOH, dioxane, Δ) or even slightly milder conditions (TsOH, CH₂Cl₂, RT) did not furnish the expected 4-hydroxytetrahydroisoquinolinone 243, but resulted in decomposition of the glyoxamide. On treatment of glyoxamide 232 with 20 mol% Sc(OTf)₃, the only compound isolated from the complex reaction mixture was a tetrahydroisoquinoline 244 bearing a methylsulfanyl group at the 4 position rather than the expected alcohol 243. This product is thought to have formed by reaction of residual DMS from the Swern oxidation with the glyoxamide (Scheme 47).
In order to discover the source of the problem, the reaction was broken down into its component steps. Glyoxamide 232 was treated with fluorous thiol and complete conversion (by $^1$H NMR) to the hemithioacetal 245 occurred. On treatment of the hemithioacetal 245 with TsOH, no reaction occurred, but in the presence of 100 mol% Sc(OTf)$_3$, ~20 % conversion to the tetrahydroisoquinolinone 242 was observed by $^1$H NMR after 1 h. Although this result was encouraging, work on optimising the cyclisation of the capped hemithioacetal was prioritised. A separate portion of hemithioacetal 245 was capped with TFAA to give 246, which was washed to remove excess reagent and its structure confirmed by $^1$H NMR. No reaction occurred after addition of TsOH to 246. The desired product 242 was, however, isolated in 31 % and 21 % yield when a fresh portion of capped hemithioacetal 246 was treated with Sc(OTf)$_3$ (100 mol%) and BF$_3$•OEt$_2$ respectively. The capping and Sc(OTf)$_3$-mediated cyclisation steps were combined in one-pot and the tetrahydroisoquinolinone product 242 was isolated in 15 % yield from hemithioacetal 245 (Scheme 48).

Unfortunately, combining hemithioacetal formation, capping and cyclisation using Sc(OTf)$_3$ gave irreproducible yields of 242. In some cases, hemithioacetal formation was observed to be
incomplete and unreacted glyoxamide and thiol (when used as the limiting reagent) could be observed by TLC and \(^1\)H NMR.

Concerned that poor glyoxamide quality could be affecting the reaction, different methods for the synthesis of glyoxamides were examined. Oxidation of hydroxyamide 240 using Dess-Martin periodinane was tried, both with and without pyridine to buffer the reaction, but the glyoxamide thus formed was contaminated with unreacted hydroxyacetamide and periodinane by-products. In order to attempt the synthesis of a glyoxamide by oxidative cleavage of a diol, the use of bis-acetonide of L-(+)-tartaric acid 247 to make a diol was explored. On treatment of 247 with an excess of alkylbenzylamine 239 under microwave conditions, the expected diamide 248 was unfortunately not observed. The major product of the complex reaction mixture was a pyruvamide 249 (Scheme 49).

**Scheme 49 – Attempted diol synthesis**

The pyruvamide is believed to form following attack of the amine on one of the carbonyl groups of 247, elimination of the resulting intermediate, tautomerisation and decarboxylation (elimination of the bis-acetonide is known to occur with \(t\)-BuOK at low temperatures\(^{93}\) and an observed build-up of pressure in the microwave vial lends support to a mechanism involving the evolution of a gas) (Scheme 50).

**Scheme 50 – Proposed mechanism for the formation of pyruvamide 249**
As the PMB and \(n\)-Bu protected hydroxyacetamides, glyoxamides and hemithioacetals exist as a mixture of rotamers (1:1.2 by \(^1\)H NMR for \(n\)-Bu hydroxyacetamide 240 and 1:1.1 for PMB hydroxyacetamide 238); it was thought it may be possible that the existence of rotamers could be affecting the connective Pummerer reaction. In an attempt to bias rotamer populations towards one favouring cyclisation, a substrate 250 bearing a bulkier protecting group on nitrogen, \(i\)-Pr, was synthesised. Of two attempts at hydroxyamide formation using acetonide 241 under the previously optimised conditions, both were low yielding with large amounts of unreacted amine remaining, presumably due to the increased steric bulk around the amine. The ratio of rotamers for the \(i\)-Pr hydroxyacetamide 250 was however similar to the \(n\)-Bu and PMB substrates (~1.1:1 by \(^1\)H NMR). Nevertheless, Swern oxidation and a connective Pummerer reaction using the best conditions found thus far (R\(^7\)SH, TFAA then Sc(OTf)\(_3\)) were carried out to give the cyclised product 251 in 5 % yield.

Scheme 51 – Synthesis and cyclisation of a \(N\)-\(i\)-Pr substrate

Taking inspiration from initial work on pyruvamide substrates, in which a Lewis acid (ZnCl\(_2\)) was used to promote hemithioacetal formation, glyoxamide 232 was treated with thiol and a sub-stoichiometric amount of Lewis acid (20 mol % Sc(OTf)\(_3\) or ZnCl\(_2\)). Pleasingly, \(^1\)H NMR monitoring of the reaction after 18 h indicated that not only had the hemithioacetal 245 formed, but partial conversion to the desired tetrahydroisoquinolinone product 242 had also occurred (~65 % conversion for Sc(OTf)\(_3\) and ~25 % conversion for ZnCl\(_2\). After extended reaction times, complete consumption of the hemithioacetal had occurred and the product was isolated in moderate to good yield. Further experiments indicated that the use of stoichiometric Lewis acid led to a small increase in yield with decreased reaction times, although it was felt this improvement was not sufficient to justify the use of equimolar quantities of an expensive reagent. ZnCl\(_2\) gave moderate yields (Table 8, entry 1 and 4). BF\(_3\)\(\cdot\)OEt\(_2\) was also evaluated, but proved to be the worst Lewis acid of those tried (Table 8, entry 3). The best results were obtained using Sc(OTf)\(_3\) (Table 8, entry 2 and 5).
<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5 equiv R^F SH, 0.2 equiv ZnCl_2, CH_2Cl_2, 64 h</td>
<td>49 %</td>
</tr>
<tr>
<td>2</td>
<td>1.5 equiv R^F SH, 0.2 equiv Sc(OTf)_3, CH_2Cl_2, 40 h</td>
<td>67 %</td>
</tr>
<tr>
<td>3</td>
<td>1.5 equiv R^F SH, 0.2 equiv BF_3·OEt_2, CH_2Cl_2, 44 h</td>
<td>26 %</td>
</tr>
<tr>
<td>4</td>
<td>1.5 equiv R^F SH, 1.0 equiv ZnCl_2, CH_2Cl_2, 19 h</td>
<td>56 %</td>
</tr>
<tr>
<td>5</td>
<td>1.5 equiv R^F SH, 1.0 equiv Sc(OTf)_3, CH_2Cl_2, 19 h</td>
<td>74 %</td>
</tr>
</tbody>
</table>

**Table 8 – Lewis acid screen for the connective Pummerer reaction**

**Scheme 52 – Application of optimised connective Pummerer conditions to the synthesis of 4-sulfanyltetrahydroisoquinolinones.**

Having established optimum conditions (1.5 equiv thiol and 20 mol% Sc(OTf)_3), the reaction was carried out on glyoxamide 232 using methyl 3-mercapto propanoate 252 as the thiol and the product 253 was isolated in good yield. A slight reduction in yield was observed when 1.0 equiv...
of thiol was used. The conditions were found to be compatible with the PMB protected substrate 233 as well as a range of thiols, including, importantly, a cysteine derivative 256 (Scheme 52). In some cases, a 4-methylsulfanyl by-product 258 was also isolated.

In order to further probe the scope of the new connective Pummerer conditions, hydroxyamides 259 and 260 which bear less electron-rich aromatic rings were prepared, oxidised under Swern conditions then treated with thiol and 20 mol% Sc(OTf)_3. However, only hemithioacetals and no cyclised material were detected by ^1H NMR. This suggests that a highly activated aromatic ring is necessary for cyclisation to occur (Scheme 53).

![Scheme 53 - Synthesis and attempted cyclisation of substrates with less electron-rich aromatic rings.](image)

The competency of hemithioacetals and acylated hemithioacetals as reaction intermediates is suggestive of a connective Pummerer-type mechanism (Scheme 54). Hemithioacetal 245 was synthesised by trapping the newly formed glyoxamide with thiol at the end of the Swern reaction. Following partial characterisation, it was treated with ZnCl_2 to give tetrahydroisoquinolinone 242 in good yield. A similar portion of hemithioacetal was treated with TFAA to give a capped hemithioacetal 246 which cannot revert to glyoxamide, so any cyclisation which takes place must occur via a thionium ion. On treatment with ZnCl_2, this gave tetrahydroisoquinolinone 242 in moderate yield, which suggests that thionium ions do play a role in the reaction mechanism. Additionally, as 4-hydroxytetrahydroisoquinolinone 243 was not observed when glyoxamides were treated with protic or Lewis acid, it seems unlikely to be a reaction intermediate.
Prior to completing the optimisation of connective Pummerer conditions for glyoxamides, cyclisation of an accidentally-synthesised pyruvamide 249 was attempted. Following the reaction by $^1$H NMR, it appeared that no hemithioamide formation occurred on treatment of the ketone with fluorous thiol. On addition of ZnCl$_2$ (0.7 equiv),$^{94}$ the equilibrium was shifted towards hemithioamide 261 and a $\sim$3:2 mixture of ketone and hemithioamide was observed by $^1$H NMR. Despite the significant amount of unreacted starting material remaining, the next stage of the reaction was carried out, and following treatment with TFAA and Sc(OTf)$_3$, a 4-methyl-4-sulfanyl tetrahydroisoquinolinone 262 was isolated, albeit in low yield; this constituted the first example of a connective Pummerer reaction on a ketone substrate (Scheme 55).

Following this small success, an improved method for the synthesis of pyruvamide starting materials was sought to allow further investigation of connective Pummerer cyclisations involving ketones. Reaction between $n$-Bu benzylamine 239 and pyruvic acid in the presence of EDCI was low-yielding (24 %), but a reagent not so dissimilar to the bisacetonide 247 originally used proved superior. Hydroxymaleic anhydride pyridinium salt 263,$^{95,96}$ was synthesised from L- (+)-tartaric acid and produced pyruvamides cleanly in good yield on exposure to amines 237 and 239, and at lower temperatures than were required for 247 (Scheme 56).
Scheme 56 – Improved synthesis of pyruvamides

This reaction bears some similarity to that of 247 as described earlier in section 2.1. Elimination of one of the hydroxyl groups occurs following acetylation and exposure to pyridine during the synthesis of the reagent rather than after attack of the amine, but a similar β-keto-acid which undergoes decarboxylation is invoked in the proposed mechanism (Scheme 57).

Scheme 57 – Proposed mechanism for reaction of 256 with amines to form pyruvamides

With pyruvamide substrates and new connective Pummerer reaction conditions in hand, the two were brought together and a range of 4-methyl-4-sulfanyl tetrahydroisoquinoliones 265-269 were thus synthesised in moderate to good yields (Scheme 58).
Scheme 58 – Synthesis of 4-methyl-4-sulfanyl tetrahydroisoquinolinones

The use of chiral scandium complexes to catalyse organic reactions and give enantioenriched products is well established. The first example was reported by Kobayashi, who used Sc(OTf)₃ with BINOL and a tertiary amine to catalyse a Diels-Alder reaction between an acryloyl oxazolidin-2-one 270 and cyclopentadiene 271. Evans has employed scandium-PyBox complexes to promote enantioselective addition of a range of nucleophiles, including allyl silanes 272, to electrophiles, including glyoxylates and glyoxamides 273. These complexes have also been used to control 1,4-additions onto acryloyl oxazolidinone derivatives using thiol nucleophiles and asymmetric Friedel-Crafts reactions of indoles with 2-oxo-4-aryl-3-butenoate esters. The reactions all involve 1,2- or 1,3-dicarbonyl species which can chelate to scandium, while the chiral ligand blocks one face from the reaction partner (Scheme 59). Other ligands, including bipyridyl derivatives and N-oxides, have also been used.
Scheme 59 – Reactions catalysed by chiral scandium complexes.

Tetrahydroisoquinolinone products derived from glyoxamides have an acidic proton at the stereogenic centre and therefore may readily epimerise, but 4-methyl tetrahydroisoquinolinone products from pyruvamides lack this proton and should be more configurationally stable. Pyruvamides 249 and 264 were treated with Sc(OTf)$_3$ and a chiral ligand (either (S)-PyBox 274 or (S)-BINOL 275 with a tertiary amine), molecular sieves and thiol in the hope that the products would be enantioenriched. Disappointingly, even with stoichiometric Sc(OTf)$_3$ and ligand, neither pyruvamide 249 or 264 underwent any reaction (Scheme 60). This may be due to either increased steric hindrance around the metal (making co-ordination of the pyruvamide more difficult), or an increase in electron density at the metal (making it less Lewis acidic) or a combination of the two factors. However, further work should allow an asymmetric variant of the work to be developed.
Scheme 60 – Attempts at an asymmetric cyclisation

For 4-methyl-4-sulfanyl tetrahydroisoquinolinone 269, it was found that the chemical yield was dependent on the duration of the reaction, although starting material had been consumed (TLC) in both cases. A by-product, 4-hydroxy-4-methyl tetrahydroisoquinolinone 276, was isolated, resulting in a roughly equal mass balance across both reactions (Scheme 61).

Scheme 61 – Variation of chemical yield with time in the cyclisation of pyruvamides

This result indicated that an alternative reaction mechanism which does not invoke a thionium ion could be operating for pyruvamide substrates (Scheme 62). Instead, direct cyclisation of the pyruvamide to 4-hydroxy-4-methyl tetrahydroisoquinolinone and a S_N1-type substitution could potentially give identical reaction products. This alternative mechanism seems more favourable in the pyruvamide case than in the glyoxamide case as a more-stabilised tertiary carbocation is invoked.
Due to the position of equilibrium between ketone and thiol, a cross over experiment could not be carried out as in the glyoxamide case to test the competency of hemithioacetals and capped hemithioacetals as reaction intermediates. However, testing the competency of 4-hydroxy-4-methyl tetrahydroisoquinolinone 276 was possible: in the absence of thiol, pyruvamide 264 was treated with Sc(OTf)$_3$ and cyclised to give 276. However this reaction was much slower than the reaction performed in the presence of thiol: just under half of the starting material was recovered after the 72 h reaction, compared to the formation of 269 where the starting material was completely consumed within 18 h. The hydroxy compound 276 was successfully converted to a sulfanyl compound 266 on treatment with thiol and Sc(OTf)$_3$, suggesting that the alternative reaction mechanism is plausible, but its initial cyclisation is far slower than reaction in the presence of thiol (Scheme 63).

Taking the results of these experiments into account, it is believed that a connective Pummerer mechanism is in operation, but the alternative pathway also occurs as a background reaction.
2.3 Synthesis of an Et 597 ABH ring system analogue

Having established reaction conditions for the synthesis of simple tetrahydroisoquinolinones, attention was turned to more complex, branched systems (TBS-protected, enantioenriched hydroxyamide 277) which could be used in an approach to Et 597 analogues. Starting from aldehyde 278, Wittig olefination gave styrene 279 which was oxidised under Sharpless AA conditions\(^{105,106}\) using benzylcarbamate (CbzNH\(_2\)) or \(\alpha\)-butylcarbamate (BocNH\(_2\)) as the nitrogen source to give the desired aminoalcohols 280 (92 % ee by chiral HPLC) and 281; regioisomers 282 and 283 were also formed in the reaction, but were discarded (Scheme 64).

![Scheme 64 – Synthesis of an enantioenriched aminoalcohol using Sharpless AA.](image)

As hydrogenolysis of the Cbz protecting group of 280 proved problematic, we focused on Boc-protected amine 281. Following cleavage of the Boc protecting group with TFA, \(\alpha\)-butyldimethylsilyl (TBS) protection of the resulting aminoalcohol 284 was initially attempted using typical conditions (TBSCI, imidazole) but the product could not be extracted from the aqueous layer on work-up. The use of modified conditions (TBSCI, NEt\(_3\), DMAP\(^{107}\)) allowed successful isolation of 285, which was subjected to reductive amination conditions to install the PMB group to give 286.\(^2\) Direct 2-hydroxyacetylation with acetonide 241 was unsuccessful (presumably due to the increased steric bulk of the amine decreasing the rate of reaction and the increased molecular complexity leading to greater potential for side reactions), but after carbodiimide coupling of amine 286 with acetoxyacetic acid and careful hydrolysis, the 2-hydroxyacetamide 277 was isolated in moderate yield (Scheme 65).
Scheme 65 – Synthesis of enantioenriched hydroxyamide 277

2-Hydroxyacetamide 277 was oxidised under Swern conditions then exposed to thiol and 20 mol% Sc(OTf)_3 but, disappointingly, the reaction mixture was complex and the isolated yield of the desired product 287 was low. In one case a single diastereoisomer was isolated but in another both possible diastereoisomers were present as an inseparable mixture. Although many of the by-products could not be separated from one another, a hydroxymorpholinone by-product 288 was isolated from a reaction mixture. It was presumed to have formed by loss of the TBS group from the glyoxamide and attack of the resulting alcohol on the glyoxamide, and it was decided that the use of a more stable protecting group would be beneficial (Scheme 66).

Scheme 66 – Attempted connective Pummerer cyclisation of 277

A 2-hydroxyacetamide 289 bearing the more robust tri-/iso-propylsilyl (TIPS) protecting group was synthesised by modification of the route used to access TBS ether 277. Following Sharpless AA, the TIPS group could be installed before removal of the Boc group due to its increased stability towards acidic conditions, giving 290. The desired amino alcohol regioisomer 281 bearing a less hindered primary alcohol was selectively silylated, facilitating separation from the undesired regioisomer 283. PMB protection was carried out as before to give amine 291, but optimisation of the acylation and hydrolysis conditions was required. Amine 291 was not totally consumed on treatment with 2-acetoxyacetic acid, EDCI and HOBt (~30% of amine 292 was recovered), but complete conversion was achieved using 2-acetoxyacetyl chloride. The resulting
2-acetoxyacetamide had low solubility in the 2:1 MeOH-H$_2$O solvent mixture previously used for the hydrolysis step, necessitating the use of different conditions: LiOH$\cdot$H$_2$O in THF-MeOH-H$_2$O (12:2:3) (Scheme 67).

Scheme 67 – Synthesis of TIPS-protected hydroxyamide 289

As the Sharpless asymmetric aminohydroxylation proved unreliable on a larger scale, an alternative route based on literature precedent was explored.\textsuperscript{92} Although this increased the step-count of the synthesis and slightly decreased the overall yield, this was compensated for by greater dependability.

Scheme 68 – Sharpless AD-Mitsunobu route to amine 292. AD mix-$\alpha$ consists of (DHQ)$_2$PHAL, K$_2$CO$_3$, K$_3$Fe(CN)$_6$, K$_2$OsO$_6$$\cdot$2H$_2$O.

Sharpless asymmetric dihydroxylation (AD) of styrene 279 using the (DHQ)$_2$PHAL ligand\textsuperscript{108} and regioselective TIPS-protection of the primary alcohol gave silyl ether 293. A Mitsunobu reaction
with amide 294 was attempted in the hope of reducing the step-count of the synthesis, but was unsuccessful (presumably as the amide nitrogen is not acidic enough to act as a nucleophile). Using phthalimide, the Mitsunobu reaction proceeded in modest yield then hydrazinolysis of the resulting phthalimide 295 gave amine 291 in ~85 % ee (chiral HPLC) and reductive amination under improved conditions furnished amine 292 in excellent yield (Scheme 68).

Hydroxyamide 289 was oxidised under Swern conditions and the resulting glyoxamide treated with methyl 3-mercaptopropanoate 252 and 20 mol% Sc(OTf)3. Unfortunately the yield was poor once again, although the TIPS group was largely retained. The main component of the crude reaction mixture was 4-hydroxy tetrahydroisoquinolinone 296 as a single diastereoisomer. Small amounts (~4 %) of the desired products 297a and b and methyl sulfide 298 were also isolated. Changing the Lewis acid to ZnCl2 (20 mol%) improved the yield of the desired tetrahydroisoquinolines to 36 %, then using stoichiometric ZnCl2 increased the yield further to 58 %. However, this result was not reproducible, with yields in subsequent experiments ranging from 30-60 %, and similarly when cysteine derivative 256 was used as the thiol, yields of tetrahydroisoquinoline 299 varied from 15-58 %. Morpholinone 288 was also isolated from some reaction mixtures (Scheme 69).

Scheme 69 – Initial attempts at cyclisation on the branched TIPS substrate.

Methyl sulfide 298 is believed to result from the reaction of methyl sulfide contaminants from the Swern oxidation which were trapped in the glyoxamide 300. Alcohol 296 is generated by direct cyclisation of the glyoxamide (Scheme 70).
Scheme 70 – Formation of by-products in the connective Pummerer reaction.

Both the 4-hydroxytetrahydroisoquinolone 296 and the 2-hydroxymorpholin-3-one 288 by-products could be converted to useful sulfanyl products. 4-Hydroxytetrahydroisoquinolone 296 reacted slowly (<50 % conversion in 24 h) to give 297 as a mixture of diastereoisomers on stirring with thiol 252 and 20 mol% Sc(OTf)₃. Using 100 mol% ZnCl₂ and thiol 252, alcohol 296 was converted to a mixture of sulfide diastereoisomers 297 (~70 % conversion in 20 h) in 58 % yield. A similar transformation could also be accomplished by converting the hydroxyl group of 296 to a better leaving group: mesylation of 296 and displacement with cysteine derivative 256 gave the desilylated tetrahydroisoquinolinone 301 in 61 % yield (Scheme 71).

Scheme 71 – Conversion of 4-hydroxytetrahydroisoquinolone 296 to 4-sulfanyltetrahydroisoquinolones 297

2-Hydroxymorpholin-3-one 288 was converted to 302 upon treatment with thiol 252 and 100 mol% ZnCl₂ (~66 % conversion in 20 h), or Sc(OTf)₃. When the reaction was performed in refluxing MeCN with 10 mol% Sc(OTf)₃, the reaction time decreased to 3 h and the sulfide product was isolated in 55 % yield (Scheme 72).
Scheme 72 - Conversion of hydroxymorpholinone 288 to tetrahydroisoquinolinone 302.

Due to glyoxamide decomposition during Swern reactions to give either hydroxytetrahydroisoquinolinone 296 or a complex mixture of compounds, an alternative oxidation reaction was sought, and Parikh-Doering reactions (DMSO, SO$_3$•Py, NEt$_3$) were found to proceed cleanly. Additionally, N-Troc cysteine methyl ester 256 was exchanged at this stage for N-Troc cysteine t-butyl ester 303 due to problems with deprotection reactions later in the synthetic sequence. Trapping the glyoxamide as a hemithioacetal 304 or 305 by addition of thiol directly to the oxidation reaction mixture before work up, then treating the resulting hemithioacetal with Lewis acid gave cleaner reaction mixtures – no methyl sulfide by-products were observed (presumably the less viscous hemithioacetals did not trap as much Me$_2$S as the gummy glyoxamide did). Yields of 297 and 306 were still low when using stoichiometric or sub-stoichiometric ZnCl$_2$, but the use of 1.5 or 2 equivalents ZnCl$_2$ increased yields dramatically and no by-products were observed by $^1$H NMR in the crude reaction mixture (Scheme 73).

Scheme 72 – Conversion of hydroxymorpholinone 288 to tetrahydroisoquinolinone 302.

Scheme 73 – Connective Pummerer cyclisations with thiol trapping

297; $R^1 = H$, $R^2 = Me$ 81 %, dr = 1:1 (using 2.0 equiv ZnCl$_2$)
306; $R^1 = NHTroc$, $R^2 = t$-Bu 57 %, dr = 1:1 (using 1.5 equiv ZnCl$_2$)
It is uncertain whether the reaction occurs completely via a connective Pummerer pathway. The desired 4-sulfanyltetrahydroisoquinolinone product 297 was isolated in 22% when hemithioacetal 303 was treated with TFAA, indicating that the connective Pummerer pathway is feasible. However, monitoring the progress of the cyclisation reaction promoted by ZnCl₂ using ³H NMR suggested that some cyclisation-substitution was taking place. The spectrum of an aliquot taken 25 minutes after ZnCl₂ addition revealed complete consumption of the hemithioacetal and formation of both diastereoisomers of product 297 in addition to another compound. The peaks of this third component correspond to those of 4-hydroxytetrahydroisoquinolinone 296 in the presence of ZnCl₂. Over the course of the reaction, the peaks of the 4-hydroxytetrahydroisoquinolinone-Zn complex decayed until only 297a and b were present after 3.5 h (Figure 1).

Figure 1 – Following the cyclisation by ³H NMR.

To continue the synthesis of the ABH ring system analogue, treatment of a mixture of diastereoisomers of tetrahydroisoquinolinone 297 with TBAF produced alcohol 302 as a mixture of diastereoisomers, which were then subjected to ester hydrolysis conditions to give ω-hydroxyacid 307 as a single diastereoisomer in moderate yield. Epimerisation was thought to occur via reversible formation of enolate 308 (Scheme 74).
Scheme 74 – Deprotection of tetrahydroisoquinolinone 297

Macromodel computational modelling and conformational energy minimisation using an MM2* forcefield suggested that the cis isomer 307 was lower in energy than the trans-isomer and would be the major product of thermal equilibration (Figure 2). A single crystal X-ray structure confirmed the isolated ω-hydroxyacid 307 did indeed have cis stereochemistry (Figure 3).

Figure 2 – Molecular modelling of ω-hydroxyacid 307
Figure 3 – X-ray structure of ω-hydroxyacid 307 (2 conformations were present within the crystal)

Table 9 – Attempted optimisation of the Yamaguchi macrolactonisation. *by \(^1\)H NMR

<table>
<thead>
<tr>
<th>Entry</th>
<th>Addition time/h</th>
<th>Equiv. DMAP</th>
<th>309 : 310*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3.0</td>
<td>1 : 1</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>6.0</td>
<td>2.6 : 1</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>6.0</td>
<td>2.6 : 1</td>
</tr>
</tbody>
</table>
As it is difficult to predict the optimum macrolactonisation conditions for a novel ω-hydroxyacid, a screen of conditions for closing the macrolactone was carried out, starting with the Yamaguchi conditions (2,4,6-trichlorobenzoyl chloride, NEt₃; filtration to remove salts then slow addition of the resulting mixed anhydride to excess DMAP in refluxing PhMe). Initially, a 1:1 mixture of the desired product 309 and a diolide 310 was obtained (Table 9, entry 1). This could be improved to 2.6:1 by modification of the reaction conditions, (Table 9, entries 2 and 3) but since 309 and 310 were almost completely inseparable by flash chromatography and reverse phase-HPLC, a different approach was pursued.

No reaction occurred when macrolactonisation under Mitsunobu conditions (di-t-butylazodicarboxylate [DTBAD], PPh₃, high dilution, THF) was attempted (Table 10, entry 1). Corey-Nicolaou conditions (di(2-pyridyl)disulfide, PPh₃, PhMe then slow addition of the resulting thioester to refluxing PhMe), were more successful: the ¹H NMR spectrum of the crude reaction mixture revealed 70 % chemical conversion and an improvement in product ratio (Table 10, entry 2). Finally, Shiina’s conditions (2-methyl-6-nitrobenzoic anhydride [MNBA], DMAP, high dilution) were tried and furnished the desired macrolactone 309 with excellent selectivity in 65 % yield after chromatography (Table 10, entry 3).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Addition time / h</th>
<th>309 : 310</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>PPh₃, DTBAD, PhMe, RT</td>
<td>6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>PPh₃, 2,2′-dipyridyl disulfide, PhMe, RT then Δ</td>
<td>~12</td>
<td>20 : 1</td>
<td>70 %⁸</td>
</tr>
<tr>
<td>3</td>
<td>MNBA, DMAP, CH₂Cl₂, RT</td>
<td>7</td>
<td>40 : 1</td>
<td>65 %⁹</td>
</tr>
</tbody>
</table>

Table 10 – Screening conditions for macrolactonisation. ⁸conversion by ¹H NMR, ⁹isolated yield.

Treatment of cysteinyl tetrahydroisoquinolinone 290 with TBAF gave variable yields (8-65 %) of the desired alcohol 301, and in one case a compound believed to be amine 311 was also detected, perhaps by attack of the silanol by-product on the carbamate (TMSOK is known to cleave Troc groups)⁷⁰. Although it couldn’t be isolated cleanly for characterisation, treatment of
amine 311 with TrocCl gave the desired carbamate 301 (Scheme 75). Basic hydrolysis of methyl ester 301 proved low yielding, thus the use of an ester which could be cleaved under different conditions was explored instead.

More acidic conditions were investigated for the deprotection of silyl ether 306 in an effort to prevent loss of the Troc group. Addition of a trace of AcOH to the reaction did not improve the yield, so alternative fluoride sources were then tried; reaction using KF+H₂O in MeOH–H₂O with a small amount of AcOH was very slow and 87 % of the silyl ether was recovered after 6 days. Finally, careful treatment of a mixture of diastereoisomers of 306 with 60 % aqueous HF in MeCN gave a single diastereoisomer of alcohol 312 in 64 % yield (the ¹H NMR spectrum of the crude reaction mixture suggested some cleavage of the t-Bu ester may have occurred under these conditions, but no carboxylic acid could not be isolated). Cleavage of the t-butyl ester was accomplished under acidic conditions, and Shiina macrolactonisation gave the model ABH ring system 313 in moderate yield (Scheme 76).

2.4 Synthesis and cyclisation of acetals: towards a one-pot synthesis of ABH ring system analogues

In addition to sequential formation of the B and H rings in our model system, it was desirable to form both rings in a one-pot reaction. In order to achieve this, the acetate protecting group on
the glycolic acid residue during amide formation need to be changed, as there would now be a second ester group present in the molecule which could give rise to issues with regioselectivity during hydrolysis. The use of a protected glyoxyllic acid derivative was also desirable, as it would already be at the correct oxidation level, allowing omission of the oxidation step and possibly a deprotection step (Scheme 77). With these criteria in mind, acetal substrates and conditions for connective Pummerer cyclisations were investigated.

Scheme 77 – Advantages of a protected glyoxamide in the proposed one-pot synthesis of the ABH-ring system analogue.

Aldehydes can be protected as 1,1-diacyloxy derivatives, also known as acylals, in the presence of the corresponding acid anhydride and a Lewis acid. These protecting groups are more stable under aqueous acidic conditions than conventional acetals but can be cleaved under mild alkaline conditions. Some carboxylic acid-containing pharmaceuticals (such as cephalosporin antibiotics) are orally administered in the form of acylal pro-drugs which display improved bioavailability and are hydrolysed following absorption to reveal the active compound. Acylals have been used as formaldehyde equivalents, electrophiles in Friedel-Crafts reactions and as precursors to S,O-acetals and oximes.

1,1-Diacetoxyacetamide 314 was prepared by reaction of 2,2-diacetoxyacetyl chloride 315 with amine 237. The reaction was sufficiently clean by 1H NMR for the product to be used without purification (Scheme 78). Flash chromatography was carried out on a sample for characterisation, but less than 50 % recovery was achieved, suggesting that the acylal 314
might not be stable towards silica and might not easily be carried through several steps of the synthesis of a branched substrate.

Scheme 78 – Synthesis of acylal derivative 314

Acylal 314 did not cyclise under the connective Pummerer conditions developed for aldehydes and ketones using Sc(OTf)₃ or ZnCl₂ (20 mol% Lewis acid was used initially but as no product formation was observed by TLC after 24 h, Lewis acid loading was increased to 100 mol% but still no conversion was detected) (Table 11, entry 1 and 2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield of 254</th>
<th>Yield of 237</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5 equiv 252, 0.2 equiv Sc(OTf)₃, CH₂Cl₂, RT, 24 h then 1.0 equiv Sc(OTf)₃, 24 h</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>1.5 equiv 252, 0.2 equiv ZnCl₂, CH₂Cl₂, RT, 24 h then 1.0 equiv ZnCl₂, 24 h</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>1.5 equiv 252, 0.2 equiv Sc(OTf)₃, MeCN, Δ, 4.5 h (29 % SM recovered)</td>
<td>20 %</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>1.5 equiv 252, 0.5 equiv Sc(OTf)₃, MeCN, Δ, 3 h</td>
<td>26 %</td>
<td>b</td>
</tr>
<tr>
<td>5</td>
<td>1.5 equiv 252, 1.0 equiv Sc(OTf)₃, MeCN, Δ, 1 h</td>
<td>47 %</td>
<td>b</td>
</tr>
<tr>
<td>6</td>
<td>1.5 equiv 252, 2.0 equiv Sc(OTf)₃, MeCN, Δ, 2.5 h</td>
<td>33 %</td>
<td>65 %</td>
</tr>
<tr>
<td>7</td>
<td>1.5 equiv 252, 1.0 equiv ZnCl₂, MeCN, Δ, 7 h (47 % SM recovered)</td>
<td>19 %a</td>
<td>8 %</td>
</tr>
<tr>
<td>8</td>
<td>1.5 equiv 252, 0.15 equiv TsOH, MeCN, Δ, 2 h</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 11 – Attempted optimisation of connective Pummerer acylal cyclisation. a by-products still present after flash chromatography. b detected in the ¹H NMR of the crude product mixture but not isolated.
On switching the reaction solvent to MeCN and carrying out the reaction at reflux with 20 mol% Sc(OTf)$_3$, around 30 % conversion was observed by $^1$H NMR, and the product 254 could be isolated along with unreacted starting material (Table 11, entry 3).

Increasing the ratio of Sc(OTf)$_3$ to 50 mol% brought about a small increase in yield, along with the presence of amine 237 in the $^1$H NMR of the crude product mixture (Table 11, entry 4). In the absence of thiol, heating the acylal substrate with 200 mol% Sc(OTf)$_3$ caused decomposition to give amine 237 plus impurities.

Using 100 mol% Sc(OTf)$_3$ gave the product in 47 % isolated yield, the highest achieved using this substrate. Amine 237 was also detected by $^1$H NMR (Table 11, entry 5). With 200 mol% Sc(OTf)$_3$, the yield of tetrahydroisoquinolinone dropped again, and amine 237 was isolated in 65 % yield, perhaps due to competing decomposition of the starting material (Table 11, entry 6).

Changing the Lewis acid to ZnCl$_2$ decreased the rate of reaction significantly, with <50 % acylal 314 remaining after 7 h and no reaction was observed using TsOH (Table 11, entries 7 and 8).

As the best yield obtained in the cyclisation was fairly poor and acylal 314 was prone to decomposition under the reaction conditions, this method of glyoxamide protection was abandoned in favour of dialkyl acetals.

Cyclic acetal 316 was synthesised but did not undergo reaction in the presence of thiol and 1.0 equiv Sc(OTf)$_3$ in refluxing MeCN, presumably due to its cyclic nature and gem-dimethyl group making thiolysis of the acetal unfavourable (Scheme 79). Unlike acylal 314, no decomposition of the substrate was observed, suggesting that dialkyl acetals were more compatible with these more forcing reaction conditions.

Scheme 79 – Synthesis and attempted cyclisation of cyclic acetal 316.

In the hope that they would be more reactive under the modified connective Pummerer conditions, dialkyl acetals 317 and 318 were synthesised. Initially, dichloroacetamide 319 was synthesised then treated with sodium alkoxide salts to access both acetals 317 and 318.
However, 318 could be prepared more easily by EDCI-coupling of amine 237 with diethoxycetic acid 320 (which was formed in quantitative yield by hydrolysis of commercially-available ethyl diethoxyacetate) (Scheme 80).

![Scheme 80 – Synthesis of acetal substrates 317 and 318.](image)

On treatment of dimethyl acetal 317 with thiol 252 and 100 mol% Sc(OTf)$_3$ in refluxing MeCN for 5 h, a ~4:1 ratio (by $^1$H NMR) of starting material to product 254 was obtained. Increasing the quantity of Lewis acid to 150 mol% resulted in ~60% conversion by $^1$H NMR after 4.5 h. The product was, however, inseparable from the unreacted starting material. By contrast, the diethoxy acetal 318 was consumed within 2.5 h under the same conditions and 254 was isolated in good yield (Scheme 81). Greater stability of dimethyl acetals relative to their diethyl counterparts has also been observed in other systems, such as acetals of acetylene dicarboxaldehyde.$^{121}$ The diethyl acetal was therefore selected for use in the attempted one-pot ABH ring system formation.

Treatment of diethyl acetal 318 with cysteine derivative 256 gave a mixture of desired product 257 (22%) and an ethyl carbamate analogue 321 (18%) (which was presumably formed by attack of ethanol on the trichloroethylcarbamate group under Lewis acid activation). An attempt to inhibit the formation of by-product 321 by performing the reaction at a lower temperature was unsuccessful; product formation was not observed by TLC analysis after 2 h at 60 °C. After 3.5 h at 70 °C, both the desired product and by-product were detected by TLC along with unreacted acetal. Using a larger excess of thiol 256 (2.0 equiv instead of 1.5 equiv) did improve the yield to 57% (although impurities were present in the product after chromatography). Addition of a ten-fold excess of 2,2,2-trichloroethanol (TCE) to the reaction mixture did appear to suppress by-product 321 formation, although the yield of the isolated product 257 decreased to around 39%, suggesting that in order to pursue this chemistry further, changing the protecting group on the cysteine nitrogen would be necessary (Scheme 81).
Scheme 81 – Cyclisation of dialkyl acetal substrates.

No tetrahydroisoquinolinone product was observed on heating diethyl acetal 318 with thiol 252 and TsOH or ZnCl₂. Treatment of acetal 318 with Sc(OTf)₃ in the absence of thiol gave a complex reaction mixture in which only the starting material was readily detected by ¹H NMR or mass spectroscopy, which suggests that 4-hydroxy or 4-alkoxy tetrahydroisoquinolinones are not readily formed under these reaction conditions.

Branched model 2,2-diethoxyacetamides 322 and 323 bearing different O-protecting groups were synthesised. Amine 292 reacted with diethoxycetic acid in good yield to furnish 322, and 323 was then obtained by protecting group manipulation (Scheme 82).

Scheme 82 – Synthesis of branched acetal substrates 322 and 323.
Acetal 322 was submitted to the modified connective Pummerer conditions for acetals, but the desired product was not detected and the major component of the reaction mixture was 2-ethoxymorpholinone 325, formed by loss of TIPS and cyclisation of the resulting alcohol onto the acetal. Despite the use of extended reaction times, it was not possible to convert this morpholinone to tetrahydroisoquinolinone 302. On replacement of TIPS with the more acid-stable acetate protecting group, acetal 323 did cyclise in good yield to give tetrahydroisoquinolinone 326 after treatment with thiol and Sc(OTf)_3 (Scheme 83).

Scheme 83 – Connective Pummerer cyclisations of branched acetals.

To synthesise a substrate for a one-pot synthesis of the model ABH ring system, alcohol 324 was coupled with TMTr-protected 3-thiopropanoic acid 327 (having ensured the acetal moiety of simple acetal 318 was stable under the acidic conditions required to cleave the TMTr protecting group). Poor conversion in the deprotection to give thiol 328 was observed using TFA in TFE, but switching the solvent to CH_2Cl_2 and addition of Et_3SiH to the reaction to quench the TMTr-cation improved the yield dramatically. The intramolecular cyclisation was initially attempted using 1.5 equiv Sc(OTf)_3, at a substrate concentration of 0.01 M in refluxing MeCN and the starting material was consumed after 1 h but no macrolactone was observed. Low concentration was employed to disfavour potential intermolecular reactions. A compound which we believed to be thioacetal 329 due to consistent MS and ^1H NMR was formed, but could not be isolated sufficiently cleanly for full characterisation. Modification of the reaction conditions by increasing the reaction time, replacing MeCN with PhMe or increasing the concentration ten-fold produced the same result (Scheme 84).
Scheme 84 – Attempted one-pot synthesis of the model ABH ring system

Molecular modelling indicated that in the lowest energy conformation of thioacetal 329, the distance between the acetal centre and the aromatic nucleophile is quite large, and folding the ring to reduce this distance may require twisting the amide bond, potentially requiring a large amount of energy (Figure 4). This meant that, although connective Pummerer reactions had been successfully carried out on simpler branched and unbranched substrates, the development of an intramolecular reaction to form both the B and H rings of the Et 597 skeleton is unlikely to be possible.

Figure 4 – Computational model of the lowest-energy conformation of thioacetal 329. (enantiomer shown is the opposite to that synthesised)

2.5 Synthesis and cyclisation of N,O-acetal protected branched glyoxamides

In the proposed synthesis, conversion of the model ABH ring systems 309 and 313 to Et 597 analogues requires partial lactam reduction and addition of a one-carbon acyl anion equivalent (such as cyanide, which can be readily converted to a carboxaldehyde group with SnCl₂) to the
resulting hemiaminal. Removal of the PMB protecting group would then furnish aminoaldehyde 212, which could be converted to Et 597 analogues (Scheme 85).

Scheme 85 – Proposed conversion of macrolactones 309 and 313 to Et 597 analogues

Attempted reduction of macrolactone 309 using LiBHEt3 or DiBAL gave mixtures of compounds from which the desired hemiaminal was not isolated. The presence of aldehyde peaks in 1H NMR spectra of reaction mixtures suggested that lactone reduction had occurred preferentially.

Scheme 86 – Attempted reduction of tetrahydroisoquinolinones.

Reduction of tetrahydroisoquinoline 289 was also attempted, but the only compound isolated from the reaction mixture was alcohol 330. Activation of the lactam carbonyl of simple tetrahydroisoquinoline 254 by treatment with Tf2O followed by nucleophile addition (TMSCN) and reduction was investigated. A 1H NMR spectrum of the reaction mixture indicated that the benzylic C-S bond had been reduced instead of the lactam, as peaks corresponding to the
sulfanyl moiety were not present. However, as diethylene glycol dimethylether could not be removed by chromatography or distillation, the products could not be characterised (Scheme 86).

Attention was turned briefly to removal of the PMB group, hoping that it could be replaced with an electron-withdrawing protecting group, such as a carbamate, which would facilitate lactam reduction. However, cleavage of PMB groups from tetrahydroisoquinolinones is known to be difficult, and in this case, typical reagents such as CAN would have caused unwanted Pummerer reactions. Treatment of 297 with DDQ, another reagent known to cleave PMB groups, had no effect.

A new protecting group strategy was then investigated. As the hydroxyamide used in the connective Pummerer reaction was synthesised from a 1,2-aminoalcohol, the use of a cyclic N,O-acetal or carbamate was appealing. Synthesis of acetalts and an oxazolidinone from a common precursor, amide 332 (synthesised by acylation and deprotection of amine 291), was desirable. However, instead of the desired N,O-acetonide, isochroman 333 was the major product when acetal formation was attempted, and the yield of oxazolidinone 334 was poor when 332 was treated with carbonyldiimidazole (CDI) (Scheme 87).

Scheme 87 – Initial attempts to form N,O-acetal and cyclic carbamate-protected 2-acetoxyacetamides.

Formation of an acetonide from aminoalcohol 284 was more successful; condensation of 284 with acetone followed by acylation with 2-acetoxyacetyl chloride then ester hydrolysis furnished 2-hydroxyacetamide 335 in moderate yield. Parikh-Doering oxidation of hydroxyamide 335, thiol addition and exposure to ZnCl₂ gave tetrahydroisoquinolinone 336 as a single diastereoisomer in good yield. However, deprotection to give 337 could not be accomplished as the acetal protecting group was unaffected by treatment with TFA, HCl or AcOH at RT, and heating with HCl led to decomposition (Scheme 88).
Scheme 88 – Formation and cyclisation of an acetonide-protected substrate

Molecular modelling predicted that in the lowest energy conformations of the two possible diastereoisomers of 336, the 1,4-\textit{trans} isomer would be the more stable (Figure 5). However, as 336 was not a solid, its stereochemistry could not be determined by X-ray diffraction.

Figure 5 – Modelling of the two possible diastereoisomers of acetonide 336.
Oxazolidinone 338 was synthesised from aminoalcohol 284 and was successfully acylated with acetoxyacetyl chloride to give carbamate 334 in superior yield. However, selective cleavage of the ester moiety to furnish 339 was not possible by basic hydrolysis or by DiBAL reduction, the only product observed in both cases was oxazolidinone 338. Acrylamide 340 was also synthesised in the hope that glyoxamide 341 could be formed by oxidative alkene cleavage, but the dihydroxylation conditions used led to decomposition (perhaps due to amide hydrolysis under the aqueous reaction conditions). Attempts to form an oxazolidinone substrate for the connective Pummerer reaction were abandoned and finding a acetal with the required stability became the main focus (Scheme 89).

Scheme 89 – Attempted formation of an oxazolidinone-protected glyoxamide

Synthesis of a benzylidene acetal was unsuccessful under the conditions used for acetonide formation as several by-products were also formed and the product decomposed during attempted characterisation. A 4-nitrobenzylidene acetal was then tried, as it would be more stable than a benzylidene but hopefully less stable than an acetonide. Initially, the yield of 2-aceoxygenacetamide 342 was low, but modification of the reaction conditions gave the desired product 342 in 5:1 dr by \(^1\)H NMR and in excellent overall yield. The two isomers were separated and hydrolysed to give diastereoisomeric hydroxamides 343a and 343b, which were individually oxidised and treated with thiol 252 then ZnCl\(_2\). From each reaction, a single diastereoisomer of tetrahydroisoquinolinone product 344a or 344b was isolated in good or moderate yield for the major and minor diastereoisomers 343a and 343b respectively. \(^1\)H NMR
analysis of an incomplete reaction showed only hemithioacetal and tetrahydroisoquinolinone were present, supporting a connective Pummerer pathway (Scheme 90).

Scheme 90 – Formation and cyclisation of a 4-nitrobenzylidene protected hydroxyamides 343a and 343b

The product from the major diastereoisomer 344a was subjected to acidic conditions (TFA in CH₂Cl₂, c. HCl in MeOH-H₂O, AcOH in MeCN) but was untouched at room temperature. Attempted reduction of the nitro group using indium and NH₄Cl in EtOH resulted in conversion to a compound which could not be sufficiently purified for characterisation, but upfield movement of the benzylidene peaks in the ¹H NMR spectrum suggested a species containing a more electron-rich aromatic ring and MS was consistent with aniline 345. After treatment of the intermediate with TFA, deprotected tetrahydroisoquinolinone 337 was isolated in 23 % yield. Interestingly, no sulfanyl-cleavage by-products resulting from electron transfer to the carbon-sulfur bond were observed (Scheme 91).

Scheme 91 – Attempted deprotection of the nitrobenzylidene
Using the modified conditions, benzylidene acetal-protected hydroxyamide 346 was finally synthesised in moderate yield as an inseparable mixture of diastereoisomers. Oxidation, hemithioacetal formation and treatment with 2 equiv ZnCl₂ gave a mixture of products: 2 diastereoisomers of tetrahydroisoquinoline 347 (15 %, believed to differ at the benzylidene centre), deprotected tetrahydroisoquinolinone 337 (24 %) and isochroman 348 (18 %; presumably formed by opening of the oxazolidine ring and attack of the aromatic ring on the oxonium ion intermediate) (Scheme 92).

![Scheme 92: Synthesis and cyclisation of a benzylidene acetal-protected hydroxyamide 346.](image)

Decreasing the amount of ZnCl₂ used, changing the Lewis acid to Sc(OTf)₃, increasing the amount of thiol and altering the reaction time had little effect on the combined yield of tetrahydroisoquinolines 347 and 337, whilst changing the solvent to THF or MeCN impeded cyclisation.

The structure and stereochemistry of by-product 348 was confirmed by a single crystal X-ray structure. The trans-relationship between the oxymethyl and sulfanyl substituents is the same as that predicted for acetonide-protected tetrahydroisoquinoline 336, suggesting that this may indeed be correct for all of the acetal-protected connective Pummerer products (Figure 6).
Lastly, a 4-bromobenzylidene acetal-protected hydroxyacetamide 349 was synthesised in the hope that its stability would be midway between a 4-nitrobenzylidene and benzylidene. However, the $^1$H NMR spectrum of the crude connective Pummerer reaction mixture showed a mixture of products and tetrahydroisoquinolinone 350 was isolated as a mixture of diastereoisomers in only 23 % yield. Although they were not isolated, peaks corresponding to isochroman 351 and tetrahydroisoquinoline 337 were visible in other fractions (Scheme 93).
Whilst these acetal protecting groups have shown some potential, further work would be necessary in order for this approach to be synthetically useful.

2.6 Future Work

Although attempts to perform asymmetric connective Pummerer cyclisations on pyruvamides were unsuccessful under the conditions tried, reactions involving glyoxamide substrates similar to those used by Evans and a non-tethered nucleophile may have the potential to be successful (Scheme 94).

Scheme 93 — Synthesis and cyclisation of bromobenzylidene protected 2-hydroxyacetamide 349.

Scheme 94 — Proposed asymmetric Pummerer-type reaction

Further studies are required to optimise a protecting group strategy for the synthesis of the Et ABH ring system. If an acetal which is stable to cyclisation conditions but can be removed afterwards is not found, two separate protecting groups will be required. Silyl groups have been shown here to be adequate for the protection of the alcohol moiety, whilst literature precedent
suggests that an allyl group may be suitable for the amide. Following connective Pummerer cyclisation to give 210, replacement of the amide protecting group with an electron-withdrawing group such as a carbamate would facilitate lactam reduction. Once aldehyde 212 was obtained, coupling to phenylalanine derivative 213 would allow completion of the Et 597 skeleton and deprotection would provide completed analogues (Scheme 95).

Scheme 95 – Proposed completion of Et 597 analogues.
3. Experimental

3.1 General Experimental

All experiments were performed under an atmosphere of nitrogen, using anhydrous solvents, unless stated otherwise. THF was distilled from sodium and benzophenone; CH$_2$Cl$_2$, NEt$_3$ and PhMe were distilled from CaH$_2$. ZnCl$_2$ was dried in the oven at 120 °C. Microwave reactions were carried out using a Biotage Initiator. Room temperature (RT) varied from 5–30 °C. R$^5$SH = 3,3,4,4,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecane-1-thiol. $^1$H NMR and $^{13}$C NMR spectra were recorded using 300, 400 and 500 MHz spectrometers, with chemical shift values reported in ppm relative to residual chloroform (δ$_H$ = 7.27 or δ$_C$ = 77.2) or DMSO (δ$_H$ = 2.50 or δ$_C$ = 39.5) as internal standards. All coupling constants (J) are reported in Hertz (Hz). Mass spectra were obtained using positive and negative electrospray (ES±) methodology. Infra-red spectra were recorded as evaporated films or neat using a FT-IR spectrometer. Flash chromatography was carried out using 35–70 μm, 60 Å silica gel. Routine TLC analysis was carried out on aluminium sheets coated with silica gel 60 F254, 0.2 mm thickness. Plates were viewed using a 254 mm wavelength ultraviolet lamp and stained using p-anisaldehyde or phosphomolybdic acid.

General Procedure 1: Swern Oxidation

A solution of oxalyl chloride (0.096 ml/mmol, 1.1 equiv) in CH$_2$Cl$_2$ (4 ml/mmol) was cooled to –78 °C. DMSO (0.142 ml/mmol, 2.0 equiv) was added and the solution stirred for 5 minutes. A solution of 2-hydroxyacetamide in CH$_2$Cl$_2$ (4 ml/mmol) was added and the reaction stirred for 30 minutes. NEt$_3$ (0.695 ml/mmol, 5.0 equiv) was added and the solution allowed to warm to RT. After 3 h the reaction mixture was washed with sat. NaHCO$_3$ solution (3 × 10 ml/mmol) then dried (MgSO$_4$). The crude glyoxamide was used without further purification.

3.2 Synthesis and cyclisation of simple glyoxamides

(3,5-Dimethoxybenzyl)(4-methoxybenzyl)-amine 237

3,5-Dimethoxybenzaldehyde (3.32 g, 20 mmol) was dissolved in dry PhMe (100 ml) and 4-methoxybenzylamine (3.02 g, 22 mmol) was added. The mixture was heated at reflux under Dean-Stark conditions for 5 h then cooled and the solvent removed in vacuo. The residue was dissolved in dry MeOH (100 ml) and NaBH$_4$ (0.834 g, 22 mmol) was added portionwise. The solution was stirred at RT overnight then concentrated. The residue was taken up in EtOAc (100 ml) and washed with water (2 × 50 ml) then with brine (50 ml) and dried (MgSO$_4$). Flash chromatography (40 % EtOAc–pet. ether) gave 237 (5.42 g, 94 %) as a pale yellow oil.
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.27 (2 H, d, \(J = 8.6\) Hz, aromatic C-H of PMB), 6.88 (2 H, d, \(J = 8.6\) Hz, aromatic C-H of PMB), 6.52 (2 H, d, \(J = 2.3\) Hz, aromatic C-H), 3.82 (3 H, s, OCH\(_3\)), 3.80 (6 H, s, OCH\(_3\)), 3.75 (4 H, s, 2 \times CH\(_2\)).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 160.8 (aromatic C-O), 158.6 (aromatic C-O), 142.9 (aromatic C-C), 132.4 (aromatic C-C), 129.4 (aromatic C-H of PMB), 113.8 (aromatic C-H of PMB), 105.9 (aromatic C-H), 98.9 (aromatic C-H), 55.3 (3 \times OCH\(_3\)), 53.2 (CH\(_2\)), 52.5 (CH\(_2\)).

MS (ES+) \(m/z\) 288 [M+H]\(^+\). HRMS 288.1588; C\(_{17}\)H\(_{22}\)NO\(_3\) requires 288.1595.

IR (thin film) \(\nu\) max (cm\(^{-1}\)) 3323 (N-H), 2937 (C-H).

\(N\)-(3,5-Dimethoxybenzyl)-2-hydroxy-\(N\)-(4-methoxybenzyl)acetamide 238

\[
\begin{align*}
\text{MeO} & \quad \text{N} \\
\text{MeO} & \quad \text{OH} \\
\end{align*}
\]

**Method A – EDCI coupling with acetoxyacetic acid**

Amine 237 (861 mg, 3.0 mmol) was dissolved in CH\(_2\)Cl\(_2\) (15 ml) and acetoxyacetic acid (425 mg, 3.6 mmol), HOBT-H\(_2\)O (81 mg, 0.6 mmol) and EDCI (690 mg, 3.6 mmol) were added and the solution was stirred at RT for 20 h. The organic layer was washed with 1N HCl (3 \times 20 ml) then dried (MgSO\(_4\)) and concentrated \textit{in vacuo}. The residue was dissolved in MeOH (12 ml) and water (6 ml) then K\(_2\)CO\(_3\) (553 mg, 12 mmol) was added. The solution was stirred for 16 h and the volatiles evaporated. The residue was diluted with water (10 ml) and extracted with EtOAc (3 \times 15 ml). The organic extracts were washed with brine (10 ml) then dried (MgSO\(_4\)). Flash chromatography (50 % EtOAc–pet. ether) gave 238 (859 mg, 83 %) as a pale yellow oil.

**Method B – EDCI coupling with glycolic acid**

Amine 237 (861 mg, 3.0 mmol) was dissolved in CH\(_2\)Cl\(_2\) (15 ml) and glycolic acid (274 mg, 3.6 mmol), HOBT-H\(_2\)O (81 mg, 0.6 mmol) and EDCI (690 mg, 3.6 mmol) were added. The solution was stirred at RT for 18 h. The organic layer was washed with 1M HCl (3 \times 10 ml) (separation of the layers was difficult due to the presence of solid in the aqueous layer) then dried (MgSO\(_4\)). Flash chromatography (40–50 % EtOAc–pet. ether) gave 238 (176 mg, 18 %).

**Method C – EDCI coupling with glycolic acid**

Amine 237 (287 mg, 1.0 mmol) was dissolved in CH\(_2\)Cl\(_2\) (6 ml) and THF (3 ml) and glycolic acid (76.1 mg, 1.0 mmol), HOBT-H\(_2\)O (38 mg, 0.2 mmol) and EDCI (211 mg, 1.1 mmol) were added. The solution was stirred at RT for 17 h. The reaction mixture was poured into EtOAc (15 ml), washed with water (10 ml) and brine (10 ml) then dried (Na\(_2\)SO\(_4\)). Flash chromatography (40 %–50 % EtOAc–pet. ether) gave 238 (66 mg, 18 %).

**Method D – EDCI coupling with glycolic acid under basic conditions**

Amine 237 (287 mg, 1.0 mmol) was dissolved in CH\(_2\)Cl\(_2\) (5 ml) and \(N\)-methyl morpholine (222 mg, 2.2 mmol), glycolic acid (76.1 mg, 1.0 mmol), HOBT-H\(_2\)O (149 mg, 1.1 mmol), and EDCI (288 mg, 1.5 mmol) were added. The solution was stirred at RT for 17 h. The reaction mixture
was washed with 1N HCl (3 x 5 ml) then dried (Na₂SO₄). Flash chromatography (40 % EtOAc–pet. ether) gave 238 (66 mg, 20 %).

**Method E – Reaction with 2,2-dimethyl-1,3-dioxolan-4-one under thermal conditions**

Amine 237 (95 mg, 0.33 mmol) was dissolved in dry PhMe (1 ml) and 2,2-dimethyl-1,3-dioxolan-4-one (20 mg, 0.17 mmol) was added. The solution was heated to 100 °C for 16 h then cooled and concentrated in vacuo. Flash chromatography (40 % EtOAc–pet. ether) gave 238 (19 mg, 34 %).

**Method F – Microwave reactions with 2,2-dimethyl-1,3-dioxolan-4-one – General procedure for solvent screen**

Amine 237 (287 mg, 1.0 mmol) was dissolved in dry solvent (1 ml) in an oven dried microwave vial and 2,2-dimethyl-1,3-dioxolan-4-one 241 (0.175 ml, 1.5 mmol or 0.235 ml, 2.0 mmol) was added. The vial was flushed with nitrogen then sealed and the reaction heated to 150 or 160 °C in the microwave reactor for 1-2 h. The solvent was evaporated and flash chromatography (50 % EtOAc–pet. ether) gave 238.

**Method G – Best microwave conditions**

Amine 237 (574 mg, 2.0 mmol) was placed in an oven-dried microwave vial and 2,2-dimethyl-1,3-dioxolan-4-one 241 (0.352 ml, 4.0 mmol) was added. The vial was flushed with N₂ then sealed and heated to 150 °C in the microwave reactor for 1 h. The acetone generated in the reaction was removed in vacuo and the residue purified by flash chromatography (50 % EtOAc–pet. ether) to give 238 (494 mg, 74 %).

**¹H NMR (400 MHz, CDCl₃)** δ ppm 7.17 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB of one rotamer), 7.06 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB of one rotamer), 6.90 (4 H, d, J = 8.6 Hz, aromatic C-H of PMB of one rotamer), 6.87 (4 H, d, J = 8.8 Hz, aromatic C-H of PMB of one rotamer), 6.39 (2 H, t, J = 2.0 Hz, aromatic C-H), 6.35 (2 H, d, J = 2.3 Hz, aromatic C-H), 6.24 (2 H, d, J = 2.0 Hz, aromatic C-H), 4.59 (2 H, s, ArCH₂N of one rotamer), 4.54 (2 H, s, ArCH₂N of one rotamer), 4.32 (3 H, d, J = 4.3 Hz, CH₂O of one rotamer), 4.24 (4 H, d, J = 4.3 Hz, CH₂O of one rotamer), 4.21 (2 H, s, CH₂ of PMB of one rotamer), 4.18 (2 H, s, CH₂ of PMB of one rotamer), 3.82 (3 H, s, OCH₃), 3.81 (3 H, s, OCH₃), 3.78 (6 H, s, OCH₃), 3.72 (1 H, t, J = 4.3 Hz, OH of one rotamer), 3.68 (1 H, t, J = 4.3 Hz, OH of one rotamer).

**¹³C NMR (100 MHz, CDCl₃)** δ ppm 172.2 (C=O of one rotamer), 172.1 (C=O of one rotamer), 161.4 (aromatic C-O), 161.0 (aromatic C-O), 159.3 (aromatic C-O), 159.2 (aromatic C-O), 138.6 (aromatic C=C of one rotamer), 137.7 (aromatic C=C of one rotamer), 129.9 (aromatic C-H of PMB of one rotamer), 128.3 (aromatic C=C of one rotamer), 128.0 (aromatic C-H of PMB of one rotamer), 126.8 (aromatic C=C of one rotamer), 114.4 (aromatic C-H of PMB of one rotamer), 114.0 (aromatic C-H of PMB of one rotamer), 106.2 (2 × aromatic C-H of one rotamer), 104.5 (2 × aromatic C-H of one rotamer), 99.3 (aromatic C-H of one rotamer), 99.3 (aromatic C-H of one rotamer), 60.0 (CH₃OH of one rotamer), 60.0 (CH₃OH of one rotamer), 55.3 (OCH₃), 55.2 (OCH₃), 48.3 (CH₂N), 47.9 (CH₂N of one rotamer), 47.4 (CH₂N of one rotamer).
n-Butyl(3,5-dimethoxybenzyl)amine 239

3,5-Dimethoxybenzaldehyde (1.66 g, 10.0 mmol) was dissolved in dry MeOH (50 ml) under N₂ and n-butylamine (1.30 ml, 11.0 mmol) added. The solution was heated at reflux for 2 h then cooled to RT and NaBH₄ (417 mg, 11.0 mmol) added portionwise. The solution was stirred for 1 h then the solvent evaporated and the residue dissolved in 1 M HCl (100 ml) and extracted with EtOAc (20 ml). The aqueous layer was basified with sat. Na₂CO₃ solution then extracted with EtOAc (3 × 50 ml). The extracts were washed with brine (50 ml) then dried (MgSO₄) and evaporated to give 239 (2.05 g, 94 %) as a pale yellow oil which was used without further purification.

¹H NMR (300 MHz, CDCl₃) δ ppm 6.51 (2 H, d, J = 2.3 Hz, aromatic C-H), 3.80 (6 H, s, OCH₃), 3.75 (2 H, s, ArCH₂N), 2.63 (3 H, t, J = 7.1 Hz, CH₂N), 1.44 - 1.57 (2 H, m, CH₂), 1.28 - 1.43 (2 H, m, CH₂), 0.91 (3 H, t, J = 7.2 Hz, CH₃).

¹³C NMR (75 MHz, CDCl₃) δ ppm 160.9 (aromatic C-O), 142.9 (aromatic C-C), 106.0 (aromatic C-H), 99.0 (aromatic C-H), 55.3 (2 × OCH₃), 54.1 (ArCH₂N), 49.1 (CH₂N), 32.2 (CH₂), 20.5 (CH₂), 14.0 (CH₃).

IR (thin film) v max (cm⁻¹) 3426 (OH), 2936 (C-H), 1651 (C=O).

n-Butyl-N-(3,5-dimethoxybenzyl)-2-hydroxyacetamide 240

Method A – EDCI coupling with acetoxyacetic acid

Amine 239 (669 mg, 3.0 mmol) was dissolved in CH₂Cl₂ (15 ml) and acetoxyacetic acid (425 mg, 3.6 mmol), HOBt•H₂O (81 mg, 0.6 mmol) and EDCI (690 mg, 3.6 mmol) were added and the solution was stirred at RT for 20 h. The organic layer was washed with 1N HCl (3 × 20 ml) then dried (MgSO₄) and concentrated in vacuo. The residue was dissolved in MeOH (12 ml) and water (6 ml) then K₂CO₃ (553 mg, 12 mmol) was added. The solution was stirred for 18 h and the volatiles evaporated. The residue was diluted with water (10 ml) and extracted with EtOAc (3 × 15 ml). The organic extracts were washed with brine (10 ml) then dried (MgSO₄). Flash chromatography (40 % EtOAc–pet. ether) gave 240 (651 mg, 77 %) as a pale yellow oil.

Method B – EDCI coupling with glycolic acid
Amine 239 (669 mg, 3.0 mmol) was dissolved in CH₂Cl₂ (15 ml) and glycolic acid (274 mg, 3.6 mmol), HOBT•H₂O (81 mg, 0.6 mmol) and EDCI (690 mg, 3.6 mmol) were added. The solution was stirred at RT for 18 h. The organic layer was washed with 1M HCl (3 × 10 ml) then dried (MgSO₄). Flash chromatography (40 % EtOAc–pet. ether) gave 240 (175 mg, 21 %).

Method C – Best microwave conditions

Amine 239 (223 mg, 1.0 mmol) was placed in an oven-dried microwave vial and 2,2-dimethyl-1,3-dioxolan-4-one 241 (0.235 ml, 2.0 mmol) added. The vial was flushed with N₂ then sealed and heated to 150 °C in the microwave reactor for 1 h. The acetone generated in the reaction was removed in vacuo and the residue purified by flash chromatography (50 % EtOAc–pet. ether) to give 240 (191 mg, 68 %) as a pale yellow oil.

¹H NMR (400 MHz, CDCl₃) δ ppm 6.38 (2 H, s, aromatic C-H), 6.27 (1 H, s, aromatic C-H), 4.59 (2 H, s, ArCH₂N of one rotamer), 4.29 (2 H, s, ArCH₂N of one rotamer), 4.24 (2 H, d, J = 4.3 Hz CH₂OH of one rotamer), 4.17 (2 H, d, J = 4.3 Hz CH₂OH of one rotamer), 3.78 (6 H, s, 2 × OCH₃), 3.70 (1 H, t, J = 4.3 Hz, OH of one rotamer), 3.65 (1 H, t, J = 4.3 Hz, OH of one rotamer), 3.43 (1 H, t, J = 7.7 Hz, CH₂N of one rotamer), 3.04 (2 H, t, J = 7.7 Hz, CH₂N of one rotamer), 1.48 - 1.58 (2 H, m, CH₂), 1.24 - 1.34 (2 H, m, CH₂), 0.92 (3 H, t, J = 7.3 Hz, CH₃).

¹³C NMR (100 MHz, CDCl₃) δ ppm 171.7 (C=O). 161.4 (aromatic C-O of one rotamer), 161.1 (aromatic C-O of one rotamer), 139.1 (aromatic C=C of one rotamer), 138.2 (aromatic C=C of one rotamer), 106.0 (aromatic C-H of one rotamer), 104.3 (aromatic C-H), 99.2 (aromatic C-H of one rotamer), 55.4 (2 × OCH₃), 59.9 (CH₂OH), 49.1 (ArCH₂N of one rotamer), 48.6 (ArCH₂N of one rotamer), 46.5 (CH₂N of one rotamer), 44.8 (CH₂N of one rotamer), 29.4 (CH₂), 20.1 (CH₂), 13.7 (CH₃).

MS (ES+) m/z 304 [M+Na]⁺. HRMS 304.1522; C₁₅H₂₃O₄NNa⁺ requires 304.1519. IR (thin film) νmax (cm⁻¹) 3417 (OH), 2956 (C-H), 1645 (C=O).

2-Butyl-5,7-dimethoxy-4-(methylsulfanyl)-1,2-dihydroisoquinolin-3(4H)-one 244

Hydroxamide 240 (0.5 mmol) was oxidised according to the Swern general procedure 1 and the resulting glyoxamide was dissolved in CH₂Cl₂ (6 ml) and Sc(OTf)₃ (49 mg, 0.1 mmol) was added. The solution was stirred at RT for 2 days then diluted with CH₂Cl₂ (5 ml) and washed with water (10 ml) then brine (10 ml) and dried (MgSO₄). Flash chromatography (5 % MeOH–CH₂Cl₂) gave 244 (20 mg, 13 %) as a pale yellow oil.

¹H NMR (300 MHz, CDCl₃) δ ppm 6.38 (1 H, d, J = 1.9 Hz, aromatic C-H), 6.31 (1 H, d, J = 1.9 Hz, aromatic C-H), 4.80 (1 H, d, J = 15.5 Hz, ArCHH₂N), 4.71 (1 H, s, ArCHS), 4.06 (1 H, d, J = 15.5 Hz, ArCHH₂N), 3.86 (3 H, s, OCH₃), 3.80 (3 H, s, OCH₃), 3.70 (1 H, dt, J = 13.7, 7.3 Hz, 0.92 (3 H, t, J = 7.3 Hz, CH₃).
Hydroxyamide 240 was oxidised according to general procedure 1. The crude glyoxamide was dissolved in CH₂Cl₂ (12 ml/mmole) and HSCH₂CH₂C₈F₁₇ (1.5 equiv) and Lewis acid were added. The solution was stirred at RT until the reaction was complete (TLC) then the reaction mixture was washed with water then brine and dried (MgSO₄). Purification then gave 242 as a yellow oil.

**1H NMR (400 MHz, CDCl₃) δ ppm**: 6.40 (1 H, d, J = 2.3 Hz, aromatic C-H), 6.33 (1 H, d, J = 2.3 Hz, aromatic C-H), 4.81 (1 H, s, ArCHS), 4.77 (1 H, d, J = 15.6 Hz, ArCHHN), 4.09 (1 H, d, J = 15.6 Hz, ArCHHN), 3.81 (3 H, s, OCH₃), 3.85 (3 H, s, OCH₃), 3.68 (1 H, dt, J = 13.6, 7.6 Hz, NCH₃), 3.36 (1 H, dt, J = 13.6, 7.6 Hz, NCH₃), 3.04 - 3.13 (1 H, m, SCH₂), 2.82 - 2.91 (1 H, m, SCH₂), 2.46 - 2.64 (2 H, m, CH₃C₈F₁₇), 1.56 - 1.64 (2 H, m, CH₃), 1.28 - 1.43 (2 H, m, CH₂), 0.95 (3 H, t, J = 7.3 Hz, CH₃).

**13C NMR (100 MHz, CDCl₃) δ ppm**: 167.7 (C=O), 160.3 (aromatic C-O), 157.3 (aromatic C-O), 135.4 (aromatic C-C), 113.4 (aromatic C-C), 101.8 (aromatic C-H), 97.5 (aromatic C-H), 55.7 (OCH₃), 55.5 (OCH₃), 50.3 (ArCH₂N), 47.0 (CH₂N), 41.0 (ArCHS), 31.8 (t, J = 21.2 Hz, CH₂C₈F₁₇), 29.4 (CH₂), 23.0 (t, J = 3.7 Hz, SCH₂), 19.9 (CH₂), 13.8 (CH₂).

**MS (ES+) m/z**: 764 [M+Na]⁺. HRMS 764.1068; C₂₃H₂₄F₁₇NO₃SNa⁺ requires 764.1098. IR (thin film) ν max (cm⁻¹) 2962 (C-H), 1653 (C=O).

**N-Butyl-\(N\)(3,5-dimethoxybenzyl)-2-oxopropionamide 249**
Amine 239 (345 mg, 1.5 mmol) was dissolved in PhMe (0.5 ml) in a microwave vial and bisacetonide 247 (736 mg, 3.3 mmol) was added. The mixture was heated to 140 °C for 30 minutes in the microwave reactor. During heating, the reaction mixture turned bright red. The solvent was evaporated and flash chromatography (30 % EtOAc–pet. ether) gave 249 (194 mg, 44 %) as a pale yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 6.39 - 6.42 (2 H, m, aromatic C-H), 6.36 - 6.39 (4 H, m, aromatic C-H), 4.54 (2 H, s, ArCH$_2$N of one rotamer), 4.43 (2 H, s ArCH$_2$N of one rotamer), 3.78 (6 H, s, OCH$_3$ of one rotamer), 3.78 (6 H, s, OCH$_3$ of one rotamer), 3.35 (2 H, t, $J$ = 7.6 Hz, NCH$_2$ of one rotamer), 3.19 (2 H, t, $J$ = 7.6 Hz, NCH$_2$ of one rotamer), 2.46 (3 H, s, COCH$_3$ of one rotamer), 2.36 (3 H, s, COCH$_3$ of one rotamer), 1.49 - 1.67 (4 H, m, CH$_2$), 0.91 (3 H, t, $J$ = 7.3 Hz, CH$_3$ of one rotamer), 0.88 (3 H, t, $J$ = 7.3 Hz, CH$_3$ of one rotamer).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 198.7 (C=O of one rotamer), 198.4 (C=O of one rotamer), 167.2 (C=O of one rotamer), 167.2 (C=O of one rotamer), 161.2 (aromatic C-O), 161.0 (aromatic C-O), 138.5 (aromatic C=C), 105.9 (aromatic C-H of one rotamer), 105.3 (aromatic C-H of one rotamer), 99.5 (aromatic C-H of one rotamer), 99.4 (aromatic C-H of one rotamer), 55.3 (OCH$_3$ of one rotamer), 55.3 (OCH$_3$ of one rotamer), 50.8 (ArCH$_2$ of one rotamer), 47.4 (ArCH$_2$ of one rotamer), 46.6 (NCH$_2$ of one rotamer), 44.8 (NCH$_2$ of one rotamer), 30.5 (CH$_2$ of one rotamer), 29.0 (CH$_3$ of one rotamer), 27.8 (COCH$_3$ of one rotamer), 27.6 (COCH$_3$ of one rotamer), 20.0 (CH$_2$ of one rotamer), 19.8 (CH$_2$ of one rotamer), 13.7 (CH$_3$ of one rotamer), 13.6 (CH$_3$ of one rotamer).

MS (ES+) m/z 264 [M+H$^+$], 316 [M+Na$^+$]. HRMS 316.1524; C$_{16}$H$_{23}$NO$_4$Na$^+$ requires 316.1519. IR (thin film) $\nu$ max (cm$^{-1}$) 2933 (C-H), 1798 (C=O) 1713 (ketone C=O), 1652 (amide C=O).

$N$-(3,5-Dimethoxybenzyl)-2-hydroxy-$N$-isopropylacetamide 250

3,5-Dimethoxybenzaldehyde (664 mg, 4.0 mmol) was dissolved in dry MeOH (12 ml) and i-propylamine (0.44 ml, 5.2 mmol) added. The solution was stirred at RT for 2 h, then NaBH$_4$ (112 mg, 4.0 mmol) was added and the solution stirred at RT for a further 16 h. The solvent was evaporated and the residue taken up in EtOAc (20 ml) and washed with 1 M HCl (2 x 20 ml). The aqueous phase was then basified and extracted with EtOAc (3 x 15 ml). The extracts were dried (MgSO$_4$) and concentrated in vacuo to give (3,5-dimethoxybenzyl)isopropylamine (813 mg, 97 %) as a pale yellow oil, which was used without further purification. (3,5-Dimethoxybenzyl)isopropylamine (239 mg, 1.14 mmol) was placed in a microwave vial and 2,2-dimethyl-1,3-dioxolan-4-one (0.2 ml, 1.75 mmol) was added. The reaction mixture was heated to
150 °C for 1 h in the microwave reactor. Flash chromatography (30-40 % EtOAc–pet. ether) gave 250 (67 mg, 22 %) as a pale yellow oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 6.37 (2 H, s, aromatic C-H of one rotamer), 6.34 (1 H, s, aromatic C-H of one rotamer), 6.31 (3 H, s, aromatic C-H), 4.74 (1 H, apparent quin, \(J = 6.6\) Hz, NCH of one rotamer), 4.52 (2 H, s, ArCH\(_2\)N of one rotamer), 4.29 (2 H, s, ArCH\(_2\)OH of one rotamer), 4.25 (2 H, s, ArCH\(_2\)N of one rotamer), 4.04 (2 H, s, ArCH\(_2\)OH of one rotamer), 3.80 (1 H, apparent q, \(J = 6.2\) Hz, NCH of one rotamer), 3.76 (6 H, s, OCH\(_3\) of one rotamer), 3.75 (6 H, s, OCH\(_3\) of one rotamer), 3.66 (1 H, br. s, OH), 1.17 (6 H, d, \(J = 6.2\) Hz, CH\(_3\)), 1.16 (6 H, d, \(J = 6.6\) Hz, CH\(_3\)).

\(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 172.5 (C=O of one rotamer), 171.8 (C=O of one rotamer), 161.3 (aromatic C-O of one rotamer), 160.9 (aromatic C-O of one rotamer), 141.1 (aromatic C-C of one rotamer), 139.7 (aromatic C-C of one rotamer), 105.1 (aromatic C-H of one rotamer), 103.9 (aromatic C-H of one rotamer), 98.9 (aromatic C-H of one rotamer), 98.5 (aromatic C-H of one rotamer), 60.1 (CH\(_2\)OH of one rotamer), 60.5 (CH\(_2\)OH of one rotamer), 55.3 (OCH\(_3\)), 47.4 (NCH of one rotamer), 47.2 (NCH of one rotamer), 45.1 (ArCH\(_2\)N of one rotamer), 44.6 (ArCH\(_2\)N of one rotamer), 21.2 (CH\(_3\) of \(\gamma\)-Pr of one rotamer), 20.1 (CH\(_3\) of \(\gamma\)-Pr of one rotamer).

MS (ES+) \(m/z\) 290.2 [M+Na]. HRMS 268.1557; \(C_{14}H_{13}NO_4^-\) requires 268.1543. IR (thin film) \(\nu_{max}\) (cm\(^{-1}\)) 3424 (OH), 2936 (C-H), 1640 (amide C=O).

4-(3,3,4,4,5,5,6,7,8,9,10,10-Heptadecafluorodecylsulfanyl)-2-isopropyl-5,7-dimethoxy-1,4-dihydro-2 \(H\)-isoquinolin-3-one 251

![Image of chemical structure](image)

Hydroxyamide 250 (64 mg, 0.25 mmol) was oxidised according to general procedure 1 and the crude glyoxamide was dissolved in CH\(_2\)Cl\(_2\) (4 ml) and R\(^\text{f}\)SH (0.05 ml, 0.25 mmol) was added. The solution was stirred at RT for 45 h then TFAA (0.31 ml, 2.2 mmol) was added and stirring was continued for a further 1 h after which Sc(OTf)\(_3\) (123 mg, 0.25 mmol) was added. After 2 h, the solution was diluted with CH\(_2\)Cl\(_2\) (5 ml), washed with sat. NaHCO\(_3\) solution (10 ml) then brine (10 ml) and dried (MgSO\(_4\)). Flash chromatography (20 % EtOAc–petrol. ether) gave 251 (17 mg, 5.6 %) as a pale yellow gum.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 6.40 (1 H, d, \(J = 2.3\) Hz, aromatic C-H), 6.37 (1 H, d, \(J = 2.3\) Hz, aromatic C-H), 4.90 (1 H, apparent quint., \(J = 6.9\) Hz, NCH), 4.85 (1 H, s, ArCHS), 4.52 (1 H, d, \(J = 15.6\) Hz, ArCHN), 4.13 (1 H, d, \(J = 15.6\) Hz, ArCHN), 3.84 (3 H, s, OCH\(_3\)), 3.82 (3 H, s, OCH\(_3\)), 3.01 - 3.10 (1 H, m, SCH\(_2\)H of fluorous tag), 2.86 (1 H, ddd, \(J = 13.8, 10.0, 5.9\) Hz, SCH\(_2\)H of fluorous tag), 2.46 - 2.63 (2 H, m, CH\(_2\) of fluorous tag), 1.23 (3 H, d, \(J = 6.9\) Hz, CH\(_3\) of \(\gamma\)-Pr group), 1.16 (3 H, d, \(J = 6.9\) Hz, CH\(_3\) of \(\gamma\)-Pr group).
$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 167.4 (C=O), 160.6 (aromatic C-O), 157.3 (aromatic C-O), 135.7 (aromatic C-C), 113.4 (aromatic C-C), 101.9 (aromatic C-H), 97.5 (aromatic C-H), 55.7 (OCH$_3$), 55.5 (OCH$_3$), 44.4 (CH of i-Pr), 43.3 (ArCH$_2$N), 41.5 (ArCHS), 23.2 (t, $J = 4.6$ Hz, CH$_2$S), 19.5 (CH$_3$ of i-Pr group), 19.3 (CH$_3$ of i-Pr group). (CH$_2$ of fluorous tag not observed due to small amount of material)

MS (ES+) $m/z$ 750.3 [M+Na]$^+$. HRMS 750.0952; C$_{24}$H$_{22}$F$_{17}$NO$_3$Na$^+$ requires 750.0941.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 2973 (C-H), 1651 (C=O).

Methyl 3-(2-butyl-5,7-dimethoxy-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-ylsulfanyl) propanoate 253

[Chemical structure image]

Hydroxyamide 240 (143 mmol, 0.5 mmol) was oxidised according to general procedure 1. The crude glyoxamide was dissolved in CH$_2$Cl$_2$ (6 ml) and methyl 3-mercaptopropanoate (81 µl, 0.75 mmol) and Sc(OTf)$_3$ (49 mg, 0.1 mmol) were added. The solution was stirred at RT for 40 h then washed with water (2 × 10 ml) then brine (10 ml) and dried (MgSO$_4$). Flash chromatography (30 % EtOAc–pet. ether) gave 253 (150 mg, 79 %) as a yellow oil.

$^1$H NMR (300 MHz, CDCl$_3$) δ ppm 6.34 (1 H, d, $J = 1.9$ Hz, aromatic C-H), 6.27 (1 H, d, $J = 1.7$ Hz, aromatic C-H), 4.75 (1 H, s, ArCH$_2$N), 4.75 (2 H, d, $J = 15.5$ Hz, ArCHHN), 4.03 (1 H, d, $J = 15.5$ Hz, ArCH$_2$N), 3.80 (3 H, s, OCH$_3$), 3.75 (3 H, s, OCH$_3$), 3.65 (3 H, s, CO$_2$CH$_3$), 3.56 - 3.68 (1 H, m, NC$_2$H$_2$), 3.31 (1 H, dt, $J = 13.7$, 7.0 Hz, NCHH), 3.02 - 3.15 (1 H, m, SCH$_2$), 2.80 - 2.94 (1 H, m, SCH$_2$), 2.70 - 2.79 (2 H, m, CH$_2$CO$_2$Me), 1.48 - 1.62 (2 H, m, CH$_2$), 1.24 - 1.39 (2 H, m, CH$_2$), 0.90 (3 H, t, $J = 7.2$ Hz, CH$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 172.4 (C=O), 168.1 (C=O), 160.4 (aromatic C-O), 157.2 (aromatic C-O), 135.3 (aromatic C-C), 113.7 (aromatic C-C), 101.7 (aromatic C-H), 97.5 (aromatic C-H), 55.7 (OCH$_3$), 55.4 (OCH$_3$), 51.6 (CO$_2$CH$_3$), 50.2 (ArCH$_2$N), 46.9 (NCH$_2$), 40.7 (ArCHS), 34.4 (CH$_2$CO$_2$Me), 29.4 (CH$_2$), 27.2 (SCH$_2$), 23.9 (CH$_2$), 19.9 (CH$_2$), 13.9 (CH$_3$).

MS (ES+) $m/z$ 404.2 [M+Na]$^+$. HRMS 404.1497, C$_{19}$H$_{27}$NO$_3$Na$^+$ requires 404.1502. IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 2954 (C-H), 1734 (ester C=O), 1653 (amide C=O).

Methyl 3-[5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-ylsulfanyl] propanoate 254

[Chemical structure image]
Hydroxyamide 238 (166 mg, 0.5 mmol) was oxidised according to general procedure 1. The crude glyoxamide was dissolved in CH₂Cl₂ (6 ml) and methyl 3-mercaptopropionate (0.08 ml, 0.75 mmol) and Sc(OTf)₃ (49 mg, 0.1 mmol) were added. The reaction mixture was stirred at RT for 15 h then washed with water (10 ml) then brine (10 ml) and dried (MgSO₄). Flash chromatography (30 % EtOAc-pet. ether) gave 254 (277 mg, 64 %) as a pale yellow gum.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.22 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB), 6.87 (2 H, d, J = 8.6 Hz, aromatic C-H of PMB), 6.37 (1 H, d, J = 2.3 Hz, aromatic C-H), 6.20 (1 H, d, J = 2.3 Hz, aromatic C-H), 4.86 (1 H, s, ArCHS), 4.76 (1 H, d, J = 14.9 Hz, CHH of PMB), 4.62 (1 H, d, J = 15.5 Hz, ArCH(HN)), 4.59 (1 H, d, J = 14.9 Hz, CHH of PMB), 4.02 (1 H, d, J = 15.5 Hz, ArCH(HN)), 3.86 (3 H, s, OCH₃), 3.80 (3 H, s, OCH₃), 3.76 (3 H, s, OCH₃), 3.71 (3 H, s, CO₂CH₃), 3.19 (1 H, ddd, J = 13.6, 7.6, 6.2 Hz, SCH₂), 2.96 (1 H, dt, J = 13.6, 7.6 Hz, SCH₂), 2.77 - 2.83 (2 H, m, CH₃CO₂Me).

¹³C NMR (75 MHz, CDCl₃) δ ppm 172.4 (C=O), 168.3 (C=O), 160.4 (aromatic C-O), 159.1 (aromatic C-O), 157.2 (aromatic C-O), 135.0 (aromatic C-C), 129.2 (aromatic C-H of PMB), 128.7 (aromatic C-C), 114.1 (aromatic C-H of PMB), 113.6 (aromatic C-C), 101.6 (aromatic C-H), 97.6 (aromatic C-H), 55.8 (OCH₃), 55.4 (OCH₃), 55.3 (OCH₃), 51.7 (CO₂CH₃), 49.6 (CH₂N), 49.5 (CH₂N), 40.7 (ArCHS), 34.5 (CH₃CO₂Me), 27.3 (SCH₂).

MS (ES+) m/z 468 [M+Na]+.

HRMS 468.1457; C₂₂H₂₃NO₃SNa+ requires 468.1451. IR (thin film) νₘₓ (cm⁻¹) 3460, 2951 (C-H), 1737 (ester C=O), 1660 (amide C=O).

5,7-Dimethoxy-2-(4-methoxybenzyl)-4-(phenylsulfanyl)-1,2-dihydroisoquinolin-3(4H)-one 255

\[
\begin{array}{c}
\text{MeO} \quad \text{S} \quad \text{Ph} \\
\text{MeO} \\
\text{N} \quad \text{PMB}
\end{array}
\]

Hydroxyamide 238 (166 mg, 0.5 mmol) was oxidised according to general procedure 1. The crude glyoxamide was dissolved in CH₂Cl₂ (6 ml) and thiophenol (77 µl, 0.75 mmol) and Sc(OTf)₃ (49 mg, 0.1 mmol) were added. The reaction mixture was stirred at RT for 30 h then diluted with CH₂Cl₂ (5 ml) washed with water (10 ml) then brine (10 ml) and dried (MgSO₄). Flash chromatography (33 % EtOAc-pet. ether) gave 255 (168 mg, 78 %) as a yellow gum.

¹H NMR (500 MHz, CDCl₃) δ ppm 7.25 - 7.35 (3 H, m, aromatic C-H), 7.14 - 7.20 (4 H, m, aromatic C-H), 6.85 (2 H, d, J = 8.5 Hz, aromatic C-H of PMB), 6.38 (1 H, d, J = 1.8 Hz, aromatic C-H), 6.07 (1 H, d, J = 1.8 Hz, aromatic C-H), 5.09 (1 H, s, ArCHS), 4.62 (1 H, d, J = 14.5 Hz, ArCH(HN)), 4.48 (1 H, d, J = 14.5 Hz, ArCH(HN)), 3.81 - 3.86 (5 H, m, CH₂ and OCH₃), 3.80 (3 H, s, OCH₃), 3.76 (3 H, s, OCH₃).

¹³C NMR (100 MHz, CDCl₃) δ ppm 167.4 (C=O), 159.9 (aromatic C-O), 158.6 (aromatic C-O), 156.9 (aromatic C-O), 135.0 (aromatic C-H), 134.5 (aromatic C-S), 131.7 (aromatic C-C), 129.2
(aromatic C-H), 128.2 (aromatic C-C), 128.1 (aromatic C-H), 128.0 (aromatic C-H), 113.5 (aromatic C-H), 113.3 (aromatic C-C), 100.3 (aromatic C-H), 97.1 (aromatic C-H), 55.3 (OCH$_3$), 55.0 (OCH$_3$), 54.9 (OCH$_3$), 49.2 (CH$_2$), 49.1 (CH$_2$), 45.1 (ArCHS).

MS (ES+) m/z 458.4 [M+Na]$^+$. HRMS 458.1390; C$_{25}$H$_{25}$O$_4$NNaS$^+$ requires 458.1397. IR (thin film) $\nu$$_{\text{max}}$ (cm$^{-1}$) 2928 (C-H), 1651 (C=O), 1610.

N-Troc Cysteine methyl ester 256

![Chemical structure image]

L-Cystine dimethyl ester dihydrochloride salt (683 mg, 2.0 mmol) was dissolved in water (100 ml) and the solution cooled to 0 °C. NaHCO$_3$ (672 mg, 8.0 mmol) was added and the solution stirred for 5 minutes. 2,2,2-Trichloroethyl chloroformate (0.825 ml, 6.0 mmol) was added dropwise and the mixture stirred at 0 °C for 2 h then at RT for 5 h. The reaction mixture was then saturated with NaCl and extracted with EtOAc (4 × 20 ml). The organic extracts were combined, washed with water (20 ml) then brine (20 ml) then dried (Na$_2$SO$_4$). Flash chromatography (50 % Et$_2$O–petrol. ether) gave bis-N-Troc cystine dimethyl ester (1.14g, 92 %) as a viscous, colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 5.95 (2 H, d, $J$ = 7.8 Hz, NH), 4.79 (2 H, d, $J$ = 11.9 Hz CHHCCl$_3$), 4.74 (2 H, d, $J$ = 11.9 Hz, CHHCCl$_3$), 4.71 (2 H, dt, $J$ = 7.8, 5.3 Hz, CHNHTroc O) 3.81 (6 H, s, CH$_3$), 3.24 (4 H, d, $J$ = 5.3 Hz, SCH$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 170.4 (ester C=O), 154.0 (carbamate C=O), 95.2 (CCl$_3$), 75.1 (CHNHTroc), 53.4 (CH$_2$CCl$_3$), 53.0 (OCH$_3$), 41.0 (SCH$_2$).

MS (ES+) m/z 604 [M+Na]$^+$. Bis-N-Troc cystine dimethyl ester (619 mg, 1.0 mmol) was dissolved in dry CH$_2$Cl$_2$ (15 ml) under N$_2$ and DL-dithiothreitol (238 mg, 1.5 mmol) and NEt$_3$ (0.417 ml, 3.0 mmol) were added. The solution was stirred at RT for 3 h then washed with 5 %w/v degassed citric acid solution (3 × 15 ml) and degassed water (15 ml) then dried (MgSO$_4$) and concentrated in vacuo to give 256 (537 mg, 86 %) a pale yellow solid, melting point 47-48 °C, which was used without further purification.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ ppm 5.92 (1 H, d, $J$ = 7.6 Hz, NH), 4.78 (1 H, d, $J$ = 12.0 Hz, CHHCCl$_3$), 4.74 (1 H, d, $J$ = 12.0 Hz, CHHCCl$_3$), 4.70 (1 H, dt, $J$ = 7.6, 4.1 Hz, NCHCO), 3.83 (3 H, s, CH$_3$), 3.06 (1 H, dd, $J$ = 9.0, 4.1 Hz, CHHS), 3.05 (1 H, dd, $J$ = 9.0, 4.1 Hz, CHHS), 1.42 (1 H, t, $J$ = 9.0 Hz, SH).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ ppm 170.0 (ester C=O), 154.0 (carbamate C=O), 95.2 (CCl$_3$), 55.4 (Cl$_3$CCl$_2$), 53.0 (OCH$_3$), 26.9 (SCH$_2$).

MS m/z (ES+) 331.9 [M+Na]$^+$. HRMS 331.9293; C$_{17}$H$_{10}$NO$_4$Cl$_3$SNa$^+$ requires 331.9288. IR (thin film) $\nu$$_{\text{max}}$ (cm$^{-1}$) 3340 (N-H), 2954 (C-H), 1732 (ester C=O), 1530 (carbamate C=O). $\lbrack\alpha\rbrack$_{D}^{32}$ = −15.7 (c = 1.2, EtOH).
(2R)-Methyl 3-((5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)sulfanyl)-2-(((2,2,2-trichloroethoxy)carbonyl)amino)propanoate 257

Hydroxyamide 238 (166 mg, 0.5 mmol) was oxidised according to general procedure 1. The crude glyoxamide was dissolved in CH$_2$Cl$_2$ (6 ml) and L-N-Troc Cysteine methyl ester 256 (204 mg, 0.66 mmol) and Sc(OTf)$_3$ (49 mg, 0.1 mmol) were added and the reaction mixture stirred at RT for 15 h. The solution was washed with water (10 ml) then brine (10 ml) and dried (MgSO$_4$). Flash chromatography (40 % EtOAc–pet. ether) gave 257 (163 mg, 52 %, 1:1 dr) as a pale yellow gum.

$^1$H NMR (500 MHz, CDCl$_3$) δ ppm 7.21 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB of one diastereoisomer), 7.21 (3 H, d, J = 8.8 Hz, aromatic C-H of PMB of one diastereoisomer and NH of one diastereoisomer), 6.86 (2 H, d, J = 8.2 Hz, aromatic C-H of PMB), 6.73 (1 H, d, J = 8.8 Hz, NH of one diastereoisomer), 6.39 (1 H, d, J = 1.9 Hz, aromatic C-H of one diastereoisomer), 6.37 (1 H, d, J = 2.2 Hz, aromatic C-H of one diastereoisomer), 6.18 (2 H, s, aromatic C-H), 4.95 (1 H, s, ArCHS of one diastereoisomer), 4.51 - 4.89 (6 H, m, ArCHS of one diastereoisomer, ArCH$_2$N, OCH$_2$CCl$_3$, CH$_2$NHTroc), 3.96 (3 H, s, OCH$_3$), 3.86 (3 H, s, OCH$_3$), 3.80 (3 H, s, OCH$_3$), 3.79 (6 H, s, 2 × OCH$_3$), 3.75 (9 H, s, 3 × OCH$_3$), 3.66 (1 H, dd, J = 14.7, 3.9 Hz, SCH$_2$ of one diastereoisomer), 3.44 (1 H, dd, J = 14.7, 6.8 Hz, SCH$_2$ of one diastereoisomer), 3.19 (1 H, dd, J = 14.5, 8.5 Hz, SCH$_2$ of one diastereoisomer), 3.18 (1 H, dd, J = 14.7, 6.8 Hz, SCH$_2$ of one diastereoisomer).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ ppm 170.8 (C=O of one diastereoisomer), 170.7 (C=O of one diastereoisomer), 168.4 (C=O of one diastereoisomer), 168.3 (C=O of one diastereoisomer), 160.6 (aromatic C-O), 160.5 (aromatic C-O), 159.03 (aromatic C-O), 159.0 (aromatic C-O), 157.3 (aromatic C-O), 157.2 (aromatic C-O), 154.5 (carbamate C=O of one diastereoisomer), 154.4 (carbamate C=O of one diastereoisomer), 134.4 (aromatic C-C of one diastereoisomer), 134.3 (aromatic C-C of one diastereoisomer), 129.2 (aromatic C-H of PMB of one diastereoisomer), 129.1 (aromatic C-H of PMB of one diastereoisomer), 128.3 (aromatic C-C of one diastereoisomer), 128.3 (aromatic C-C of one diastereoisomer), 114.0 (aromatic C-H of PMB), 112.8 (aromatic C-C of one diastereoisomer), 112.4 (aromatic C-C of one diastereoisomer), 101.5 (aromatic C-H), 97.7 (aromatic C-H of one diastereoisomer), 97.6 (aromatic C-H of one diastereoisomer), 95.5 (CCl$_3$ of one diastereoisomer), 95.3 (CCl$_3$ of one diastereoisomer), 74.8 (OCH$_2$CCl$_3$ of one diastereoisomer), 74.5 (OCH$_2$CCl$_3$ of one diastereoisomer), 55.7 (OCH$_3$), 55.4 (OCH$_3$), 55.2 (OCH$_3$), 55.2 (OCH$_3$), 54.9 (OCH$_3$), 52.6 (CH$_2$NHTroc), 49.5 (ArCH$_2$N), 49.4
(ArCH₂N), 41.2 (ArCHS of one diastereoisomer), 40.8 (ArCHS of one diastereoisomer), 34.2 (CH₂S of one diastereoisomer), 33.7 (CH₂S of one diastereoisomer).

MS (ES+) m/z 657 [M+Na]⁺. HRMS 657.0597; C₂₆H₂₉O₈N₂Cl₃SNa⁺ requires 657.0602. IR (thin film) vₘₐₓ (cm⁻¹) 3340 (N-H), 2953 (C-H), 1736 (C=O), 1647 (C=O), 1611 (C=O).

**5,7-Dimethoxy-2-(4-methoxybenzyl)-4-methylsulfanyl-1,4-dihydro-2H-isoquinolin-3-one 258**

![Chemical Structure](image)

Tetrahydroisoquinolinone 258 (20 mg, 11 %) was isolated as a by-product from the reaction to form 257.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.22 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB), 6.87 (1 H, d, J = 2.2 Hz, aromatic C-H), 6.38 (1 H, d, J = 2.2 Hz, aromatic C-H), 4.81 (1 H, d, J = 14.6 Hz, CH₃H of PMB), 4.78 (1 H, s, ArCHS), 4.63 (1 H, d, J = 15.7 Hz, ArCHN), 3.86 (3 H, s, OCH₃), 3.80 (3 H, s, OCH₃), 3.76 (3 H, s, OCH₃), 2.32 (3 H, s, SMe).

¹³C NMR (100 MHz, CDCl₃) δ ppm 168.0 (C=O), 160.3 (aromatic C-O), 159.0 (aromatic C-O), 157.3 (aromatic C-O), 135.0 (aromatic C-C), 129.1 (aromatic C-H of PMB), 128.8 (aromatic C-C), 114.1 (aromatic C-H of PMB), 113.7 (aromatic C-C), 101.6 (aromatic C-H), 113.7 (aromatic C-C), 101.6 (aromatic C-H), 97.6 (aromatic C-H), 55.8 (OCH₃), 55.4 (OCH₃), 55.3 (OCH₃), 49.6 (CH₂), 49.5 (CH₂), 42.5 (ArCHS), 15.8 (SCH₃).

MS (ES+) m/z 396 [M+Na]⁺. HRMS 396.1246; C₂₀H₂₁NOSNa⁺ requires 396.1240. IR (thin film) vₘₐₓ (cm⁻¹) 2918 (C-H), 1737, 1650 (C=O), 1610.

**n-Butyl-N-(3,5-dimethoxybenzyl)-2-((3,3,4,4,5,6,6,7,7,8,8,9,9,10,10-heptadecafluorodecyl)sulfanyl)-2-hydroxyacetamide 245**

![Chemical Structure](image)

DMSO (147 µl, 2.06 mmol) was added to a solution of (COCl)₂ (99 µl, 1.13 mmol) in CH₂Cl₂ (4 ml) at −78 °C. After 15 minutes, a solution of 2-hydroxyacetamide 240 (290 mg, 1.03 mmol) in CH₂Cl₂ (4 ml) was added and the solution stirred for a further 35 minutes. NEt₃ (695 µl, 5.0 mmol) was added then the reaction mixture allowed to warm to RT. HSCH₂CH₂C₆F₁₇ (354 µl, 1.24 mmol) was added after 3 h and the reaction was allowed to stir for a further 20 minutes then washed with water (10 ml), sat. NaHCO₃ solution (2 × 10 ml) and dried (MgSO₄) to give crude 245 which was used without further purification.
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 6.27 - 6.42 (6 H, m, aromatic C-H), 5.49 (1 H, d, \(J = 9.1\) Hz, SCH\(\text{OH}\) of one rotamer), 5.34 (1 H, d, \(J = 8.8\) Hz, SCH\(\text{OH}\) of one rotamer), 4.99 (1 H, d, \(J = 15.1\) Hz, ArCH\(\text{HN}\) of one rotamer), 4.82 (1 H, d, \(J = 17.0\) Hz, ArCH\(\text{HN}\) of one rotamer), 4.65 (1 H, d, \(J = 8.8\) Hz, OH of one rotamer), 4.63 (1 H, d, \(J = 9.1\) Hz, OH of one rotamer), 4.31 (1 H, d, \(J = 17.0\) Hz ArCH\(\text{HN}\) of one rotamer), 4.21 (1 H, d, \(J = 15.1\) Hz ArCH\(\text{HN}\) of one rotamer), 3.79 (6 H, s, OCH\(_3\) of one rotamer), 3.77 (6 H, s, OCH\(_3\) of one rotamer), 3.44 - 3.55 (1 H, m, NC\(\text{H}\)\(\text{H}\) of one rotamer), 2.98 - 3.16 (3 H, m, NCH\(_2\) of one rotamer and NCH\(_2\)), 2.83 - 2.99 (4 H, m, SCH\(_2\)), 2.35 - 2.56 (4 H, m, C\(_2\)H\(_2\)C\(_8\)F\(_{17}\)), 1.58 (4 H, m, CH\(_2\)), 1.26 - 1.38 (4 H, m, CH\(_2\)), 0.90 - 0.97 (6 H, m, CH\(_3\)).

2-Butyl-4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10-heptadecafluorodecylsulfanyl)-5,7-dimethoxy-1,4-dihydro-2\(\text{H}\)-isoquinolin-3-one 242 from hemithioacetal 245

Hemithioacetal 245 (0.51 mmol) was dissolved in CH\(_2\)Cl\(_2\) (6 ml) and ZnCl\(_2\) (70 mg, 0.51 mmol) was added. The solution was stirred for 26 h then washed with sat. NaHCO\(_3\) solution (10 ml) and dried (MgSO\(_4\)). Flash chromatography (20 % EtOAc–pet. ether) gave 242 (290 mg, 77 %) as a yellow oil.

2-(Butyl(3,5-dimethoxybenzyl)amino)-1-((3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10-heptadecafluorodecyl)sulfanyl)-2-oxoethyl 2,2,2-trifluoroacetate 246

Hemithioacetal 245 (0.275 mmol) was dissolved in CDCl\(_3\) (3.3 ml) and TFAA (57\(\mu\)l, 0.413 mmol) was added. After 3 h the reaction was complete (NMR) and the solution was diluted with CH\(_2\)Cl\(_2\) (5 ml), washed with water (10 ml) then dried (MgSO\(_4\)) and concentrated \textit{in vacuo} to give crude 246 as a pale yellow oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 6.44 (1 H, s, aromatic C-H), 6.44 (1 H, s, aromatic C-H), 6.41 (1 H, d, \(J = 2.3\) Hz, aromatic C-H), 6.37 (3 H, s, aromatic C-H), 6.29 (1 H, s, SCHOCOCF\(_3\) of one rotamer), 6.14 (1 H, s, SCHOCOCF\(_3\) of one rotamer), 4.89 (1 H, d, \(J = 17.3\) Hz, ArCH\(\text{HN}\) of one rotamer), 4.71 (1 H, d, \(J = 15.1\) Hz, ArCH\(\text{HN}\) of one rotamer), 4.44 (1 H, d, \(J = 15.1\) Hz, ArCH\(\text{HN}\) of one rotamer), 4.33 (1 H, d, \(J = 17.3\) Hz, ArCH\(\text{HN}\) of one rotamer), 3.81 (6 H, s, OCH\(_3\) of one rotamer), 3.77 (6 H, s, OCH\(_3\) of one rotamer), 3.42 (1 H, m, ArCH\(\text{HN}\) of one rotamer), 3.28 - 3.33 (2 H, m), 3.16 - 3.25 (1 H, m ArCH\(\text{HN}\) of one rotamer), 2.95 - 3.13 (4 H, m), 2.81 - 2.93 (3
H, m), 2.40 - 2.57 (4 H, m CH$_3$C$_8$F$_{17}$), 1.68 (3 H, dt, J = 15.6, 7.8 Hz, CH$_2$ of one rotamer), 1.57 (3 H, dt, J = 15.1, 7.7 Hz, CH$_2$ of one rotamer), 1.33 (4 H, m, CH$_2$), 0.87 - 0.99 (6 H, m, CH$_3$).

2-Butyl-4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-decylsulfanyl)-5,7-dimethoxy-1,4-dihydro-2H-isooquinolin-3-one 242 from trifluoroacetylated hemithioacetal 246

Trifluoroacetylated hemithioacetal 246 (0.275 mmol) was dissolved in CH$_2$Cl$_2$ (3.0 ml) and ZnCl$_2$ (7.5 mg, 0.055 mmol) was added. The solution was stirred for 21 h then washed with water (10 ml) and dried (MgSO$_4$). Flash chromatography (20 % EtOAc–pet. ether) gave 242 (85 mg, 42 %) as a yellow oil.

$N$-Benzyl-$N$-butyl-2-hydroxyacetamide 259

Benzaldehyde (1.06 g, 10 mmol) was dissolved in dry EtOH (50 ml) then n-butylamine (1.19 ml, 12 mmol) was added and the solution was heated under reflux for 1.5 h then cooled to RT. NaBH$_4$ (378 mg, 10 mmol) was added portionwise then the solution was stirred for 1 h. The solvent was evaporated and the residue taken up in 1 M HCl (40 ml), washed with EtOAc (15 ml) then the aqueous layer was basified with sat. Na$_2$CO$_3$ solution and extracted with EtOAc (2 × 50 ml). The organic extracts were washed with brine (20 ml), dried (MgSO$_4$) and concentrated in vacuo to give crude amine (1.78 g, quant.) A portion of the crude amine (489 mg, 3.0 mmol) was dissolved in CH$_2$Cl$_2$ (15 ml) and acetoxyacetic acid (425 mg, 3.6 mmol), EDCI (690 mg, 3.6 mmol) and HOBt·H$_2$O (81 mg, 0.6 mmol) were added. The solution was stirred for 18 h then diluted with CH$_2$Cl$_2$ (15 ml) and washed with 1 M HCl (3 × 20 ml), dried (MgSO$_4$) and concentrated in vacuo. The residue was dissolved in MeOH (12 ml) and water (6 ml) then K$_2$CO$_3$ (550 mg, 4.0 mmol) was added. The solution was stirred for 20 h then concentrated in vacuo, diluted with water (20 ml) and extracted with EtOAc (3 × 20 ml). The extracts were combined and dried (MgSO$_4$). Flash chromatography (40 % EtOAc–pet. ether) gave 259 (333 mg, 50 % over 2 steps) as a pale yellow oil and mixed fractions (130 mg).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.28 - 7.40 (m, 3 H, aromatic C-H), 7.22 - 7.26 (m, 1 H, aromatic C-H), 7.13 - 7.18 (m, 1 H, aromatic C-H), 4.66 (ArCH$_2$N of one rotamer), 4.36 (ArCH$_2$N of one rotamer), 4.25 (CH$_2$OH of one rotamer), 4.19 (CH$_2$OH of one rotamer), 3.43 (m, 2 H, NCH$_2$ of one rotamer), 3.03 (m, 2 H, NCH$_2$ of one rotamer), 1.48 - 1.59 (m, 2 H, CH$_3$CH$_2$CH$_3$ of
both rotamers), 1.24 - 1.36 (m, 2 H, CH₂CH₃ of both rotamers), 0.92 (t, J = 7.4 Hz, 3 H, CH₃ of one rotamer), 0.91 (t, J = 7.3 Hz, 3 H, CH₃ of one rotamer).

¹³C NMR (100 MHz, CDCl₃) δ ppm 171.5 (C=O of one rotamer), 171.3 (C=O of one rotamer), 136.3 (aromatic C-C of one rotamer), 135.2 (aromatic C-C of one rotamer), 128.7 (aromatic C-H of one rotamer), 128.3 (aromatic C-H of one rotamer), 127.7 (aromatic C-H of one rotamer), 127.6 (aromatic C-H of one rotamer), 127.3 (aromatic C-H of one rotamer), 126.0 (aromatic C-H of one rotamer), 59.6 (CH₂OH of one rotamer), 59.5 (CH₂OH of one rotamer), 48.7 (ArCH₂N of one rotamer), 48.3 (ArCH₂N of one rotamer), 45.9 (CH₂N of one rotamer), 44.5 (CH₂N of one rotamer), 29.7 (CH₂CH₂CH₃ of one rotamer), 29.0 (CH₂CH₂CH₃ of one rotamer), 19.8 (CH₂CH₃ of one rotamer), 19.6 (CH₂CH₃ of one rotamer), 13.5 (CH₃ of one rotamer), 13.3 (CH₃ of one rotamer).

MS (ES+) m/z 244 [M+Na]⁺. HRMS 244.1317; C₁₃H₁₉O₂NNa⁺ requires 244.1308. IR (thin film) ν max (cm⁻¹) 3412 (br., O-H) 2957 (C-H), 2930 (C-H), 1653 (C=O), 1647 (C=O).

Hydroxyamide 259 (221 mg, 1.0 mmol) was oxidised according to general procedure 1. The resulting glyoxamide was dissolved in CH₂Cl₂ (12 ml) and methyl 3-mercaptopropanoate (162 μl, 1.5 mmol) and Sc(OTf)₃ (98 mg, 0.2 mmol) were added. The solution was stirred at RT for 16.5 hours then a 1 ml aliquot was removed, evaporated under a stream of nitrogen then redissolved in CDCl₃, filtered and submitted for ¹H NMR analysis. No tetrahydroisoquinolinone was observed in the ¹H NMR spectrum.

N-Butyl-2-hydroxy-N-(3-methoxybenzyl)acetamide 260

3-Methoxybenzaldehyde (582 μl, 4.0 mmol) was dissolved in EtOH (20 ml), n-butylamine (475 μl, 4.8 mmol) was added and the solution heated under reflux for 2 h. The solution was cooled to RT and NaBH₄ (167 mg, 4.4 mmol) was added portionwise and the solution stirred for 1 h. The solvent was evaporated and the residue taken up in 1 M HCl (20 ml) and washed with EtOAc (3 × 20). The extracts were washed with brine (20 ml) then dried (MgSO₄) to give the crude amine (554 mg, 63 %) as a pale yellow oil. A portion of the crude amine (330 mg, 1.5 mmol) was dissolved in CH₂Cl₂ (7 ml) and acetoxyacetic acid (212 mg, 1.8 mmol), EDCI (345 mg, 1.8 mmol) and HOBt•H₂O (40 mg, 0.3 mmol) were added. The solution was stirred for 20 h then diluted with CH₂Cl₂ (10 ml) and washed with 1 M HCl (3 × 10 ml) then dried (MgSO₄) and concentrated in vacuo. The residue was dissolved in MeOH (6 ml) and H₂O (3 ml) and K₂CO₃ (621 mg, 4.5 mmol) was added. The solution was stirred for 16 h then the volatiles were evaporated and the residue diluted with water (10 ml) then extracted with EtOAc (3 × 15 ml). The extracts were
washed with brine (10 ml) then dried (MgSO₄). Flash chromatography (30 % EtOAc–pet. ether) gave 260 (349 mg, 92 % over 2 steps) as a pale yellow oil.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.21 - 7.32 (1 H, m, aromatic C-H of both rotamers), 6.65 - 6.87 (3 H, m, aromatic C-H of both rotamers), 4.63 (2 H, s, ArCH₂N of one rotamer), 4.33 (2 H, s, ArCH₂N of one rotamer), 4.24 (2 H, d, J = 4.5 Hz, CH₂OH of one rotamer), 4.18 (2 H, d, J = 4.3 Hz, CH₂OH of one rotamer), 3.81 (3 H, s, OCH₃ of one rotamer), 3.80 (3 H, s, OCH₃ of one rotamer), 3.71 (1 H, t, J = 4.3 Hz, OH of one rotamer), 3.66 (1 H, t, J = 4.4 Hz, OH of one rotamer), 3.38 - 3.47 (2 H, m, NCH₂ of one rotamer), 3.03 (2 H, dd, J = 8.6, 7.1 Hz, NCH₂ of one rotamer), 1.47 - 1.60 (2 H, m, NCH₂C₂H₅), 1.23 - 1.38 (2 H, m, NCH₂CH₂C₂H₅), 0.92 (6 H, t, J = 7.3 Hz, CH₃).

¹³C NMR (100 MHz, CDCl₃) δ ppm 171.85 (C=O of one rotamer), 171.64 (C=O of one rotamer), 160.15 (aromatic C-O of one rotamer), 159.86 (aromatic C-O of one rotamer), 138.69 (aromatic C-C of one rotamer), 137.28 (aromatic C-C of one rotamer), 130.15 (aromatic C-H), 129.69 (aromatic C-H), 120.25 (aromatic C-H), 118.44 (aromatic C-H), 113.71 (aromatic C-H), 112.80 (aromatic C-H), 112.42 (aromatic C-H), 59.91 (CH₂OH of one rotamer), 59.77 (CH₂OH of one rotamer), 55.25 (OCH₃ of one rotamer), 55.21 (OCH₃ of one rotamer), 48.94 (ArCH₂N of one rotamer), 48.51 (ArCH₂N of one rotamer), 46.35 (CH₂N of one rotamer), 44.77 (CH₂N of one rotamer), 30.01 (CH₂CH₂CH₃ of one rotamer), 29.37 (CH₂CH₂CH₃ of one rotamer), 20.09 (CH₂CH₃ of one rotamer), 19.96 (CH₂CH₃ of one rotamer), 13.83 (CH₃ of one rotamer), 13.69 (CH₃ of one rotamer).

MS m/z (ES+) 274.2 [M+Na]+. HRMS 274.1413; C₁₄H₂₁O₃NNa+ requires 274.1414. IR (thin film) νₘₐₓ (cm⁻¹) 3421 (br., OH), 2957 (C-H), 1644 (C=O), 1601.

Hydroxamide 260 (126 mg, 0.5 mmol) was oxidised according to general procedure 1. The resulting glyoxamide was dissolved in CH₂Cl₂ (6 ml) and methyl 3-mercaptopropanoate (81 µl, 0.75 mmol) and Sc(OTf)₃ (49 mg, 0.1 mmol) were added. The solution was stirred at RT for 16.5 hours then a 1 ml aliquot removed, evaporated under a stream of nitrogen then redissolved in CDCl₃, filtered and submitted for ¹H NMR analysis. No tetrahydroisoquinolinone was observed in the ¹H NMR spectrum.

### 3.3 Synthesis and cyclisation of pyruvamides

**N-Butyl-N-(3,5-dimethoxybenzyl)-2-oxo-propionamide 249**

![N-Butyl-N-(3,5-dimethoxybenzyl)-2-oxo-propionamide](image)

Method A – coupling with pyruvic acid
Amine 239 (350 mg, 1.5 mmol) was dissolved in CH₂Cl₂ (4.5 ml) and pyruvic acid (0.125 ml, 1.8 mmol), HOBt•H₂O (40 mg, 0.3 mmol) and EDCI (345 mg, 1.8 mmol) were added. The reaction was stirred at RT for 20 h then diluted with CH₂Cl₂ (5 ml) and washed with 1 M HCl (3 × 10 ml) then dried (MgSO₄). Flash chromatography (30 % EtOAc–pet. ether) gave 249 (107 mg, 21 %) as a pale yellow oil.

**Method B – reaction with hydroxymaleic anhydride-pyridine complex.**

Amine 239 (242 mg, 1.08 mmol) was dissolved in MeCN (3 ml) and hydroxymaleic anhydride–pyridine complex (prepared according to a literature procedure)³⁶ (251 mg, 1.32 mmol) was added. The solution was stirred for 26 h at 40 °C then evaporated, taken up in EtOAc (20 ml) and washed with 1 M HCl (10 ml) then sat. NaHCO₃ solution (10 ml) then water (10 ml), and dried (MgSO₄). Flash chromatography (30 % EtOAc–pet. ether) gave 249 (225 mg, 70%) as a pale yellow oil.

Data were consistent with those previously recorded.

4-((3,3,4,4,5,5,6,6,7,7,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-2-butyl-5,7-dimethoxy-4-methyl-1,4-dihydro-2H-isoquinolin-3-one 262

Pyruvamide 249 (94 mg, 0.32 mmol) was dissolved in CH₂Cl₂ (3 ml) and RᵗSH (65 μl, 0.22 mmol) and ZnCl₂ (8 mg, 0.03 mmol) were added. The solution was stirred at RT for 17 h. A further portion of RᵗSH (65 μl) was then added and the solution stirred for 24 h. TFAA (0.4 ml, 2.88 mmol) was added and after 1 h, Sc(OTf)₃ (80 mg, 0.16 mmol) was added. After 1 h, the reaction mixture was diluted with CH₂Cl₂ (10 ml), neutralised by slow addition of sat. NaHCO₃ solution then the organic layer was washed with sat. NaHCO₃ solution (3 × 10 ml) and dried (MgSO₄). Flash chromatography (15 % EtOAc–pet. ether) gave 262 (30 mg, 12 %) as a pale yellow gum.

¹H NMR (400 MHz, CDCl₃) δ ppm 6.43 (1 H, d, J = 2.6 Hz, aromatic C-H), 6.25 (1 H, d, J = 16.1 Hz, ArCHHN), 4.26 (1 H, d, J = 16.1 Hz, ArCHHN), 3.85 (3 H, s, OCH₃), 3.81 (3 H, s, OCH₃), 3.69 (1 H, dt, J = 13.5, 7.6 Hz, NCH₃H), 3.38 (1 H, dt, J = 13.5, 7.3 Hz, NCH₃H), 2.70 - 2.84 (2 H, m, SCH₂), 2.18 - 2.28 (2 H, m, CH₂C₁₈F₁₇), 2.16 (3 H, s, CH₃), 1.58 - 1.68 (2 H, m, CH₂), 1.32 - 1.43 (2 H, m, CH₂), 0.95 (3 H, t, J = 7.4 Hz, CH₃CH₃).

¹³C NMR (100 MHz, CDCl₃) δ ppm 169.0 (C=O), 160.1 (aromatic C-O), 159.7 (aromatic C-O), 134.1 (aromatic C-C), 116.8 (aromatic C=C), 101.4 (aromatic C-H), 99.2 (aromatic C-H), 55.7 (OCH₃), 55.3 (OCH₃), 50.5 (ArCH₃N), 49.4 (quaternary ArCS), 47.8 (CH₂N), 31.7 (t, J = 22.1 Hz, CH₂C₁₈F₁₇), 29.1 (CH₂), 21.2 (t, J = 4.6 Hz, CH₂S), 23.6 (CH₂), 20.1 (CH₂), 13.8 (CH₃ of n-Bu group).
Amine 237 (574 mg, 2.00 mmol) was dissolved in MeCN (3 ml) and hydroxymaleic anhydride–pyridine complex (prepared according to a literature procedure)\(^6\) (425 mg, 2.2 mmol) was added. The solution was stirred for 26 h at 40 °C then evaporated, taken up in EtOAc (20 ml) and washed with 1 M HCl (10 ml) then sat. NaHCO\(_3\) solution (10 ml) then water (10 ml), and dried (MgSO\(_4\)) and concentrated to give 264 (683 mg, 95%) as a pale yellow oil which was used without further purification.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.19 (2 H, d, \(J = 8.6\) Hz, aromatic C-H of PMB of one rotamer), 7.15 (2 H, d, \(J = 8.6\) Hz, aromatic C-H of PMB of one rotamer), 6.89 (2 H, d, \(J = 8.6\) Hz, aromatic C-H of PMB of one rotamer), 6.88 (2 H, d, \(J = 8.6\) Hz, aromatic C-H of PMB of one rotamer), 6.37 - 6.42 (2 H, m, aromatic C-H), 6.34 (1 H, d, \(J = 2.5\) Hz, aromatic C-H), 4.50 (2 H, s, CH\(_2\) of PMB of one rotamer), 4.46 (2 H, s, ArCH\(_2\) of one rotamer), 4.33 (2 H, s, CH\(_2\) of PMB of one rotamer), 4.31 (2 H, s, ArCH\(_2\) of one rotamer), 3.82 (3 H, s, OCH\(_3\)), 33.79 (3 H, s, OCH\(_3\)), 3.78 (3 H, s, OCH\(_3\)), 2.41 (3 H, s, COCH\(_3\) of one rotamer), 2.41 (3 H, s, COCH\(_3\) of one rotamer).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) ppm 198.5 (ketone C=O), 167.3 (amide C=O), 161.2 (aromatic C-O), 161.1 (aromatic C-O), 159.4 (aromatic C-O), 159.3 (aromatic C-O), 138.1 (aromatic C-C of one rotamer), 138.0 (aromatic C-C of one rotamer), 130.0 (aromatic C-H of PMB of one rotamer), 129.3 (aromatic C-H of PMB of one rotamer), 127.8 (aromatic C-C of one rotamer), 127.3 (aromatic C-C of one rotamer), 114.2 (aromatic C-H of PMB of one rotamer), 114.1 (aromatic C-H of PMB of one rotamer), 106.3 (aromatic C-H of one rotamer), 105.6 (aromatic C-H of one rotamer), 99.7 (aromatic C-H of one rotamer), 99.6 (aromatic C-H of one rotamer), 55.3 (OCH\(_3\)), 55.3 (OCH\(_3\)), 49.7 (ArCH\(_2\) of one rotamer), 49.4 (ArCH\(_2\) of PMB of one rotamer), 46.9 (ArCH\(_2\) of one rotamer), 46.7 (ArCH\(_2\) of PMB of one rotamer), 27.8 (COCH\(_3\) of one rotamer), 27.7 (COCH\(_3\) of one rotamer).

MS (ES+) \(m/z\) 778.5 [M+Na]\(^+\). HRMS 778.1253; \(\text{C}_{26}\text{H}_{38}\text{O}_{3}\text{F}_1\text{SNa}^+\) requires 778.1254. IR (thin film) \(v_{\text{max}}\) (cm\(^{-1}\)) 2935 (C-H), 1797, 1644 (C=O), 1690.

\(N(3,5\text{-dimethoxybenzyl})-N(4\text{-methoxybenzyl})-2\text{-oxopropanamide} 264\)

![Chemical Structure](https://example.com/structure.png)

Methyl 3-(2-butyl-5,7-dimethoxy-4-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-ylsulfanyl)-propanoate 265
Pyruvamide 249 (110 mg, 0.375 mmol) was dissolved in CH₂Cl₂ (4.5 ml) and methyl 3-mercaptopropanoate (0.061 ml, 0.56 mmol) and Sc(OTf)₃ (36.8 mg, 0.074 mmol) were added. The solution was stirred at RT for 16 h then washed with water then brine and dried (MgSO₄). Flash chromatography (30 % EtOAc–pet. ether) gave 265 (76 mg, 51 %) as a pale yellow oil.

³¹H NMR (300 MHz, CDCl₃) δ ppm 6.40 (1 H, d, J = 2.2 Hz, aromatic C-H), 6.23 (1 H, d, J = 2.2 Hz, aromatic C-H), 4.73 (1 H, d, J = 16.0 Hz, ArCH₂HN), 4.20 (1 H, d, J = 16.0 Hz, ArCH₂HN), 3.83 (3 H, s, OCH₃), 3.79 (3 H, s, OCH₃), 3.64 (3 H, s, CO₂CH₃), 3.54 - 3.68 (1 H, m, CH₂HN), 3.40 (1 H, dt, J = 13.2, 7.4 Hz, CH₂HN), 2.69 - 2.93 (2 H, m, SCH₂), 2.48 (2 H, t, J = 7.4 Hz, CH₂CO₂CH₃), 2.15 (3 H, s, CH₃), 1.54 - 1.67 (2 H, m, CH₂), 1.27 - 1.43 (2 H, m, CH₂), 0.95 (3 H, t, J = 7.3 Hz, CH₃CH₂).

³¹C NMR (75 MHz, CDCl₃) δ ppm 172.3 (C=O), 169.2 (C=O), 159.9 (aromatic C-O), 159.7 (aromatic C-O), 134.5 (aromatic C-C), 117.3 (aromatic C-C), 101.6 (aromatic C-H), 99.2 (aromatic C-H), 55.7 (OCH₃), 55.3 (OCH₃), 51.6 (CO₂CH₃), 50.5 (ArCH₃N), 49.1 (ArCS), 47.8 (NCH₂), 34.5 (CH₂CO₂Me), 29.1 (CH₃), 25.4 (SCH₂), 23.5 (SCCH₂), 20.1 (CH₃), 13.9 (CH₃).

MS (ES+) m/z 418 [M+Na]⁺. HRMS 418.1650; C₂₀H₂₉NO₅SNa⁺ requires 418.1659. IR (thin film) νmax (cm⁻¹) 3466, 2958 (C=O), 1738 (ester C=O), 1645 (amide C=O).

Methyl 3-((5,7-dimethoxy-2-(4-methoxybenzyl)-4-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)sulfanyl)propanoate 268

Pyruvamide 264 (179 mg, 0.5 mmol) was dissolved in CH₂Cl₂ (6 ml) and methyl 3-mercaptopropanoate (82 µl, 0.75 mmol) and Sc(OTf)₃ (0.1 mmol, 49 mg) were added. The solution was stirred at RT for 18 h then diluted with CH₂Cl₂ (5 ml) and washed with water (10 ml) then brine (10 ml) and dried (MgSO₄). Flash chromatography (33 % EtOAc–pet. ether) gave 268 (138 mg, 60 %) as a pale yellow oil.

³¹H NMR (400 MHz, CDCl₃) δ ppm 7.28 (2 H, d, J = 8.8 Hz, PBM aromatic C-H), 6.89 (2 H, d, J = 8.6 Hz, PBM aromatic C-H), 6.41 (1 H, d, J = 2.3 Hz, aromatic C-H), 6.16 (1 H, d, J = 2.3 Hz, aromatic C-H), 4.82 (2 H, d, J = 14.5 Hz, CH₂ of PBM), 4.63 (2 H, d, J = 14.5 Hz, CH₂ of PBM), 4.60 (1 H, d, J = 16.1 Hz, ArCH₂HN), 4.18 (1 H, d, J = 16.1 Hz, ArCH₂HN), 3.85 (3 H, s, OCH₃), 3.81 (3 H, s, OCH₃), 3.77 (3 H, s, OCH₃), 3.66 (3 H, s, OCH₃), 2.72 - 2.91 (2 H, m, CH₂), 2.43 - 2.51 (2 H, m, CH₂), 2.22 (3 H, s, CH₃).

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$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 172.6 (ester C=O), 169.9 (amide C=O), 160.1 (aromatic C-O), 159.8 (aromatic C-O), 159.3 (aromatic C-O), 134.2 (aromatic C-C), 129.8 (aromatic C-H), 128.9 (aromatic C=C), 117.1 (aromatic C-C), 114.3 (aromatic C-H), 101.7 (aromatic C-H), 99.4 (aromatic C-H), 55.9 (OCH$_3$), 55.5 (OCH$_2$), 55.5 (OCH$_3$), 51.9 (CO$_2$CH$_3$), 50.6 (ArCH$_2$N), 49.9 (CH$_2$ of PMB), 49.3 (ArCS), 34.6 (CH$_2$CO$_2$Me), 25.7 (SCH$_2$), 23.8 (CH$_3$).

MS (ES+) $m/z$ 482 [M+Na]$^+$. HRMS 482.1605; C$_{24}$H$_{29}$O$_6$NNaS$^+$ requires 482.1608. IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 2950 (C-H), 1736 (C=O), 1644 (C=O), 159.8 (C=O), 159.3 (C=O), 159.1 (C=O), 153.4 (carbamate C=O of one diastereoisomer), 133.3 (aromatic C=C of one diastereoisomer), 129.5 (aromatic C-H of PMB), 129.4 (aromatic C-C), 116.1 (aromatic C-C), 114.1 (aromatic C-H of PMB), 101.2 (aromatic

(2R)-Methyl 3-(((5,7-dimethoxy-2-(4-methoxybenzyl)-4-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)sulfanyl)-2-(((2,2,2-trichloroethoxy)carbonyl)amino)propanoate

Pyruvamide 264 (143 mg, 0.4 mmol) was dissolved in CH$_2$Cl$_2$ (6 ml) and N-Troc cysteine methyl ester (163 mg, 0.6 mmol) and Sc(OTf)$_3$ (40 mg, 0.08 mmol) were added. The solution was stirred at RT for 21 h then diluted with CH$_2$Cl$_2$ (5 ml) and washed with water (10 ml) then brine (10 ml) and dried (MgSO$_4$). Flash chromatography (40 % EtOAc–pet. ether) gave 267 (129 mg, 49 %, 1:1 dr) as a pale yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.23 - 7.26 (4 H, m, aromatic C-H of PMB), 6.87 (4 H, d, $J$ = 8.6 Hz, aromatic C-H of PMB), 6.40 (1 H, s, aromatic C-H of one diastereoisomer), 6.40 (1 H, s, aromatic C-H of one diastereoisomer), 6.12 (2 H, s, aromatic C-H), 6.02 (1 H, d, $J$ = 8.1 Hz, NH of one diastereoisomer), 5.98 (1 H, d, $J$ = 8.1 Hz, NH of one diastereoisomer), 4.82 (1 H, d, $J$ = 14.4 Hz, OCH$_2$HCCl$_3$ of one diastereoisomer), 4.64 - 4.77 (6 H, m, 2 × ArCH$_2$N and OCH$_2$CCl$_3$ of one diastereoisomer), 4.61 (1 H, d, $J$ = 14.4 Hz, OCH$_2$HCCl$_3$ of one diastereoisomer), 4.55 (2 H, d, $J$ = 16.4 Hz, CH$_2$ of PMB), 4.39 - 4.46 (2 H, m, CH$_2$NHTroc), 4.21 (2 H, d, $J$ = 16.4 Hz, CH$_2$ of PMB), 3.86 (6 H, s, 2 × OCH$_3$), 3.79 (6 H, s, 2 × OCH$_3$), 3.75 (3 H, s, OCH$_3$), 3.73 (3 H, s, OCH$_3$), 3.71 (3 H, s, OCH$_3$), 3.21 (1 H, dd, $J$ = 12.5, 4.9 Hz, SCH$_2$ of one diastereoisomer), 3.12 (1 H, dd, $J$ = 13.9, 6.3 Hz, SCH$_2$ of one diastereoisomer), 3.00 (1 H, dd, $J$ = 13.9, 7.3 Hz, SCH$_2$ of one diastereoisomer), 2.97 (1 H, dd, $J$ = 13.9, 4.3 Hz, SCH$_2$ of one diastereoisomer), 2.16 (3 H, s, CH$_3$ of one diastereoisomer), 2.16 (3 H, s, CH$_3$ of one diastereoisomer).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 170.8 (C=O), 170.6 (C=O), 169.9 (C=O), 160.1 (aromatic C-O), 159.5 (aromatic C-O), 159.4 (aromatic C-O), 159.1 (aromatic C-O), 154.1 (carbamate C=O of one diastereoisomer), 154.0 (carbamate C=O of one diastereoisomer), 133.4 (aromatic C=C of one diastereoisomer), 133.3 (aromatic C=C of one diastereoisomer), 129.5 (aromatic C-H of PMB), 129.4 (aromatic C-C), 116.1 (aromatic C-C), 114.1 (aromatic C-H of PMB), 101.2 (aromatic
C-H), 99.3 (aromatic C-H), 99.2 (CCl₃ of one diastereoisomer), 95.3 (CCl₃ of one diastereoisomer), 74.6 (OCH₂CCl₃ of one diastereoisomer), 74.6 (OCH₂CCl₃ of one diastereoisomer), 55.6 (OCH₃), 55.3 (OCH₃), 55.2 (OCH₃), 53.9 (CHNHTroc of one diastereoisomer), 53.7 (CHNHTroc of one diastereoisomer), 52.6 (OCH₃), 50.2 (NCH₂), 49.5 (NCH₂), 49.4 (ArCS of one diastereoisomer), 49.0 (CH₂), 48.7 (ArCS of one diastereoisomer), 32.2 (SCH₂), 23.5 (CH₃ of one diastereoisomer), 23.4 (CH₃ of one diastereoisomer).

MS (ES+) m/z 671 [M+Na]⁺. HRMS 671.0766; C₁₁₈H₁₁₈N₂O₂₃SNa requires 671.0759. IR (thin film) νmax (cm⁻¹) 3321 (br., NH), 2953 (C=O), 1736 (C=O), 1640 (C=O).

5,7-Dimethoxy-2-(4-methoxybenzyl)-4-methyl-4-phenylsulfanyl-1,2-dihydroisoquinoline-3(4H)-one 266

![Structure of 5,7-Dimethoxy-2-(4-methoxybenzyl)-4-methyl-4-phenylsulfanyl-1,2-dihydroisoquinoline-3(4H)-one](image-url)

**Method A**

Pyruvamide 264 (143 mg, 0.4 mmol) was dissolved in CH₂Cl₂ (4.8 ml) and thiophenol (62 µl, 0.6 mmol) and Sc(OTf)₃ (40 mg, 0.084 mmol) were added. The solution was stirred at RT for 15 h then diluted with CH₂Cl₂ (5 ml) and washed with water (10 ml) then brine (10 ml) and dried (MgSO₄). Flash chromatography (30 % EtOAc–pet. ether) gave 266 (145 mg, 80 %) as a pale yellow oil.

**Method B**

4-Hydroxytetrahydroisoquinoline 276 (20 mg, 0.056 mmol) was dissolved in CH₂Cl₂ (0.67 ml) and thiophenol (10 µl, 0.084 mmol) and Sc(OTf)₃ (0.084 mmol, 28 mg) were added. The solution was stirred at RT for 6 h then diluted with CH₂Cl₂ (3 ml) and washed with water (3 ml) then brine (3 ml) and dried (MgSO₄). Flash chromatography (30 % EtOAc–pet. ether) gave 266 (7 mg, 28 %) as a pale yellow oil.

¹H NMR (500 MHz, CDCl₃) δ ppm 7.22 - 7.26 (1 H, m aromatic C-H of Phenyl group), 7.19 (2 H, d, J = 8.2 Hz, aromatic C-H of PMB), 6.97 - 7.05 (4 H, m, aromatic C-H of phenyl group), 6.84 (2 H, d, J = 8.5 Hz, aromatic C-H of PMB), 6.42 (1 H, s, aromatic C-H), 5.88 (1 H, s, aromatic C-H), 4.74 (1 H, d, J = 14.3 Hz, CHH of PMB), 4.21 (1 H, d, J = 14.3 Hz, CHH of PMB), 3.88 (3 H, s, OCH₃), 3.85 (1 H, d, J = 16.4 Hz, ArCHHN), 3.79 (3 H, s, OCH₃), 3.73 (3 H, s, OCH₃), 3.24 (1 H, d, J = 16.4 Hz, ArCHHN), 2.21 (3 H, s, CH₃).

¹³C NMR (126 MHz, CDCl₃) δ ppm 169.7 (C=O), 159.5 (aromatic C-O), 159.3 (aromatic C-O), 159.0 (aromatic C-O), 137.0 (aromatic C-H of phenyl), 133.4 (aromatic C=C), 132.1 (aromatic C=S), 129.9 (aromatic C-H of phenyl), 129.0 (aromatic C-H of PMB), 128.3 (aromatic C=C), 127.8 (aromatic C-H of phenyl), 117.4 (aromatic C=C), 113.8 (aromatic C-H of PMB), 99.9 (aromatic C-H), 98.8 (aromatic C-H), 55.6 (OCH₃), 55.2 (OCH₃), 55.1 (OCH₃), 53.6 (ArCH₃N), 50.2 (CH₂), 49.1 (ArCS), 23.8 (CH₃).
MS m/z (ES+) 472.5 [M+Na]^+. HRMS 450.1744 C_{26}H_{28}O_{4}NS^+ requires 450.1734. IR (thin film) ν_{max} (cm^{-1}) 2935 (C-H), 1646 (amide C=O), 1610.

Ethyl 2-((5,7-dimethoxy-2-(4-methoxybenzyl)-4-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)sulfanyl)acetate 269

Pyruvamide 264 (179 mg, 0.5 mmol) was dissolved in CH$_2$Cl$_2$ (6 ml) and ethyl 2-mercaptoacetate (82 μl, 0.75 mmol) and Sc(OTf)$_3$ (0.1 mmol, 49 mg) were added. The solution was stirred at RT for 66 h then diluted with CH$_2$Cl$_2$ (5 ml) and washed with water (10 ml) then brine (10 ml) and dried (MgSO$_4$). Flash chromatography (30 % EtOAc–pet. ether) gave 269 (172 mg, 75 %) as a pale yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.24 (2 H, d, J = 8.6 Hz, aromatic C=H of PMB), 6.85 (2 H, d, J = 8.6 Hz, aromatic C=H of PMB), 6.12 (1 H, d, J = 2.5 Hz, aromatic C-H), 4.75 (1 H, d, J = 14.6 Hz, CH$_2$ of PMB), 4.62 (1 H, d, J = 14.6 Hz, CH$_2$ of PMB), 4.59 (1 H, d, J = 16.1 Hz, ArCH$_2$HN), 4.16 (d, J = 16.1 Hz, 1 H, ArCH$_2$HN), 3.83 (3 H, s, OCH$_3$), 3.77 (3 H, s, OCH$_3$), 3.73 (3 H, s, OCH$_3$), 3.40 (1 H, d, J = 15.5 Hz, SCH$_2$CO), 3.33 (1 H, d, J = 15.5 Hz, SCH$_2$CO), 2.18 (3 H, s, CH$_3$), 1.21 (3 H, t, J = 7.2 Hz, CH$_2$C$_6$H$_5$).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 170.1 (C=O), 169.0 (C=O), 159.9 (aromatic C=O), 159.6 (aromatic C-O), 158.9 (aromatic C-O), 134.0 (aromatic C-C), 129.3 ( aromatic C-H of PMB), 128.5 (aromatic C-C), 116.0 (aromatic C=C), 113.9 (aromatic C-H of PMB), 101.2 (aromatic C-H), 99.0 (aromatic C-H), 61.1 (CO$_2$CH$_2$CH$_3$), 55.6 (OCH$_3$), 55.2 (OCH$_3$), 55.1 (OCH$_3$), 50.0 (ArCH$_2$N), 49.4 (ArCH$_2$N), 49.0 (ArCS), 33.2 (SCH$_2$), 23.4 (CH$_3$), 14.0 (CH$_2$C$_6$H$_5$).

MS (ES+) m/z 482 [M+Na]$^+$. HRMS 482.1622; C$_{24}$H$_{29}$O$_6$NSNa$^+$ requires 482.1608. IR (thin film) ν$_{max}$ (cm$^{-1}$) 2935 (C-H), 2837, 1734 (ester C=O), 1642 (amide C=O), 1610.

4-Hydroxy-5,7-dimethoxy-2-(4-methoxybenzyl)-4-methyl-1,2-dihydroisoquinolin-3(4H)-one 276

Pyruvamide 264 (179 mg, 0.5 mmol) was dissolved in CH$_2$Cl$_2$ (6 ml) and Sc(OTf)$_3$ (0.1 mmol, 49 mg) was added. The solution was stirred at RT for 72 h then diluted with CH$_2$Cl$_2$ (5 ml) and washed with water (10 ml) then brine (10 ml) and dried (MgSO$_4$). Flash chromatography (30 %
EtOAc–pet. ether then 10 % MeOH–CH₂Cl₂ gave recovered starting material (88 mg, 49 %) and 276 (84 mg, 47 %) as a pale yellow oil.

¹H NMR (500 MHz, CDCl₃) δ ppm 7.22 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB), 6.86 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB), 6.44 (1 H, d, J = 1.3 Hz, aromatic C-H), 6.13 (1 H, d, J = 1.3 Hz, aromatic C-H), 4.71 (2 H, s, CH₂ of PMB), 4.35 (1 H, d, J = 16.4 Hz, ArCH=HN), 4.21 (1 H, d, J = 16.4 Hz, ArCH=HN), 3.90 (3 H, s, OCH₃), 3.79 (3 H, s, OCH₃), 3.75 (3 H, s, OCH₃), 1.64 (3 H, s, CH₃).

¹³C NMR (126 MHz, CDCl₃) δ ppm 172.8 (C=O), 159.8 (aromatic C-O), 159.2 (aromatic C-O), 158.7 (aromatic C-O), 130.7 (aromatic C-C), 129.4 (aromatic C-H of PMB), 128.1 (aromatic C-C), 118.7 (aromatic C-C), 114.1 (aromatic C-H of PMB), 100.9 (aromatic C-H), 98.9 (aromatic C-H), 70.4 (ArC(OH)), 55.8 (OCH₃), 55.3 (OCH₃), 55.2 (OCH₃), 49.9 (CH₂), 49.0 (CH₂), 27.7 (CH₃).

MS (ES+) m/z 380 [M+Na]⁺. HRMS 380.1468 C₂₀H₂₃O₅NNa⁺ requires 380.1468.

IR (thin film) ν_max (cm⁻¹) 3498 (br., OH), 2936 (C-H), 1649 (amide C=O), 1612.

3.4 Synthesis of an Et 597 ABH ring system analogue

1,3-Dimethoxy-5-vinyl-benzene 279¹²³

Methyltriphenylphosphonium bromide (15.5 g, 43.2 mmol) was suspended in dry THF (67 ml) under N₂ and KOt-Bu (5.7 g, 50.4 mmol) added and the mixture stirred at RT for 30 minutes then cooled to ~78 °C. A solution of 3, 5-dimethoxybenzaldehyde (6.0 g, 36.1 mmol) in dry THF (33 ml) was added dropwise and the reaction mixture was allowed to warm to RT. The reaction was quenched with MeOH (10 ml) and the solvent evaporated. The crude material was filtered through a short silica column (6 % Et₂O–pet. ether) to give 279 (5.90 g, 99 %) as a colourless oil.

¹H NMR (400 MHz, CDCl₃) δ ppm 6.66 (1 H, dd, J = 17.4, 10.8 Hz, ArCH=CH₂), 6.58 (2 H, d, J = 2.3 Hz, aromatic C-H), 6.40 (1 H, t, J = 2.3 Hz, aromatic C-H), 5.74 (1 H, d, J = 17.4 Hz, ArCH=CH₂), 5.26 (1 H, d, J = 10.8 Hz, ArCH=CH₂), 3.82 (6 H, s, OCH₃).

¹³C NMR (100 MHz, CDCl₃) δ ppm 160.5 (aromatic C-O), 139.3 (aromatic C-C), 136.5 (ArCH=CH₂), 114.0 (CH₂), 103.9 (aromatic C-H), 99.7 (aromatic C-H), 55.0 (OCH₃).

IR (thin film) ν_max (cm⁻¹) 2930 (C-H), 2357, 2339, 1592.

Data was consistent with literature values.¹²³

(R)-Benzyl (1-(3,5-dimethoxyphenyl)-2-hydroxyethyl)carbamate 280¹⁰⁵
Benzylcarbamate (470 mg, 3.05 mmol) was dissolved in \( n\)-PrOH (4 ml) and a solution of NaOH (122 mg, 3.05 mmol) in water (7.5 ml) was added, followed by freshly prepared \( t\)-butyl hypochlorite (331 mg, 3.05 mmol). The solution was stirred at RT for 5 minutes. A solution of \((\text{DHQD})_2\text{PHAL}\) (40 mg, 0.05 mmol) in \( n\)-PrOH (4 ml) was then added, followed by a solution of styrene 279 (164 mg, 1.0 mmol) in \( n\)-PrOH (7 ml) and then \( K_2\text{OsO}_4\cdot2\text{H}_2\text{O}\) (14.7 mg, 0.04 mmol). The solution was stirred for 1 hour then cooled to 0 °C and quenched with sat. NaSO\(_3\) solution (10 ml) and stirred for 15 minutes. The phases were separated and the aqueous layer extracted with EtOAc (3 × 10 ml). The organic phases were combined and washed with water (10 ml) then brine (25 ml) and dried (MgSO\(_4\)). Flash chromatography (20–40 % EtOAc–pet. ether) gave 280 (151 g, 45 %) as a colourless solid, melting point 117-118 °C; literature value 109-110 °C.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm 7.36 (5 H, br. s, aromatic C-H of Cbz), 6.44 (2 H, d, \( J = 2.3 \) Hz, aromatic C-H), 6.39 (1 H, t, \( J = 2.3 \) Hz, aromatic C-H), 5.57 (1 H, d, \( J = 1.0 \) Hz, NH), 5.13 (1 H, d, \( J = 12.4 \) Hz, PhCH\(_2\)OH), 5.09 (1 H, d, \( J = 12.4 \) Hz, PhCH\(_2\)OH), 4.78 (1 H, br. s, ArCHN), 3.84 (2 H, br. s, C\(_\text{H}_2\)OH), 3.77 (6 H, s, OCH\(_3\)).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) ppm 161.1 (aromatic C-O), 156.3 (carbamate C=O), 141.5 (aromatic C-C), 136.2 (aromatic C-C), 128.5 (aromatic C-H of Cbz), 128.2 (2 × aromatic C-H of Cbz), 104.6 (aromatic C-H), 99.5 (aromatic C-H), 67.0 (CH\(_2\) of Cbz), 66.4 (CH\(_3\)OH), 57.1 (ArCHN), 55.3 (OCH\(_3\)).

\([\alpha]_{D}^{28} = -24.8 \) (c = 0.98, EtOH); literature value for (S)-isomer \([\alpha]_{D}^{25} = +32.6 \) (c = 0.5, EtOH). Data was consistent with literature values.\(^{105}\)

Enantiomeric excess was measured as 92 % using chiral HPLC (ChiralPak OD column, 80:20 hexane–isopropanol, 40°C, see appendix 4.1 for trace).

\((R)-\text{tert-Butyl} (1-(3,5\text{-dimethoxyphenyl})-2\text{-hydroxyethyl})\text{carbamate} \text{ 281}\(^{105}\)
Na$_2$SO$_3$ solution (50 ml) and stirred for 15 minutes. The phases were separated and the aqueous layer extracted with EtOAc (3 × 20 ml). The organic phases were combined and washed with water (30 ml), brine (30 ml) then dried (MgSO$_4$). Flash chromatography (20–45 % EtOAc–pet. ether) gave 281 (942 mg, 65 %) as a white solid, melting point 113-114 °C; literature value 97-98 °C.

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 6.45 (2 H, d, $J = 2.3$ Hz, aromatic C-H), 6.39 (1 H, t, $J = 2.3$ Hz, aromatic C-H), 5.23 (1 H, br. s, NH), 4.71 (1 H, br. s, CHN), 3.84 (2 H, m, CH$_2$O), 3.79 (6 H, s, OCH$_3$), 2.23 (1 H, br. s, OH), 1.45 (9 H, s, C(CH$_3$)$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 161.2 (aromatic C-O), 156.5 (C=O), 141.7 (aromatic C-C), 104.6 (aromatic C-H), 99.4 (aromatic C-H), 80.0 (OCC(CH$_3$)$_3$), 66.9 (CH$_2$O), 56.9 (CHN), 55.4 (OCH$_3$), 28.3 (CH$_3$).

[α]$_D^{28}$ = –36.6 (c = 0.94, EtOH); literature value for (S)-isomer [α]$_D^{25}$ = +44.6 (c = 0.5, EtOH).

Data was consistent with literature values.$^{105}$

(R)-2-Amino-2-(3,5-dimethoxyphenyl)ethanol 284

Carbamate 281 (942 mg, 3.17 mmol) was dissolved in CH$_2$Cl$_2$ (45 ml) and TFA (11 ml) was added. The solution was stirred for one hour then evaporated. The residue was dissolved in sat. NaHCO$_3$ solution (20 ml) and extracted with CH$_2$Cl$_2$ (3 × 15 ml). The extracts were combined, dried (MgSO$_4$) and concentrated in vacuo to give 284 (588 mg, 94 %) as a pale yellow, amorphous solid which was used without further purification.

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 6.49 (2 H, d, $J = 2.3$ Hz, aromatic C-H), 6.38 (1 H, t, $J = 2.3$ Hz, aromatic C-H), 4.00 (1 H, dd, $J = 8.0$, 4.5 Hz, ArCHN), 3.80 (6 H, s, OCH$_3$), 3.74 (1 H, dd, $J = 10.7$, 4.5 Hz, CH$_2$O), 3.55 (1 H, dd, $J = 10.7$, 8.0 Hz, CH$_2$O).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 161.0 (aromatic C-O), 145.0 (aromatic C-C), 104.5 (aromatic C-H), 99.3 (aromatic C-H), 67.8 (OCH$_3$), 57.5 (NCH), 55.4 (OCH$_3$).

MS (ES+) m/z 198 [M+H]$^+$. HRMS 198.1124; C$_{10}$H$_{16}$NO$_3$ requires 198.1125. IR (thin film) $\nu_{max}$ (cm$^{-1}$) 3362, 2936 (C-H), 1597. [α]$_D^{30}$ = +49.8 (c = 0.72, EtOH).

(R)-2-(tert-Butyldimethylsilyloxy)-1-(3,5-dimethoxyphenyl)ethylamine 285
Aminoalcohol 284 (566 mg, 2.87 mmol) was dissolved in dry CH₂Cl₂ (35 ml) and TBSCI (476 mg, 3.16 mmol), NEt₃ (0.8 ml, 5.74 mmol) and DMAP (10 mg, 0.08 mmol) were added. The solution was stirred at RT for 20 h then washed with sat. NaHCO₃ solution (2 × 15 ml) and dried (MgSO₄). Flash chromatography (50 % EtOAc–petrol. ether) gave 285 (735 mg, 82 %) as a pale yellow oil.

³¹H NMR (400 MHz, CDCl₃) δ ppm 6.56 (2 H, d, J = 2.3 Hz, aromatic C-H), 6.37 (1 H, t, J = 2.3 Hz, aromatic C-H), 4.03 (1 H, dd, J = 8.3, 3.8 Hz, ArCHN), 3.79 (6 H, s, OCH₃), 3.73 (1 H, dd, J = 9.8, 3.8 Hz, CH-OH), 3.53 (1 H, dd, J = 9.8, 8.3 Hz, CH₃OH), 0.90 (9 H, s, C(CH₃)₃), 0.04 (6 H, s, SiCH₃).

¹³C NMR (100 MHz, CDCl₃) δ ppm 160.8 (aromatic C-O), 144.8 (aromatic C=C), 104.9 (aromatic C-H), 99.4 (aromatic C-H), 69.2 (OCH₃), 57.8 (NCH), 55.4 (OCH₃), 25.9 (C(CH₃)₃), 18.3 (SiCMes₂), -5.39 (SiCH₃).

MS (ES+) m/z 312 [M+H]⁺. HRMS requires 312.1990. IR (thin film) νmax (cm⁻¹) 3387 (N-H), 2954 (C-H), 1579. [α]D²⁰⁻³⁰ = -3.6 (c = 0.91, EtOH).

(R)-[2-(tert-Butyldimethylsilyloxy)-1-(3,5-dimethoxyphenyl)ethyl]-4-methoxybenzyl)amine 286

Amine 285 (725 mg, 2.33 mmol) was dissolved in dry MeOH (2 ml) and 4-methoxybenzaldehyde (0.29 ml, 2.56 mmol), NaBH₃CN (161 mg, 2.56 mmol) and AcOH (0.05 ml) were added. The solution was stirred at RT for 16 h then quenched with sat. NaHCO₃ solution (5 ml) and the aqueous phase extracted with CH₂Cl₂ (4 × 5 ml) and the extracts dried (MgSO₄). Flash chromatography (15 % EtOAc–petrol. ether) gave 286 (640 mg, 64 %) as a pale yellow oil.

³¹H NMR (400 MHz, CDCl₃) δ ppm 7.21 (2 H, d, J = 8.7 Hz, aromatic C-H of PMB), 6.87 (2 H, d, J = 8.7 Hz, aromatic C-H of PMB), 6.61 (2 H, d, J = 2.3 Hz, aromatic C-H), 6.40 (1 H, t, J = 2.3 Hz, ArCH), 3.81 (9 H, s, OCH₃), 3.75 (1 H, dd, J = 9.3, 4.0 Hz, ArCHN), 3.71 (1 H, d, J = 13.4 Hz, CH₃ of PMB), 3.66 (1 H, dd, J = 9.8, 4.0 Hz, CH₂OSi), 3.57 (1 H, dd, J = 9.8, 9.3 Hz, CH₂OSi), 3.51 (1 H, d, J = 13.4 Hz, CH₂ of PMB), 2.19 (1 H, br. s, NH), 0.89 (9 H, m, C(CH₃)₃), 0.03 (3 H, s, SiCH₃), 0.02 (3 H, s, SiCH₃).

¹³C NMR (100 MHz, CDCl₃) δ ppm 158.5 (aromatic C-O), 143.5 (aromatic C=C), 132.9 (aromatic C=C), 129.2 (aromatic C-H of PMB), 113.7 (aromatic C-H of PMB), 105.6 (aromatic C-H), 99.4 (aromatic C-H), 68.4 (ArCHN), 63.4 (OCH₃), 55.3 (OCH₃), 50.7 (CH₂ of PMB), 25.9 (C(CH₃)₃), 18.3 (SiCMes₂), -5.3 (SiCH₃), -5.4 (SiCH₃).

MS (ES+) m/z 432 [M+H]⁺. HRMS requires 432.2565. IR (thin film) νmax (cm⁻¹) 3331 (N-H), 2954 (C-H), 1609. [α]D²⁰⁻³⁰ = -39.9 (c = 0.95, EtOH).
(R)-N\([2-(\text{tert-Butyldimethylsilyloxy})-1-(3,5-\text{dimethoxyphenyl})\text{ethyl}]\)-2-hydroxy-N-(4-methoxybenzyl)acetamide 277

![Structure of the compound](image)

Amine 286 (436 mg, 1.0 mmol) was dissolved in CH$_2$Cl$_2$ (5 ml) and acetoxyacetic acid (142 mg, 1.2 mmol), EDCI (230 mg, 1.2 mmol) and HOBt-H$_2$O (24 mg, 0.2 mmol) were added. The solution was stirred at RT for 20 h then washed with 0.5 M HCl (3 × 10 ml) then sat. NaHCO$_3$ solution (10 ml) and dried (MgSO$_4$). The crude amide was dissolved in MeOH (4 ml) and water (2 ml) then K$_2$CO$_3$ (414 mg, 3.0 mmol) was added. The solution was stirred for 3 h at RT then concentrated under reduced pressure and the residue diluted with water (5 ml) and extracted with EtOAc (3 × 10 ml). The extracts were combined and dried (MgSO$_4$). Flash chromatography (20–25 % EtOAc–petrol. ether) gave 277 (299 mg, 61 %) as a pale yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.06 (2 H, d, $J = 8.1$ Hz, aromatic C-H of PMB of one rotamer), 7.03 (2 H, d, $J = 7.8$ Hz, aromatic C-H of PMB of one rotamer), 6.78 (2 H, d, $J = 8.1$ Hz, aromatic C-H of PMB of one rotamer), 6.72 (2 H, d, $J = 7.8$ Hz, aromatic C-H of PMB of one rotamer), 6.43 (2 H, s, aromatic C-H of one rotamer), 6.36 (1 H, br. s, aromatic C-H of one rotamer), 6.34 (1 H, br. s, aromatic C-H of one rotamer), 6.25 (2 H, s, aromatic C-H of one rotamer), 5.48 (1 H, t, $J = 6.4$ Hz, ArCHN of one rotamer), 4.66 (2 H, d, $J = 14.8$ Hz, CH$_2$ of PMB of one rotamer), 4.64 - 4.68 (1 H, m, ArCHN of one rotamer), 4.52 (1 H, d, $J = 15.0$ Hz, CH$_2$ of PMB of one rotamer), 4.34 (1 H, d, $J = 14.8$ Hz, CH$_2$ of PMB of one rotamer), 4.26 (2 H, s, CH$_2$OH of one rotamer), 4.16 (2 H, d, $J = 15.0$ Hz, CH$_3$ of PMB of one rotamer), 4.06 (2 H, s, CH$_2$OH of one rotamer), 4.00 (1 H, dd, $J = 10.6$, 5.5 Hz, CH$_2$OHSi), 3.93 (1 H, dd, $J = 10.1$, 4.8 Hz, CH$_2$OHSi), 3.88 (1 H, d, $J = 9.3$ Hz), 3.74 (3 H, s, OCH$_3$), 3.72 (3 H, s, OCH$_3$), 3.71 (5 H, s, OCH$_3$), 3.70 (7 H, s, OCH$_3$), 0.85 (9 H, s C(CH$_3$)$_3$), 0.02 (6 H, s, SiCH$_3$), -0.01 (3 H, s, SiCH$_3$), -0.06 (3 H, s, SiCH$_3$).

$^13$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 173.3 (C=O), 161.1 (aromatic C-O of one rotamer), 160.8 (aromatic C-O of one rotamer), 159.0 (aromatic C-O of one rotamer), 158.6 (aromatic C-O of one rotamer), 139.7 (aromatic C=C of one rotamer), 138.3 (aromatic C=C of one rotamer), 130.6 (aromatic C=C of one rotamer), 129.3 (aromatic C-H of PMB of one rotamer), 128.6 (aromatic C=C of one rotamer), 127.8 (aromatic C-H of PMB of one rotamer), 114.2 (aromatic C-H of PMB of one rotamer), 113.7 (2 × aromatic C-H of PMB of one rotamer), 106.2 (aromatic C-H of one rotamer), 106.1 (aromatic C-H of one rotamer), 99.7 (aromatic C-H), 62.4 (CH$_2$OSi of one rotamer), 62.0 (CH$_2$OSi of one rotamer), 61.1 (ArCHN of one rotamer), 60.7 (CH$_2$OH of one rotamer), 59.9 (CH$_3$OH of one rotamer), 55.4 (2 × OCH$_3$), 47.4 (CH$_3$ of PMB of one rotamer), 45.9 (CH$_2$ of PMB of one rotamer), 25.8 (C(CH$_3$)$_3$), 18.1 (SiCMe$_3$), -5.5 (SiCH$_3$), -5.6 (SiCH$_3$).
MS (ES+) m/z 512 [M+Na]+. HRMS 512.2448; C_{26}H_{39}NO_{3}SiNa^{+} requires 512.2439. IR (thin film) ν_{\text{max}} (cm\(^{-1}\)) 3433 (br., OH), 2953 (C-H), 1650 (C=O), 1610, 1513. [α]D^{32} = -29.7 (c = 0.86, EtOH).

*Methyl 3-(((1R,4S)-4-(((tert-butyldimethylsilyl)oxy)methyl)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)sulfonyl)propanoate 287*

Hydroxyamide 277 (157 mg, 0.32 mmol) was oxidised according the Swern oxidation general procedure 1 using oxalyl chloride (32 μl), DMSO (47 μl), CH\(_2\)Cl\(_2\) (2.6 ml) and NEt\(_3\) (0.23 ml). The resulting glyoxamide was dissolved in CH\(_2\)Cl\(_2\) (4 ml) and methyl 3-mercaptopropanoate (52 μl, 0.45 mmol) and Sc(OOTf)\(_3\) (31 mg, 0.064 mmol) were added. The solution was stirred at RT for 17 h then heated to 25 °C for 7 h (as RT had dropped to 14 °C overnight). The solution was washed with water (10 ml) then brine (10 ml) and dried (MgSO\(_4\)). Flash chromatography (20 % EtOAc–petrol. ether) gave 287 (12 mg, 8 %) as a pale yellow gum.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) δ ppm 7.29 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB), 6.88 (2 H, d, J = 8.5 Hz, aromatic C-H of PMB), 6.38 (1 H, d, J = 2.0 Hz, aromatic C-H), 6.23 (1 H, d, J = 2.0 Hz, aromatic C-H), 5.57 (1 H, d, J = 15.7 Hz, CH=H of PMB), 4.63 (1 H, s, ArCHS), 4.52 (1 H, br. s, ArCHN), 4.07 (1 H, d, J = 15.7 Hz, CH=H of PMB), 4.04 (1 H, m, CHHOSi), 3.86 (3 H, s, OCH\(_3\)), 3.80 (3 H, s, OCH\(_3\)), 3.76 (3 H, s, OCH\(_3\)), 3.71 - 3.79 (1 H, m, CHHOSi), 3.69 (3 H, s, OCH\(_3\)), 3.28 (1 H, dt, J = 13.9, 6.9 Hz, SCH=H), 2.90 - 3.00 (1 H, m, SCH=H), 2.75 (2 H, td, J = 7.3, 2.4 Hz, CH\(_2\)CO\(_2\)Me), 0.76 (9 H, s, C(CH\(_3\))\(_3\)), -0.06 (3 H, s, SiCH\(_3\)), -0.18 (3 H, s, SiCH\(_3\)).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ ppm 172.6 (C=O), 170.7 (C=O), 160.2 (aromatic C-O), 158.8 (aromatic C-O), 157.3 (aromatic C-O), 134.8 (aromatic C=C), 129.4 (aromatic C-H of PMB), 128.8 (aromatic C=C), 114.7 (aromatic C-H on PMB), 114.1 (aromatic C=C), 101.3 (aromatic C-H), 97.9 (aromatic C-H), 63.2 (CH\(_3\)OSi), 59.8 (ArCHN), 55.8 (OCH\(_3\)), 55.4 (OCH\(_3\)), 55.3 (OCH\(_3\)), 51.7 (OCH\(_3\)), 45.8 (CH\(_2\) of PMB), 41.2 (ArCHS), 34.4 (CH\(_2\)CO\(_2\)Me), 28.0 (SCH\(_3\)), 25.6 (C(CH\(_3\))\(_3\)), 18.0 (Si(CH\(_3\))\(_3\)), -5.6 (SiCH\(_3\)), -5.8 (SiCH\(_3\)).

MS (ES+) m/z 612 [M+Na]+. HRMS 590.2599, C\(_{30}\)H\(_{44}\)NO\(_3\)SSi\(^+\) requires 590.2602. IR (thin film) ν_{\text{max}} (cm\(^{-1}\)) 3417, 2952 (C-H), 1738 (ester C=O), 1644 (amide C=O), 1610. [α]D^{32} = +99.8 (c = 1.6, EtOH).

*5R)-5-(3,5-Dimethoxyphenyl)-2-hydroxy-4-(4-methoxybenzyl)morpholin-3-one 288*
Morpholinone 288 (1.7:1 dr) was isolated as a by-product from the exposure of branched glyoxamides derived from 277 or 289 under connective Pummerer conditions. 

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.14 (2 H, d, $J = 8.6$ Hz, aromatic C-H of PMB of one diastereoisomer), 7.04 (2 H, d, $J = 8.6$ Hz, aromatic C-H of PMB of one diastereoisomer), 6.86 (2 H, d, $J = 8.6$ Hz, aromatic C-H of PMB of one diastereoisomer), 6.82 (1 H, d, $J = 8.6$ Hz, aromatic C-H of one diastereoisomer), 6.45 (1 H, t, $J = 2.3$ Hz, aromatic C-H of one diastereoisomer), 6.37 (2 H, d, $J = 2.3$ Hz, aromatic C-H of one diastereoisomer), 6.35 (2 H, d, $J = 2.3$ Hz, aromatic C-H of one diastereoisomer), 5.50 (1 H, s, OCH$_2$OH of one diastereoisomer), 5.45 (1 H, s, OCH$_2$OH of one diastereoisomer), 5.46 (1 H, d, $J = 14.5$ Hz, C-HH of PMB of one diastereoisomer), 5.35 (1 H, d, $J = 14.5$ Hz, C-HH of PMB of one diastereoisomer), 4.43 (1 H, dd, $J = 12.2, 3.9$ Hz, ArCHN of one diastereoisomer), 4.39 (1 H, dd, $J = 8.8, 4.9$ Hz, ArCHN of one diastereoisomer), 4.25 (1 H, dd, $J = 12.2, 8.8$ Hz, C-HHO of one diastereoisomer), 4.20 (1 H, dd, $J = 3.9, 2.5$ Hz, C-HHO of one diastereoisomer), 3.85 (1 H, dd, $J = 12.2, 4.9$ Hz, C-HHO of one diastereoisomer), 3.80 (12 H, s, OCH$_3$), 3.79 (6 H, s, OCH$_3$), 3.72 (1 H, dd, $J = 12.1, 2.5$ Hz, C-HHO of one diastereoisomer), 3.54 (1 H, d, $J = 14.5$ Hz, CH$_2$ of PMB of one diastereoisomer), 3.46 (1 H, d, $J = 14.5$ Hz, CH$_2$ of PMB of one diastereoisomer).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 167.2 (C=O) 161.3 (aromatic C-O), 159.3 (aromatic C-O), 139.9 (aromatic C of one diastereoisomer), 137.5 (aromatic C of one diastereoisomer), 130.1 (aromatic C-H of PMB of one diastereoisomer), 129.9 (aromatic C-H of PMB of one diastereoisomer), 128.0 (aromatic C of one diastereoisomer), 127.8 (aromatic C of one diastereoisomer), 114.1 (aromatic C-H of PMB of one diastereoisomer), 113.9 (aromatic C-H of PMB of one diastereoisomer), 105.8 (aromatic C-H of one diastereoisomer), 105.3 (aromatic C-H of one diastereoisomer), 100.4 (aromatic C-H of one diastereoisomer), 99.7 (aromatic C-H of one diastereoisomer), 91.0 (OCH$_2$OH of one diastereoisomer), 90.5 (OCH$_2$OH of one diastereoisomer), 64.1 (CH$_2$O of one diastereoisomer), 63.4 (CH$_2$O of one diastereoisomer), 59.4 (ArCHN of one diastereoisomer), 58.2 (ArCHN of one diastereoisomer), 55.4 (OCH$_3$), 55.4 (OCH$_3$), 55.3 (OCH$_3$), 46.6 (CH$_2$ of PMB of one diastereoisomer), 45.7 (CH$_2$ of PMB of one diastereoisomer).

MS (ES+) $m/z$ 396.1 [M+Na]$^+$. HRMS 396.1425; C$_{20}$H$_{23}$O$_6$NNa$^+$ requires 396.1418. IR (thin film) $\nu_{max}$ (cm$^{-1}$) 3308 (br., OH), 2926 (C-H), 1643 (C=O), 1610, 1597. [\(\alpha\)]$^D_{30}$ = +32.0 (c = 0.50, CHCl$_3$).

(R)-tert-Butyl (1-(3,5-dimethoxyphenyl)-2-((triisopropylsilanyloxy)ethyl)carbamate 290
NaOH (732 mg, 18 mmol) and BocNH₂ (2.19 g, 18 mmol) were dissolved in water (45 ml) and n-PrOH (24 ml) at 0 °C. Freshly-prepared t-BuOCl (2.14 ml, 18.0 mmol) in n-PrOH (24 ml) was added followed by a solution of (DHQD)₂PHAL (144 mg, 0.18 mmol) in n-PrOH (24 ml) and K₂OsO₄·H₂O (40 mg, 0.1 mmol). The solution was stirred at 0 °C for 1 h then sat. aq. Na₂SO₃ solution (60 ml) was added. The layers were separated then the aqueous layer extracted with EtOAc (2 × 50 ml). The organic layers were combined and washed with water (50 ml) then brine (50 ml) and dried (MgSO₄) and the solvent evaporated. The residue was dissolved in dry CH₂Cl₂ (60 ml) then imidazole (1.02 g, 15 mmol) and TIPSCl (1.67 ml, 7.8 mmol) were added and the solution stirred for 21 h then washed with sat. NH₄Cl solution (2 × 30 ml) then brine (30 ml) and dried (MgSO₄). Flash chromatography (10 % EtOAc–pet. ether) gave 290 (1.71 g, 63 % over 2 steps) as a pale yellow oil.

**{(R)}-1-(3,5-Dimethoxyphenyl)-2-((triisopropylsila)oxy)ethanamine 291**

Carbamate 290 (1.71 g, 3.8 mmol) was dissolved in CH₂Cl₂ (50 ml) and TFA (14 ml) was added dropwise over 2 minutes. The reaction was stirred for 2 h then quenched slowly with sat. Na₂CO₃ solution (30 ml), the layers separated and the aqueous phase extracted with CH₂Cl₂ (4 × 50 ml). The organic layers were combined and dried (MgSO₄) to give 291 (1.27 g, 95 %) as a brown oil.

**{(R)}-1-(3,5-Dimethoxyphenyl)-2-((triisopropylsila)oxy)ethanamine 291**
1H NMR (400 MHz, CDCl₃) δ ppm 6.55 (2 H, d, J = 2.4 Hz, aromatic C-H), 6.40 (1 H, t, J = 2.4 Hz, aromatic C-H), 4.73 (1 H, dd, J = 8.9, 3.4 Hz, ArCHO), 3.85 (1 H, dd, J = 10.0, 3.4 Hz, CHOSi), 3.81 (6 H, s, 2 × OCH₃), 3.61 (1 H, dd, J = 10.0, 8.9 Hz, CH(OSi), 3.09 (1 H, br. s, OH), 1.05 - 1.11 (21 H, m, SiCH and SiCH(CH₃)₂)

13C NMR (100 MHz, CDCl₃) δ ppm 160.7 (aromatic C-O), 142.7 (aromatic C-C), 104.4 (aromatic C-H), 104.1 (aromatic C-H), 99.7 (aromatic C-H), 74.5 (ArCHO), 69.2 (CH₂OSi), 55.3 (OCH₃), 17.9 (SiCH(CH₃)₂), 11.9 (SiCH).

MS (ES+) m/z 377 [M+Na]⁺. HRMS 377.2218, C₁₉H₃₄O₄Si requires 377.2219. IR (thin film) νmax (cm⁻¹) 3460 (br., OH), 2642 (C-H), 2866, 1598. [α]D₃⁴ = -1.2 (c = 3.18, EtOH).

2-(4-Methoxybenzylamino)-2-oxoethyl acetate 294

4-Methoxybenzylamine (130 µl, 1.0 mmol) was dissolved in CH₂Cl₂ (1.5 ml) and acetoxyacetyl chloride (118 µl, 1.1 mmol) and NE₃ (153 µl, 1.1 mmol) were added. The solution was stirred for 2.5 h then diluted with CH₂Cl₂ (10 ml) and washed with 1 M HCl (10 ml) then sat. NaHCO₃
solution (10 ml) and dried (MgSO₄). Flash chromatography (60 % EtOAc–pet. ether) gave 294 as a colourless solid (221 mg, 93 %), melting point 75-77 °C.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.24 (2 H, d, J = 8.6 Hz, aromatic C-H), 6.89 (2 H, d, J = 8.6 Hz, aromatic C-H), 6.34 (1 H, br. s, NH), 4.61 (2 H, s, CH₂O), 4.45 (2 H, d, J = 5.8 Hz, CH₂NH), 3.82 (3 H, s, OCH₃), 2.14 (3 H, s, COCH₃).

³¹C NMR (100 MHz, CDCl₃) δ ppm 169.3 (C=O), 166.7 (C=O), 159.2 (aromatic C-O), 129.6 (aromatic C-C), 129.2 (aromatic C-H), 114.2 (aromatic C-H), 63.1 (CH₂O), 55.3 (OCH₃), 42.6 (CH₂N), 20.7 (COCH₃).

MS (ES+) m/z 238 [M+H]⁺, 260 [M+Na]⁺. HRMS 238.1072; C₁₂H₁₆NO₄⁺ requires 238.1072.

IR (thin film) νmax (cm⁻¹) 3266 (N-H), 3089, 2961 (C-H), 1746 (ester C=O), 1667 (amide (C=O)).

Alcohol 293 (5.11 g, 14.4 mmol) was dissolved in THF (85 ml) and phthalimide (2.97 g, 20.2 mmol), DIAD (3.98 ml, 20.2 mmol) and PPh₃ (5.30 g, 20.2 mmol) were added. The solution was stirred at RT for 90 h then concentrated in vacuo. The residue was dissolved in Et₂O (100 ml) then hexane (50 ml) was added. The mixture was triturated then filtered through a plug of silica and the precipitate was washed with Et₂O-hexane (40:60). The filtrate was concentrated in vacuo and purified by flash chromatography (10-15 % Et₂O–pet. ether) to give 295 (4.34 g, 62 %) as a colourless solid, melting point 62-65 °C.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.83 (2 H, dd, J = 5.4, 3.0 Hz, phthalimide aromatic C-H), 7.70 (2 H, dd, J = 5.4, 3.0 Hz, phthalimide aromatic C-H), 6.71 (2 H, d, J = 2.4 Hz, aromatic C-H), 6.39 (1 H, t, J = 2.4 Hz, aromatic C-H), 5.41 (1 H, dd, J = 10.2, 5.7 Hz, ArCHN), 4.78 (1 H, t, J = 10.4 Hz, CHOSi), 4.20 (1 H, dd, J = 10.0, 5.7 Hz, CH₂OSi), 3.78 (6 H, s, 2 × OCH₃), 0.92 - 1.00 (21 H, m, SiCH and SiCH(C₃H₇)₂).

³¹C NMR (100 MHz, CDCl₃) δ ppm 168.6 (C=O), 160.8 (aromatic C-O), 139.3 (aromatic C-C), 133.9 (phthalimide aromatic C-H), 131.9 (phthalimide aromatic C-C), 123.1 (phthalimide aromatic C-H), 106.3 (aromatic C-H), 99.9 (aromatic C-H), 66.8 (ArCHN), 57.4 (CH₂OSi), 55.3 (OCH₃), 17.8 (CH(CH₃)₂), 11.8 (SiCH).

MS (ES+) m/z 506 M+Na⁺. HRMS 506.2330; C₂₇H₃₇O₅NNaSi⁺ requires 506.2333. IR (thin film) νmax (cm⁻¹) 3470, 2943 (C-H), 2865, 1774 (C=O), 1712, 1598. [α]D₃₀ = +15.5 (c = 1.17, EtOH).

(R)-1-(3,5-Dimethoxyphenyl)-2-((triisopropylsilanyl)oxy)ethanamine 291
Phthalimide 294 (4.34 g, 8.98 mmol) was dissolved in EtOH (60 ml) and hydrazine (62 % aq. solution, 1.8 ml, 35 mmol) was added. The solution was heated under reflux for 2 h then cooled, diluted with Et₂O (150 ml) and filtered through celite. The precipitate was washed with Et₂O (200 ml) and the combined filtrate was concentrated in vacuo to give 291 (3.15 g, 99 %) as a pale yellow oil which was used without further purification.

Data was consistent with that of the material obtained using the asymmetric aminohydroxylation route. A racemic sample was also synthesised using a similar route. Enantiomeric excess was measured as approximately 84 % using chiral HPLC (ChiralPak AD column, 90:10 hexane–isopropanol).

(R)-1-(3,5-Dimethoxyphenyl)-N-(4-methoxybenzyl)-2-((triisopropylsilanyl)oxy)ethanamine 292

Method A

Amine 291 (1.28 g, 3.6 mmol) was dissolved in MeOH (4 ml) and 4-methoxybenzaldehyde (484 μl, 4.0 mmol), NaBH₃CN (249 mg, 4.0 mmol) and AcOH (1 drop) were added. The solution was stirred at RT for 22 h then NaBH₄ (50 mg) was added to destroy the remaining 4-methoxybenzaldehyde. The reaction was quenched with sat. sodium carbonate solution (20 ml) then extracted with EtOAc (3 × 20 ml), then the extracts were dried (MgSO₄). Flash chromatography (40 % EtOAc–pet. ether) gave impure 292 (1.19 g, 70 %).

Method B

Amine 291 (3.02 g, 8.56 mmol) was dissolved in dry MeOH (15 ml) under N₂, 4-methoxybenzaldehyde (1.14 ml, 9.41 mmol) was added and the solution heated under reflux for 2 h. The solution was cooled to RT and NaBH₄ (356 mg, 9.41 mmol) was added portionwise and the solution stirred for 75 minutes. The reaction was quenched with water (50 ml) then extracted with EtOAc (3 × 50 ml). The extracts were washed with brine (20 ml) and dried (MgSO₄). Flash chromatography (10 % EtOAc–pet. ether) gave 292 (3.88 g, 96 %) as a pale yellow oil.

¹H NMR (500 MHz, CDCl₃) δ ppm 7.20 (2 H, d, J = 8.6 Hz, aromatic C-H of PMB), 6.86 (2 H, d, J = 8.6 Hz, aromatic C-H of PMB), 6.61 (2 H, d, J = 2.4 Hz, aromatic C-H), 6.39 (1 H, t, J = 2.4 Hz, aromatic C-H), 3.81 (6 H, s, 2 × OCH₃), 3.81 (3 H, s, OCH₃), 3.74 - 3.80 (2 H, m, CH₂O),

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3.72 (1 H, d, J = 13.0 Hz, CHH of PMB), 3.64 (1 H, t, J = 9.5 Hz, CHN), 3.51 (1 H, d, J = 13.0 Hz, CHH of PMB), 1.00 - 1.11 (21 H, m, SiCH and SiCH(CH₃)₂).

13C NMR (126 MHz, CDCl₃) δ ppm 160.5 (aromatic C-O), 158.2 (aromatic C-O), 143.3 (aromatic C-C), 132.7 (aromatic C-C), 128.9 (aromatic C-H of PMB), 113.5 (aromatic C-H of PMB), 105.4 (aromatic C-H), 99.1 (aromatic C-H), 68.4 (ArCHN), 64.3 (CH₂O), 55.1 (OCH₃), 55.0 (OCH₃), 50.5 (CH₂ of PMB), 17.7 (SiCH(CH₃)₂), 11.6 (SiCH(CH₃)₂).

MS (ES+) m/z 474 [M+H]⁺. HRMS 474.3045; C₂₉H₄₄O₄NSi⁺ requires 474.3034. IR (thin film) v_max (cm⁻¹) 2940 (C-H), 2864, 1609, 1596. [α]ᵢₒ³⁴ = −45.6 (c = 1.05, EtOH).

(R)-N(1-(3,5-Dimethoxyphenyl)-2-((triisopropylsilanyloxy)ethyl)-2-hydroxy-N(4-methoxybenzyl)acetamide 289

Amine 292 (1.73 g, 3.7 mmol) was dissolved in CH₂Cl₂ (7.4 ml) and AcOCH₂COCl (0.44 ml, 4.07 mmol) and NEt₃ (0.57 ml, 4.07 mmol) were added. The solution was stirred for 15 h then diluted with CH₂Cl₂ (20 ml) and washed with sat. NaHCO₃ solution (2 × 20 ml) then dried (MgSO₄) and concentrated in vacuo. The residue was dissolved in THF (24 ml), MeOH (4 ml) and water (6 ml) and LiOH·H₂O (311 mg, 7.4 mmol) was added. The solution was stirred for 26 h then the volatiles evaporated and the aqueous layer diluted with water (50 ml) and extracted with EtOAc (3 × 50 ml) and dried (MgSO₄). Flash chromatography (30 % EtOAc–pet. ether) gave 289 (1.75 g, 89 %) as a pale yellow oil.

1H NMR (400 MHz, DMSO-d₆, 120 °C) δ ppm 7.06 (2 H, d, J = 8.6 Hz, aromatic C-H of PMB), 6.79 (2 H, d, J = 8.6 Hz, aromatic C-H of PMB), 6.48 (2 H, d, J = 2.2 Hz, aromatic C-H), 6.40 (1 H, t, J = 2.2 Hz, aromatic C-H), 5.13 (1 H, t, J = 6.3 Hz, ArCHN), 4.52 (1 H, d, J = 16.2 Hz, CHH of PMB), 4.33 (1 H, d, J = 16.2 Hz, CHH of PMB), 4.16 - 4.25 (2 H, m, CH₂OSi), 4.12 (2 H, d, J = 6.8 Hz, CH₂OH), 3.73 (3 H, s, OCH₃), 3.71 (6 H, s, OCH₃), 0.97 - 1.09 (21 H, m, SiCH and CH(CH₃)₂).

13C NMR (100 MHz, CDCl₃) δ ppm 173.3 (C=O of one rotamer), 173.2 (C=O of one rotamer), 161.0 (aromatic C-O of one rotamer), 160.6 (aromatic C-O of one rotamer), 158.9 (aromatic C-O of one rotamer), 158.5 (aromatic C-O of one rotamer), 139.6 (aromatic C-C of one rotamer), 138.2 (aromatic C-C of one rotamer), 130.4 (aromatic C-C of one rotamer), 129.1 (aromatic C-H of PMB of one rotamer), 128.5 (aromatic C-C of one rotamer), 127.8 (aromatic C-H of PMB of one rotamer), 114.0 (aromatic C-H of PMB of one rotamer), 113.5 (aromatic C-H of PMB of one rotamer), 106.5 (aromatic C-H of one rotamer), 105.9 (aromatic C-H of one rotamer), 99.5 (aromatic C-H of one rotamer), 99.5 (aromatic C-H of one rotamer), 62.7 (CH₂O of one rotamer), 62.5 (CH₂O of one rotamer), 61.0 (ArCHN of one rotamer), 60.8 (ArCHN of one rotamer), 60.7
(CH₂O of one rotamer), 60.4 (CH₂O of one rotamer), 55.3 (OCH₃ of one rotamer), 55.2 (OCH₃ of one rotamer), 47.2 (CH₂ of PMB of one rotamer), 45.9 (CH₂ of PMB of one rotamer), 17.9 (CH(CH₃)₂), 11.8 (SiCH₃ of one rotamer), 11.7 (SiCH₃ of one rotamer).

MS (ES⁺) m/z 554.6 [M+Na]+. HRMS 554.2904 C₂₉H₴₅O₆NNaS⁺ requires 554.2908. IR (thin film) νmax (cm⁻¹) 3431 (br., OH), 2943 (C-H), 2865, 1650 (amide C=O), 1610.

Methyl 3-(((1'R,4'S)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1-(((triisopropylsilanyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)sulfanyl)propanoate 297a and methyl 3-(((1'R,4'R)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1-(((triisopropylsilanyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)sulfanyl)propanoate 297b

Method A – connective Pummerer reaction
Hydroxyamide 289 (274 mg, 0.52 mmol) was dissolved in CH₂Cl₂ (1.4 ml) and DMSO (1.4 ml) at 0 °C and NEt₃ (0.36 ml, 2.60 mmol) and SO₃·py (325 mg, 2.1 mmol) were added. The solution was stirred for 2 h then methyl 3-mercaptopropanoate (84 μl, 0.78 mmol) was added. After 15 minutes, the solution was diluted with Et₂O (10 ml) and washed with 1 M HCl (10 ml), sat. NaHCO₃ solution (10 ml) then brine (10 ml) and dried (MgSO₄). The crude hemithioacetal was dissolved in CH₂Cl₂ (6 ml) and ZnCl₂ (141 mg, 1.04 mmol) was added. The solution was stirred at RT for 22 h then diluted with CH₂Cl₂ (10 ml) and washed with water (10 ml) then brine (10 ml) and dried (MgSO₄). Flash chromatography (30 % EtOAc–pet. ether) gave 297a and 297b (267 mg, 81 %) as pale yellow gums.

Method B – Substitution of hydroxytetrahydroisoquinolinone 296
Hydroxytetrahydroisoquinolinone 296 (94 mg, 0.18 mmol) was dissolved in CH₂Cl₂ (2 ml) and thiol 252 (29 μl, 0.27 mmol) and ZnCl₂ (24 mg, 0.18 mmol) were added and the solution was stirred at RT for 20 h then diluted with CH₂Cl₂ (5 ml) and washed with water (5 ml) then brine (5 ml) and dried (MgSO₄). Flash chromatography (30 % EtOAc–pet. ether) gave 297a and 297b (65 mg, 58 %) as a pale yellow gum.

MS (ES⁺) m/z 654 [M+Na]+. HRMS 654.2891, C₃₃H₴₉O₇NNaSSi⁺ requires 654.2891.

Analytically pure samples of the individual diastereoisomers were obtained by further chromatography.

For 297a ¹H NMR (400 MHz, CDCl₃) δ ppm 7.30 (2 H, d, J = 8.6 Hz, aromatic C-H of PMB), 6.87 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB), 6.36 (1 H, d, J = 2.2 Hz, aromatic C-H), 6.22 (1 H, d,
J = 2.2 Hz, aromatic C-H), 5.62 (1 H, d, J = 15.4 Hz, CH₃ of PMB), 4.57 (1 H, s, ArCHS), 4.49 (1 H, br. s, ArCH=NO), 4.15 (1 H, dd, J = 10.3, 3.3 Hz, CH(HOSi)), 3.99 (1 H, d, J = 15.4 Hz, CH₃ of PMB), 3.85 (3 H, s, OCH₃), 3.80 (3 H, s, OCH₃), 3.75 - 3.79 (1 H, m, CH(HOSi)), 3.73 (3 H, s, OCH₃), 3.68 (3 H, s, CO₂CH₃), 3.29 (1 H, dt, J = 13.6, 7.6 Hz, SCH(H)), 2.95 (1 H, dt, J = 13.6, 7.6 Hz, SCH(H)), 2.73 (2 H, t, J = 7.6 Hz, CH₃CO₂Me), 0.82 - 0.94 (21 H, m, SiCH and SiCH(CH₃)₂).

¹³C NMR (100 MHz, CDCl₃) δ ppm 172.6 (C=O), 170.7 (C=O), 160.1 (aromatic C-O), 158.8 (aromatic C-O), 157.3 (aromatic C-O), 134.3 (aromatic C-C), 129.1 (aromatic C-H of PMB), 129.1 (aromatic C-C), 114.7 (aromatic C-C), 114.1 (aromatic C-H of PMB), 101.0 (aromatic C-H), 98.0 (aromatic C-H), 64.5 (CH₂OSi), 60.2 (ArCHN), 55.7 (OCH₃), 55.3 (OCH₃), 55.2 (OCH₃), 51.6 (CO₂CH₃), 45.9 (CH₂ of PMB), 41.1 (ArCHS), 34.3 (CH₂CO₂CH₃), 28.2 (SCH₂), 17.7 (SiCH(CH₃)₂), 11.8 (SiCH(CH₃)₂).

IR (thin film) νmax (cm⁻¹) 2925 (C-H), 2865, 1739 (ester C=O), 1651 (amide C=O). [α]D²⁰ = −129.3 (c = 2.61, EtOH).

For 297b ¹H NMR (400 MHz, CDCl₃) δ ppm 7.14 (2 H, d, J = 8.6 Hz, aromatic C-H of PMB), 6.80 (2 H, d, J = 8.6 Hz, aromatic C-H of PMB), 6.37 (1 H, d, J = 2.3 Hz, aromatic C-H), 6.23 (1 H, d, J = 2.3 Hz, aromatic C-H), 5.43 (1 H, d, J = 15.0 Hz, CH₃ of PMB), 4.72 (1 H, s, ArCHS), 4.40 (1 H, dd, J = 7.7, 5.8 Hz, ArCHN), 4.39 (1 H, d, J = 15.0 Hz, CH₃ of PMB), 4.27 (1 H, dd, J = 9.9, 7.7Hz, CH(HOSi)), 3.91 (1 H, dd, J = 9.9, 5.8 Hz, CH(HOSi)), 3.86 (3 H, s, OCH₃), 3.76 (3 H, s, OCH₃), 3.75 (3 H, s, OCH₃), 3.72 (3 H, s, OCH₃), 3.38 (1 H, dt, J = 13.9, 6.7 Hz, SCHOH), 3.00 - 3.13 (1 H, m, SCHOH), 2.85 - 2.92 (2 H, m, CH₂CO₂Me), 1.01 - 1.10 (21 H, m, Si(CH(CH₃)₂)₃).

¹³C NMR (100 MHz, CDCl₃) δ ppm 172.5 (C=O), 169.1 (C=O), 160.0 (aromatic C-O), 158.8 (aromatic C-O), 157.2 (aromatic C-O), 136.1 (aromatic C-C), 129.4 (aromatic C-C), 129.1 (aromatic C-H of PMB), 113.9 (aromatic C-H of PMB), 113.5 (aromatic C-C), 102.9 (aromatic C-H), 98.0 (aromatic C-H), 68.8 (CH₂OSi), 62.6 (ArCHN), 55.7 (OCH₃), 55.3 (OCH₃), 55.2 (OCH₃), 51.7 (CO₂CH₃), 49.1 (CH₂ of PMB), 39.8 (ArCHS), 34.4 (CH₂CO₂Me), 28.5 (SCH₂), 18.0 (SiCH(CH₃)₂), 11.7 (SiCH(CH₃)₂).

IR (thin film) νmax (cm⁻¹) 2926 (C-H), 2865, 1740 (ester C=O), 1648 (amide C=O). [α]D²⁰ = +32.5 (c = 2.14, EtOH).

(1R)-4-Hydroxy-5,7-dimethoxy-2-(4-methoxybenzyl)-1-(((triisopropylsilanyl)oxy)-methyl)-1,2-dihydroisoquinolin-3(4H)-one 296

Alcohol 296 was isolated as a by-product from the exposure of branched glyoxamides derived from 289 under connective Pummerer conditions.
1H NMR (400 MHz, CDCl3) δ ppm 7.20 (2 H, d, J = 8.7 Hz, aromatic C-H of PMB), 6.83 (2 H, d, J = 8.7 Hz, aromatic C-H of PMB), 6.45 (1 H, d, J = 2.4 Hz, aromatic C-H), 6.16 (1 H, d, J = 2.4 Hz, aromatic C-H), 5.47 (1 H, d, J = 14.9 Hz, CH$_3$H of PMB), 5.29 (1 H, s, ArCH$_2$OH), 4.36 (1 H, dd, J = 4.2, 3.5 Hz, ArCHN), 4.26 (1 H, d, J = 14.9 Hz, CH$_2$H of PMB), 3.92 (1 H, dd, J = 9.2, 3.5 Hz, CH$_2$HO), 3.89 (3 H, s, OCH$_3$), 3.78 (3 H, s, OCH$_3$), 3.76 (3 H, s, OCH$_3$), 3.67 (1 H, dd, J = 9.2, 4.2 Hz, CH$_2$O), 0.89 - 0.94 (21 H, m, SiCH and CH(CH$_3$)$_2$).

13C NMR (100 MHz, CDCl3) δ ppm 171.0 (C=O), 160.1 (2 × aromatic C-O), 159.1 (aromatic C-O), 133.9 (aromatic C-C), 129.3 (aromatic C-H of PMB), 128.4 (aromatic C-C), 116.4 (aromatic C-C), 114.1 (aromatic C-H of PMB), 101.9 (aromatic C-H), 98.7 (aromatic C-H), 66.5 (CH$_2$O), 65.2 (ArCHOH), 61.5 (ArCHN), 56.1 (OCH$_3$), 55.4 (OCH$_3$), 55.3 (OCH$_3$), 48.1 (CH$_2$ of PMB), 17.7 (C(CH$_3$)$_2$), 11.8 (SiCH).

MS (ES+) m/z 552.5 [M+Na]$^+$. HRMS 552.2774; C$_{29}$H$_{33}$O$_8$NNaSi$^+$ requires 552.2763. IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 3419 (br., O-H), 2940 (C-H), 2863, 1655 (C=O), 1651, 1644, 1615. $\left[\alpha\right]_D^{30} = -11.8$ (c = 1.16, EtOH).

(1R,4S)-5,7-Dimethoxy-2-(4-methoxybenzyl)-4-(methylsulfonyl)-1-(((triisopropylsilanyloxy)methyl)-1,2-dihydroisoquinolin-3(4H)-one 298a

Sulfide 298a was isolated as a by-product from the exposure of branched glyoxamides derived from 289 under connective Pummerer conditions.

1H NMR (500 MHz, CDCl3) δ ppm 7.28 (2 H, d, J = 8.5 Hz, aromatic C-H of PMB), 6.88 (2 H, d, J = 8.5 Hz, aromatic C-H of PMB), 6.38 (1 H, d, J = 2.0 Hz, aromatic C-H), 6.23 (1 H, d, J = 2.0 Hz, aromatic C-H), 5.64 (1 H, d, J = 15.4 Hz, CH$_2$H of PMB), 4.56 (1 H, s, ArCH$_5$S), 4.50 (1 H, br. s, ArCHN), 4.16 (1 H, dd, J = 10.3, 3.3 Hz, CH$_2$HO), 3.99 (1 H, d, J = 15.4 Hz, CH$_2$H of PMB), 3.86 (3 H, s, OCH$_3$), 3.80 (3 H, s, OCH$_3$), 3.77 (1 H, dd, J = 10.3, 1.3 Hz, CH$_2$HO), 3.74 (3 H, s, OCH$_3$), 2.20 (3 H, s, SCH$_3$), 0.86 - 0.94 (21 H, m, SiCH and CH(CH$_3$)$_2$).

13C NMR (126 MHz, CDCl3) δ ppm 172.0 (C=O), 159.7 (aromatic C-O), 158.6 (aromatic C-O), 157.2 (aromatic C-O), 134.2 (aromatic C-C), 129.0 (aromatic C-H of PMB), 128.9 (aromatic C-C), 114.9 (aromatic C-C), 113.8 (aromatic C-H of PMB), 100.6 (aromatic C-H), 97.8 (aromatic C-H), 64.3 (CH$_2$O), 59.9 (ArCHN), 55.7 (OCH$_3$), 55.1 (OCH$_3$), 55.0 (OCH$_3$), 45.7 (CH$_2$ of PMB), 42.4 (SCH$_3$), 17.4 (CH$_2$(CH$_3$)$_2$), 15.6 (SCH$_3$), 11.5 (SiCH).

MS m/z (ES+) 582.4 [M+Na]$^+$ (both diastereoisomers). HRMS 582.2629; C$_{30}$H$_{33}$O$_8$NNaSi$^+$ requires 582.2691. IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 2925 (C-H), 2862, 1739, 1647 (C=O), 1611. $\left[\alpha\right]_D^{30} = -103.0$ (c = 0.83, CHCl$_3$).
(1R,4R)-5,7-Dimethoxy-2-(4-methoxybenzyl)-4-(methylsulfanyl)-1-
(((triisopropylsilanilyl)-oxy)methyl)-1,2-dihydroisoquinolin-3(4H)-one 298b

Sulfide 298b was isolated as a by-product from the exposure of branched glyoxamides derived from 289 under connective Pummerer conditions.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ ppm 7.15 (2 H, d, $J = 8.7$ Hz, aromatic C-H of PMB), 6.81 (1 H, d, $J = 2.5$ Hz, aromatic C-H), 6.25 (1 H, d, $J = 2.5$ Hz, aromatic C-H), 5.44 (1 H, d, $J = 14.8$ Hz, C-H of PMB), 4.68 (1 H, s, ArCHS), 4.40 (2 H, d, $J = 14.8$ Hz, CH of PMB), 4.33 - 4.44 (2 H, m, CHN and C-HO), 3.95 (1 H, dd, $J = 9.6, 5.5$ Hz, CHO), 3.87 (3 H, s, OCH$_3$), 3.77 (3 H, s, OCH$_3$), 3.76 (3 H, s, OCH$_3$), 2.48 (3 H, s, SCH$_3$), 0.82 - 1.14 (21 H, m, SiCH and CH(CH$_3$)$_2$).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ ppm 168.7 (C=O), 158.1 (aromatic C-O), 157.4 (C-O), 136.2 (aromatic C-C), 129.5 (aromatic C-C), 129.1 (aromatic C-H of PMB), 114.1 (aromatic C-C), 113.9 (aromatic C-H of PMB), 103.0 (aromatic C-H), 98.0 (aromatic C-H), 68.6 (CH$_2$O), 62.6 (ArCHN), 55.9 (OCH$_3$), 55.3 (OCH$_3$), 55.2 (OCH$_3$), 49.0 (CH$_2$ of PMB), 41.9 (CHS), 17.9 (CH(CH$_3$)$_2$), 17.4 (SCH$_3$), 11.8 (SiCH).

MS m/z (ES+) 582.4 [M+Na]$^+$ (both diastereoisomers) HRMS 582.2629; $C_{30}H_{45}O_5NNaSSi$ requires 582.2691. IR (thin film) $\nu_{max}$ (cm$^{-1}$) 2942 (C-H), 2865, 1739, 1649 (C=O), 1610.

[α]$_D^{30}$ = -4.4 (c = 0.60, CHCl$_3$).

(R)-Methyl 3-(((1R,4R)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1-(((tri-isopropylsilanilyl)oxy)methyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)sulfanyl)-2-(((2,2,2-trichloro-ethoxy)carbonyl)amino)propanoate 299

Hydroxyamide 289 (0.85 mmol) was oxidised according to general procedure A then the corresponding glyoxamide was dissolved in CH$_2$Cl$_2$ (10 ml) and methyl N-Troc-cysteine (1.28 mmol, 396 mg) and ZnCl$_2$ (116 mg, 0.85 mmol) were added. The solution was stirred at RT for 15 h then washed with water (10 ml) then brine (10 ml) and dried (MgSO$_4$). Flash chromatography (25 % EtOAc–pet. ether) gave 299a and 299b (399 mg, 57 %, ~3.5:1 dr) as a pale yellow gum. Morpholinone 288 (63 mg, 20 %) was also isolated.
299a Major syn diastereoisomer

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm: 7.72 (1 H, d, $J = 8.6$ Hz, NH), 7.14 (2 H, d, $J = 8.6$ Hz, aromatic C-H of PMB), 6.80 (2 H, d, $J = 8.8$ Hz, aromatic C-H of PMB), 6.39 (1 H, d, $J = 2.2$ Hz, aromatic C-H), 6.22 (1 H, d, $J = 2.2$ Hz, aromatic C-H), 5.47 (1 H, d, $J = 14.8$ Hz, CH=H of PMB), 4.87 (1 H, d, $J = 12.1$ Hz, OCH=HCCl$_3$), 4.85 (1 H, s, ArCHS), 4.81 - 4.84 (1 H, m, CH=NHTroc), 4.73 (1 H, d, $J = 12.1$ Hz, OCH=HCCl$_3$), 4.39 (1 H, dd, $J = 7.6, 5.8$ Hz, ArCHN), 4.38 (2 H, d, $J = 14.8$ Hz, CH=H of PMB), 4.13 (1 H, dd, $J = 10.0, 7.6$ Hz, CH=HOSi), 3.88 (3 H, s, OCH$_3$), 3.86 (1 H, m, CH=HOSi), 3.81 (3 H, s, OCH$_3$), 3.77 (3 H, s, OCH$_3$), 3.75 (3 H, s, OCH$_3$), 3.64 (1 H, dd, $J = 14.9, 5.8$ Hz, CH=HS), 3.29 (1 H, dd, $J = 14.9, 4.3$ Hz, CH=HS), 0.99 - 1.08 (21 H, m, SiCH and SiCH(CH$_3$)$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm: 170.9 (C=O), 169.3 (C=O), 160.1 (aromatic C=O), 158.9 (C=O), 157.4 (aromatic C=O), 154.7 (C=O), 135.72 (aromatic C=C), 129.2 (aromatic C=H of PMB), 129.1 (aromatic C=C), 113.9 (aromatic C=H of PMB), 113.5 (aromatic C=C), 102.9 (aromatic C-H), 98.0 (aromatic C-H), 95.6 (CCl$_3$), 77.2 (CH=NHTroc), 74.6 (OCH$_2$CCl$_3$), 69.2 (CH$_2$O), 62.3 (CHN), 55.7 (OCH$_3$), 55.4 (OCH$_3$), 55.2 (OCH$_3$), 52.6 (OCH$_3$), 49.2 (CH$_2$ of PMB), 40.4 (CHS), 35.6 (CH$_2$S), 17.9 (CH$_2$(CH$_3$)$_2$), 11.7 (SiCH).

MS (ES+) m/z 843 [M+Na]+. HRMS 843.2042; C$_{36}$H$_{53}$Cl$_3$N$_2$O$_5$SSiNa$^+$ requires 843.2042. IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 2944 (C-H), 2865, 1740 (ester C=O), 1635 (amide C=O), 1612 (carbamate C=O), 1512. [$\alpha$]$_D^{30} = -0.3$ (c = 0.98, CHCl$_3$).

(R)-tert-Butyl 3-mercapto-2-(((2,2,2-trichloroethoxy)carbonyl)amino)propanoate 303

L-cystine (10 g, 41.6 mmol) was dissolved in 60 % HClO$_4$ (16.6 ml, 276 mmol) then t-butyl acetate (100 ml) was slowly added. The solution was stirred at RT for 16 h then cooled in an ice bath and water (100 ml) and EtOAc (100 ml) were added. 10 M NaOH solution was added slowly with stirring until a white precipitate formed then redissolved, then the layers were separated. The aqueous layer was extracted with EtOAc (2 × 50 ml) and the combined organic layers were washed with brine (50 ml), dried (MgSO$_4$) and concentrated in vacuo. The crude product (4.61 g) was suspended in water (100 ml) and NaHCO$_3$ (4.38 g, 52.2 mmol) then 2,2,2-trichloroethylethchloroformate (5.39 ml, 39.1 mmol) were added. The mixture was stirred at RT for 18 h then sat. with NaCl and extracted with CH$_2$Cl$_2$ (3 × 50 ml). The extracts were washed with brine (50 ml) then dried (MgSO$_4$). Flash chromatography (20 % EtOAc-pet. ether) gave the desired disulfide (7.27 g, 25 % over 2 steps) as a colourless gum. A portion of disulfide (746 mg, 1.061 mmol) was dissolved in CH$_2$Cl$_2$ (20 ml) under N$_2$ and NEt$_3$ (0.44 ml, 3.18 mmol) and dithiothreitol (245 mg, 1.591 mmol) were added. The solution was stirred for 3 h then washed with 15% w/v citric acid solution (3 × 15 ml), dried (MgSO$_4$) and concentrated in vacuo to give
303 (671 mg, 90 %) as a pale yellow solid (melting point 43-45 °C) which was used without further purification.

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 5.91 (1 H, s, NH), 4.77 (1 H, d, $J$ = 12.5 Hz, OCH$_2$HCCl$_3$), 4.72 (1 H, d, $J$ = 12.5 Hz, OCH$_2$HCCl$_3$), 4.55 (1 H, dd, $J$ = 9.1, 5.3 Hz, CHNH Troc), 3.03 (1 H, dd, $J$ = 9.1, 5.3 Hz, CH$_2$SH), 3.02 (1 H, dd, $J$ = 9.1, 5.3 Hz, CH$_2$SH), 1.51 (9 H, s, C(CH$_3$)$_3$), 1.38 (1 H, t, $J$ = 9.1 Hz, SH).

$^{31}$C NMR (100 MHz, CDCl$_3$) δ ppm 168.5 (C=O), 153.9 (carbamate C=O), 95.3 (CCl$_3$), 83.4 (OCC(CH$_3$)$_3$), 74.6 (OCH$_2$CCl$_3$), 55.6 (CHNH Troc), 28.0 (C(CH$_3$)$_3$), 27.1 (CH$_2$S).

MS (ES+) m/z 374 [M+Na]$^+$. HRMS 373.9749; $C_{16}H_{18}NO_SClNa^+$ requires 373.9758. IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 3415, 3342, 3063, 2920, 2852, 1726, 1685, 1539, 1253, 1141, 953, 918, 865 [M+Na]$^+$. HRMS 863.2709; $C_{30}H_{32}N_{2}O_SSiCl_3^+$ requires 863.2693.

(R)-tert-Butyl 3-(((1R,4S)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1-(((tri-isopropylsilanyloxy)methyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)sulfanyl)-2-((2,2,2-trichloroethoxy)carbonyl)amino)propanoate 306a and (R)-tert-buty1 3-(((1R,4S)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1-(((trisopropylsilanyloxy)methyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)sulfanyl)-2-((2,2,2-trichloroethoxy)carbonyl)amino)-propanoate 306b

Hydroxyamide 289 (141 mg, 0.27 mmol) was dissolved in CH$_2$Cl$_2$ (0.7 ml) and DMSO (0.7 ml) at 0 °C and NEt$_3$ (0.18 ml, 1.32 mmol) and SO$_2$-py (126 mg, 0.79 mmol) were added. The solution was stirred for 2 h then a solution of 303 (280 mg, 0.79 mmol) in CH$_2$Cl$_2$ (2 ml) was added. After 30 minutes, the solution was diluted with Et$_2$O (10 ml) and washed with 1 M HCl (10 ml), sat. NaHCO$_3$ solution (10 ml) then brine (10 ml) and dried (MgSO$_4$). The crude hemithioacetal was dissolved in CH$_2$Cl$_2$ (3 ml) and ZnCl$_2$ (54 mg, 0.397 mmol) was added. The solution was stirred for 23 h then diluted with CH$_2$Cl$_2$ (10 ml) and washed with water (10 ml) then brine (10 ml) and dried (MgSO$_4$). Flash chromatography (30 % EtOAc–pet. ether) gave 306a and 306b (130 mg, 57 %) as a pale yellow gum. Analytically pure samples of the individual diastereoisomers were obtained by further chromatography.

MS (ES+) m/z 865 [M+Na]$^+$. HRMS 863.2709; $C_{30}H_{32}N_{2}O_SSiCl_3^+$ requires 863.2693.

For 306a $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.29 (2 H, d, $J$ = 8.6 Hz, aromatic C-H of PMB), 6.96 (1 H, d, $J$ = 9.1 Hz, NH), 6.88 (2 H, d, $J$ = 8.6 Hz, aromatic C-H of PMB), 6.41 (1 H, d, $J$ = 2.0 Hz, aromatic C-H), 6.18 (1 H, d, $J$ = 2.0 Hz, aromatic C-H), 5.63 (1 H, d, $J$ = 15.3 Hz, CH$_2$ of PMB), 4.85 (1 H, d, $J$ = 11.9 Hz, OCH$_2$HCCl$_3$), 4.66 (1 H, d, $J$ = 11.9 Hz, OCH$_2$HCCl$_3$), 4.63 - 4.68
(1 H, m, CHNHTroc), 4.59 (1 H, s, ArCHS), 4.43 (1 H, br. s, ArCHN), 4.13 (1 H, dd, J = 10.2, 2.6 Hz, CH-HO), 4.00 (3 H, s, OCH3) 3.94 (1 H, d, J = 15.3 Hz, CH of PMB), 3.86 (1 H, dd, J = 14.7, 4.0 Hz, CHHS), 3.80 (3 H, s, OCH3), 3.73 (3 H, s, OCH3), 3.68 (1 H, d, J = 10.2 Hz, CH-HO), 3.32 (1 H, dd, J = 14.7, 4.4 Hz, CHH-S), 1.44 (9 H, s, C(CH3)3), 0.82 - 0.94 (21 H, m, Si[CH2(CH3)]3).

13C NMR (100 MHz, CDCl3) δ ppm 171.5 (C=O), 169.5 (C=O), 160.3 (aromatic C-O), 158.9 (aromatic C-O), 157.6 (aromatic C-O), 154.6 (carbamate C=O), 134.2 (aromatic C-C), 129.2 (aromatic C-H of PMB), 128.8 (aromatic C-C), 114.1 (aromatic C-C), 113.9 (aromatic C-C), 101.2 (aromatic C-H), 98.1 (aromatic C-H), 95.5 (CCl3), 82.2 (OC(CH3)3), 74.7 (OCH2CCl3), 64.9 (CH2OSi), 60.4 (ArCHN), 55.9 (CHNHTroc), 55.4 (OCH3), 55.3 (OCH3), 55.2 (OCH3), 45.8 (CH2 of PMB), 42.3 (ArCHS), 35.7 (CH3S), 27.9 (C(CH3)3), 17.6 (CH(CH3)2), 11.7 (SiCH).

IR (thin film) νmax (cm⁻¹) 3350 (N-H), 2941 (C-H), 2865, 1738 (ester C=O), 1651 (amide C=O), 1612 (carbamate C=O). [α]D 30 = -96.7 (c = 1.04, EtOH)

For 306b 1H NMR (500 MHz, CDCl3) δ ppm 7.57 (1 H, d, J = 8.2 Hz, NH), 7.15 (2 H, d, J = 8.5 Hz, aromatic C-H of PMB), 6.80 (2 H, d, J = 8.5 Hz, aromatic C-H of PMB), 6.39 (1 H, d, J = 2.1 Hz, aromatic C-H), 6.23 (1 H, d, J = 2.1 Hz, aromatic C-H), 5.42 (1 H, d, J = 14.8 Hz, CH of PMB), 4.86 (1 H, s, ArCHS), 4.86 (2 H, d, J = 12.0 Hz, OCHHCCl3), 4.73 (1 H, d, J = 12.0 Hz, OCHHCCl3), 4.67 (1 H, m, CHNHTroc), 4.42 (1 H, d, J = 14.8 Hz, CH of PMB), 4.38 (1 H, t, J = 6.6 Hz, ArCHN), 4.12 (1 H, dd, J = 9.8, 7.6 Hz, CH-HO), 3.87 (3 H, s, OCH3), 3.83 - 3.86 (1 H, m, CH-HO), 3.77 (3 H, s, OCH3), 3.75 (3 H, s, OCH3), 3.56 (1 H, dd, J = 14.5, 6.0 Hz, SCHH), 3.31 (1 H, dd, J = 14.5, 4.1 Hz, SCHH), 1.50 (9 H, s, C(CH3)3), 1.00 - 1.08 (21 H, m, Si[CH2(CH3)]3).

13C NMR (126 MHz, CDCl3) δ ppm 169.4 (C=O), 169.1 (C=O), 160.0 (aromatic C-O), 158.8 (aromatic C-O), 157.3 (aromatic C-O), 154.7 (carbamate C=O), 135.7 (aromatic C-C), 129.2 (aromatic C-H of PMB), 129.1 (aromatic C-C), 113.9 (aromatic C-H of PMB), 113.8 (aromatic C-C), 102.9 (aromatic C-H), 98.0 (aromatic C-H), 95.7 (CCl3), 82.3 (OC(C-H2)), 74.5 (OCH2CCl3), 69.1 (CH2OSi), 62.4 (ArCHN), 55.9 (CHNHTroc), 55.7 (OCH3), 55.3 (OCH3), 55.2 (OCH3), 49.2 (CH2 of PMB), 40.9 (CHS), 36.3 (CH3S), 28.0 (C(CH3)3), 17.9 (CH(CH3)2), 11.7 (SiCH).

IR (thin film) νmax (cm⁻¹) 3215 (N-H), 2942 (C-H), 2865, 1737 (ester C=O), 1637 (amide C=O), 1611 (carbamate C=O). [α]D 30 = +8.8 (c = 1.06, EtOH).

Methyl 3-(((1R,4R)-1-((hydroxymethyl)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)sulfanyl)propanoate 302a and methyl 3-(((1R,4S)-1-((hydroxymethyl)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)sulfanyl)propanoate 302b
Silyl ether 297 (1.3:1 dr, 183 mg, 0.3 mmol) was dissolved in CH₂Cl₂ (1.5 ml) and TBAF (1 M solution in THF, 0.6 mmol, 0.6 ml) was added. The solution was stirred for 6.5 h then quenched with sat. NaHCO₃ solution and extracted with CH₂Cl₂ (2 × 20 ml). The extracts were combined, dried (MgSO₄) and concentrated in vacuo. Flash chromatography (60 % EtOAc–pet. ether) gave 302a and 302b (108 mg, 78 %, 1:2 dr) as a pale yellow gum. Analytically pure samples of the individual diastereoisomers were obtained by further chromatography.

For 302a ¹H NMR (400 MHz, CDCl₃) δ ppm 7.31 (2 H, d, J = 8.7 Hz, aromatic C-H of PMB), 6.89 (2 H, d, J = 8.7 Hz, aromatic C-H of PMB), 6.41 (1 H, d, J = 2.4 Hz, aromatic C-H), 6.30 (1 H, d, J = 2.4 Hz, aromatic C-H), 5.55 (1 H, d, J = 15.4 Hz, CH₂ of PMB), 4.71 (1 H, s, ArCHS), 4.58 (1 H, s, ArCHN), 4.25 (1 H, d, J = 15.4 Hz, CH₃ of PMB), 4.18 (1 H, m, CH₂OH), 3.92 (1 H, dd, J = 12.7, 3.4 Hz, CH₂OH), 3.88 (3 H, s, OCH₃), 3.80 (3 H, s, OCH₃), 3.77 (3 H, s, OCH₃), 3.70 (3 H, s, OCH₃), 3.28 (1 H, dt, J = 13.8, 6.8 Hz, SCH₂), 2.97 (1 H, dt, J = 13.8, 7.5 Hz, SCH₂), 2.78 (2 H, m, CH₂CO₂Me), 1.79 (1 H, s, OH).

¹³C NMR (100 MHz, CDCl₃) δ ppm 172.5 (C=O), 170.5 (C=O), 160.4 (aromatic C-H of PMB), 158.9 (aromatic C-O), 157.6 (aromatic C-O), 133.6 (aromatic C-C), 129.1 (aromatic C-H of PMB), 128.7 (aromatic C-C), 114.4 (aromatic C-H of PMB), 114.3 (aromatic C-C), 101.0 (aromatic C-H), 98.0 (aromatic C-H), 59.2 (ArCHN), 55.8 (OCH₃), 55.3 (OCH₃), 51.7 (OCH₃), 45.9 (CH₂ of PMB), 40.5 (CHS), 34.3 (CH₂CO₂CH₂), 28.0 (CH₂S).

MS (ES+) m/z 498 [M+Na]+. HRMS 498.1560; C₂₄H₂₅O₂NNaS requires 498.1557. [α]D³⁰ = +30.6 (c = 0.57, EtOH).

For 302b ¹H NMR (400 MHz, CDCl₃) δ ppm 7.17 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB), 6.81 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB), 6.39 (1 H, d, J = 2.3 Hz, aromatic C-H), 6.21 (1 H, d, J = 2.3 Hz, aromatic C-H), 5.35 (1 H, d, J = 14.9 Hz, CH₂ of PMB), 4.74 (1 H, s, ArCHS), 4.40 (1 H, t, J = 6.2 Hz, ArCHN), 4.31 (1 H, d, J = 14.9 Hz, CH₂ of PMB), 4.08 (1 H, dd, J = 11.3, 6.3 Hz, CH₂OH), 3.93 (1 H, dd, J = 11.3, 6.1 Hz, CH₂OH), 3.87 (3 H, s, OCH₃), 3.77 (3 H, s, OCH₃), 3.75 (3 H, s, OCH₃), 3.71 (3 H, s, OCH₃), 3.34 (1 H, dt, J = 13.9, 7.1 Hz, SCH₂), 3.13 (1 H, dt, J = 13.9, 7.1 Hz, SCH₂), 2.86 (2 H, t, J = 7.1 Hz, CH₂CO₂CH₂).

¹³C NMR (100 MHz, CDCl₃) δ ppm 172.7 (C=O), 169.2 (C=O), 160.4 (aromatic C-O), 157.6 (aromatic C-O), 135.7 (aromatic C-C), 129.2 (aromatic C-H of PMB), 129.0 (aromatic C-C), 114.1 (aromatic C-H of PMB), 113.4 (aromatic C-C), 102.4 (aromatic C-H), 98.1 (aromatic C-H), 66.3 (CH₂OH), 62.4 (CHN), 55.8 (OCH₃), 55.5 (OCH₃), 55.3 (OCH₃), 51.8 (OCH₃), 48.8 (CH₂ of PMB), 39.9 (CHS), 34.4 (CH₂CO₂CH₂), 28.9 (CH₂S).

MS (ES+) m/z 476 [M+H]+, 498 [M+Na]+. HRMS 476.1728 C₂₄H₂₅O₂N₂S requires 476.1737. IR (thin film) vₘₐₓ (cm⁻¹) 3400 (br., OH), 2951 (C-H), 1737 (ester C=O), 1612 (amide C=O). [α]D³² = -222.7 (c = 0.90, EtOH).

3-(((1R,4R)-1-(Hydroxymethyl)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)sulfanyl)propanoic acid 307
Ester 302 (108 mg, 0.23 mmol, 1:2 dr) was dissolved in THF (1.4 ml) and water (0.4 ml) and LiOH·H₂O (19 mg, 0.46 mmol) was added. The solution was stirred at RT for 18 h then acidified with 1 M HCl (5 ml) and extracted with EtOAc (2 × 10 ml). The extracts were washed with brine (5 ml), dried (MgSO₄) and concentrated in vacuo. Flash chromatography (10 % MeOH−CH₂Cl₂) gave 307 (87 mg, 82 %) as a pale yellow solid, melting point 70–73 °C. Recrystallization from EtOH gave crystals for single crystal X-ray diffraction analysis.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.14 (2 H, d, J = 8.6 Hz, aromatic C-H of PMB), 6.79 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB), 6.37 (1 H, d, J = 2.3 Hz, aromatic C-H), 6.20 (1 H, d, J = 2.3 Hz, aromatic C-H), 5.39 (1 H, d, J = 15.0 Hz, C-H of PMB), 4.75 (1 H, s, ArCHS), 4.41 (1 H, apparent t, J = 6.2 Hz, ArCHN), 4.29 (1 H, d, J = 15.0 Hz, CH of PMB), 4.10 (1 H, dd, J = 11.5, 6.7 Hz, CHOH), 3.90 (1 H, dd, J = 11.5, 5.7 Hz, CHOH), 3.84 (3 H, s, OCH₃), 3.74 (3 H, s, OCH₃), 3.73 (3 H, s, OCH₃), 3.31 (1 H, dt, J = 13.9, 6.8 Hz, SCH), 3.11 (1 H, dt, J = 13.9, 7.1 Hz, SCH), 2.78–2.98 (2 H, m, C₂H₂CO₂H).

¹³C NMR (100 MHz, CDCl₃) δ ppm 175.8 (CO₂H), 170.0 (C=O), 160.3 (aromatic C-O), 158.9 (aromatic C-O), 157.4 (aromatic C-O), 135.4 (aromatic C-C), 129.2 (aromatic C-H of PMB), 128.6 (aromatic C-C), 114.0 (aromatic C-H of PMB), 113.3 (aromatic C-C), 102.3 (aromatic C-H), 98.0 (aromatic C-H), 66.5 (CH₂OH), 62.3 (ArCHN), 55.71 (OCH₃), 55.41 (OCH₃), 55.21 (OCH₃), 49.1 (CH₂ of PMB), 40.0 (ArCHS), 34.4 (CH₂CO₂H), 28.7 (CH₂S).

MS (ES+) m/z 484.1 [M+Na]+. HRMS 484.1393, C₂₃H₂₇O₇NSNa+ requires 484.1400. IR (thin film) νmax (cm⁻¹) 3400 (br.), 2938 (C-H), 1705 (acid C=O), 1634 (amide C=O). [α]D³⁰ = +14.2 (c = 0.90, EtOH).

(1R,8R)-10,12-Dimethoxy-13-(4-methoxybenzyl)-3,4,7,8-tetrahydro-8,1-(epimino-methano)benzo[g][1,5]oxathiecine-5,14(1H)-dione 309

Method A – Yamaguchi (representative procedure)
ω-Hydroxyacid 307 (25 mg, 0.054 mmol) and NEt₃ (8.3 μl, 0.06 mmol) were dissolved in dry THF (1 ml) under N₂ and 2,4,6-trichlorobenzoyl chloride (8.4 μl, 0.054 mmol) was added. The solution was stirred for 40 minutes then filtered and diluted with PhMe (27 ml). The solution was added to a refluxing solution of DMAP (40 mg, 0.324 mmol) in PhMe (5.4 ml) via syringe pump.
over 6 h. After the addition was complete, the solution was allowed to cool to RT then concentrated, diluted with Et²O (10 ml), washed with 1 M HCl (5 ml) then sat. NaHCO₃ solution (5 ml) then water (5 ml) and dried (MgSO₄). Purification by flash chromatography (15 % EtOAc–CH₂Cl₂) was attempted, but only small amounts of the desired macrolactone could be separated from the diolide.

**Method B – Mitsunobu conditions**

PPh₃ (39 mg, 0.150 mmol) was dissolved in PhMe (60 ml) and DTBAD (35 mg, 0.150 mmol) was added. The solution was stirred at RT for 30 minutes then a solution of ω-hydroxyacid 307 (46 mg, 0.1 mmol) in THF (2 ml) and PhMe (40 ml) was added via syringe pump over 6 hours. After 3 h of starting the addition, a 1 ml aliquot was taken and analysed by LC-MS but only starting material and reagents were detected. Following completion of the addition, the solution was stirred for a further 17 h before a second aliquot was analysed by LC-MS but no product was detected. After a further 28 h, a solution of PPh₃ (57 mg, 0.150 mmol) and DTBAD (42 mg, 0.15 mmol) in PhMe (9 ml) was added. After a further 24 hours, the solution was concentrated *in vacuo* and the residue analysed by ¹H NMR, but none of the desired product was present.

**Method C – Corey-Nicolaou conditions**

ω-Hydroxyacid 307 (24 mg, 0.052 mmol) and PPh₃ (20 mg, 0.078 mmol) were dissolved in dry PhMe (1 ml) under N₂ then di(2-pyridyl)disulfide (17 mg, 0.078 mmol) was added. After 1 h, THF (1 ml) was added due to low solubility of the substrate in PhMe. After a further 4 h, PhMe (2 ml) was added and the solution added to refluxing PhMe (10 ml) *via* syringe pump over ~12 h. The solution was refluxed for a further 9 h, cooled to RT and concentrated *in vacuo* and the residue analysed by ¹H NMR.

**Method D – Shiina conditions**

A solution of ω-hydroxyacid 307 (46 mg, 0.10 mmol) in CH₂Cl₂ (22 ml) was added *via* pressure-equalizing dropping funnel over 2.5 h to a solution of MNBA (41.3 mg, 0.12 mmol) and DMAP (29 mg, 0.24 mmol) in CH₂Cl₂ (36 ml) at RT. The solution was stirred for a further 3.5 h then concentrated *in vacuo* and the residue taken up in CH₂Cl₂ (10 ml), washed with sat. NaHCO₃ solution (10 ml) then brine (10 ml) and dried (MgSO₄). Flash chromatography (15 % EtOAc–CH₂Cl₂) gave 309 (29 mg, 65 %) as a pale yellow solid.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.18 (2 H, d, J = 8.6 Hz, aromatic C-H of PMB), 6.84 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB), 6.42 (1 H, d, J = 2.3 Hz, aromatic C-H), 6.20 (1 H, d, J = 2.3 Hz, aromatic C-H), 5.60 (1 H, d, J = 15.2 Hz, CH₂ of PMB), 5.00 (1 H, s, ArCHS), 4.89 (1 H, dd, J = 11.4, 1.8 Hz, CH₃), 4.43 (1 H, br. s, ArCHN), 4.28 (1 H, dd, J = 11.4, 1.6 Hz, CHCH₂), 3.98 (1 H, d, J = 15.2 Hz, CH₂ of PMB), 3.87 (3 H, s, OCH₃), 3.78 (3 H, s, OCH₃), 3.78 (3 H, s, OCH₃), 2.91 (1 H, m, CHHS) and 2.42 - 2.63 (3 H, m, CH₂HS and CH₂CO₂R).

¹³C NMR (100 MHz, CDCl₃) δ ppm 170.7 (C=O), 168.6 (C=O), 160.9 (aromatic C=O), 159.4 (aromatic C=O), 158.2 (aromatic C=O), 134.6 (aromatic C=C), 129.8 (aromatic C=H of PMB), 128.4 (aromatic C=C), 114.5 (aromatic C=H of PMB), 112.7 (aromatic C=C), 102.0 (aromatic C=H), 98.2
(aromatic C-H), 63.4 (CH₂O), 59.9 (ArCHN), 55.7 (OCH₃), 55.6 (OCH₃), 47.2 (CH₂ of PMB), 41.3 (ArCHS), 38.8 (C₆H₄CO₂R), 26.5 (CH₂S).

MS (ES+) m/z 466 [M+Na]⁺. HRMS 466.1292, C₂₃H₂₅O₆N₂SNa⁺ requires 466.1295. IR (thin film) \( \nu_{max} (\text{cm}^{-1}) \) 2394 (C-H), 1742 (ester C=O), 1640 (amide C=O).

(\( R \))-Methyl 3-(((1R,4R)-1-(hydroxymethyl)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)sulfanyl)-2-(((2,2,2-trichloroethoxy)carbonyl)amino)propanoate 301

Method A – Substitution of hydroxy tetrahydroisoquinolinone 295
Hydroxytetrahydroisoquinolinone 295 (100 mg, 0.19 mmol) was dissolved in Et₂O (1 ml) and NEt₃ (80 \( \mu l \), 0.57 mmol) and MsCl (29 \( \mu l \), 0.38 mmol) were added. The solution was stirred at RT for 1 h then diluted with Et₂O (10 ml), washed with 1 M HCl (10 ml), water (10 ml), brine (10 ml) then dried (MgSO₄) and concentrated in vacuo. The residue was dissolved in DMF (2 ml) and cysteine 256 (62 mg, 0.20 mmol) and Cs₂CO₃ (65 mg, 0.20 mmol) were added. The solution was stirred at RT for 17 h then heated to 50 °C for 7 h. The solution was cooled to RT, diluted with Et₂O (10 ml), washed with water (2 x 10 ml), brine (10 ml) then dried (MgSO₄). Flash chromatography (60 % EtOAc–pet. ether) gave 301 (77 mg, 61 %) as a pale yellow oil.

Method B – Deprotection of silyl ether 299
Silyl ether 290 (62 mg, 0.076 mmol, ~3.5:1 dr) was dissolved in CH₂Cl₂ (0.4 ml) and a solution of TBAF (1 M in THF, 0.15 ml, 0.15 mmol) was added. The solution was stirred at RT for 3 h then quenched with sat. NaHCO₃ solution and extracted with CH₂Cl₂ (3 x 2 ml), then the combined extracts were dried (MgSO₄). Flash chromatography (30–60 % EtOAc–pet. ether) gave alcohol 301 (33 mg, 65 %, 2.5:1 dr) as a pale yellow gum.

Method C – Troc protection of amine 311.
Amine 311 (54 mg, 0.11 mmol) was dissolved in CH₂Cl₂ (2 ml) and TrocCl (25 \( \mu l \), 0.19 mmol) and NaHCO₃ (55 mg, 0.66 mmol) were added and the mixture was stirred at RT for 5 h. The mixture was diluted with CH₂Cl₂ (2 ml) and washed with water (3 ml) then dried (MgSO₄). Flash chromatography (50 % EtOAc–pet. ether) gave 301 (20 mg, 27 %) as a pale yellow gum.

For major diastereoisomer, \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) ppm 7.28 - 7.36 (1 H, d, J = 9.1 Hz, NH), 7.16 (2 H, d, J = 8.7 Hz, aromatic C-H of PMB), 6.80 (2 H, d, J = 8.7 Hz, aromatic C-H of PMB), 6.40 (1 H, d, J = 2.2 Hz, aromatic C-H), 6.19 (1 H, d, J = 2.2 Hz, aromatic C-H), 5.49 (1 H, d, J = 15.1 Hz, CHH of PMB), 4.88 - 4.92 (1 H, m, CHNHTroc), 4.87 (1 H, s, ArCHS), 4.83 (1 H, d, J
= 12.2 Hz, OCH\(_{\text{HCl}}\), 4.74 (1 H, d, J = 12.2 Hz, OCH\(_{\text{HCl}}\)), 4.37 - 4.46 (1 H, m, ArCHN), 4.33 (1 H, d, J = 15.1 Hz, CH\(_{\text{H}}\) of PMB), 4.07 (1 H, dd, J = 11.6, 7.1 Hz, CH\(_{\text{H}}\)O), 3.88 (3 H, s, OCH\(_{3}\)), 3.82 - 3.86 (1 H, m, CH\(_{\text{H}}\)O), 3.80 (3 H, s, OCH\(_{3}\)), 3.77 (3 H, s, OCH\(_{3}\)), 3.76 (3 H, s, OCH\(_{3}\)), 3.39 - 3.50 (2 H, m, SCh\(_{2}\)).

\(^{13}\text{C} \text{ NMR} \) (100 MHz, CDCl\(_{3}\)) \(\delta\) ppm 170.8 (C=O), 169.3 (C=O), 160.2 (aromatic C-O), 158.6 (aromatic C-O), 157.4 (aromatic C-O), 154.7 (C=O of carbamate), 135.1 (aromatic C-C), 128.9 (aromatic C-H of PMB), 128.8 (aromatic C-C), 113.7 (aromatic C-H of PMB), 112.8 (aromatic C-C), 101.9 (aromatic C-H), 97.7 (aromatic C-H), 95.1 (CCl\(_{3}\)), 74.3 (OCH\(_{2}\)CCl\(_{3}\)), 66.4 (CH\(_{2}\)OH), 61.8 (ArCHN), 55.5 (OCH\(_{3}\)), 55.1 (OCH\(_{3}\)), 54.9 (OCH\(_{3}\)), 54.7 (OCH\(_{3}\)), 52.4 (CH\(_{2}\) of PMB), 40.8 (ArCHS), 36.1 (CH\(_{2}\)S).

MS (ES+) \(m/z\) 687 [M+Na]\(^+\). HRMS 687.0713; C\(_{2}\)\(_{2}\)H\(_{2}\)N\(_{2}\)O\(_{3}\)Cl\(_{3}\)SNa\(^+\) requires 687.0709. IR (thin film) \(\nu_{\text{max}}\) (cm\(^{-1}\)) 3374 (br., O-H) 2953 (C-H), 2840, 1738 (ester C=O), 1625 (amide C=O), 1613 (carbamate C=O).

\((R)\)-Methyl 2-amino-3-((1R,4R)-1-(hydroxymethyl)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)sulfanyl)propanoate 311

\[
\text{H}_2\text{N} \text{CO}_{2}\text{Me}
\]

\text{MeO} \text{S} \text{O} \text{PMB}

\text{MeO} \text{N} \text{OH}

Amine 311 (54 mg, 25 %) was isolated as a by-product following exposure of silyl ether 290 to TBAF.

\(^{1}\text{H} \text{NMR} \) (500 MHz, CDCl\(_{3}\)) \(\delta\) ppm 7.14 (2 H, d, J = 8.5 Hz, aromatic C-H of PMB), 6.80 (3 H, d, J = 8.5 Hz, aromatic C-H of PMB), 5.97 (1 H, d, J = 1.9 Hz, aromatic C-H), 6.20 (1 H, d, J = 1.9 Hz, aromatic C-H), 5.37 (1 H, d, J = 14.8 Hz, CH\(_{\text{H}}\) of PMB), 4.78 (1 H, s, ArCHS), 4.39 (1 H, dd, J = 5.7, 6.6 Hz, ArCHN), 4.29 (1 H, d, J = 14.8 Hz, CH\(_{\text{H}}\) of PMB), 4.09 (1 H, dd, J = 11.5, 6.6 Hz, CH\(_{\text{H}}\)O), 4.01 (1 H, dd, J = 7.1, 4.5 Hz, NCH\(_{2}\)CO\(_{2}\)Me), 3.91 (1 H, dd, J = 11.5, 5.7 Hz, CH\(_{\text{H}}\)O), 3.87 (3 H, s, OCH\(_{3}\)), 3.81 - 3.86 (1 H, m, CH\(_{\text{H}}\)O), 3.76 (3 H, s, OCH\(_{3}\)), 3.76 (3 H, s, OCH\(_{3}\)), 3.75 (3 H, s, OCH\(_{3}\)), 3.41 (1 H, dd, J = 14.1, 4.5 Hz, CH\(_{\text{H}}\)S), 3.31 (1 H, dd, J = 14.1, 7.1 Hz, CH\(_{\text{H}}\)S).

MS (ES+) \(m/z\) 491 [M+H]\(^+\), 513 [M+H]\(^+\). HRMS 513.1666; C\(_{24}\)H\(_{30}\)O\(_{7}\)SNa\(^+\) requires 513.1666.

\((R)-\text{t}-\text{Butyl} \ 3-((1R,4R)-1-(hydroxymethyl)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)sulfanyl)-2-(((2,2,2-trichloroethoxy)carbonyl)-amino)propanoate 312
Silyl ether 306 (190 mg, 0.23 mmol, 1:1 dr) was dissolved in MeCN (2.3 ml) at 0 °C and 60 % aqueous HF (0.23 ml) was added. The solution was stirred for 30 minutes then allowed to warm to RT and stirred for a further 90 minutes. The solution was neutralised by dropwise addition of sat. NaHCO₃ solution then extracted with EtOAc (3 × 15 ml). The extracts were washed with brine (20 ml), dried (MgSO₄) and concentrated in vacuo. Flash chromatography (40 % EtOAc–pet. ether) gave 312 (99 mg, 64 %, single diastereoisomer) as a pale yellow gum.

³H NMR (400 MHz, CDCl₃) δ ppm 7.22 (1 H, d, J = 8.6 Hz, NH), 7.16 (2 H, d, J = 8.7 Hz, aromatic C-H of PMB), 6.81 (2 H, d, J = 8.7 Hz, aromatic C-H of PMB), 6.40 (1 H, d, J = 2.3 Hz, aromatic C-H), 6.19 (1 H, d, J = 2.3 Hz, aromatic C-H), 5.46 (1 H, d, J = 14.9 Hz, CHH of PMB), 4.88 (1 H, s, ArCHS), 4.79 (1 H, d, J = 12.1 Hz, OCHHCCI₃), 4.77 (1 H, d, J = 12.1 Hz, OCHHCCI₃), 4.70 (1 H, ddd, J = 8.4, 6.2, 4.3 Hz, CHNH Troc), 4.41 (1 H, m, ArCHN), 4.38 (1 H, d, J = 14.9 Hz, CHH of PMB), 4.09 (1 H, m, CHH OH), 3.87 (3 H, s, OCH₃), 3.76 (3 H, s, OCH₃), 3.76 (3 H, s, OCH₃), 3.43 (2 H, m, CH₂S), 2.75 (1 H, m, OH), 1.49 (9 H, s, C(CH₃)₃).

¹³C NMR (100 MHz, CDCl₃) δ ppm 169.4 (C=O), 169.1 (C=O), 160.18 (aromatic C-O), 158.6 (aromatic C-O), 157.3 (aromatic C=O), 154.6 (carbamate C=O), 135.2 (aromatic C-O), 154.6 (carbamate C=O), 135.2 (aromatic C-O), 128.9 (aromatic C-H of PMB), 128.5 (aromatic C-C), 113.7 (aromatic C-H of PMB), 112.9 (aromatic C-C), 101.9 (aromatic C-H), 97.7 (aromatic C-H), 95.2 (CCl₃), 82.3 (OCC(CH₃)₃), 74.3 (OCCCl₃), 66.3 (CH₂OH), 61.8 (ArCHN), 55.5 (OCH₃), 55.3 (OCH₃), 55.1 (OCH₃), 54.9 (CHNH Troc), 48.8 (CH₂ of PMB), 40.9 (ArCHS), 36.1 (CH₂S), 27.7 (C(CH₃)₃).

MS (ES+) m/z 707 [M+H]⁺, 729 [M+Na]⁺. HRMS 707.1356; C₃₀H₂₈N₂O₃SCl₃⁺ requires 707.1359.

IR (thin film) νmax (cm⁻¹) 3400-3300 (br., OH), 2935 (C-H), 1737 (ester C=O), 1732 (amide C=O), 1612 (carbamate C=O). [α]D 30 = –13.6 (c = 0.76, EtOH).

(R)-3-(((1R,4R)-1-(Hydroxymethyl)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)sulfonyl)-2-(((2,2,2-trichloroethoxy)carbonyl)amino)propanoic acid 353
Ester 312 (35 mg, 0.05 mmol) was dissolved in CH₂Cl₂ (1.3 ml) and TFA (0.44 mmol) was added. The solution was stirred at RT for 2 h then evaporated and the residue dried in vacuo to give crude 353 as a yellow gum which was used without further purification.

¹H NMR (500 MHz, CDCl₃) δ ppm 7.33 (1 H, d, J = 8.8 Hz, NH), 7.15 (2 H, d, J = 8.6 Hz, aromatic C-H of PMB), 6.80 (2 H, d, J = 8.6 Hz, aromatic C-H of PMB), 6.36 (1 H, d, J = 1.9 Hz, aromatic C-H), 4.93 (1 H, s, ArCHS), 4.85 (1 H, d, J = 12.0 Hz, OC₃HCl₂), 4.68 (1 H, d, J = 12.0 Hz, OCH₂CCl₃), 4.46 (1 H, dd, J = 7.6, 4.5 Hz, ArCHN), 4.33 (1 H, d, J = 14.8 Hz, CH₂H of PMB), 3.83 (3 H, s, OCH₃), 3.76 (3 H, s, OCH₃), 3.75 (3 H, s, OCH₃), 3.55 (1 H, d, J = 14.8 Hz, CH₂H of PMB), 3.34 (1 H, dd, J = 15.1, 6.9 Hz, CHHS), 3.25 (1 H, d, J = 15.1, 6.9 Hz, CHHS).

¹³C NMR (126 MHz, CDCl₃) δ ppm 172.2 (C=O), 171.1 (C=O), 160.6 (aromatic C-O), 157.6 (aromatic C-O), 157.2 (carbamate C=O), 153.0 (aromatic C=C), 129.4 (aromatic C-H of PMB), 128.0 (aromatic C=C), 113.9 (aromatic C-H of PMB), 113.1 (aromatic C=C), 102.1 (aromatic C-H), 98.1 (aromatic C-H), 95.4 (CCl₃), 74.7 (OCH₂CCl₃), 66.8 (CH₂O), 62.2 (ArCHN), 55.8 (OCH₃), 55.4 (OCH₃), 55.3 (C₃HNTroc), 55.2 (OCH₃), 49.7 (CH₂ of PMB), 41.9 (ArCHS), 37.3 (CH₂S).

MS (ES+) m/z 673 [M+Na]⁺. HRMS 673.0549; C₂₆H₃₉N₂O₉SCl₃Na⁺ requires 673.0552. IR (thin film) v_max (cm⁻¹) 3400-3300 (br., OH), 2932 (C-H), 1731 (acid C=O), 1612 (carbamate C=O).

2,2,2-Trichloroethyl (((1R,4R8R)-10,12-dimethoxy-13-(4-methoxybenzyl)-5,14-dioxo-1,3,4,5,7,8-hexahydro-8,1-(epiminomethano)benzo[g][1,5]oxathiecin-4-yl)carbamate 313

ω-Hydroxyacid 353 (0.05 mmol) was dissolved in CH₂Cl₂ (11 ml) and added via syringe pump over 5.5 h to a solution of MNBA (21 mg, 0.06 mmol) and DMAP (14.6 mg, 0.12 mmol) in CH₂Cl₂ (17 ml). After the addition was complete the reaction was stirred for a further 19 h then concentrated and the residue taken up in CH₂Cl₂ (10 ml) and washed with sat. NaHCO₃ solution.
(10 ml) then brine (10 ml) and dried (MgSO₄) before concentration in vacuo. Flash chromatography (10 % EtOAc–CH₂Cl₂) gave 313 (18 mg, 57 % for 2 steps) as a pale yellow foam.

^1^H NMR (400 MHz, DMSO-d₆, 120 °C) δ ppm 7.24 (1 H, d, J = 8.0 Hz, NH), 7.19 (2 H, d, J = 8.5 Hz, aromatic C-H of PMB), 6.87 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB), 6.58 (1 H, d, J = 2.3 Hz, aromatic C-H), 6.56 (1 H, d, J = 2.3 Hz, aromatic C-H), 5.23 (1 H, dd, J = 11.8, 2.0 Hz, CH₂O), 5.21 (1 H, d, J = 15.1 Hz, C=H of PMB), 4.81 (1 H, s, ArCHS), 4.77 (2 H, s, OCH₂CCl₃), 4.67 (1 H, br. s, ArCHN), 4.22 (1 H, td, J = 7.0, 2.9 Hz, C=HONHTroc), 4.16 (1 H, dd, J = 11.8, 1.8 Hz, CHH₂O), 4.03 (1 H, d, J = 15.1 Hz, CHH of PMB), 3.86 (3 H, s, OCH₃), 3.74 (3 H, s, OCH₃), 3.04 (1 H, dd, J = 15.8, 7.0 Hz, CH₂S).

^13^C NMR (100 MHz, DMSO-d₆, 120 °C) δ ppm 168.3 (C=O), 165.9 (C=O), 160.0 (aromatic C=O), 158.3 (aromatic C=O), 157.2 (aromatic C=O), 152.9 (carbamate C=O), 134.2 (aromatic C=C), 128.5 (aromatic C-H of PMB), 128.3 (aromatic C=C), 113.7 (aromatic C-H of PMB), 113.2 (aromatic C=C), 102.4 (aromatic C-H), 98.0 (aromatic C-H), 95.4 (CCl₃), 73.6 (OCH₂CCl₃), 64.3 (CH₂O), 59.0 (ArCHN), 55.5 (OCH₃), 55.4 (CHNHTroc), 54.9 (OCH₃), 54.6 (OCH₃), 46.0 (CH₂ of PMB), 30.6 (CH₂S).

MS (ES+) m/z 655 [M+Na]^+. HRMS 633.0598; C$_{26}$H$_{28}$N$_{2}$O$_8$SCl$_3$+ requires 633.0627. IR (thin film) νmax (cm$^{-1}$) 3410 (N-H), 1737 (ester C=O), 1643 (amide C=O), 1611 (carbamate C=O). [α]D$^{34}$ = +76.8 (c = 1.25, EtOH).

3.5 Synthesis and cyclisation of acetals: towards a one-pot synthesis of ABH ring system analogues

2-((3,5-Dimethoxybenzyl)(4-methoxybenzyl)amino)-2-oxoethane-1,1-diyl diacetate 314

Amine 237 (287 mg, 1.0 mmol) was dissolved in CH₂Cl₂ (5 ml) and (AcO)$_2$HCCOCl 315 (300 mg, 1.5 mmol, prepared according to a literature procedure)$^{120}$ and K$_2$CO$_3$ (276 mg, 2.0 mmol) were added. The solution was stirred for 19 h then diluted with CH₂Cl₂ (20 ml), filtered through celite and evaporated to give 314 (410 mg, 92 %) as a yellow oil which was used without further purification.

A sample was purified for characterisation as follows: a portion of the crude material (150 mg) was dissolved in CH₂Cl₂ (10 ml), washed with sat. NaHCO₃ solution (2 × 5 ml) then dried (MgSO₄). Flash chromatography (30–40 % EtOAc–pet. ether) gave the purified product (64 mg) as a colourless oil.
$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.25 (1 H, s, CH(OAc)$_2$ one rotamer), 7.19 (1 H, s, CH(OAc)$_2$ one rotamer), 7.16 (2 H, d, $J$ = 8.6 Hz, aromatic C-H of PMB of one rotamer), 7.13 (2 H, d, $J$ = 8.6 Hz, aromatic C-H of PMB of one rotamer), 6.90 (2 H, d, $J$ = 8.8 Hz, aromatic C-H of PMB of one rotamer), 6.86 (2 H, d, $J$ = 8.6 Hz, aromatic C-H of PMB of one rotamer), 6.37 - 6.40 (2 H, m, Ar-H), 6.34 - 6.37 (3 H, m, Ar-H), 4.55 (2 H, s, ArCH$_2$N of one rotamer), 4.53 (2 H, s, ArCH$_2$N of one rotamer), 4.37 (2 H, s, CH$_2$ of PMB of one rotamer), 4.33 (2 H, s, CH$_2$ of PMB of one rotamer), 3.81 (3 H, s, OCH$_3$ of one rotamer), 3.80 (3 H, s, OCH$_3$ of one rotamer), 3.78 (6 H, s, OCH$_3$), 3.77 (6 H, s, OCH$_3$ of one rotamer), 2.08 (6 H, s, COCH$_3$ of one rotamer), 2.07 (6 H, s, COCH$_3$ of one rotamer).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 168.4 (C=O of one rotamer), 164.1 (C=O of one rotamer), 160.9 (aromatic C-O of one rotamer), 160.7 (aromatic C-O of one rotamer), 158.9 (aromatic C-O of one rotamer), 158.8 (aromatic C-O of one rotamer), 138.0 (aromatic C-C of one rotamer), 137.5 (aromatic C-C of one rotamer), 129.5 (aromatic C-H of PMB of one rotamer), 127.7 (aromatic C-H of PMB of one rotamer), 126.8 (aromatic C-C), 113.9 (aromatic C-H of PMB of one rotamer), 113.7 (aromatic C-H of PMB of one rotamer), 105.4 (aromatic C-H of one rotamer), 104.3 (aromatic C-H of one rotamer), 99.5 (aromatic C-H of one rotamer), 99.3 (aromatic C-H of one rotamer), 83.9 (CH(OAc)$_2$), 55.1 (OCH$_3$), 55.0 (OCH$_3$), 54.9 (OCH$_3$), 48.6 (CH$_2$ of one rotamer), 48.2 (CH$_2$ of one rotamer), 48.1 (CH$_2$ of one rotamer), 47.9 (CH$_2$ of one rotamer), 20.1 (COCH$_3$).

MS (ES+) m/z 468 M+Na$. HRMS 468.1634; C$_{23}$H$_{27}$O$_8$NNa$^+$ requires 468.1629. IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 2936 (C-H), 1770 (ester C=O), 1681 (amide C=O), 1614, 1514.

**Methyl 3-[5,7-Dimethoxy-2-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-ylsulfanyl]propanoate 254 from acylal 314**

![Methyl 3-[5,7-Dimethoxy-2-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-ylsulfanyl]propanoate 254 from acylal 314](image)

Acylal 314 (78 mg, 0.18 mmol) was dissolved in MeCN (2.1 ml) and methyl 3-mercaptopropanoate 252 (29 µl, 0.26 mmol) and Sc(OTf)$_3$ (87 mg, 0.18 mmol) were added and the solution was heated at reflux for 1 h. The solution was allowed to cool to RT, diluted with EtOAc (10 ml), washed with water (5 ml) then brine (5 ml) and dried (MgSO$_4$). Flash chromatography (50 % EtOAc–pet. ether) gave 254 (36 mg, 47 %). Data was identical to that previously recorded.

**N-(3,5-Dimethoxybenzyl)-N-(4-methoxybenzyl)-5,5-dimethyl-1,3-dioxane-2-carboxamide 316**
Amine 237 (726 mg, 2.53 mmol) was dissolved in CH₂Cl₂ (12 ml) then 5,5-dimethyl-1,3-dioxo-
2-carboxylic acid (377 mg, 2.3 mmol, prepared according to a literature procedure),¹²⁵
EDCI (486 mg, 2.53 mmol) and HOBT·H₂O (70 mg, 0.46 mmol) and NE₃ (0.35 ml, 2.53 mmol) were added.
The solution was stirred for 3 h, diluted with CH₂Cl₂ (10 ml), washed with 1 M HCl (3 × 10 ml)
then sat. NaHCO₃ solution (10 ml) and dried (MgSO₄). Flash chromatography (30 % EtOAc–pet.
ether) gave 316 (392 mg, 37 %) as a colourless oil.
¹H NMR (400 MHz, CDCl₃) δ ppm 7.21 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB of one rotamer),
7.16 (2 H, d, J = 8.6 Hz, aromatic C-H of PMB of one rotamer), 6.88 (2 H, d, J = 8.6 Hz,
aromatic C-H of PMB of one rotamer), 6.84 (2 H, d, J = 8.6 Hz, aromatic C-H of PMB of one
rotamer), 6.43 (2 H, d, J = 2.3 Hz, aromatic C-H of one rotamer), 6.40 (1 H, t, J = 2.3 Hz,
aromatic C-H of one rotamer), 6.36 (3 H, s, aromatic C-H), 5.19 (1 H, s, COCH(OR)₂ of one
rotamer), 5.15 (1 H, s, COCH(OR)₂ of one rotamer), 4.65 (2 H, s, ArCH₂N of one rotamer), 4.61
(2 H, s, ArCH₂N of one rotamer), 4.44 (2 H, s, ArCH₂N of one rotamer), 4.39 (2 H, s, ArCH₂N of
one rotamer), 3.83 (3 H, s, OCH₃ of one rotamer), 3.80 (3 H, s, OCH₃ of one rotamer), 3.78 (6
H, s, OCH₃ of one rotamer), 3.76 (6 H, s, OCH₃ of one rotamer), 3.54 (4 H, d, J = 11.8 Hz, OCH₃
of both rotamers), 3.53 (4 H, d, J = 11.8 Hz, OCH₃ of both rotamers), 1.21 (3 H, s, CH₃ of one
rotamer), 1.20 (3 H, s, CH₃ of one rotamer), 0.77 (3 H, s, CH₃ of one rotamer), 0.76 (3 H, s, CH₃
of one rotamer).
¹³C NMR (100 MHz, CDCl₃) δ ppm 165.8 (C=O), 160.9 (aromatic C-O of one rotamer), 160.8
(aromatic C-O of one rotamer), 159.0 (aromatic C-O of one rotamer), 158.8 (aromatic C-O
of one rotamer), 139.1 (aromatic C-C of one rotamer), 138.9 (aromatic C-C of one rotamer), 129.7
(aromatic C-H of PMB of one rotamer), 129.1 (aromatic C-H of PMB of one rotamer), 128.6
(aromatic C-C of one rotamer), 128.3 (aromatic C-C of one rotamer), 113.9 (aromatic C-H
of PMB of one rotamer), 113.8 (aromatic C-H of PMB of one rotamer), 105.9 (aromatic C-H of
one rotamer), 105.5 (aromatic C-H of one rotamer), 100.2 (aromatic C-H of one rotamer), 100.1
(aromatic C-H of one rotamer), 99.3 (CH(OR)₂), 77.5 (OCH₂), 55.2 (OCH₃ of one rotamer), 55.2
(OCH₃ of one rotamer), 55.1 (OCH₃ of one rotamer), 55.1 (OCH₃ of one rotamer), 48.9 (ArCH₂N
of one rotamer), 48.4 (ArCH₂N of one rotamer), 46.9 (ArCH₂N of one rotamer), 46.8 (ArCH₂N of
one rotamer), 30.4 (C(Me)₂), 23.5 (CH₃ of one rotamer), 21.8 (CH₃ of one rotamer).
MS (ES+) m/z 430 [M+H]+, 452 [M+Na]+. HRMS 430.2218; C₂₇H₂₂NO₄ requires 430.2224. IR
(thin film) νmax (cm⁻¹) 2955 (C-H), 2837 (C-H), 1649 (amide C=O), 1610.

2,2-Dichloro-Ν(3,5-dimethoxybenzyl)-Ν(4-methoxybenzyl)acetamide 319
A mixture of dry DMF (0.8 ml) and CH₂Cl₂ (16 ml) was cooled to 0 °C and oxalyl chloride (342 μl, 4.04 mmol) was added dropwise and the solution stirred for 5 minutes. Dichloroacetic acid (330 μl, 4.00 mmol) was then added and the solution stirred for a further 15 minutes. A solution of amine 237 (1.148 g, 4.00 mmol) and NEt₃ (840 μl, 6.00 mmol) in CH₂Cl₂ (8 ml) was added and the solution was allowed to stir at RT for 2 h. The solution was then concentrated in vacuo, taken up in EtOAc (30 ml) and washed with water (15 ml), sat. NaHCO₃ solution (15 ml) and brine (15 ml) then dried (MgSO₄). Flash chromatography (30 % EtOAc–pet. ether) gave 319 (996 mg, 62 %) as a colourless oil.

¹H NMR (500 MHz, CDCl₃) δ ppm 7.17 (2 H, d, J = 8.5 Hz, aromatic C-H of PMB of one rotamer), 7.12 (2 H, d, J = 8.5 Hz, aromatic C-H of PMB of one rotamer), 6.92 (2 H, d, J = 8.5 Hz, aromatic C-H of PMB of one rotamer), 6.87 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB of one rotamer), 6.41 (1 H, s, aromatic C-H), 6.40 (1 H, s, aromatic C-H of one rotamer), 6.35 (2 H, d, J = 2.5 Hz, aromatic C-H of one rotamer), 6.32 (1 H, s, CHCl₂ of one rotamer), 6.30 (2 H, d, J = 1.9 Hz, aromatic C-H), 6.24 (1 H, s, CHCl₂ of one rotamer), 4.57 (4 H, s, ArCH₂N), 4.53 (2 H, s, ArCH₂N of one rotamer), 4.52 (2 H, s, ArCH₂N of one rotamer), 3.83 (3 H, s, OCH₃), 3.81 (3 H, s, OCH₃), 3.78 (6H, s, OCH₃), 3.77 (6H, s, OCH₃).

¹³C NMR (126 MHz, CDCl₃) δ ppm 164.4 (C=O), 161.5 (aromatic C-O of one rotamer), 161.1 (aromatic C-O of one rotamer), 159.5 (aromatic C-O of one rotamer), 159.3 (aromatic C-O of one rotamer), 138.2 (aromatic C-C of one rotamer), 137.6 (aromatic C-C of one rotamer), 129.8 (aromatic C-H of PMB of one rotamer), 128.0 (aromatic C-H of PMB of one rotamer), 127.9 (aromatic C-C of one rotamer), 126.8 (aromatic C-C of one rotamer), 114.5 (aromatic C-H of PMB of one rotamer), 114.2 (aromatic C-H of PMB of one rotamer), 105.7 (aromatic C-H of one rotamer), 104.4 (aromatic C-H of one rotamer), 99.8 (aromatic C-H of one rotamer), 99.7 (aromatic C-H of one rotamer), 65.3 (CHCl₂ of one rotamer), 65.1 (CHCl₂ of one rotamer), 55.4 (OCH₃), 55.3 (OCH₃), 50.1 (CH₂ of one rotamer), 49.8 (CH₂ of one rotamer), 49.1 (CH₂ of one rotamer), 48.9 (CH₂ of one rotamer).

MS (ES+) m/z 420 [M+Na⁺]. HRMS 420.0756; C₁₉H₂₆O₅NCl₂Na⁺ requires 420.0740. IR (thin film) v_max (cm⁻¹) 3002, 2934 (C-H), 1675 (C=O), 1610, 1597.

N(3,5-Dimethoxybenzyl)-2,2-dimethoxy-N-(4-methoxybenzyl)acetamide 317

Dichloroacetamide 319 (160 mg, 0.4 mmol) and NaOMe (25-30 wt% solution in MeOH, 1.0 ml) were placed in a microwave vial which was sealed and heated to 110 °C in a microwave reactor.
for 10 minutes. The reaction mixture was diluted with EtOAc (10 ml) then washed with water (2 × 10 ml) then brine (10 ml) then dried (MgSO₄) to give 317 (119 mg, 76%) as a pale yellow oil which was used without further purification.

¹H NMR (500 MHz, CDCl₃) δ ppm 7.16 (2 H, d, J = 8.5 Hz, aromatic C-H of PMB), 7.14 (2 H, d, J = 8.5 Hz, aromatic C-H of PMB), 6.89 (2 H, d, J = 8.5 Hz, aromatic C-H of PMB), 6.85 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB), 6.39 (1 H, s, aromatic C-H of one rotamer), 6.34 - 6.37 (5 H, m, aromatic C-H), 5.00 (1 H, s, CH(OCH₃)₂ of one rotamer), 4.96 (1 H, s, CH(OCH₃)₂ of one rotamer), 4.56 (2 H, s, ArCH₂N of one rotamer), 4.53 (2 H, s, ArCH₂N of one rotamer), 4.46 (2 H, s ArCH₂N of one rotamer), 4.42 (2 H, s, ArCH₂N of one rotamer), 3.82 (3 H, s, OCH₃), 3.80 (6 H, s, OCH₃), 3.78 (6 H, s, OCH₃), 3.76 (6 H, s, OCH₃), 3.49 (6 H, s, CH(OCH₃)₂ of one rotamer), 3.46 (6 H, s, CH(OCH₃)₂ of one rotamer).

¹³C NMR (126 MHz, CDCl₃) δ ppm 167.2 (C=O), 161.2 (aromatic C=O of one rotamer), 161.1 (aromatic C=O of one rotamer), 159.1 (aromatic C=O of one rotamer), 158.9 (aromatic C=O of one rotamer), 139.2 (aromatic C=C of one rotamer), 139.2 (aromatic C=C of one rotamer), 129.8 (aromatic C-H of PMB of one rotamer), 128.9 (aromatic C=C of one rotamer), 128.7 (aromatic C-H of PMB of one rotamer), 128.4 (aromatic C=C of one rotamer), 114.1 (aromatic C-H of PMB of one rotamer), 113.9 (aromatic C-H of PMB of one rotamer), 106.1 (aromatic C-H of one rotamer), 105.2 (aromatic C-H of one rotamer), 102.3 (CH(OMe)₂ of one rotamer), 102.1 (CH(OMe)₂ of one rotamer), 99.4 (aromatic C-H of one rotamer), 99.3 (aromatic C-H of one rotamer), 55.6 (OCH₃), 55.3 (OCH₃), 55.3 (OCH₃), 55.2 (OCH₃), 54.9 (OCH₃), 54.8 (OCH₃), 48.7 (CH₂ of one rotamer), 48.3 (CH₂ of one rotamer), 47.2 (CH₂ of one rotamer), 47.0 (CH₂ of one rotamer).

MS (ES⁺) m/z 412 M+Na⁺. HRMS 412.1731; C₂₁H₂₇NO₆Na⁺ requires 412.1731. IR (thin film) νₘₐₓ (cm⁻¹) 2933 (C-H), 2836, 1650 (C=O), 1610, 1597.

**Diethoxyacetic acid 320**

\[
\text{HO-CH₂-OEt} \\
\text{HO-CH₂-OEt}
\]

Ethyl diethoxyacetate (1.79 ml, 10 mmol) was dissolved in THF (50 ml) and water (15 ml). NaOH pellets (0.80 g, 20 mmol) were added and the solution stirred at RT for 24 h. The solution was diluted with water (50 ml), washed with ether (20 ml) then acidified with 2 M HCl and extracted with ether (3 × 50 ml). The organic extracts were dried (MgSO₄) and concentrated in vacuo to give 320 (1.42 g, 96%) as a pale yellow oil which was used without further purification.

¹H NMR (400 MHz, CDCl₃) δ ppm 4.97 (1 H, s, CH) 3.72 (4 H, m, 2 × CH₃) 1.29 (6 H, t, J = 7.05 Hz, 2 × CH₃).

¹³C NMR (100 MHz, CDCl₃) δ ppm 168.7 (CO₂H) 96.8 (CH(OME)₂) 62.9 (OCH₃) 15.0 (CH₃).
MS (ES−) m/z 147 [M-H]−. HRMS 147.0663; C₆H₁₁O₄− requires 147.0662. Data was consistent with literature values.¹²⁶

\( N(3,5-\text{Dimethoxybenzyl})-2,2-\text{diethoxy-}N(4-\text{methoxybenzyl})\text{acetamide} \) 318

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

**Method A – from dichloroacetamide 319**

Dichloroacetamide 319 (200 mg, 0.5 mmol) was placed in a microwave vial, NaOEt (21 wt% solution in EtOH, 1.5 ml) was added and the vial was sealed. The mixture was heated to 110 °C in a microwave reactor for 15 minutes. The reaction mixture was diluted with EtOAc (10 ml) then washed with water (2 × 10 ml) then brine (10 ml) then dried (MgSO₄) to give 318 (184 mg, 87%) as a pale yellow oil which was used without further purification.

**Method B – from amine 237**

Amine 237 (287 mg, 1.0 mmol) was dissolved in CH₂Cl₂ (5 ml) and diethoxycetic acid (222 mg, 1.5 mmol), EDCI (288 mg, 1.5 mmol), HOBt▪H₂O (27 mg, 0.2 mmol) and NEt₃ (0.21 ml, 1.5 mmol) were added. The solution was stirred for 16 h then diluted with CH₂Cl₂ (10 ml) then washed 1 M HCl (3 × 10 ml) then sat. NaHCO₃ solution (10 ml) then dried (MgSO₄) and concentrated in vacuo to give 318 (422 mg, quant.) as a pale yellow oil which was used without further purification.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.17 (2 H, d, J = 9.3 Hz, aromatic C-H of PMB of one rotamer), 7.13 (2 H, d, J = 8.8, aromatic C-H of PMB of one rotamer), 6.87 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB of one rotamer), 6.84 (2 H, d, J = 8.6 Hz, aromatic C-H of PMB of one rotamer), 6.33 - 6.39 (3 H, m, aromatic C-H), 5.11 (1 H, s, CH(OEt)₂ of one rotamer), 5.07 (1 H, s, CH(OEt)₂ of one rotamer), 4.62 (2 H, s, ArCH₂N of one rotamer), 4.58 (2 H, s, ArCH₂N of one rotamer), 4.43 (2 H, s, ArCH₂N of one rotamer), 4.40 (2 H, s, ArCH₂N of one rotamer), 3.82 (3 H, s, OCH₃ of one rotamer), 3.80 (6 H, s, OCH₃ of one rotamer), 3.77 (6 H, s, OCH₃ of one rotamer), 3.76 (3 H, s, OCH₃ of one rotamer), 3.74 - 3.79 (4 H, m, OCH₂ of one rotamer), 3.58 - 3.70 (4 H, m, OCH₂ of one rotamer), 1.24 (6 H, t, J = 7.1 Hz, CH₃ of one rotamer), 1.21 (6 H, t, J = 7.1 Hz, CH₃ of one rotamer).

¹³C NMR (75 MHz, CDCl₃) δ ppm 167.9 (C=O of one rotamer), 160.9 (aromatic C-O of one rotamer), 160.8 (aromatic C-O of one rotamer), 158.9 (aromatic C-O of one rotamer), 158.8 (aromatic C-O of one rotamer), 158.8 (aromatic C-O of one rotamer), 158.8 (aromatic C-O of one rotamer), 139.4 (aromatic C-C of one rotamer), 139.3 (aromatic C=C of one rotamer), 129.6 (aromatic C-H of PMB of one rotamer), 129.0 (aromatic C-C of one rotamer), 128.8 (aromatic C-H of PMB of one rotamer), 128.7 (aromatic C-C of one rotamer), 113.8 (aromatic C-H of PMB of one rotamer), 105.8 (aromatic C-H of one rotamer), 105.4 (aromatic C-H of one rotamer), 102.1 (CH(OEt)₂ of one rotamer), 101.8 (CH(OEt)₂ of one rotamer), 99.4 (aromatic C-H of one rotamer).
rotamer), 99.2 (aromatic C-H of one rotamer), 63.7 (CH$_2$O of one rotamer), 63.5 (CH$_2$O of one rotamer), 55.2 (OCH$_3$ of one rotamer), 55.1 (OCH$_3$ of one rotamer), 48.8 (NCH$_2$ of one rotamer), 48.3 (NCH$_2$ of one rotamer), 46.9 (NCH$_2$ of one rotamer), 46.7 (NCH$_2$ of one rotamer), 15.0 (CH$_3$ of one rotamer).

MS (ES$^+$) $m/z$ 440 [M+Na]$^+$. HRMS 440.2034; C$_{23}$H$_{31}$O$_6$NNa$^+$ requires 440.2044.

IR (thin film) $\nu_{max}$ (cm$^{-1}$) 3055, 2975 (C-H), 1723, 1653 (C=O).

**Methyl 3-[5,7-Dimethoxy-2-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-ylsulfanyl]-propanoate 254 from acetal 318**

Diethyl acetal 318 (126 mg, 0.30 mmol) was dissolved in MeCN (3.6 ml) then methyl 3-mercaptopropanoate (49 µl, 0.45 mmol) and Sc(OTf)$_3$ (221 mg, 0.45 mmol) were added and the solution was heated at reflux for 2.5 h. The solution was allowed to cool to RT, diluted with EtOAc (10 ml), washed with water (10 ml) then brine (10 ml) and dried (MgSO$_4$). Flash chromatography (50 % EtOAc–pet. ether) gave 254 (91 mg, 70 %). Data was identical to that previously recorded.

**(2R)-Methyl 3-((5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)sulfanyl)-2-((ethoxycarbonyl)amino)propanoate 321**

When cysteine derivative 256 was substituted for thiol 252 in the above procedure (using 0.2 mmol acetal 318), by-product 321 (20 mg, 18 %, pale yellow gum) eluted after the desired product (28 mg, 22 %, data was identical to that previously recorded) during flash chromatography (50 % EtOAc–pet. ether).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.21 (2 H, d, $J = 8.8$ Hz, aromatic C-H of PMB), 6.87 (2 H, d, $J = 8.8$ Hz, aromatic C-H of PMB), 6.56 (1 H, d, $J = 7.8$ Hz, NH), 6.37 (1 H, d, $J = 2.3$ Hz, aromatic C-H), 6.18 (1 H, d, $J = 2.3$ Hz, aromatic C-H), 4.93 (1 H, s, ArCHS), 4.78 (1 H, d, $J = 14.8$ Hz, CH$_2$ of PMB), 4.71 (1 H, m, CHNHCO$_2$Et), 4.59 (2 H, d, $J = 14.8$ Hz, CH$_2$ of PMB), 4.57 (1 H, d, $J = 15.9$ Hz, ArCH$_2$N), 4.17 (2 H, q, $J = 7.2$ Hz, OCH$_3$CH$_3$), 4.02 (1 H, d, $J = 15.9$ Hz, ArCH$_2$N), 3.87 (3 H, s, OCH$_3$), 3.84 (3 H, s, OCH$_3$), 3.80 (3 H, s, OCH$_3$), 3.78 (3 H, s, OCH$_3$), 3.42 (1 H, dd, $J = 14.5, 6.7$ Hz, CH$_2$HS), 3.14 (1 H, dd, $J = 14.5, 4.0$ Hz, CH$_2$HS), 1.27 (3 H, t, $J = 7.2$ Hz, CH$_3$CH$_3$).
13C NMR (100 MHz, CDCl₃) δ ppm 174.1 (C=O), 171.5 (C=O), 160.5 (aromatic C-O), 159.1 (aromatic C-O), 157.3 (aromatic C-O), 156.4 (carbamate C=O), 135.3 (aromatic ζ-C), 129.2 (aromatic C-H of PMB), 128.4 (aromatic ζ-C), 114.1 (aromatic C-H of PMB), 113.7 (aromatic ζ-C), 101.5 (aromatic C-H), 97.6 (aromatic C-H), 61.1 (CH₂OCON), 55.7 (OCH₃), 55.4 (OCH₃), 55.2 (OCH₃), 55.0 (OCH₃), 53.2 (CHNHTroc), 49.5 (CH₂N), 49.4 (CH₂N), 40.9 (ArCHS), 31.7 (CH₂S), 14.6 (CH₃).

MS (ES+) m/z 555 [M+Na]+. HRMS 555.1778; C₂₆H₃₂O₈NaS⁺ requires 555.1772. IR (thin film) νmax (cm⁻¹) 3355, 2954, 1746, 171.5 (C=O), 171.5 (C=O), 160.5 (C=O), 158.8 (aromatic C-O), 158.3 (aromatic C-O), 140.6 (aromatic ζ-C), 140.0 (aromatic ζ-C), 131.4 (aromatic ζ-C), 130.1 (aromatic ζ-C), 129.3 (aromatic C-H of PMB), 128.8 (aromatic C-H of PMB), 113.8 (aromatic ζ-C), 113.7 (aromatic C-H of PMB), 113.4 (aromatic C-H

(R)-N(1-(3,5-Dimethoxyphenyl)-2-((tri-iso-propylsilanyl)oxy)ethyl)-2,2-diethoxy-N(4-methoxybenzyl)acetamide 322

Amine 237 (473 mg, 1.0 mmol) was dissolved in CH₂Cl₂ (5 ml) and diethoxyacetic acid (222 mg, 1.5 mmol), DCC (309 mg, 1.5 mmol) and HOBt·H₂O (27 mg, 0.2 mmol) were added. The solution was stirred for 1 h then concentrated in vacuo. Flash chromatography (20 % EtOAc–pet. ether with 1 % NEt₃) gave 322 (563 mg, 93 %) as a colourless oil.

1H NMR (500 MHz, CDCl₃) δ ppm 7.17 (2 H, d, J = 8.5 Hz, aromatic C-H of PMB of one rotamer), 7.03 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB of one rotamer), 6.81 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB of one rotamer), 6.70 (2 H, d, J = 8.5 Hz, aromatic C-H of PMB of one rotamer), 6.55 (2 H, d, J = 1.6 Hz, aromatic C-H of one rotamer), 6.44 (2 H, d, J = 2.2 Hz, aromatic C-H of one rotamer), 6.37 (1 H, s, aromatic C-H of one rotamer), 6.33 (1 H, s aromatic C-H of one rotamer), 5.53 (1 H, t, J = 6.6 Hz, CHN of one rotamer), 5.33 (1 H, s, CH(OEt)₂ of one rotamer), 5.17 (1 H, t, J = 6.6 Hz, CHN of one rotamer), 4.98 (1 H, s, CH(OEt)₂ of one rotamer), 4.73 (1 H, d, J = 16.4 Hz, CHH of PMB of one rotamer), 4.63 (1 H, d, J = 14.9 Hz, CHH of PMB of one rotamer), 4.54 (1 H, d, J = 16.4 Hz, CHH of PMB of one rotamer), 4.15 (1 H, dd, J = 10.2, 6.9 Hz, CHHO of one rotamer), 4.08 (1 H, d, J = 14.9 Hz, CHH of PMB of one rotamer), 4.02 - 4.06 (2 H, m, CH₂O of both rotamers), 3.98 (1 H, dd, J = 10.2, 6.9 Hz, CHHO of one rotamer), 3.79 (3 H, s, OCH₃), 3.75 (3 H, s, OCH₃), 3.73 (6 H, s, OCH₃), 3.72 (6 H, s, OCH₃), 3.56 - 3.67 (8 H, m, OCH₂CH₃), 1.29 (6 H, t, J = 7.1 Hz, CH₂CH₃ of one rotamer), 1.20 (6 H, t, J = 7.1 Hz, CH₂CH₃ of one rotamer), 1.03 (42 H, m, SiCH and CH(CH₃)₂).

13C NMR (126 MHz, CDCl₃) δ ppm 168.4 (C=O), 168.2 (C=O), 160.7 (aromatic C-O), 160.5 (aromatic C-O), 158.8 (aromatic C-O), 158.3 (aromatic C-O), 140.6 (aromatic ζ-C), 140.0 (aromatic ζ-C), 131.4 (aromatic ζ-C), 130.1 (aromatic ζ-C), 129.3 (aromatic C-H of PMB), 128.8 (aromatic C-H of PMB), 113.8 (aromatic ζ-C), 113.7 (aromatic C-H of PMB), 113.4 (aromatic C-H
of PMB), 106.6 (aromatic C-H), 106.4 (aromatic C-H), 100.7 (CH(OEt)₂), 100.1 (CH(OEt)₂), 99.8 (aromatic C-H), 99.7 (aromatic C-H), 63.64 (CH₂OSi), 63.48 (CH₂OSi), 63.32 (OCH₂CH₃), 63.06 (OCH₂CH₃), 61.49 (ArCHN), 60.17 (ArCHN), 55.3 (OCH₃), 55.2 (OCH₃), 48.7 (CH₂ of PMB), 45.8 (CH₃ of PMB), 17.9 (CH(CH₃)₂), 15.1 (CH₃CH₂), 15.0 (CH₃CH₂), 11.9 (SiCH), 11.8 (SiCH).

MS (ES⁺) m/z 626 [M+Na]⁺. HRMS 626.3500; C₃₃H₆₅O₇NSiNa⁺ requires 626.3484. IR (thin film) vₘₙₙ (cm⁻¹) 2939 (C-H), 2865, 1651 ν(C=O). [α]_D²⁸ = −9.9 (c = 1.76, CHCl₃).

(5R)-5-(3,5-Dimethoxyphenyl)-2-ethoxy-4-(4-methoxybenzyl)morpholin-3-one 325

Acetal 322 (60.3 mg, 0.10 mmol) was dissolved in MeCN (1.2 ml) and methyl 3-mercaptopropanoate (16 µl, 0.15 mmol) and Sc(OTf)₃ (74 mg, 1.5 mmol) were added. The solution was heated under reflux for 75 minutes then cooled, diluted with EtOAc (10 ml) and washed with water (5 ml) then brine (5 ml). Flash chromatography (30 % EtOAc–pet. ether) gave 325 (35 mg, 87 %, 1:1.7 dr) as a pale yellow oil.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.15 (2 H, d, J = 8.6 Hz, aromatic C-H of PMB of one diastereoisomer), 7.03 (2H, d, J = 8.6 Hz, aromatic C-H of PMB of one diastereoisomer), 6.85 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB of one diastereoisomer), 6.80 (2H, d, J = 8.6 Hz, aromatic C-H of PMB of one diastereoisomer), 6.44 (4 H, t, J = 2.3 Hz, aromatic C-H of both diastereoisomers), 6.36 (2H, d, J = 2.3 Hz, aromatic C-H of both diastereoisomers), 5.49 (1 H, d, J = 14.5 Hz, CH of PMB of one diastereoisomer), 5.35 (1 H, d, J = 14.4 Hz, CH of PMB of one diastereoisomer), 5.12 (1 H, s, CHOEt), 5.06 (1 H, s, CHOEt), 4.43 (1 H, dd, J = 10.7, 5.5 Hz, ArCHN of one diastereoisomer), 4.38 (1 H, d, J = 3.6 Hz ArCHN of one diastereoisomer), 4.16 (1 H, dd, J = 11.9, 10.7 Hz, CHHO of one diastereoisomer), 4.10 (1 H, d, J = 3.6 Hz, CHHO of one diastereoisomer), 3.82 - 3.89 (2 H, m CH₂O), 3.80 (6H, s, OCH₃), 3.79 (6H, s, OCH₃), 3.78 (6 H, s, OCH₃), 3.68 - 3.75 (4H, m, OCH₂CH₃ of both diastereoisomers), 3.52 (1 H, d, J = 14.4 Hz, CH of PMB of one diastereoisomer), 3.40 (1 H, d, J = 14.5 Hz, CH of PMB of one diastereoisomer), 1.28 - 1.33 (6H, m, CH₂CH₃ of both diastereoisomers)

¹³C NMR (100 MHz, CDCl₃) δ ppm 165.3 (C=O of one diastereoisomer), 164.7 (C=O of one diastereoisomer), 161.3 (aromatic C-O of one diastereoisomer), 161.2 (aromatic C-O of one diastereoisomer), 159.2 (aromatic C-O of one diastereoisomer), 159.0 (aromatic C-O of one diastereoisomer), 140.8 (aromatic C=C of one diastereoisomer), 138.2 (aromatic C=C of one diastereoisomer), 130.1 (aromatic C-H of PMB of one diastereoisomer), 130.0 (aromatic C-H of PMB of one diastereoisomer), 128.3 (aromatic C-C), 114.1 (aromatic C-C), 113.8 (aromatic C-H of PMB), 105.8 (aromatic C-H of one diastereoisomer), 105.2 (aromatic C-H of one diastereoisomer), 100.5 (aromatic C-H of one diastereoisomer), 99.6 (aromatic C-H of one
diastereoisomer), 96.3 (CHOEt of one diastereoisomer), 95.6 (CHOEt of one diastereoisomer),
64.8 (OCH₃ of one diastereoisomer), 64.8 (OCH₂ of one diastereoisomer), 62.9 (OCH₂CH₃ of one
diastereoisomer), 62.7 (OCH₃CH₃ of one diastereoisomer), 59.4 (ArCHN of one diastereoisomer),
57.9 (ArCHN of one diastereoisomer), 55.4 (OCH₃ of one diastereoisomer), 55.4 (OCH₂ of one
diastereoisomer), 55.2 (OCH₂ of one diastereoisomer), 55.2 (OCH₃ of one diastereoisomer), 46.4
(CH₂ of PMB of one diastereoisomer), 45.3 (CH₂ of PMB of one diastereoisomer), 15.1 (CH₂CH₃ of
one diastereoisomer), 15.0 (CH₂CH₂ of one diastereoisomer).

MS (ES+) m/z 424 [M+Na]+. HRMS 424.1738; C₂₂H₂₂O₈Na requires 424.1731. IR (thin film)
νmax (cm⁻¹) 2938 (C-H), 2836 (C-H), 1666 (C=O), 1609, 1597.

(R)-N-(1-(3,5-Dimethoxyphenyl)-2-hydroxyethyl)-2,2-diethoxy-N-(4-methoxybenzyl)-
acetamide 324

Silyl ether 322 (673 mg, 1.11 mmol) was dissolved in dry THF (10 ml) and TBAF (1 M solution in
THF, 1.2 ml, 1.2 mmol) was added. The solution was stirred for 45 minutes then diluted with
water (15 ml) and extracted with EtOAc (2 × 15 ml) and the extracts were dried (MgSO₄). Flash
chromatography (60 % EtOAc–pet. ether with 1 % NEt₃) gave 324 (445 mg, 90 %) as a pale
yellow oil.

¹H NMR (500 MHz, CDCl₃) δ ppm 7.18 (2 H, d, J = 8.5 Hz, aromatic C-H of PMB of one rotamer),
7.10 (2 H, d, J = 8.5 Hz, aromatic C-H of PMB of one rotamer), 6.87 (2 H, d, J = 8.5 Hz,
aromatic C-H of PMB of one rotamer), 6.76 (2 H, d, J = 8.5 Hz, aromatic C-H of PMB of one
rotamer), 6.48 (2 H, d, J = 2.2 Hz, aromatic C-H of one rotamer), 6.38 (4 H, s, aromatic C-H of
both rotamers), 5.81 (1 H, dd, J = 9.9, 4.9 Hz, ArCHN of one rotamer), 5.17 (1 H, s, CH(OEt)₂ of
one rotamer), 5.06 (1 H, s, CH(OEt)₂ of one rotamer), 4.86 (1 H, d, J = 16.4 Hz, C₆H₆ of PMB of
one rotamer), 4.82 (1 H, dd, J = 7.6, 3.8 Hz, ArCHN of one rotamer), 4.61 (1 H, d, J = 15.1 Hz,
C₆H₆ of PMB of one rotamer), 4.34 (1 H, d, J = 16.4 Hz, C₆H₆ of PMB of one rotamer), 3.95 (1 H,
d, J = 15.1 Hz, C₆H₆ of PMB of one rotamer), 3.87 - 3.93 (4 H, m, CH₂OH), 3.81 (3 H, s, OCH₃),
3.76 (15 H, s, OCH₃), 3.71 - 3.75 (4 H, m, OCH₂CH₃ of one rotamer), 3.65 (4 H, dd, J = 9.3, 7.1
Hz, OCH₂CH₃), 3.43 (1 H, dd, J = 8.4, 4.6 Hz, OH of one rotamer), 2.65 (1 H, dd, J = 7.3, 4.1
Hz, OH of one rotamer), 1.32 (6 H, t, J = 7.1 Hz, CH₂CH₃ of one rotamer), 1.25 (3 H, t, J = 7.1
Hz, CH₂CH₃ of one rotamer), 1.23 (3 H, t, J = 7.1 Hz, CH₃CH₃ of one rotamer).

¹³C NMR (126 MHz, CDCl₃) δ ppm 169.7 (C=O of one rotamer), 168.6 (C=O of one rotamer),
160.9 (aromatic C-O), 159.0 (aromatic C-O of one rotamer), 158.4 (aromatic C-O of one
rotamer), 139.1 (aromatic C-C of one rotamer), 139.0 (aromatic C-C of one rotamer), 130.6
(aromatic C-C of one rotamer), 129.1 (aromatic C-C of one rotamer), 128.9 (aromatic C-H of
PMB of one rotamer), 128.5 (aromatic C-H of PMB of one rotamer), 114.0 (aromatic C-H of PMB of one rotamer), 113.6 (aromatic C-H of PMB of one rotamer), 106.2 (aromatic C-H of one rotamer), 105.9 (aromatic C-H of one rotamer), 104.6 (CH(OEt)₂ of one rotamer), 101.6 (CH(OEt)₂ of one rotamer), 99.8 (aromatic C-H of one rotamer), 99.6 (aromatic C-H of one rotamer), 65.4 (OCH₂ of one rotamer), 65.1 (OCH₂ of one rotamer), 63.7 (OCH₂CH₃ of one rotamer), 63.5 (OCH₂CH₃ of one rotamer), 61.4 (ArCHN of one rotamer), 59.5 (ArCHN of one rotamer), 55.3 (OCH₃), 55.3 (OCH₃), 55.2 (OCH₃), 49.5 (CH₂ of PMB of one rotamer of one rotamer), 45.4 (CH₂ of PMB of one rotamer of one rotamer), 15.3 (CH₃CH₃ of one rotamer), 15.1 (CH₃CH₃ of one rotamer).

MS (ES⁺) m/z 470 [M+Na]⁺. HRMS 470.2148; C₂₄H₂₆O₄Na⁺ requires 470.2149. IR (thin film) νmax (cm⁻¹) 3300-3500 (br. OH), 2974 (C-H), 1646 (C=O). [α]D²⁶ = -11.3 (c = 2.14, CHCl₃).

(R)-2-(2,2-Diethoxy-N(4-methoxybenzyl)acetamido)-2-(3,5-dimethoxyphenyl)ethyl acetate 323

Alcohol 324 (80 mg, 0.18 mmol) was dissolved in CH₂Cl₂ (0.5 ml) and Ac₂O (20 µl, 0.21 mmol) and pyridine (29 µl, 0.38 mmol) were added. The solution was stirred at RT for 25 h then diluted with Et₂O (5 ml), washed with 1 M HCl (5 ml) then sat. NaHCO₃ solution (5 ml) and dried (MgSO₄). Flash chromatography (40 % EtOAc–pet. ether) gave 323 (49 mg, 55 %) as a pale yellow oil.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.11 (2 H, d, J = 8.6 Hz, aromatic C-H of PMB of one rotamer), 7.03 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB of one rotamer), 6.81 (2 H, d, J = 8.6 Hz, aromatic C-H of PMB of one rotamer), 6.74 (2 H, d, J = 8.6 Hz, aromatic C-H of PMB of one rotamer), 6.52 (2 H, d, J = 2.0 Hz, aromatic C-H of one rotamer), 6.41 (1 H, t, J = 2.0 Hz, aromatic C-H of one rotamer), 6.40 (2 H, d, J = 2.3 Hz, aromatic C-H of one rotamer), 6.37 (1 H, t, J = 2.3 Hz, aromatic C-H of one rotamer), 5.89 (1 H, t, J = 7.1 Hz, ArCHN of one rotamer), 5.51 (1 H, t, J = 7.1 Hz, ArCHN of one rotamer), 5.20 (1 H, s, CH(OEt)₂ of one rotamer), 4.99 (1 H, s, CH(OEt)₂ of one rotamer), 4.76 (1 H, d, J = 14.9 Hz, CH₂ of PMB of one rotamer), 4.71 (1 H, d, J = 16.1 Hz, CH₂ of PMB of one rotamer), 4.47 (1 H, d, J = 16.1 Hz, CH₂ of PMB of one rotamer), 4.41 (1 H, dd, J = 11.3, 7.3 Hz CH₂ of one rotamer), 4.27 (1 H, dd, J = 11.3, 6.8 Hz, CH₂ of one rotamer), 3.86 (1 H, d, J = 14.9 Hz, CH₂ of PMB of one rotamer), 3.86 (3 H, s, OCH₃), 3.79 (3 H, s, OCH₃), 3.77 (6 H, s, OCH₃), 3.74 (6 H, s, OCH₃), 3.67 - 3.73 (4 H, m, OCH₂CH₃ of one rotamer), 3.58 - 3.65 (4 H, m, OCH₂CH₃ of one rotamer), 1.97 (3 H, s, COCH₃ of one rotamer), 1.90 (3 H, s, COCH₃ of one rotamer), 1.28 (6 H, td, J = 7.1, 4.3 Hz, CH₃ of one rotamer), 1.22 (6 H, dt, J = 9.6, 7.1 Hz, CH₃ of one rotamer).
\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) ppm 170.5 (C=O of one rotamer), 170.3 (C=O of one rotamer), 168.6 (C=O of one rotamer), 168.6 (C=O of one rotamer), 161.0 (aromatic C=O of one rotamer), 160.8 (aromatic C=O of one rotamer), 158.9 (aromatic C-O of one rotamer), 158.5 (aromatic C-O of one rotamer), 138.8 (aromatic C-C of one rotamer), 138.7 (aromatic C-C of one rotamer), 130.5 (aromatic C-C of one rotamer), 129.4 (aromatic C-C of one rotamer), 128.8 (aromatic C-H of PMB of one rotamer), 128.5 (aromatic C-H of PMB of one rotamer), 113.7 (aromatic C-H of PMB of one rotamer), 113.6 (aromatic C-H of one rotamer), 106.2 (aromatic C-H of one rotamer), 106.2 (aromatic C-H of one rotamer), 102.5 (CH(OEt)\(_2\) of one rotamer), 100.5 (CH(OEt)\(_2\) of one rotamer), 100.1 (aromatic C-H of one rotamer), 99.8 (aromatic C-H of one rotamer), 64.2 (CH\(_2\)O of one rotamer), 63.8 (CH\(_2\)O of one rotamer), 63.2 (OCH\(_2\)CH\(_3\) of one rotamer), 63.1 (OCH\(_2\)CH\(_3\) of one rotamer), 57.4 (ArCHN of one rotamer), 56.9 (ArCHN of one rotamer), 55.3 (OCH\(_3\) of one rotamer), 55.2 (OCH\(_3\) of one rotamer), 55.2 (OCH\(_3\) of one rotamer), 47.9 (CH\(_2\) of PMB of one rotamer), 45.6 (CH\(_2\) of PMB of one rotamer), 21.2 (COCH\(_3\) of one rotamer), 15.2 (CH\(_2\)CH\(_3\) of one rotamer), 15.1 (CH\(_2\)CH\(_3\) of one rotamer).

MS (ES+) \(m/z\) 490 [M+H]\(^+\), 512 [M+Na]\(^+\). HRMS 512.2239; C\(_{26}\)H\(_{35}\)NO\(_8\)Na\(^+\) requires 512.2255.

IR (thin film) \(\nu_{\text{max}}\) (cm\(^{-1}\)) 2973 (C-H), 1741 (ester C=O), 1650 (amide C=O), 1609.

\([\alpha]_{\text{D}}^{26} = -11.2\) (c = 7.6, CHCl\(_3\)).

Methyl 3-(((1R,4R)-1-(acetoxymethyl)-5,7-dimethoxy-2-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)sulfanyl)propanoate 326

![Chemical Structure](image)

Acetal 323 (20 mg, 0.041 mmol) was dissolved in MeCN (4.1 ml) and methyl 3- mercaptopropanoate (4 \(\mu\)l, 0.041 mmol) and Sc(OTf)\(_3\) (30 mg, 0.061 mmol) were added. The solution was heated under reflux for 4 h then diluted with EtOAc (15 ml) and washed with water (10 ml) then brine (10 ml) and dried (MgSO\(_4\)). Flash chromatography (40 % EtOAc–pet. ether) gave 326 (13.4 mg, 65 %) as a pale yellow gum.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) ppm 7.15 (2 H, d, \(J = 8.7\) Hz, aromatic C-H of PMB), 6.82 (2 H, d, \(J = 8.7\) Hz, aromatic C-H of PMB), 6.40 (1 H, d, \(J = 2.2\) Hz, aromatic C-H), 6.18 (1 H, d, \(J = 2.2\) Hz, aromatic C-H), 5.45 (1 H, d, \(J = 14.9\) Hz, CH\(_2\)H of PMB), 4.73 (1 H, s, ArCHS), 4.57 (1 H, dd, \(J = 10.6, 6.3, 1.0, \) Hz, CH\(_2\)HO), 4.50 (1 H, dd, \(J = 6.6, 5.5 \) Hz, ArCHN), 4.43 (1 H, dd, \(J = 10.6, 5.5\) Hz, CH\(_2\)HO), 4.17 (1 H, d, \(J = 14.9\) Hz, CH\(_2\)H of PMB), 3.87 (3 H, s, OCH\(_3\)), 3.77 (3 H, s, OCH\(_3\)), 3.76 (3 H, s, OCH\(_3\)), 3.72 (3 H, s, OCH\(_3\)), 3.35 (1 H, dt, \(J = 14.0, 7.1\) Hz, SCCH\(_3\)), 3.09 (1 H, dt, \(J = 14.0, 7.1\) Hz, SCCH\(_3\)), 2.88 (2 H, t, \(J = 7.1\) Hz, CH\(_2\)CO\(_2\)R), 2.11 (3 H, s, COCH\(_3\)).
$^{13}\text{C NMR}$ (75 MHz, CDCl$_3$) δ ppm 172.4 (C=O), 170.5 (C=O), 169.2 (C=O), 160.4 (aromatic C-O), 159.0 (aromatic C-O), 157.4 (aromatic C-O), 135.0 (aromatic C-C), 129.2 (aromatic C-H of PMB), 128.7 (aromatic C-C), 114.1 (aromatic C-H of PMB), 113.7 (aromatic C-C), 135.0 (aromatic C-C), 129.2 (aromatic C-H of PMB), 114.1 (aromatic C-H of PMB), 113.7 (aromatic C-C), 102.6 (aromatic C-H), 98.3 (aromatic C-H), 67.7 (CH$_2$O), 59.0 (ArCHN), 55.8 (OCH$_3$), 55.4 (OCH$_3$), 51.7 (OCH$_3$), 48.6 (CH$_2$ of PMB), 39.8 (ArCHS), 34.4 (CH$_2$CO$_2$R), 28.6 (SCH$_2$), 21.0 (COCH$_3$).

MS (ES+) m/z 518 [M+Na]$^+$ HRMS 518.1840; C$_{26}$H$_{32}$NO$_8$S$^+$ requires 518.1844.

IR (thin film) ν$_{\text{max}}$ (cm$^{-1}$) 3018, 2948 (C-H), 1737 (ester C=O), 1650 (amide C=O).

$^{[\alpha]}_D^{26} = +8.7$ (c = 0.78, CHCl$_3$).

3-Tris(4-methoxyphenyl)methylsulfanylpropanoic acid 327

Methyl 3-mercaptopropanoate 252 (0.324 ml, 3.0 mmol) was dissolved in dry THF (15 ml) and TMTrCl (1.22 g, 3.3 mmol) and NEt$_3$ (0.50 ml, 3.6 mmol) were added. The solution was stirred for 20 h then MeOH (4 ml) was added and the solution stirred for a further 20 minutes. The solution was concentrated in vacuo and the residue dissolved in EtOAc (20 ml), filtered and concentrated. The residue was dissolved in THF (12 ml) and water (3 ml) and LiOH.H$_2$O (252 mg, 6.0 mmol) was added. The solution was stirred for 24 h then concentrated in vacuo. The residue was dissolved in EtOAc (15 ml) then washed with 1 M HCl (20 ml). The aqueous phase was extracted with EtOAc (20 ml) and the combined extracts were washed with brine (10 ml), dried (MgSO$_4$) and concentrated in vacuo to give 327 (1.42g, quant.) as a pale yellow orange solid which was used without further purification. Melting point (CHCl$_3$) 136 - 138 °C.

$^1\text{H NMR}$ (400 MHz, CDCl$_3$) δ ppm 7.30 (6 H, d, J = 8.8 Hz, aromatic C-H of TMTr), 6.81 (6 H, d, J = 8.8 Hz, aromatic C-H of TMTr), 3.80 (9 H, s, OCH$_3$), 2.45 - 2.50 (2 H, m, CH$_2$), 2.26 - 2.36 (2 H, m, CH$_2$).

$^{13}\text{C NMR}$ (100 MHz, CDCl$_3$) δ ppm 177.4 (CO$_2$H), 158.5 (aromatic C-O), 137.3 (aromatic C-C), 130.5 (aromatic C-H), 113.1 (aromatic C-H), 65.5 (SCAr$_3$), 55.2 (OCH$_3$), 33.4 (CH$_2$), 26.6 (CH$_2$).

MS (ES–) m/z 437 [M-H]$^–$. HRMS 437.1434; C$_{23}$H$_{29}$O$_5$S$^–$ requires 437.1428. IR (thin film) ν$_{\text{max}}$ (cm$^{-1}$) 3001, 2952 (C-H), 2932, 1709 (C=O), 1605.

(R)-2-(2,2-Diethoxy-N-(4-methoxybenzyl)acetamido)-2-(3,5-dimethoxyphenyl)ethyl 3-((tris(4-methoxyphenyl)methyl)sulfanyl)propanoate 354
Alcohol 324 (239 mg, 0.5 mmol) was dissolved in CH₂Cl₂ (12 ml) under N₂ and acid 327 (330 mg, 0.75 mmol), DCC (155 mg, 0.75 mmol) and HOBT•H₂O (0.1 mmol) were added. The solution was stirred for 1 h then concentrated in vacuo. Flash chromatography (40-50 % EtOAc–pet. ether with 1 % NEt₃) gave 354 (413 mg, 95 %) as a colourless gum.

¹H NMR (500 MHz CDCl₃) δ ppm 7.19 (6 H, d, J = 8.8, aromatic C-H of TMTr of one rotamer), 7.17 (6 H, d, J = 8.8 Hz, aromatic C-H of TMTr of one rotamer), 6.99 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB of one rotamer), 6.90 (2 H, d, J = 8.7 Hz, aromatic C-H of PMB of one rotamer), 6.71 (6 H, d, J = 8.8 Hz, aromatic C-H of TMTr of one rotamer), 6.70 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB of one rotamer), 6.69 (6 H, d, J = 8.8 Hz, aromatic C-H of TMTr of one rotamer), 6.63 (2 H, d, J = 8.7 Hz, aromatic C-H of PMB of one rotamer), 6.40 (2 H, d, J = 2.5 Hz, aromatic C-H), 6.31 (1 H, t, J = 2.2 Hz, aromatic C-H), 6.27 (3 H, s, aromatic C-H), 5.78 (1 H, t, J = 6.8 Hz, CHN of one rotamer), 5.36 (1 H, t, J = 6.8 Hz, CHN of one rotamer), 5.08 (1 H, s, CH(OEt)₂ of one rotamer), 4.90 (1 H, s, CH(OEt)₂ of one rotamer), 4.66 (1 H, d, J = 15.1 Hz, CH₂ of PMB of one rotamer), 4.65 (1 H, d, J = 16.5 Hz, CH₂ of PMB of one rotamer), 4.36 (1 H, d, J = 15.1 Hz, CH₂ of PMB of one rotamer), 4.31 - 4.40 (1 H, m, CH₂HO of one rotamer), 4.15 (1 H, dd, J = 11.5, 6.1 Hz, CH₂HO of one rotamer), 3.76 (1 H, dd, J = 9.1, 7.5 Hz, CH₂HO of one rotamer), 3.69 (12 H, s, OCH₃), 3.69 (12 H, s, OCH₃), 3.68 (3 H, s, OCH₃), 3.65 (9 H, s, OCH₃), 3.65 (9 H, s, OCH₃), 3.62 (6 H, s, OCH₃), 3.53 (4 H, m, OCH₂CH₂ of one rotamer), 2.31 (2 H, t, J = 7.6 Hz, CH₂CO₂R of one rotamer), 2.27 (2 H, t, J = 7.4 Hz, CH₂CO₂R of one rotamer), 2.09 (2 H, m, CH₂S of one rotamer), 1.99 (2 H, m, CH₂S of one rotamer), 1.20 (6 H, t, J = 6.9 Hz, CH₂CH₃ of one rotamer), 1.15 (6 H, t, J = 6.9 Hz, CH₂CH₃ of one rotamer).

¹³C NMR (126 MHz, CDCl₃) δ ppm 171.1 (C=O), 171.0 (C=O), 168.2 (C=O), 168.2 (C=O), 160.6 (aromatic C-O), 160.5 (aromatic C-O), 158.6 (aromatic C-O), 158.2 (aromatic C-O), 157.7 (aromatic C-O, both rotamers), 138.5 (aromatic C=C of one rotamer), 138.4 (aromatic C=C of one rotamer), 137.0 (aromatic C=C of one rotamer), 137.0 (aromatic C=C of one rotamer), 130.2 (aromatic C-H of TMTr), 129.0 (aromatic C=C of one rotamer), 128.5 (aromatic C-H of PMB of one rotamer), 128.2 (aromatic C-H of PMB of one rotamer), 113.5 (aromatic C-H of PMB of one rotamer), 113.3 (aromatic C-H of PMB of one rotamer), 112.8 (aromatic C-H of TMTr), 105.8 (aromatic C-H), 105.8 (aromatic C-H), 102.4 (CH(OEt)₂), 100.2 (CH(OEt)₂), 99.8 (aromatic C-H), 99.5 (aromatic C-H), 65.0 (SC₂Ar₃), 64.0 (SC₂Ar₃), 63.7 (CH₂O), 63.1 (CH₂O), 62.9 (CH₂O), 62.8 (CH₂O), 57.0 (ArCHN) 56.9 (ArCHN), 55.2 (OCH₃), 55.0 (OCH₃), 54.9 (OCH₃), 47.8 (CH₂ of PMB).
45.3 (CH₂ of PMB), 33.9 (CH₂CO₂R), 33.0 (CH₂CO₂R), 26.5 (CH₂S), 25.3 (CH₂S), 14.9 (CH₂CH₃), 14.9 (CH₃CH₂), 14.8 (CH₃CH₂).

MS (ES+) m/z 890 [M+Na]⁺. HRMS 890.3542; C₉H₇O₁₁NNaS⁺ requires 890.3545. IR (thin film) νmax (cm⁻¹) 2929 (C-H), 1737 (ester C=O), 1651 (amide C=O). [α]D²⁸ = −6.9 (c = 0.8, CHCl₃).

(R)-2-(2,2-Diethoxy-N-(4-methoxybenzyl)acetamido)-2-(3,5-dimethoxyphenyl)ethyl 3-mercaptopropanoate 328

Sulfide 354 (87 mg, 0.10 mmol) was dissolved in CH₂Cl₂-TFA (100:1, 3.3 ml) under N₂ and Et₃SiH (0.16 ml, 1.0 mmol) was added. The solution was stirred for 90 minutes then diluted with CH₂Cl₂ (15 ml), washed with sat. NaHCO₃ solution (10 ml) and dried (MgSO₄). Flash chromatography (30 % EtOAc–pet. ether with 1 % NEt₃) then gave 328 (49 mg, 91 %) as a colourless gum.

¹H NMR (500 MHz, CDCl₃) δ ppm 7.12 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB of one rotamer), 7.04 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB of one rotamer), 6.82 (2 H, d, J = 8.8 Hz, aromatic C-H of PMB of one rotamer), 6.75 (2 H, d, J = 8.5 Hz, aromatic C-H of PMB of one rotamer), 6.52 (2 H, d, J = 2.5 Hz, aromatic C-H of one rotamer), 6.41 (1 H, t, J = 1.9 Hz, aromatic C-H of one rotamer), 6.37 - 6.39 (3 H, m, aromatic C-H of one rotamer), 5.92 (1 H, t, J = 6.9 Hz, ArCHN of one rotamer), 5.49 (1 H, t, J = 7.1 Hz, ArCHN of one rotamer), 5.18 (1 H, s, CH(OEt)₂ of one rotamer), 5.00 (1 H, s, CH(OEt)₂ of one rotamer), 4.79 (1 H, d, J = 15.2 Hz, CH₂H of PMB of one rotamer), 4.72 (1 H, d, J = 16.4 Hz, 1 H, CH₃H of PMB of one rotamer), 4.43 - 4.54 (2 H, m, CH₂H), 4.41 (1 H, d, J = 16.4 Hz, CH₃H of PMB of one rotamer), 4.31 (1 H, dd, J = 11.5, 6.5 Hz, CH₃H of one rotamer), 3.84 - 3.90 (1 H, m, CH₂H of one rotamer), 3.82 (1 H, d, J = 15.2 Hz, CH₂H of one rotamer), 3.80 (3 H, s, OCH₃), 3.77 (9 H, s, OCH₃), 3.74 (6 H, s, OCH₃), 3.66 - 3.73 (4 H, m, OCH₂CH₃ of one rotamer), 3.61 (4 H, ddd, J = 9.5, 7.0, 2.7 Hz, OCH₂CH₃ of one rotamer), 3.69 (2 H, dd, J = 8.5, 1.9 Hz, CH₂CO₂R of one rotamer), 2.62 (2 H, m, CH₂CO₂R of one rotamer), 2.53 - 2.58 (2 H, m, CH₂S of one rotamer), 2.45 (2 H, td, J = 6.9, 3.6 Hz, CH₂S of one rotamer), 1.58 (1 H, t, J = 8.2 Hz, SH of one rotamer), 1.53 (1 H, t, J = 8.5 Hz, SH of one rotamer), 1.28 (6 H, m, CH₂CH₃ of one rotamer), 1.22 (6 H, dt, J = 10.7, 6.9 Hz, CH₂CH₃ of one rotamer).

¹³C NMR (75 MHz, CDCl₃) δ ppm 171.0 (C=O of one rotamer), 170.9 (C=O of one rotamer), 168.6 (C=O), 161.0 (aromatic C-O of one rotamer), 160.8 (aromatic C-O of one rotamer), 159.0 (aromatic C-O of one rotamer), 158.5 (aromatic C-O of one rotamer), 138.7 (aromatic C-C of one rotamer), 138.6 (aromatic C-C of one rotamer), 130.5 (aromatic C-C of one rotamer), 129.4
(aromatic C-C of one rotamer), 128.8 (aromatic C-H of PMB of one rotamer), 128.6 (aromatic C-H of PMB of one rotamer), 113.8 (aromatic C-H of PMB of one rotamer), 113.6 (aromatic C-H of PMB of one rotamer), 106.2 (aromatic C-H of one rotamer), 106.2 (aromatic C-H of one rotamer), 102.8 (CH(OEt) of one rotamer), 100.7 (CH(OEt) of one rotamer), 100.1 (aromatic C-H of one rotamer), 99.8 (aromatic C-H of one rotamer), 64.3 (CH₂O of one rotamer), 64.0 (CH₂O of one rotamer), 63.4 (CH₂O of one rotamer), 63.3 (CH₂O of one rotamer), 57.4 (ArCHN of one rotamer), 56.9 (ArCHN of one rotamer), 55.3 (OCH₃ of one rotamer), 55.2 (OCH₃ of one rotamer), 53.4 (OCH₃ of one rotamer), 48.0 (CH₂ of PMB of one rotamer), 45.6 (CH₂ of PMB of one rotamer), 38.4 (CH₂CO₂R of one rotamer), 38.2 (CH₂CO₂R of one rotamer), 19.5 (SCH₂ of one rotamer), 19.4 (SCH₂ of one rotamer), 15.2 (CH₃ of one rotamer), 15.1 (CH₃ of one rotamer).

MS (ES+) m/z 558 [M+Na]^+. HRMS 558.2135 C₂₇H₂₇O₈N₃NaS⁺ requires 558.2132. IR (thin film) ν_{max} (cm⁻¹) 2975 (C-H), 1737 (ester C=O), 1653 (amide C=O). [α]₂⁶ = −11.5 (c = 1.80, CHCl₃).

\((3R)-3-(3,5-Dimethoxyphenyl)-6-ethoxy-4-(4-methoxybenzyl)-1,7,4-oxathiazecane-5,10-dione\) 329

Acetal 328 (49 mg, 0.09 mmol) was dissolved in PhMe (10 ml) and Sc(OTf)₃ (67 mg, 0.137 mmol) was added. The mixture was heated to 90 °C for 5 h then cooled to RT. The mixture was diluted with EtOAc (5 ml) and washed with water (10 ml) then brine (5 ml), dried (MgSO₄) and concentrated in vacuo to give crude thiaoacetal 329 (53 mg).

\(^1\text{H} NMR (500 MHz, CDCl₃) δ ppm 7.27 (2 H, d, J = 8.2 Hz, aromatic C-H of PMB), 6.88 (2 H, d, J = 8.2 Hz, aromatic C-H of PMB), 6.58 (2 H, d, J = 1.9 Hz, aromatic C-H), 6.49 (1 H, br. s, aromatic C-H), 5.00 (1 H, s, SCHOEt), 4.49 - 4.53 (2 H, m, ArCHN and CHH of PMB), 4.10 - 4.19 (3 H, m, CH₂O and CHH of PMB), 3.81 (6 H, s, OCH₃), 3.80 (3 H, s, OCH₃), 3.78-3.79 (2 H, m, CH₂O), 3.62 (2 H, m, CH₂CO₂), 2.77 (1 H, m, CHH₂), 2.69 (1 H, t, J = 6.3 Hz, CHHS), 1.26 (3 H, t, J = 7.1 Hz, CH₃).

MS (ES+) m/z 490 [M+H]^+, 512 [M+Na]^+.

### 3.6 Synthesis and cyclisation of \(\text{NO-acetal protected branched glyoxamides}\)

\((1R,4R)-4-((3-Hydroxypropyl)sulfanyl)-5,7-dimethoxy-2-(4-methoxybenzyl)-1-(((\text{tri}-\text{isopropyl}silanyloxy)methyl)-1,2-dihydroisoquinolin-3(4\text{H})-one\) 330
Tetrahydroisoquinolinone 297 (63 mg, 0.1 mmol, 1:1 dr) was dissolved in dry THF (2 ml), the solution was cooled to −78 °C and a 1 M solution of DIBAL in hexane (0.15 ml, 0.15 mmol) was added. After 2.5 h, the reaction was quenched with 2 M NaOH solution (1 ml) then allowed to warm to RT. The mixture was diluted with water (1 ml) then extracted with CH₂Cl₂ (3 × 3 ml) then the combined extracts were washed with brine (3 ml) and dried (MgSO₄). Flash chromatography (60 % EtOAc–pet. ether) gave 330 (17 mg, 28 %) as a pale yellow gum.

³¹H NMR (400 MHz, CDCl₃) δ ppm 7.14 (2 H, d, J = 8.7 Hz, aromatic C-H of PMB), 6.81 (2 H, d, J = 8.7 Hz, aromatic C-H of PMB), 6.39 (1 H, d, J = 2.3 Hz, aromatic C-H), 6.24 (1 H, d, J = 2.3 Hz, aromatic C-H), 5.46 (1 H, d, J = 14.9 Hz, C-HH of PMB), 4.82 (1 H, s, ArCHS), 4.40 - 4.45 (1 H, m, ArCHN), 4.42 (1 H, d, J = 14.9 Hz, CHH of PMB), 3.94 (1 H, dd, J = 9.8, 9.6 Hz, CHHOSi), 3.84 - 3.89 (5 H, m, OCH₃ and CH₂OH), 3.76 (OCH₃), 3.76 (OCH₃), 3.28 (1 H, dt, J = 14.1, 6.1 Hz, CH₂S), 2.89 (1 H, dt, J = 14.1, 7.1 Hz, CHHS), 2.03 (2 H, quin, J = 6.1 Hz, CH₂), 1.03 - 1.09 (21 H, m, SiCH).

¹³C NMR (100 MHz, CDCl₃) δ ppm 169.3 (C=O), 160.1 (aromatic C-O), 158.8 (aromatic C-O), 157.3 (aromatic C-O), 136.0 (aromatic C-C), 129.2 (aromatic C-C), 129.1 (aromatic C-H of PMB), 113.9 (aromatic C-H of PMB), 113.5 (aromatic C-C), 103.0 (aromatic C-H), 98.0 (aromatic C-H), 68.8 (CH₂O), 62.6 (ArCHN), 61.0 (CH₂OH), 55.8 (OCH₃), 55.4 (OCH₃), 49.2 (CH₂ of PMB), 40.1 (ArCHS), 32.5 (CH₂), 30.0 (CH₂S), 18.0 (CH(C(CH₃)₂)), 11.8 (SiCH).

MS (ES+) m/z 626 [M+Na]+. HRMS 604.3127; C₃₂H₅₀NO₆SiS⁺ requires 601.3123. IR (thin film) νmax (cm⁻¹) 3350-3450 (br.) 2940 (C-H), 2864 (C-H), 1633 (C=O), 1610, 1511. [α]D³₀ = +20.8 (c = 1.18, CHCl₃).

(R)-2-((1-(3,5-Dimethoxyphenyl)-2-((triisopropylsilanyl)oxy)ethyl)amino)-2-oxoethyl acetate 355

Amine 291 (706 mg, 2.0 mmol) was dissolved in anhydrous THF (10 ml) then NEt₃ (0.33 ml, 2.4 mmol) and acetoxyacetyl chloride (0.26 ml, 2.4 mmol) were added and the solution was stirred at RT for 1 h. Et₂O (50 ml) was added and the solution was washed with 1 M HCl (25 ml) then sat. NaHCO₃ solution (25 ml) and dried (MgSO₄) to give 355 (882 mg, 97 %) as a yellow oil which was used without further purification.
\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) ppm 7.10 (1 H, d, \(J = 7.7\) Hz, NH), 6.49 (2 H, d, \(J = 2.2\) Hz, ArCH), 6.37 (1 H, t, \(J = 2.2\) Hz, aromatic C-H), 5.02 (1 H, ddd, \(J = 7.7, 4.0, 3.8\) Hz, ArCHN), 4.61 (2 H, s, CH\(_2\)OAc), 4.03 (1 H, dd, \(J = 10.1, 2.2\) Hz, CH\(_2\)OAc), 3.94 (1 H, dd, \(J = 10.1, 3.8\) Hz, CH\(_2\)OSi), 3.79 (6 H, s, OCH\(_3\)), 2.17 (3 H, s, COCH\(_3\)), 1.05 - 1.11 (3 H, m, SiCH), 0.99 - 1.04 (18 H, m, CH(CH\(_3\))\(_2\)).

\(^1^3\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) ppm 169.2 (C=O), 166.3 (C=O), 160.8 (aromatic C-O), 142.2 (aromatic C-C), 105.0 (aromatic C-H), 99.3 (aromatic C-H), 66.4 (CH\(_2\)OSi), 63.2 (CH\(_2\)OAc), 55.3 (OCH\(_3\)), 54.0 (ArCHN), 20.7 (COCH\(_3\)), 17.9 (CH(C\(_6\)H\(_5\))), 11.7 (SiCH).

MS (ES+) \(m/z\) 454 [M+H]\(^+\), 479 [M+Na]\(^+\). HRMS 476.2427; C\(_{23}\)H\(_{39}\)NO\(_6\)SiNa\(^+\) requires 476.2439.

IR (thin film) \(\nu_{max}\) (cm\(^{-1}\)) 3300 - 3400 (br., N-H), 2942 (C-H), 1749 (ester C=O), 1667 (amide C=O), 1608.

\([\alpha]D_{29} = -27.7\) (c = 0.99, CHCl\(_3\)).

\((R)-2-((1-(3,5-Dimethoxyphenyl)-2-hydroxyethyl)amino)-2-oxoethyl acetate 332

Silyl ether 355 (830 mg, 1.8 mmol) was dissolved in MeCN (20 ml) at 0 °C then 60 % aq HF solution (2.0 ml) was added. After 30 minutes the solution was allowed to warm to RT, stirred for a further 30 minutes then neutralised by dropwise addition of sat. NaHCO\(_3\) solution (~20 ml). The mixture was extracted with EtOAc (3 \(\times\) 20 ml) then the extracts were combined, washed with water (10 ml) then brine (10 ml) and dried (MgSO\(_4\)). The crude product was triturated with Et\(_2\)O (10 ml), collected by filtration and dried to give 332 (413 mg, 77 %) as a colourless solid, melting point 91-93 °C.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) ppm 6.81 (1 H, d, \(J = 6.9\) Hz, NH), 6.44 (2 H, d, \(J = 2.2\) Hz, aromatic C-H), 6.40 (1 H, t, \(J = 2.2\) Hz, aromatic C-H), 5.03 - 5.07 (1 H, m, ArCHN), 4.63 (1 H, d, \(J = 15.7\) Hz, CH\(_2\)OAc), 4.59 (1 H, d, \(J = 15.7\) Hz, CH\(_2\)OAc), 3.90 (2 H, br. s, CH\(_2\)OH), 3.80 (6 H, s, OCH\(_3\)), 2.19 (3 H, s, COCH\(_3\)), 1.67 (1 H, br. s, OH).

\(^1^3\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) ppm 169.3 (C=O), 167.0 (C=O), 161.0 (aromatic C-O), 140.5 (aromatic C-C), 104.5 (aromatic C-H), 99.1 (aromatic C-H), 65.8 (CH\(_2\)OH), 62.8 (CH\(_2\)OAc), 55.1 (OCH\(_3\)), 55.0 (ArCHN), 20.5 (COCH\(_3\)).

MS (ES+) \(m/z\) 298 [M+H]\(^+\), 320 [M+Na]\(^+\). HRMS 320.1108; C\(_{14}\)H\(_{19}\)NO\(_6\)Na\(^+\) requires 320.1105.

\([\alpha]D_{29} = -36.6\) (c = 0.82, CHCl\(_3\)).

\((R)-2-((6,8-Dimethoxy-1,1-dimethylisoisochroman-4-yl)amino)-2-oxoethyl acetate 333

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Amide 332 (200 mg, 0.67 mmol) was suspended in PhMe (12 ml) and 2-methoxypropene (640 μl, 6.7 mmol) and PPTS (6 mg, 0.02 mmol) were added and the mixture heated at reflux for 16 h then cooled to RT. Sat. NaHCO₃ solution (10 ml) was added then the mixture was extracted with Et₂O (3 × 15 ml) then the combined extracts were washed with brine (15 ml) and dried (MgSO₄). Flash chromatography (50 % EtOAc–pet. ether) gave a trace of the desired N,O-acetal 356 and 333 (187 mg, 83 %) as a pale yellow oil.

1H NMR (500 MHz, CDCl₃) δ ppm 6.72 (1 H, d, J = 8.8 Hz, NH), 6.52 (1 H, d, J = 1.9 Hz, aromatic C-H), 6.43 (1 H, d, J = 1.9 Hz, aromatic C-H), 5.00 (1 H, d, J = 8.8 Hz, ArCHN), 4.58 (2 H, s, CH₂OAc), 4.01 (1 H, dd, J = 11.7, 1.6 Hz, C-HO), 3.81 (3 H, s, OCH₃), 3.79 (3 H, s, OCH₃), 3.77 - 3.83 (1 H, m, CHH₂O), 2.12 (3 H, s, COCH₃), 1.62 (3 H, s, CH₃), 1.56 (3 H, s, CH₃).

13C NMR (126 MHz, CDCl₃) δ ppm 169.3 (C=O), 166.1 (C=O), 159.2 (aromatic C-O), 157.0 (aromatic C-O), 135.2 (aromatic C-C), 123.5 (aromatic C-C), 104.5 (aromatic C-H), 99.7 (aromatic C-H), 74.8 (OCC₂(CH₃)₂), 63.2 (CH₂OC), 63.0 (CH₂OAc), 55.4 (OCH₃), 55.3 (OCH₃), 46.5 (ArCHN), 28.4 (CH₃), 24.1 (CH₃), 20.7 (COCH₃).

MS (ES+) m/z 338 [M+H]+, 360 [M+Na]+. HRMS 338.1589; C₁₇H₂₄NO₆ requires 338.1599. IR (thin film) νmax (cm⁻¹) 3300-3400 (br., N-H), 2969 (C-H), 2939, 1751 (ester C=O), 1664 (amide C=O), 1609. [α]D²⁹ = -110.8 (c = 1.51, CHCl₃).

(R)-2-Amino-2-(3,5-dimethoxyphenyl)ethanol 284

Silyl ether 291 (692 mg, 1.96 mmol) was dissolved in MeCN (20 ml) and the solution was cooled to 0 °C then 60 % aq HF (0.5 ml) was added. The solution was allowed to warm to RT over 5 h then quenched with sat. Na₂CO₃ solution (TLC monitoring was unhelpful due to salt formation). The mixture was extracted with EtOAc (4 × 15 ml) and the combined extracts were washed with brine (10 ml) and dried (MgSO₄). 1H NMR revealed the presence of unreacted starting material, so the residue was dissolved in MeOH (25 ml), c. HCl (2 ml) was added and the reaction was allowed to stir at RT for 3 days. The solvent was removed in vacuo and the residue triturated with Et₂O (30 ml) and the precipitate was collected by filtration and washed with Et₂O then dried. The precipitate was dissolved in 20 % w/v NaOH solution (50 ml) and extracted with CH₂Cl₂ (4 × 20 ml). The combined extracts were dried (MgSO₄) and concentrated to give 284 (240 mg, 62 %) as a pale yellow solid. Data were identical to those obtained previously. 

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(R)-2-(4-(3,5-Dimethoxyphenyl)-2,2-dimethylxazolidin-3-yl)-2-oxoethyl acetate 356

Aminoalcohol 284 (500 mg, 2.54 mmol) was dissolved in dichloroethane (3.8 ml) and acetone (3.8 ml) then Na₂SO₄ (500 mg) was added and the mixture was heated to 80 °C for 20 h then cooled to RT. The mixture was filtered and the filtrate was concentrated in vacuo to give a brown oil (405 mg) which was dissolved in CH₂Cl₂ (3 ml) then NEt₃ (475 μl, 3.42 mmol) and acetoxyacetyl chloride (183 μl, 1.71 mmol) were added. The solution was stirred for 19 h then diluted with CH₂Cl₂ (10 ml), washed with 1 M HCl (10 ml) then sat. NaHCO₃ solution (10 ml) and dried (MgSO₄). Flash chromatography (50 % EtOAc–pet. ether) gave 356 (338 mg, 40 %) as a pale yellow solid, 83–85 °C (CH₂Cl₂).

\(^1\)H NMR (300 MHz, CDCl₃) δ ppm 6.42 (2 H, d, J = 2.2 Hz, aromatic C-H), 6.38 (1 H, t, J = 2.2 Hz, aromatic C-H), 4.80 (1 H, d, J = 14.9 Hz, CH₂OAc), 4.36 (1 H, dd, J = 8.9, 6.6 Hz, CH₂HOC), 4.03 (1 H, d, J = 15.8 Hz, CH₂HOC), 4.00 (1 H, dd, J = 8.9, 2.1 Hz, CH₂HOC), 3.78 (6 H, s, OCH₃), 2.11 (3 H, s, COCH₃), 1.85 (3 H, s, CH₃), 1.62 (3 H, s, CH₃).

\(^13\)C NMR (75 MHz, CDCl₃) δ ppm 170.4 (C=O), 164.6 (C=O), 161.4 (aromatic C-O), 142.7 (aromatic C-C), 103.8 (aromatic C-H), 99.8 (aromatic C-H), 96.8 (OCN), 71.6 (CH₂O), 62.3 (CH₂OAc), 60.4 (ArCHN), 55.3 (OCH₃), 25.2 (CH₃), 23.1(CH₃), 20.4 (COCH₃).

MS (ES+) m/z 338 [M+H]+, 360 [M+Na]+. HRMS 338.1584; C₁₇H₂₄NO₆ requires 338.1599. IR (thin film)νmax (cm⁻¹) 2985 (C-H), 2940 (C-H), 1749 (ester C=O), 1714 (amide C=O), 1608, 1597. [α]D₃₀ = −63.0 (c = 0.9, EtOH).

(R)-1-(4-(3,5-Dimethoxyphenyl)-2,2-dimethylxazolidin-3-yl)-2-hydroxyethanone 335

Ester 356 (168 mg, 0.5 mmol) was dissolved in THF (5 ml), MeOH (2.5 ml) and water (2.5 ml) then LiOH·H₂O (42 mg, 1.0 mmol) was added. The solution was stirred for 1 h then the volatiles were removed in vacuo and the residue diluted with water (15 ml) and extracted with EtOAc (3 × 15 ml). The combined extracts were washed with brine (10 ml) and dried (MgSO₄) to give the product 335 (151 mg, quant) as a pale yellow oil which was used without further purification.

\(^1\)H NMR (500 MHz, CDCl₃) δ ppm 6.40 (3 H, s, aromatic C-H), 4.63 (1 H, dd, J = 6.6, 2.1 Hz, ArCHN), 4.36 (1 H, dd, J = 8.9, 6.6 Hz, CH₂HOC), 3.99 (1 H, d, J = 15.8 Hz, CH₂HOC), 3.94 (1 H,
Methyl 3-(((6R,10bR)-7,9-dimethoxy-3,3-dimethyl-5-oxo-3,5,6,10b-tetrahydro-1H-oxazolo[4,3-a]isoquinolin-6-yl)sulfanyl)propanoate 336

Hydroxyamide 335 (74 mg, 0.25 mmol) was dissolved in CH$_2$Cl$_2$ (2 ml) and DMSO (0.7 ml) at 0 °C then NEt$_3$ (173 μl, 1.25 mmol) and SO$_3$·py (159 mg, 1.0 mmol) were added and the mixture was stirred for 1 h then methyl 3-mercaptopropanoate (55 μl, 0.5 mmol) was added and the solution stirred for a further 25 minutes. Et$_2$O (10 ml) was added and the mixture was washed with 1 M HCl (10 ml), sat. NaHCO$_3$ solution (10 ml) and brine (10 ml) then dried (MgSO$_4$). The crude hemithioacetal was dissolved in CH$_2$Cl$_2$ (3 ml) and ZnCl$_2$ (68 mg, 0.5 mmol) was added. The reaction was stirred for 17 h then diluted with CH$_2$Cl$_2$ (10 ml) and washed with water (10 ml) then brine (5 ml) and dried (MgSO$_4$). Flash chromatography (40 % EtOAc–pet. ether) gave a single diastereoisomer of 336 (68 mg, 68 %) as a yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ ppm 6.41 (1 H, d, $J = 1.7$ Hz, aromatic C-H), 6.10 (1 H, d, $J = 1.7$ Hz, aromatic C-H), 5.02 (1 H, dd, $J = 10.1$, 6.3 Hz, ArCHN), 4.78 (1 H, s, ArCHS), 4.58 (1 H, dd, $J = 8.3$, 6.3 Hz, CH$_2$O), 3.92 (1 H, dd, $J = 10.1$, 8.3 Hz, CH$_2$O), 3.85 (3 H, s, OCH$_3$), 3.80 (3 H, s, OCH$_3$), 3.69 (3 H, s, OCH$_3$), 3.11 (1 H, ddd, $J = 14.2$, 7.8, 6.8 Hz, SCH$_2$), 2.94 (1 H, dt, $J = 14.2$, 7.1 Hz, SCH$_2$), 2.78 (2 H, td, $J = 7.3$, 4.2 Hz, CH$_2$CO$_2$Me), 1.73 (3 H, s, CH$_3$), 1.57 (3 H, s, CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 172.3 (C=O), 165.0 (C=O), 160.7 (aromatic C-O), 136.4 (aromatic C-C), 114.3 (aromatic C-C), 100.4 (aromatic C-H), 97.6 (aromatic C-H), 95.2 (OCN), 67.8 (CH$_2$O), 56.7 (CHN), 55.8 (OCH$_3$), 51.7 (OCH$_3$), 42.4 (ArCHS), 34.4 (CH$_3$CO$_2$Me), 27.1 (CH$_3$S), 25.2 (CH$_3$), 23.7 (CH$_3$).

MS (ES+) m/z 396 [M+H]$^+$, 418 [M+Na]$^+$. HRMS 396.1490; C$_{19}$H$_{26}$NO$_6$S$^+$ requires 396.1476. IR (thin film) $\nu$$_{max}$ (cm$^{-1}$) 2980 (C-H), 2938 (C-H), 1737 (ester C=O), 1657 (amide C=O), 1606. [$\alpha$]$_D^{30}$ = −145.4 (c = 1.15, CHCl$_3$).
(R)-4-(3,5-Dimethoxyphenyl)oxazolidin-2-one 338

Aminoalcohol 284 (123 mg, 0.62 mmol) was dissolved in CH₂Cl₂ (2 ml) and NEt₃ (172 μl, 1.24 mmol) at 0 °C. A solution of bis(trichloromethyl) carbonate (65 mg, 0.22 mmol) in CH₂Cl₂ (1 ml) was added over 15 minutes. After 5 minutes, the solution was allowed to warm to RT and stirred for 30 minutes then quenched with sat. NH₄Cl solution (3 ml). The layers were separated and the aqueous layer extracted with CH₂Cl₂ (2 × 2 ml) and the combined organic phases were dried (MgSO₄) and concentrated in vacuo to give 338 (125 mg, 90 %) as a pale yellow solid.

¹H NMR (300 MHz, CDCl₃) δ ppm 6.47 (2 H, d, J = 2.2 Hz, aromatic C-H), 6.43 (1 H, t, J = 2.2 Hz, aromatic C-H), 5.38 (1 H, br. s, NH), 4.89 (1 H, dd, J = 8.5, 7.3 Hz, CH(OH)), 4.73 (1 H, t, J = 8.7 Hz, ArCHN), 4.18 (1 H, dd, J = 8.5, 6.8 Hz, CH(OH)), 3.81 (6 H, s, OCH₃).

¹³C NMR (100 MHz, CDCl₃) δ ppm 161.4 (aromatic C-O), 159.8 (C=O), 141.9 (aromatic C-C), 103.7 (aromatic C-H), 100.3 (aromatic C-H), 72.3 (CH₂O), 56.3 (ArCHN), 55.4 (OCH₃).

MS (ES+) m/z 224 [M+H]+, 246 [M+Na]+. HRMS 246.0734; C₁₁H₁₃NO₄Na⁺ requires 246.0737. IR (thin film) νmax (cm⁻¹) 3425 (N-H), 3329, 2938 (C-H), 1759, 1715. [α]D₃₀ = −3.5 (c = 9.7, CHCl₃).

(R)-2-(4-(3,5-Dimethoxyphenyl)-2-oxooxazolidin-3-yl)-2-oxoethyl acetate 334

Method A

Amide 332 (95 mg, 0.32 mmol) was dissolved in THF (5 ml) and CDI (104 mg, 0.64 mmol) was added and the solution was stirred at RT for 18 h then concentrated in vacuo. Flash chromatography (60 % EtOAc–pet. ether) gave 334 (39 mg, 38 %) as a pale yellow solid, melting point 103-105 °C.

Method B

Oxazolidinone 338 (125 mg, 0.56 mmol) was dissolved in CH₂Cl₂ (5 ml) and acetoxyacetyl chloride (72 μl, 0.67 mmol) and NEt₃ (94 μl, 0.67 mmol) were added. The solution was stirred for 15 h then further acetoxyacetyl chloride (30 μl, 0.28 mmol) was added. The solution was stirred for a further 1 h then diluted with CH₂Cl₂ (5 ml) and washed with water (5 ml) then brine (5 ml) and dried (MgSO₄). Flash chromatography (40–50 % EtOAc–pet. ether) gave 334 (176 mg, 87 % over 2 steps).

¹H NMR (500 MHz, CDCl₃) δ ppm 6.35 - 6.45 (3 H, m, aromatic C-H), 5.33 (1 H, dd, J = 9.0, 3.8 Hz, ArCHN), 5.30 (1 H, d, J = 17.3 Hz, CH₂OAc), 5.13 (1 H, d, J = 17.3 Hz, CH₂OAc), 4.75 (1 H,
$t, J = 9.0$ Hz, CH$_2$O), 4.31 (1 H, dd, $J = 9.0, 3.8$ Hz, CH$_2$O), 3.79 (6 H, s, OCH$_3$), 2.13 (3 H, s, COCH$_3$).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ ppm 170.3 (C=O), 166.7 (C=O), 161.5 (aromatic C-O), 153.7 (carbamate C=O), 140.5 (aromatic C-C), 103.6 (aromatic C-H), 100.3 (aromatic C-H), 71.1 (CH$_2$O), 63.2 (CH$_2$OAc), 57.3 (ArCHN), 55.4 (OCH$_3$), 20.3 (COCH$_3$).

MS (ES+) $m/z$ 324 [M+H]$^+$, 346 [M+Na]$^+$. HRMS 324.1083; C$_{15}$H$_{18}$NO$_7$ requires 324.1078.

IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 2962 (C-H), 1783, 1753 (ester C=O), 1722, 1610 (carbamate C=O).

$[^\alpha]_D^{30} = -71.0$ (c = 0.95, CHCl$_3$).

**340**

(R)-3-Acryloyl-4-(3,5-dimethoxyphenyl)oxazolidin-2-one

Oxazolidinone 338 (223 mg, 1.0 mmol) was dissolved in anhydrous THF (3 ml) and the solution cooled to $-78$ °C. n-BuLi in hexanes (1.2 M, 1 ml, 1.2 mmol) was added and the solution stirred for 20 minutes. Acryloyl chloride (122 $\mu$l, 1.5 mmol) was added and the solution was stirred for a further 15 minutes then allowed to warm to RT. After 45 minutes the reaction was quenched with sat. NH$_4$Cl solution (5 ml) and the mixture extracted with EtOAc (3 x 10 ml) and the extracts were dried (MgSO$_4$). Flash chromatography (40 % EtOAc–pet. ether) gave 340 (38 mg, 14 %) as a pale yellow solid, melting point 189-191 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm 7.52 (1 H, dd, $J = 17.0, 10.5$ Hz, NCOCH), 6.50 (1 H, dd, $J = 17.0, 1.7$ Hz, =CHH), 6.42 (2 H, d, $J = 2.2$ Hz, aromatic C-H), 5.89 (1 H, dd, $J = 10.5, 1.7$ Hz, =CHH), 5.41 (1 H, dd, $J = 8.8, 4.0$ Hz, ArCHN), 4.68 (1 H, t, $J = 8.8$ Hz, CH$_2$O), 4.25 (1 H, dd, $J = 8.8, 4.0$ Hz, CH$_2$O), 3.77 (6 H, s, OCH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 164.4 (C=O), 161.4 (aromatic C-O), 153.5 (carbamate C=O), 141.2 (aromatic C-C), 132.2 (=CH$_2$), 127.1 (NCOCH=CH$_2$), 103.7 (aromatic C-H), 100.1 (aromatic C-H), 69.9 (CH$_2$O), 57.7 (ArCHN), 55.3 (OCH$_3$).

MS (ES+) $m/z$ 278 [M+H]$^+$, 300 [M+Na]$^+$. HRMS 300.0838; C$_{14}$H$_{15}$NO$_7$Na$^+$ requires 300.0843. IR (thin film) $\nu_{\text{max}}$ (cm$^{-1}$) 2938 (C-H), 1784, 1699 (amide C=O), 1612, 1597. $[^\alpha]_D^{30} = -103.7$ (c = 0.725, CHCl$_3$).

2-((4R)-4-(3,5-Dimethoxyphenyl)-2-(4-nitrophenyl)oxazolidin-3-yl)-2-oxoethyl acetate 342
Aminoalcohol 284 (500 mg, 2.54 mmol) was dissolved in EtOH (15 ml) and 4-nitrobenzaldehyde (422 mg, 2.79 mmol) was added. The solution was stirred for 22 h then the solvent evaporated. The residue was dissolved in CH₂Cl₂ (20 ml) and acetoxyacetyl chloride (300 μl, 2.79 mmol) was added. The solution was stirred for 2 h then cooled to 0 °C and pyridine (225 μl, 2.79 mmol) was added and the reaction allowed to warm slowly to RT. After 21 h, water (20 ml) was added, the layers were separated and the aqueous phase was extracted with CH₂Cl₂ (2 × 20 ml) and the combined extracts were dried (MgSO₄) to give the crude product as a 5:1 mixture of diastereoisomers by ¹H NMR. Flash chromatography (40 % EtOAc–pet. ether) gave 342a (890 mg, 81 %) as a colourless solid, melting point 159-161 °C, and 342b (187 mg, 17 %) as a colourless solid, melting point 163-165 °C.

**Major diastereoisomer 342a**

¹H NMR (400 MHz, CDCl₃) δ ppm 8.25 (2 H, d, J = 8.6 Hz, aromatic C-H of nitrobenzylidene), 7.78 (2 H, d, J = 8.3 Hz, aromatic C-H of nitrobenzylidene), 6.68 (1 H, br. s, OCHN), 6.32 - 6.38 (2 H, m, aromatic C-H), 6.25 (1 H, br. s, aromatic C-H), 5.05 (1 H, t, J = 6.1 Hz, ArCHN), 4.75 (1 H, d, J = 15.1 Hz, CΗΟAc), 4.53 - 4.60 (1 H, m, CΗHOC), 4.21 (1 H, d, J = 15.1 Hz, CΗOAc), 4.00 (1 H, m, CHHOC), 3.66 (6 H, s, OCH₃), 2.12 (3 H, s, COCH₃).

¹³C NMR (100 MHz, CDCl₃) δ ppm 170.8 (C=O), 167.9 (C=O), 161.8 (aromatic C-O), 148.4 (aromatic C-N), 145.6 (aromatic Ζ-C), 140.2 (aromatic Ζ-C), 128.3 (aromatic C-H of benzylidene), 123.9 (aromatic C-H of benzylidene), 104.3 (aromatic C-H), 100.4 (aromatic C-H), 89.8 (OCHN), 75.1 (CH₂OC), 62.0 (CH₂OAc), 60.8 (ArCHN), 55.5 (OCH₃), 20.6 (COCH₃).

IR (thin film) νₘₐₓ (cm⁻¹) 2942 (C-H), 1749 (ester C=O), 1682 (amide C=O), 1608, 1598, 1524. [α]D₃₀ = +50.6 (c = 1.4, CHCl₃). MS (ES+) m/z 431 [M+H]⁺, 453 [M+Na]⁺. HRMS 431.1448; C₂₁H₂₃N₂O₈⁺ requires 431.1449.

**Minor diastereoisomer 342b**

¹H NMR (400 MHz, CDCl₃) δ ppm 8.23 (2 H, d, J = 8.6 Hz, aromatic C-H of nitrobenzylidene), 7.60 (2 H, d, J = 8.6 Hz, aromatic C-H of nitrobenzylidene), 6.73 (1 H, s, OCHN), 6.38 - 6.53 (3 H, m, aromatic C-H), 5.06 (1 H, apparent d, J = 5.0 Hz, ArCHN), 4.67 (1 H, d, J = 14.9 Hz, CHΗOAc), 4.27 (1 H, dd, J = 9.0, 6.4 Hz, CHΗOC), 4.00 (1 H, dd, J = 9.1, 1.5 Hz, CHΗOC), 3.94 (1 H, d, J = 14.9 Hz, CHΗOAc), 3.80 (6 H, s, OCH₃), 2.08 (3 H, s, COCH₃).

¹³C NMR (100 MHz, CDCl₃) δ ppm 170.2 (C=O), 165.5 (C=O), 161.2 (aromatic C-O), 147.7 (aromatic C-N), 144.0 (aromatic Ζ-C), 141.8 (aromatic Ζ-C), 127.2 (aromatic C-H of benzylidene), 123.3 (aromatic C-H of benzylidene), 103.5 (aromatic C-H), 99.6 (aromatic C-H), 89.6 (OCHN), 73.1 (CH₂OC), 61.9 (OCHN), 59.7 (ArCHN), 55.0 (OCH₃), 19.9 (COCH₃).
IR (thin film) ν_max (cm^{-1}) 3012, 2940 (C-H), 1749 (ester C=O), 1674 (amide C=O), 1608, 1597, 1524. [α]_D^{30} = -145.5 (c = 0.88, CHCl_3).

1-((4R)-4-(3,5-Dimethoxyphenyl)-2-(4-nitrophenyl)oxazolidin-3-yl)-2-hydroxyethanone 343

From major diastereoisomer 342a

Acetate 342a (50 mg, 0.116 mmol) was dissolved in THF-MeOH-water (2:1:1, 2 ml) and LiOH+H_2O (7 mg, 0.17 mmol) was added. The solution was stirred for 3.5 h then diluted with water (5 ml) and extracted with CH_2Cl_2 (3 × 5 ml). The extracts were washed with brine (5 ml) then dried (MgSO_4). Flash chromatography (40–60 % EtOAc–pet. ether) gave 343a (36 mg, 80 %) as a pale yellow solid, melting point 148–150 °C.

^1H NMR (500 MHz, CDCl_3) δ ppm 8.28 (2 H, d, J = 8.0 Hz, aromatic C-H of nitrobenzylidene), 7.81 (2 H, d, J = 8.0 Hz, aromatic C-H of nitrobenzylidene), 6.73 (1 H, br. s, OCHN), 6.36 (1 H, br. s, aromatic C-H), 6.18 (2 H, br. s, aromatic C-H), 4.78 - 4.96 (1 H, m, ArCHN), 4.58 (1 H, t, J = 7.5 Hz, CHHO), 4.20 (1 H, d, J = 16.6 Hz, CHHO), 3.98 (1 H, t, J = 7.5 Hz, CHCO), 3.81 (1 H, d, J = 16.6 Hz, CHHO), 3.65 (6 H, s, OCH_3), 3.16 (1 H, br. s, OH).

^13C NMR (126 MHz, CDCl_3) δ ppm 172.8 (C=O), 161.5 (aromatic C-O), 148.2 (aromatic C-N), 145.3 (aromatic C-C), 139.4 (aromatic C-C), 127.8 (aromatic C-H of benzylidene), 123.8 (aromatic C-H of benzylidene), 104.3 (aromatic C-H), 100.0 (aromatic C-H), 89.6 (OCHN), 74.7 (CHOC), 61.0 (CH_2OH), 60.3 (ArCHN), 55.2 (OCH_3).

MS (ES+) m/z 389 [M+H]^+, 411 [M+Na]^+. HRMS 389.1349; C_{19}H_{21}N_2O_5 requires 389.1344. IR (thin film) ν_max (cm^{-1}) 3476 (O-H), 2939 (C-H), 2891 (C-H), 1659 (C=O), 1607, 1596, 1523. [α]_D^{30} = +51.9 (c = 1.49, CHCl_3).

From minor diastereoisomer 342b

Acetate 342b (167 mg, 0.39 mmol) was dissolved in THF-MeOH-water (2:1:1, 6 ml) and LiOH+H_2O (24 mg, 0.60 mmol) was added. The solution was stirred for 3.5 h then diluted with water (10 ml) and extracted with CH_2Cl_2 (3 × 12 ml). The extracts were washed with brine (10 ml) then dried (MgSO_4) and concentrated in vacuo to give 343b (140 mg, 93 %) as a pale yellow solid, melting point 121-123 °C.

^1H NMR (400 MHz, CDCl_3) δ ppm 8.27 (2 H, d, J = 8.7 Hz, aromatic C-H of nitrobenzylidene), 7.59 (2 H, d, J = 8.7 Hz, aromatic C-H of nitrobenzylidene), 6.75 (1 H, s, OCHN), 6.42 - 6.46 (3 H, m, aromatic C-H), 4.88 (1 H, dd, J = 6.3, 1.9 Hz, ArCHN), 4.34 (1 H, dd, J = 9.1, 6.3 Hz, CHHO), 4.12 (1 H, d, J = 16.1 Hz, CHOOH), 4.05 (1 H, dd, J = 9.1, 1.9 Hz, CHHO), 3.82 (6 H, s, OCH_3), 3.70 (1 H, d, J = 16.1 Hz, CHOOH).
$^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 170.5 (C=O), 161.4 (aromatic C-O), 147.9 (aromatic C-N), 144.1 (aromatic C=C), 141.3 (aromatic C=C), 127.2 (aromatic C-H of nitro benzylidene), 123.5 (aromatic C-H of nitro benzylidene), 103.7 (aromatic C-H), 99.6 (aromatic C-H), 89.9 (OCHN), 73.3 (CH$_2$OC), 61.1 (CH$_2$OH), 59.4 (ArCHN), 55.1 (OCH$_3$).

MS (ES+) m/z 389 [M+H]$^+$, 411 [M+Na]$^+$. HRMS 389.1342; C$_{19}$H$_{21}$N$_2$O$_7$+$^+$ requires 389.1344.

IR (thin film) ν$_{\text{max}}$ (cm$^{-1}$) 3451 (br., OH), 2939 (C-H), 1653 (C=O), 1608, 1597, 1522.

$[\alpha]_D^{30} = -192.9$ (c = 0.92, CHCl$_3$).

**Methyl 3-(((10bR)-7,9-dimethoxy-3-(4-nitrophenyl)-5-oxo-3,5,6,10b-tetrahydro-1H-oxazolo[4,3-a]isoquinolin-6-yl)sulfanyl)propanoate 344**

![](image)

**From major diastereoisomer 343a**

Hydroxyamide 343a (97 mg, 0.25 mmol) was dissolved in a mixture of DMSO (0.5 ml) and CH$_3$Cl$_2$ (0.5 ml) at 0 °C. NEt$_3$ (174 μl, 1.25 mmol) was added, followed by SO$_3$·py (159 mg, 1.0 mmol) and the solution was stirred for 3 h before methyl 3-mercaptopropanoate (41 μl, 0.375 mmol) was added and stirring was continued for a further 30 minutes. The reaction was diluted with Et$_2$O (10 ml) and EtOAc (10 ml) then washed with 1 M HCl (10 ml), sat. NaHCO$_3$ solution (10 ml) and brine (10 ml) then dried (MgSO$_4$). The crude hemithioacetal was dissolved in CH$_2$Cl$_2$ (3 ml) and ZnCl$_2$ (85 mg, 0.625 mmol) was added. The solution was stirred for 18 hours then diluted with water (5 ml), separated and the aqueous layer extracted with CH$_2$Cl$_2$ (2 × 5 ml) then the extracts were dried (MgSO$_4$). Flash chromatography (40 % EtOAc–pet. ether) gave 344a (73 mg, 60 %) as a pale yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$) δ ppm 8.15 (2 H, d, $J = 8.5$ Hz, aromatic C-H of nitrobenzylidene), 7.39 (2 H, d, $J = 8.5$ Hz, aromatic C-H of nitrobenzylidene), 6.48 (1 H, d, $J = 1.6$ Hz, aromatic C-H), 6.41 (1 H, s, aromatic C-H), 6.17 (1 H, s, OCHN), 5.26 (1 H, dd, $J = 9.3, 6.5$ Hz, ArCHN), 4.84 (1 H, s, ArCHS), 4.70 (1 H, dd, $J = 9.3, 6.5$ Hz, CH$_2$OH), 4.09 (1 H, t, $J = 9.3$ Hz, CH$_2$OH), 3.90 (3 H, s, OCH$_3$), 3.83 (3 H, s, OCH$_3$), 3.70 (3 H, s, OCH$_3$), 3.14 (1 H, dt, $J = 13.8, 6.9$ Hz, CH$_2$S), 2.95 (1 H, td, $J = 13.8, 7.3$ Hz, CH$_2$S), 2.75 - 2.81 (2 H, m, CH$_2$CO$_2$Me).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ ppm 172.2 (C=O), 165.7 (C=O), 161.0 (aromatic C-O), 157.6 (aromatic C-O), 148.1 (aromatic C-N), 144.5 (aromatic C=C), 135.8 (aromatic C=C), 127.5 (aromatic C-H of benzylidene), 123.7 (aromatic C-H of benzylidene), 113.9 (aromatic C=C), 100.8 (aromatic C-H), 97.9 (aromatic C-H), 89.1 (OCHN), 68.8 (CH$_2$O), 56.9 (ArCHN), 55.9 (OCH$_3$), 55.5 (OCH$_3$), 51.7 (OCH$_3$), 41.3 (ArCHS), 34.2 (CH$_2$CO$_2$Me), 27.2 (CH$_2$S).
MS (ES+) m/z 489 [M+H]+, 511 [M+Na]+. HRMS 511.1156; C_{23}H_{24}N_2O_8SNa^+ requires 511.1146. IR (thin film) ν_{max} (cm\(^{-1}\)) 2949 (C-H), 1734 (ester C=O), 1664 (amide C=O), 1607 1523. [α]_D^{30} = -52.7 (c = 1.23, CHCl_3).

From minor diastereoisomer 343b

Hydroxyamide 343b (97 mg, 0.25 mmol) was dissolved in a mixture of DMSO (0.5 ml) and CH_2Cl_2 (0.5 ml) at 0 °C. NEt_3 (174 µl, 1.25 mmol) was added, followed by SO_3·py (159 mg, 1.0 mmol) and the solution was stirred for 3 h before methyl 3-mercaptopropanoate (41 µl, 0.375 mmol) was added and stirring was continued for a further 40 minutes. The reaction was diluted with Et_2O (10 ml) and EtOAc (10 ml) then washed with 1 M HCl (10 ml), sat. NaHCO_3 solution (10 ml) and brine (10 ml) then dried (MgSO_4). The crude hemithioacetal was dissolved in CH_2Cl_2 (3 ml) and ZnCl_2 (85 mg, 0.625 mmol) was added. The solution was stirred for 19 h then diluted with water (5 ml), separated and the aqueous layer extracted with CH_2Cl_2 (2 × 5 ml) then the extracts were dried (MgSO_4). Flash chromatography (40 % EtOAc–pet. ether) gave 344b (49 mg, 40 %) as a pale yellow oil.

\(^1\)H NMR (500 MHz, CDCl_3) δ ppm 8.28 (2 H, d, J = 8.5 Hz, aromatic C-H of benzylidene), 7.76 (2 H, d, J = 8.5 Hz, aromatic C-H of benzylidene), 6.45 (1 H, s, aromatic C-H), 6.41 (1 H, s, aromatic C-H), 6.16 (1 H, s, OCHN), 5.16 (1 H, dd, J = 8.8, 7.1 Hz, ArCHN), 4.83 (1 H, t, J = 7.1 Hz, CHHOC), 4.75 (1 H, s, ArCHS), 3.95 (1 H, t, J = 8.8 Hz, CHHOC), 3.88 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 3.65 (3 H, s, OCH_3), 2.96 (1 H, dt, J = 13.9, 6.9 Hz, CHHS), 2.82 (1 H, dt, J = 13.9, 7.3 Hz, CHHS), 2.47 - 2.60 (2 H, m, CH_3CO_2Me).

\(^13\)C NMR (126 MHz, CDCl_3) δ ppm 172.3 (C=O), 166.8 (C=O), 161.3 (aromatic C-O), 157.9 (aromatic C-O), 148.6 (aromatic C-N), 145.1 (aromatic C-C), 134.8 (aromatic C-C), 128.1 (aromatic C-H of benzylidene), 124.1 (aromatic C-H of benzylidene), 113.2 (aromatic C-C), 101.1 (aromatic C-H), 98.3 (aromatic C-H), 88.5 (OCHN), 72.2 (CH_2O), 57.4 (ArCHN), 56.1 (OCH_3), 56.2 (OCH_3), 55.8 (OCH_3), 41.7 (ArCHS), 34.5 (CH_3CO_2Me), 27.5 (CH_2S).

MS (ES+) m/z 489 [M+H]+, 511 [M+Na]+. HRMS 489.1320; C_{23}H_{24}N_2O_8S^+ requires 489.1327. IR (thin film) ν_{max} (cm\(^{-1}\)) 2949 (C-H), 2842 (C-H), 1735 (ester C=O), 1659 (amide C=O), 1607, 1523. [α]_D^{30} = -179.3 (c = 1.12, CHCl_3).

Methyl 3-(((1R)-1-(hydroxymethyl)-5,7-dimethoxy-3-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl)sulfanyl)propanoate 337

![Chemical Structure](image)

Tetrahydroisoquinolinone 344a (30 mg, 0.06 mmol) was dissolved in EtOH (1 ml) and indium metal and sat. NH_4Cl solution (0.3 ml) was added then the mixture was heated at reflux for 2.5 h then cooled to RT. The mixture was filtered through celite and the solid was washed with water,
MeOH then EtOAc. The collected washings were separated and the aqueous layer extracted with EtOAc (3 × 5 ml). The combined extracts were washed with brine (5 ml) and dried (MgSO₄). ¹H NMR and MS indicated reduction of the nitro group had occurred. The residue was dissolved in CH₂Cl₂ (2 ml) and TFA (0.4 ml) was added and the solution was stirred at RT for 3 days then quenched with sat. NaHCO₃ solution (5 ml) and extracted with CH₂Cl₂ (3 × 5 ml) and the extracts combined and dried (MgSO₄). Flash chromatography (3–10 % MeOH–CH₂Cl₂ with 1 % NEt₃) gave deprotected product 337 (5 mg, 23 %).

¹H NMR (500 MHz, CDCl₃) δ ppm 7.73 (1 H, d, J = 3.6 Hz, NH), 6.37 (1 H, d, J = 2.1 Hz, aromatic C-H), 6.30 (1 H, d, J = 2.1 Hz, aromatic C-H), 4.52 (1 H, s, ArCH₂), 4.48 (1 H, dt, J = 9.5, 3.6 Hz, ArCHN), 3.96 (1 H, t, J = 9.5 Hz, CH═O), 3.85 (3 H, s, OCH₃), 3.83 (1 H, m, CH═O), 3.78 (3 H, s, OCH₃), 3.75 (1 H, s, OCH₃), 3.67 (3 H, s, OCH₃), 3.28 (1 H, dt, J = 13.8, 7.3 Hz, CH═S), 3.02 (1 H, dt, J = 13.8, 7.3 Hz, CH═S), 2.80 (2 H, t, J = 7.3 Hz, CH₂CO₂Me).

¹³C NMR (75 MHz, CDCl₃) δ ppm 172.6 (C=O), 171.8 (C=O), 160.4 (aromatic C=O), 157.4 (aromatic C=O), 134.0 (aromatic C-C), 113.2 (aromatic C-C), 102.4 (aromatic C-H), 98.0 (aromatic C-H), 68.2 (CH₂OH), 59.3 (ArCHN), 55.6 (OCH₃), 55.4 (OCH₃), 51.7 (OCH₃), 39.1 (ArCHS), 34.2 (CH₂CO₂Me), 28.6 (CH₂S).

MS (ES+) m/z 356 [M+H]⁺, 378 [M+Na]⁺. HRMS 378.0985; C₁₆H₂₁NO₆SNa⁺ requires 378.0982.

IR (thin film) νmax (cm⁻¹) 3300-3400 (O-H), 2927 (C-H), 1737 (ester C=O), 1667 (amide C=O), 1608. [α]D²⁰ = +53.5 (c = 0.81, EtOH).

(R)-2-(4-(3,5-Dimethoxyphenyl)-2-phenyloxazolidin-3-yl)-2-oxoethyl acetate 357

Aminoalcohol 284 (269 mg, 1.37 mmol) was suspended in EtOH (6 ml) and benzaldehyde (153 µl, 1.50 mmol) was added. The mixture was stirred for 3 days then concentrated in vacuo. The residue was dissolved in CH₂Cl₂ (8 ml) and acetoxyacetyl chloride (121 µl, 1.50 mmol) was added. The solution was stirred at RT for 1 h then cooled in an ice bath and pyridine (121 µl, 1.50 mmol) was added. After 2 h, water (10 ml) was added and the layers were separated. The aqueous phase was extracted with CH₂Cl₂ (2 × 10 ml) and the combined extracts were dried (MgSO₄). Flash chromatography (40 % EtOAc–pet. ether) gave 257 (353 mg, 67 %, ~1.7:1 dr) as a pale yellow gum.

**Major diastereoisomer**

¹H NMR (500 MHz, CDCl₃) δ ppm 7.60 (2 H, m, aromatic C-H of benzylidene), 7.31 - 7.36 (3 H, m, aromatic C-H of benzylidene), 6.75 (1 H, br. s, OCHN), 6.32 (2 H, d, J = 2.2 Hz, aromatic C-H), 6.27 (1 H, br. s, aromatic C-H), 4.94 - 5.01 (1 H, m, ArCHN), 4.51 - 4.58 (1 H, m, CH═OAc),
4.33 (1 H, d, J = 6.9 Hz, CH\textsubscript{2}OH), 4.17 (1 H, d, J = 14.8 Hz, CH\textsubscript{2}OAc), 3.98 (1 H, br. s, CH\textsubscript{2}OH), 3.61 (6 H, s, OCH\textsubscript{3}), 2.13 (3 H, s, COCH\textsubscript{3}).

\( ^{13} \text{C} \) NMR (126 MHz, CDCl\textsubscript{3}) \( \delta \) ppm 170.5 (C=O), 167.1 (C=O), 161.3 (aromatic C-O), 138.5 (aromatic C-C), 129.0 (aromatic C-C), 128.5 (aromatic C-H of benzylidene), 126.5 (aromatic C-H of benzylidene), 104.0 (aromatic C-H), 100.5 (aromatic C-H), 90.2 (OCHN), 74.6 (CH\textsubscript{2}O), 61.8 (CH\textsubscript{2}OAc), 60.6 (ArCHN), 55.3 (OCH\textsubscript{3}), 20.4 (COCH\textsubscript{3}).

MS (ES+) m/z 386 [M+H]+, 356 [M+Na]+. HRMS 408.1411; C\textsubscript{22}H\textsubscript{23}NO\textsubscript{6}Na+ requires 408.1418. IR (thin film) \( \nu \) \text{max} (cm\textsuperscript{-1}) 2941, 2936, 2846, 1744, 1718, 1684, 1656, 1597. [\( \alpha \)]\textsubscript{D}\textsuperscript{30} = +26.7 (c = 1.07, EtOH).

\((R)-1-(4-(3,5-Dimethoxyphenyl)-2-phenyloxazolidin-3-yl)-2-hydroxyethanone 346\)

\[
\begin{align*}
\text{MeO} &\quad \text{O} &\quad \text{OH} \\
\text{MeO} &\quad \text{N} &\quad \text{O} &\quad \text{N} &\quad \text{O} &\quad \text{N} &\quad \text{O} \\
\text{Ar} &\quad \text{C} &\quad \text{N} &\quad \text{C} &\quad \text{N} &\quad \text{C} &\quad \text{N} &\quad \text{C} \\
\end{align*}
\]

Acetate 356 (353 mg, 0.91 mmol) was dissolved in THF-MeOH-water (2:1:1, 12 ml) and LiOH+H\textsubscript{2}O (42 mg, 1.0 mmol) was added. The solution was stirred for 3 h then diluted with water (12 ml) and extracted with EtOAc (3 \times 20 ml). The extracts were washed with brine (10 ml) then dried (MgSO\textsubscript{4}). Flash chromatography (50% EtOAc-pet. ether with 1 % NEt\textsubscript{3}) gave 346 (220 mg, 70 %, \textasciitilde3.5:1 dr) as a colourless, foamy solid.

MS (ES+) m/z 344 [M+H]+, 336 [M+Na]+. HRMS 344.1493; C\textsubscript{22}H\textsubscript{22}NO\textsubscript{5}Na+ requires 344.1493. IR (thin film) \( \nu \) \text{max} (cm\textsuperscript{-1}) 3400-3500 (br.), 2936 (C-H), 1656 (C=O), 1608, 1597. [\( \alpha \)]\textsubscript{D}\textsuperscript{30} = +26.7 (c = 1.07, EtOH).

Major diastereoisomer

\( ^{1}H \) NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) ppm 7.54-7.65 (2 H, m, aromatic C-H of benzylidene), 7.33 - 7.46 (3 H, m, aromatic C-H of benzylidene), 6.77 (1 H, br. s, OCH\textsubscript{3}), 6.34 (2 H, br. s, aromatic C-H), 6.22 (1 H, br. s, aromatic C-H), 4.74-4.82 (1 H, br. s, ArCHN), 4.53 (1 H, t, \( J = 7.3 \) Hz, CH\textsubscript{2}OH), 4.13 - 4.22 (1 H, m, CH\textsubscript{2}OH), 3.93 - 4.01 (1 H, m, CH\textsubscript{2}OH), 3.71 - 3.76 (1 H, m, CH\textsubscript{2}OH), 3.59 (6 H, br. s, OCH\textsubscript{3}), 3.33 (1 H, t, \( J = 4.3 \) Hz, OH).

\( ^{13} \text{C} \) NMR (75 MHz, CDCl\textsubscript{3}) \( \delta \) ppm 171.8 (C=O), 160.8 (aromatic C-O), 139.5 (aromatic C-C), 137.9 (aromatic C-C), 128.1 (aromatic C-H of benzylidene), 125.9 (aromatic C-H of benzylidene), 125.8 (aromatic C-H of benzylidene), 103.8 (aromatic C-H), 100.0 (aromatic C-H), 89.8 (OCHN), 73.9 (CH\textsubscript{2}O), 60.5 (CH\textsubscript{2}OH), 59.9 (ArCHN), 54.7 (OCH\textsubscript{3}).

Methyl 3-(((10bR)-7,9-dimethoxy-5-oxo-3-phenyl-3,5,6,10b-tetrahydro-1H-oxazolo[4,3-a]isoquinolin-6-yl)sulfanyl)propanoate 347
Hydroxyamide 346 (60 mg, 0.175 mmol) was dissolved in a mixture of DMSO (0.3 ml) and CH₂Cl₂ (0.3 ml) at 0 °C. NEt₃ (122 μl, 0.87 mmol) was added, followed by SO₃·py (111 mg, 0.7 mmol) and the solution was stirred for 2.5 h before methyl 3-mercaptopropionate 252 (39 μl, 0.35 mmol) was added and stirring was continued for a further 30 minutes. The reaction was diluted with Et₂O (5 ml) and EtOAc (5 ml) then washed with 1 M HCl (5 ml), sat. NaHCO₃ solution (5 ml) and brine (5 ml) then dried (MgSO₄). The crude hemithioacetal was dissolved in CH₂Cl₂ (2 ml) and ZnCl₂ (46 mg, 0.34 mmol) was added. The solution was stirred for 22 hours then diluted with water (5 ml), separated and the aqueous layer extracted with CH₂Cl₂ (2 × 5 ml) then the extracts were dried (MgSO₄). Flash chromatography (50 % EtOAc–pet. ether with 1 % NEt₃) gave tetrahydroisoquinoline 347 (12 mg, 15 %) as a pale yellow oil and isochroman 348 (14 mg, 18 %) as a colourless solid. Repurification of the more polar material present in the reaction mixture (flash chromatography; 20–30 % iso-propanol–pet. ether) gave deprotected tetrahydroisoquinolinone 337 (15 mg, 24 %).

For 347a ¹H NMR (500 MHz, CDCl₃) δ ppm 7.28 - 7.32 (2 H, m, aromatic C-H), 7.16 - 7.20 (3 H, m, aromatic C-H), 6.48 (1 H, d, J = 1.6 Hz, aromatic C-H), 6.39 (1 H, s, OCHN), 6.18 (1 H, d, J = 1.6 Hz, aromatic C-H), 5.24 (1 H, dd, J = 10.0, 6.5 Hz, ArCHN), 4.85 (1 H, s, ArCHS), 4.63 (1 H, dd, J = 8.3, 6.5 Hz, CH₂O), 4.12 (1 H, dd, J = 10.0, 8.3 Hz, CH₂O), 3.90 (3 H, s, OCH₃), 3.69 (3 H, s, OCH₃), 3.16 (1 H, dt, J = 13.9, 6.9 Hz, CH₃S), 2.95 (1 H, dd, J = 13.9, 7.6 Hz, CH₂S), 2.79 (2 H, td, J = 7.1, 4.7 Hz, CH₂CO₂Me).

¹³C NMR (126 MHz, CDCl₃) δ ppm 172.3 (C=O), 165.4 (C=O), 160.8 (aromatic C-O), 157.5 (aromatic C-O), 137.5 (aromatic C-C), 136.2 (aromatic C-C), 129.0 (aromatic C-H of benzylidene), 128.5 (aromatic C-H of benzylidene), 126.3 (aromatic C-H of benzylidene), 114.3 (aromatic C-C), 100.6 (aromatic C-H), 97.8 (aromatic C-H), 90.4 (OCHN), 67.9 (CH₂O), 56.8 (ArCHN), 55.9 (OCH₃), 55.5 (OCH₃), 51.8 (OCH₃), 41.3 (ArCHS), 34.2 (CH₂CO₂Me), 27.2 (CH₃S).

MS (ES+) m/z 444 [M+H]⁺, 466 [M+Na]⁺. HRMS 444.1487; C₂₃H₂₆NO₅S⁺ requires 444.1476. IR (thin film) νmax (cm⁻¹) 2927 (C-H), 1737 (ester C=O), 1667 (amide C=O), 1606. [α]D₂⁰ = −60.4 (c = 0.85, EtOH).

For 347b ¹H NMR (300 MHz, CDCl₃) δ ppm 7.51 - 7.58 (2 H, m, aromatic C-H of benzylidene), 7.36 - 7.46 (3 H, m, aromatic C-H of benzylidene), 6.44 (1 H, d, J = 2.1 Hz, aromatic C-H), 6.35 (1 H, s, OCHN), 6.17 (1 H, d, J = 2.1 Hz, aromatic C-H), 5.19 (1 H, dd, J = 9.4, 6.4 Hz, ArCHN), 4.77 (1 H, s, ArCHS), 4.74 - 4.82 (1 H, m, CH₂O), 3.88 - 3.96 (1 H, m, CH₂O), 3.87 (3 H, s, OCH₃), 3.82 (3 H, s, OCH₃), 3.66 (3 H, s, OCH₃), 2.89 - 3.04 (1 H, m, CH₂S), 2.82 (2 H, dt, J = 14.0, 7.1 Hz, CH₂S), 2.57 - 2.64 (CH₂CO₂Me).
$^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 172.3 (C=O), 166.1 (C=O), 160.9 (aromatic C-O), 157.6 (aromatic C-O), 138.1 (aromatic C=C), 135.2 (aromatic C=C), 129.1 (aromatic C-H of benzylidene), 128.6 (aromatic C-H of benzylidene), 126.5 (aromatic C-H of benzylidene), 113.3 (aromatic C=C), 100.7 (aromatic C-H), 98.0 (aromatic C-H), 89.5 (OCHN), 71.6 (CH$_2$OC), 57.3 (ArCHN), 55.9 (OCH$_3$), 55.5 (OCH$_3$), 51.6 (OCH$_3$), 41.3 (ArCHS), 34.4 (CH$_2$CO$_2$Me), 27.2 (SCH$_2$).

MS (ES+) m/z 444 [M+H]$^+$, 466 [M+Na]$^+$. HRMS 444.1487; C$_{23}$H$_{26}$NO$_6$S$^+$ requires 444.1476.

IR (thin film) $\nu_{\max}$ (cm$^{-1}$) 2949 (C-H), 1736 (ester C=O), 1660 (amide C=O), 1606.

$\text{[a]}_D^{30} = -174.7$ (c = 0.79, EtOH).

*Methyl 3-(((3S,7S,9aR)-4,6-dimethoxy-2-oxo-7-phenyl-1,2,3,7,9,9a-hexahydropyrano-[3,4,5-\beta]isoquinolin-3-yl)sulfanyl)propanoate 348*

$^1$H NMR (500 MHz, CDCl$_3$) δ ppm 7.28 - 7.32 (3 H, m, aromatic C-H of phenyl ring), 7.04 - 7.12 (2 H, m, aromatic C-H of phenyl ring), 6.41 (1 H, s, aromatic C-H), 6.04 - 6.19 (1 H, br. s, NH), 5.96 (CHPh), 4.92 (1 H, dd, J = 10.7, 6.1 Hz, ArCHN), 4.83 (1 H, s, ArCHS), 3.92 (3 H, s, OCH$_3$), 3.82 (1 H, dd, J = 10.7, 6.1 Hz, CH$_2$O), 3.72 (3 H, s, OCH$_3$), 3.63 (3 H, s, OCH$_3$), 3.42 (1 H, t, J = 10.7 Hz, CH$_2$O), 3.17 (1 H, dt, J = 13.8, 7.2 Hz, CH$_2$S), 2.99 (1 H, dt, J = 13.8, 7.2 Hz, CH$_2$S), 2.82 (2 H, td, J = 7.2, 3.5 Hz, CH$_2$CO$_2$Me).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ ppm 172.3 (C=O), 171.0 (C=O), 156.5 (aromatic C-O), 156.5 (aromatic C-O), 140.3 (aromatic C=C), 133.4 (aromatic C=C), 128.5 (aromatic C-H of phenyl ring), 128.0 (aromatic C-H of phenyl ring), 127.9 (aromatic C-H of phenyl ring), 113.8 (aromatic C=C), 112.0 (aromatic C=C), 73.9 (CHPh), 60.1 (CH$_2$O), 55.9 (OCH$_3$), 55.8 (OCH$_3$), 55.6 (OCH$_3$), 47.0 (ArCHN), 40.8 (ArCHS), 34.3 (CH$_2$CO$_2$Me), 27.3 (CH$_2$S).

MS (ES+) m/z 444 [M+H]$^+$, 466 [M+Na]$^+$. HRMS 466.1291; C$_{23}$H$_{25}$NO$_6$SNa$^+$ requires 466.1295.

IR (thin film) $\nu_{\max}$ (cm$^{-1}$) 3200-3300 (br., N-H), 2956 (C-H), 1737 (ester C=O), 1673 (amide C=O), 1607. [a]$D^{30} = -160.4$ (c = 0.64, EtOH).

*2-((4R)-2-(4-Bromophenyl)-4-(3,5-dimethoxyphenyl)oxazolidin-3-yl)-2-oxoethyl acetate 352*
Aminoalcohol 284 (197 mg, 1.0 mmol) was suspended in EtOH (6 ml) and 4-bromobenzaldehyde (203 mg, 1.1 mmol) was added and the mixture stirred at RT for 20 h then concentrated in vacuo. The residue was dissolved in CH₂Cl₂ (8 ml) and acetoxyacetyl chloride (118 μl, 1.1 mmol) was added. After 2 h the solution was cooled in an ice bath and pyridine (89 μl, 1.1 mmol) was added and the solution stirred for 1 h. The reaction was quenched with water (10 ml), the layers were separated and the aqueous phase was extracted with CH₂Cl₂ (2 × 10 ml) and the extracts were dried (MgSO₄). Flash chromatography (40–50% EtOAc–pet. ether with 1% NEt₃) gave 352 (457 mg, 98%, 5:1 dr) as a foamy solid. Analytically pure samples of the individual diastereoisomers could be obtained by further chromatography.

MS (ES+) m/z 486 [M+Na]+. HRMS 464.0706; C₂₁H₂₃BrNO₆⁺ requires 464.0704.

**Major diastereoisomer 352a**

¹H NMR (300 MHz, CDCl₃) δ ppm 7.36 - 7.59 (4 H, m, aromatic C-H of bromobenzylidene), 6.63 (1 H, br. s, OCHN), 6.35 (1 H, t, J = 1.9 Hz, aromatic C-H), 6.24 (2 H, br. s, aromatic C-H), 4.99 (1 H, m, ArCHN), 4.75 (1 H, d, J = 15.1 Hz, CHHOAc), 4.53 (1 H, m, CHHOAc), 4.16 (1 H, d, J = 15.1 Hz, CHHOAc), 3.91 - 4.02 (1 H, m, CHHOAc), 3.65 (6 H, s, OCH₃), 2.12 (3 H, s, COCH₃).

¹³C NMR (75 MHz, CDCl₃) δ ppm 170.4 (C=O), 167.1 (C=O), 161.3 (aromatic C=O), 140.3 (aromatic C=C), 137.5 (aromatic C=C), 131.6 (aromatic C-H of benzylidene), 128.5 (aromatic C-H of benzylidene), 122.7 (aromatic C-Br), 104.0 (aromatic C-H), 100.4 (aromatic C-H), 89.8 (OCHN), 74.6 (CH₂OC), 61.7 (CH₂OAc), 60.5 (ArCHN), 55.2 (OCH₃), 20.3 (COCH₃).

IR (thin film) νmax (cm⁻¹) 3445 (br.), 2937 (C-H), 1749 (ester C=O), 1673, 1667 (amide C=O), 1608, 1597. [α]D⁰ = +25.8 (c = 5.0, CHCl₃). Melting point 144-146 °C.

**Minor diastereoisomer 352a**

¹H NMR (300 MHz, CDCl₃) δ ppm 7.53 (2 H, s, aromatic C-H of benzylidene), 7.29 (1 H, d, J = 8.3 Hz, aromatic C-H of benzylidene), 6.67 (1 H, s, OCHN), 6.45 (3 H, s, aromatic C-H), 4.94 - 5.05 (1 H, m, ArCHN), 4.67 (1 H, d, J = 14.7 Hz, CHHOAc), 4.28 (1 H, dd, J = 8.8, 6.5 Hz, CHHOAc), 3.90 - 4.02 (2 H, m, CH₂OAc and CH₂OAc), 3.82 (6 H, s, OCH₃), 2.11 (3 H, s, COCH₃).

¹³C NMR (126 MHz, CDCl₃) δ ppm 170.4 (C=O), 165.3 (C=O), 161.4 (aromatic C-O), 142.4 (aromatic C=C), 136.1 (aromatic C=C), 131.5 (aromatic C-H of bromobenzylidene), 127.9 (aromatic C-H of bromobenzylidene), 122.7 (aromatic C-Br), 103.6 (aromatic C-H), 99.8 (aromatic C-H), 90.3 (OCHN), 72.8 (CH₂O), 62.1 (CH₂OAc), 59.8 (ArCHN), 55.2 (OCH₃), 20.2 (COCH₃).

IR (thin film) νmax (cm⁻¹) 2930 (C-H), 2839 (C-H), 1747 (ester C=O), 1673 (amide C=O), 1608, 1595. [α]D⁰ = -136.6 (c = 0.82, CHCl₃). Melting point 156-158 °C.
1-((4R)-2-(4-Bromophenyl)-4-(3,5-dimethoxyphenyl)oxazolidin-3-yl)-2-hydroxyethanone 349

Acetate 352 (340 mg, 0.73 mmol, 5:1 dr) was dissolved in THF-MeOH-water (2:1:1, 8 ml) and LiOH·H₂O (37 mg, 0.88 mmol) was added. The solution was stirred for 1 h then diluted with water (12 ml) and extracted with EtOAc (3 × 20 ml). The extracts were washed with brine (10 ml) then dried (MgSO₄). Flash chromatography (40–50% EtOAc–pet. ether) gave 349 (196 mg, 64 %, ~4:1 dr) as a colourless, foamy solid. Analytically pure samples of the individual diastereoisomers could be obtained by further chromatography.

MS (ES+) m/z 422 [M+H]⁺, 446 [M+Na]⁺. HRMS 422.0594; C₁₉H₂₁BrNO₅⁺ requires 422.0598. IR (thin film) νmax (cm⁻¹) 3440 (br. OH), 2936 (C-H), 1657 (C=O), 1597. [α]D30 = +34.2 (c = 1.65, CHCl₃).

Major diastereoisomer

³H NMR (400 MHz, CDCl₃) δ ppm 7.56 (2 H, d, J = 8.4 Hz, aromatic C-H of bromobenzylidene), 7.49 (2 H, d, J = 8.4 Hz, aromatic C-H of bromobenzylidene), 6.68 (1 H, br. s, OCHN), 6.35 (1 H, br. s, aromatic C-H), 6.18 (2 H, br. s, aromatic C-H), 4.79 (1 H, t, J = 7.9 Hz, ArCHN), 4.54 (1 H, t, J = 7.9 Hz, CH₂OH), 4.18 (1 H, d, J = 16.1 Hz, CH₂OH), 3.97 (1 H, t, J = 7.9 Hz, CH₂OH), 3.77 (1 H, d, J = 16.1 Hz, CH₂OH), 3.64 (6 H, s, OCH₃), 3.22 (1 H, br. s, OH).

³C NMR (75 MHz, CDCl₃) δ ppm 172.4 (C=O), 161.4 (aromatic C-O), 139.8 (aromatic C-C), 137.5 (aromatic C-H of benzylidene), 131.8 (aromatic C-C), 128.4 (aromatic C-H of benzylidene), 122.9 (aromatic C-Br), 104.3 (aromatic C-H), 100.4 (aromatic C-H), 89.9 (OCHN), 74.5 (CH₂OC), 61.0 (CH₂OH), 60.4 (ArCHN), 55.2 (OCH₃).

Methyl 3-(((10bR)-3-(4-bromophenyl)-7,9-dimethoxy-5-oxo-3,5,6,10b-tetrahydro-1H-oxazolo[4,3-a]isoquinolin-6-yl)sulfanyl)propanoate 350

Hydroxamide 349 (140 mg, 0.33 mmol, ~4:1 dr) was dissolved in a mixture of DMSO (0.7 ml) and CH₂Cl₂ (0.7 ml) at 0 °C. NEt₃ (231 μl, 1.66 mmol) was added, followed by SO₃·py (211 mg, 1.33 mmol) and the solution was stirred for 4 h before methyl 3-mercaptopropanoate (73 μl, 0.66 mmol) was added and stirring was continued for a further 30 minutes. The reaction was diluted with EtOAc (10 ml) then washed with 1 M HCl (10 ml), sat. NaHCO₃ solution (10 ml) and
brine (10 ml) then dried (MgSO₄). The crude hemithioacetal was dissolved in CH₂Cl₂ (4 ml) and ZnCl₂ (90 mg, 0.66 mmol) was added. The solution was stirred for 16 h then diluted with water (5 ml), separated and the aqueous layer extracted with CH₂Cl₂ (2 × 5 ml) then the extracts were dried (MgSO₄). Flash chromatography (40–50 % EtOAc–pet. ether) gave 350 (40 mg, 23 %, 2:1 dr) as a pale yellow oil.

¹H NMR (300 MHz, CDCl₃) δ ppm 7.55 (2 H, d, J = 8.4 Hz, aromatic C-H of benzylidene of major diastereoisomer), 7.54 (2 H, d, J = 8.6 Hz, aromatic C-H of benzylidene of minor diastereoisomer), 7.44 (2 H, d, J = 8.4 Hz, aromatic C-H of benzylidene of major diastereoisomer), 7.07 (1 H, d, J = 8.6 Hz, aromatic C-H of benzylidene of minor diastereoisomer), 6.47 (1 H, d, J = 1.9 Hz, aromatic C-H of minor diastereoisomer), 6.44 (1 H, d, J = 2.1 Hz, aromatic C-H of major diastereoisomer), 6.33 (1 H, s, OCHN of minor diastereoisomer), 6.29 (1 H, s, OCHN of major diastereoisomer), 6.14 - 6.17 (2 H, m, aromatic C-H of both diastereoisomers), 5.22 (1 H, dd, J = 10.2, 6.6 Hz, ArCHN of minor diastereoisomer), 5.15 (1 H, dd, J = 9.6, 6.4 Hz, ArCHN of major diastereoisomer), 4.83 (1 H, s, ArCHS of minor diastereoisomer), 4.78 (1 H, dd, J = 7.9, 6.4 Hz, CHH₂O of major diastereoisomer), 4.75 (1 H, s, ArCHS of major diastereoisomer), 4.63 (1 H, dd, J = 8.4, 6.5 Hz, CHH₂O of minor diastereoisomer), 4.07 (1 H, dd, J = 10.2, 8.5 Hz, CHH₂O of minor diastereoisomer), 3.89 (3 H, s, OCH₃ of minor diastereoisomer), 3.87 (3 H, s, OCH₃ of major diastereoisomer), 3.83 - 3.87 (1 H, m, CHH₂O of major diastereoisomer), 3.82 (3 H, s, OCH₃ of minor diastereoisomer), 3.81 (3 H, s, OCH₃ of major diastereoisomer), 3.69 (3 H, s, OCH₃ of minor diastereoisomer), 3.67 (3 H, s, OCH₃ of major diastereoisomer), 3.17 (1 H, dd, J = 7.4, 6.4 Hz, CHH₂S of minor diastereoisomer), 3.13 (1 H, dd, J = 7.4, 6.3 Hz, CHH₂S of minor diastereoisomer), 2.89 - 3.02 (1 H, m, CHH₂S of major diastereoisomer), 2.83 (1 H, dd, J = 14.7, 7.2 Hz, CHH₂S of major diastereoisomer), 2.78 (2 H, m, J = 5.1, 5.1, 2.6 Hz, CH₂CO₂Me of minor diastereoisomer), 2.58 (2 H, td, J = 7.2, 2.9 Hz, CH₂CO₂Me of major diastereoisomer).

¹³C NMR (75 MHz, CDCl₃) δ ppm 172.2 (C=O), 172.2 (C=O), 166.2 (C=O), 165.5 (C=O), 160.9 (aromatic C-O), 157.6 (aromatic C-O), 157.5 (aromatic C-O), 137.2 (aromatic ºC of major diastereoisomer), 136.8 (aromatic ºC of minor diastereoisomer), 136.1 (aromatic ºC of minor diastereoisomer), 134.9 (aromatic ºC of major diastereoisomer), 131.7 (aromatic C-H of benzylidene of major diastereoisomer), 131.6 (aromatic C-H of benzylidene of minor diastereoisomer), 128.4 (aromatic C-H of benzylidene of major diastereoisomer), 128.1 (aromatic C-H of benzylidene of minor diastereoisomer), 123.2 (aromatic ºBr of major diastereoisomer), 123.0 (aromatic ºBr of minor diastereoisomer), 114.2 (aromatic ºC of minor diastereoisomer), 113.1 (aromatic ºC of major diastereoisomer), 101.2 (aromatic C-H of major diastereoisomer), 101.1 (aromatic C-H of minor diastereoisomer), 98.4 (aromatic C-H of major diastereoisomer), 98.3 (aromatic C-H of minor diastereoisomer), 90.1 (OCHN of minor diastereoisomer), 89.3 (OCHN of major diastereoisomer), 71.7 (CH₂O of major diastereoisomer), 68.2 (CH₂O of minor diastereoisomer), 57.2 (ArCHN of major diastereoisomer), 56.8 (ArCHN of minor diastereoisomer).
diastereoisomer), 55.8 (OCH₃ of both diastereoisomers), 55.5 (OCH₃ of both diastereoisomers), 51.7 (OCH₃ of both diastereoisomers), 41.4 (ArCHS of both diastereoisomers), 34.3 (CH₂CO₂Me of major diastereoisomer), 34.2 (CH₂CO₂Me of minor diastereoisomer), 27.2 (CH₂S of both diastereoisomers).

MS (ES+) m/z 522 [M+H]⁺, 1065 [2M+Na]⁺. HRMS 522.0583; C₂₃H₂₅BrNO₆S⁺ requires 522.0581. IR (thin film) νmax (cm⁻¹) 2947 (C-H), 1735 (ester C=O), 1661 (amide C=O), 1607. [α]D₃₀ = −113.8 (c = 1.63, CHCl₃).
4. Appendices

4.1 Chiral HPLC traces for compound 280

**Chiral Pak OD column**

20:80 i-propanol:hexane, 40°C

Flow rate 1 ml/min

UV detection at 254, 280 nm

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***(R)-280***

\[ \text{ee} = 92\% \]

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***(S)-280***

\[ \text{ee} = 92\% \]
4.2 Chiral HPLC traces for compound 291

*(R)-291*

Chiralpak AD column
10:90 4-propanol:hexane
Flow rate 1 ml/min
UV detection at 254 nm

*rac-291*

Chiralpak AD column
10:90 4-propanol:hexane
Flow rate 1 ml/min
UV detection at 254 nm
4.3 Single crystal X-ray structure of compound 307

Cambridge Crystallographic Data Centre (CCDC) number: 808088

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  FIRST AUTHORS ADDRESS 
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  ENTER SECTION TITLE 
;
The structure was solved by the direct methods. All non-H atoms were refined anisotropically. H atoms bonded to C were included in calculated positions. Those bonded to O were found by difference Fourier techniques and refined isotropically. The absolute configuration was determined by refining the Flack parameter.


Sheldrick, G. M. (2007). TWINABS. University of G"ottingen, Germany.

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Refinement of F^2^ against ALL reflections. The weighted R-factor wR and
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F^2^ > 2sigma(F^2^) is used only for calculating R-factors(gt) etc.
and is
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on F^2^ are statistically about twice as large as those based on F,
and R-
factors based on ALL data will be even larger.

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P=(Fo^2^+2Fc^2^)/3'
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- 0.0003(9)

### C40
- 0.0176(9)  
- 0.0222(9)  
- 0.0260(10)  
- 0.0046(8)  
- 0.0049(7)  
- -0.0029(7)

### C41
- 0.0206(9)  
- 0.0249(10)  
- 0.0227(9)  
- 0.0054(7)  
- 0.0082(7)  
- 0.0006(7)

### C42
- 0.0254(9)  
- 0.0224(9)  
- 0.0175(9)  
- 0.0049(7)  
- 0.0087(8)  
- 0.0024(8)

### C43
- 0.0400(12)  
- 0.0259(11)  
- 0.0154(9)  
- -0.0019(8)  
- 0.0098(8)  
- -0.0021(9)

### C44
- 0.0235(10)  
- 0.0220(10)  
- 0.0278(11)  
- -0.0017(8)  
- 0.0078(8)  
- -0.0053(8)

### C45
- 0.0205(9)  
- 0.0234(9)  
- 0.0171(8)  
- -0.0021(7)  
- 0.0050(7)  
- -0.0019(7)

### _geom_special_details

All esds (except the esd in the dihedral angle between two l.s. planes)
are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

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O3 C20 1.209(2) . ?  
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O4 H40 0.86(3) . ?  
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O6 C22 1.424(3) . ?  
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4.4 Single crystal X-ray structure of compound 348

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The structure was solved by the direct methods and there are the molecule and a water molecule in the asymmetric unit. All non-H atoms were refined anisotropically. H atoms bonded to C were included in calculated positions. Those bonded to N and O were found by difference Fourier methods and refined isotropically. The absolute configuration was known from the synthesis.


M. C. Burla, R. Caliandro, M. Camalli, B. Carrozzini, G. L. Cascarano, L. De Caro, C. Giacovazzo, G. Polidori and R. Spagna
SIR2004: an improved tool for crystal structure determination and refinement


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; _publ_section_figureCaptions
; ENTER FIGURE CAPTIONS
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expression of
F^2 > 2sigma(F^2) is used only for calculating R-factors(gt) etc.
and is
not relevant to the choice of reflections for refinement. R-
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All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.
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C8 C3 C4 O4 -178.0(2) . . . . ?
C2 C3 C4 O4 1.5(3) . . . . ?
C8 C3 C4 C5 1.6(3) . . . . ?
C2 C3 C4 C5 -178.9(2) . . . . ?
O4 C4 C5 C6 179.9(2) . . . . ?
C3 C4 C5 C6 0.4(3) . . . . ?
C17 O5 C6 C5 0.8(3) . . . . ?
C17 O5 C6 C7 -178.22(19) . . . . ?
C4 C5 C6 O5 179.4(2) . . . . ?
C4 C5 C6 C7 -1.7(3) . . . . ?
O5 C6 C7 C8 179.94(19) . . . . ?
C5 C6 C7 C8 0.9(3) . . . . ?
O5 C6 C7 C11 0.0(3) . . . . ?
C5 C6 C7 C11 -179.0(2) . . . . ?
C6 C7 C8 C3 1.1(3) . . . . ?
C11 C7 C8 C3 -178.9(2) . . . . ?
C6 C7 C8 C9 -177.09(19) . . . . ?
C11 C7 C8 C9 2.9(3) . . . . ?
C4 C3 C8 C7 -2.4(3) . . . . ?
C2 C3 C8 C7 178.1(2) . . . . ?
C4 C3 C8 C9 175.9(2) . . . . ?
C2 C3 C8 C9 -3.6(3) . . . . ?
C1 N1 C9 C8 -36.7(3) . . . . ?
C1 N1 C9 C10 -160.0(2) . . . . ?
C7 C8 C9 N1 -142.8(2) . . . . ?
C3 C8 C9 N1 38.9(3) . . . . ?

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C7 C8 C9 C10 -19.3(3) . . . . 
C3 C8 C9 C10 162.4(2) . . . . 
C11 O6 C10 C9 -70.3(2) . . . . 
N1 C9 C10 O6 173.68(17) . . . . 
C8 C9 C10 O6 50.9(2) . . . . 
C10 O6 C11 C7 51.6(2) . . . . 
C10 O6 C11 C18 -76.3(2) . . . . 
C8 C7 C11 O6 -17.4(3) . . . . 
C6 C7 C11 O6 162.51(19) . . . . 
C8 C7 C11 C18 107.9(2) . . . . 
C6 C7 C11 C18 -72.1(3) . . . . 
C2 S1 C12 C13 -78.54(18) . . . . 
S1 C12 C13 C14 176.11(17) . . . . 
C15 O2 C14 O3 2.9(3) . . . . 
C15 O2 C14 C13 -178.5(2) . . . . 
C12 C13 C14 O3 -43.1(3) . . . . 
C12 C13 C14 O2 138.4(2) . . . . 
O6 C11 C18 C23 100.2(2) . . . . 
C7 C11 C18 C23 -25.6(3) . . . . 
O6 C11 C18 C19 -77.1(3) . . . . 
C7 C11 C18 C19 157.1(2) . . . . 
C23 C18 C19 C20 0.1(3) . . . . 
C11 C18 C19 C20 177.5(2) . . . . 
C18 C19 C20 C21 0.7(4) . . . . 
C19 C20 C21 C22 -1.4(4) . . . . 
C20 C21 C22 C23 1.2(4) . . . . 
C19 C18 C23 C22 -0.2(4) . . . . 
C11 C18 C23 C22 -177.6(2) . . . . 
C21 C22 C23 C18 -0.4(4) . . . . 

loop_
  _geom_hbond_atom_site_label_D
  _geom_hbond_atom_site_label_H
  _geom_hbond_atom_site_label_A
  _geom_hbond_distance_DH
  _geom_hbond_distance_HA
  _geom_hbond_distance_DA
  _geom_hbond_angle_DHA
  _geom_hbond_site_symmetry_A
N1 H1N O1S  0.86(2) 1.95(2) 2.805(3) 175(2) .
O1S H1O O1  0.87(3) 1.85(3) 2.713(2) 173(3) 4_455
O1S H2O O3  0.87(2) 2.02(3) 2.885(3) 174(2) 4_455

_diffrn_measured_fraction_theta_max  0.998
_diffrn_reflns_theta_full            26.42
_diffrn_measured_fraction_theta_full 0.998
_refine_diff_density_max  0.384
_refine_diff_density_min  -0.256
_refine_diff_density_rms  0.046
5. References


