Studies on the synthesis of the lasubine alkaloids

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ABSTRACT

Formal syntheses of lasubine II and subcosine II have been completed by the synthesis of epi-lasubine II. The synthesis involves diastereoselective allylation of a methoxy isoxazolidine and a tandem hydrogenation process leading stereoselectively to a trisubstituted piperidine.

Dedicated to Professor Sir Derek Barton, who taught organic chemists a new way to look at and to think about molecules, on the Centenary of his birth.

1. Introduction

Lasubine I **1** and Lasubine II **2** are diastereoisomerically related quinolizidine alkaloids isolated from *Lagerstroemia subcostata*[1] that have attracted substantial attention from synthetic chemists.[2] They are the core members of an extensive family of quinolizidine alkaloids (Fig. 1).[3] Subcosine **3** is an *O*-acylated form of lasubine I. There is a number of alkaloids which are variants of lasubine that have a biaryl substituent. In vertine **4** and lythrine **5**, a biaryl substituent is linked to the oxygen substituent to form a cyclophane moiety. It may be noted that some of these alkaloids have been reported to have interesting biological activity. Vertine **4**, for instance, has been reported to have anti-malarial activity.[4]

For a number of years, we have employed isoxazolidines as synthetic precursors of 1,3-aminoalcohols and related compounds. The isoxazolidines have mostly been formed by "non-traditional routes" involving intramolecular nucleophilic attack (or an equivalent process) of a hydroxylamine nitrogen atom onto a π-system.[5] These routes all led to *syn*-1,3-aminoalcohols. If we consider the C2-C9a fragment of either lasubine I or lasubine II, it may be considered as an anti-1,3-aminoalcohol. This stereochemistry is congruent with our recently reported allylation of isoxazolidine iminium ions.[6] The value of this methodology was shown by our recent synthesis of negamycin and 5-hydroxysedamine.[7] We, therefore, were interested to employ this chemistry in the context of the lasubines and related alkaloids. This synthetic strategy would entail a late stage introduction of the aryl moiety. We felt that this would be advantageous for generating a library of synthetic lasubine alkaloids for SAR studies.

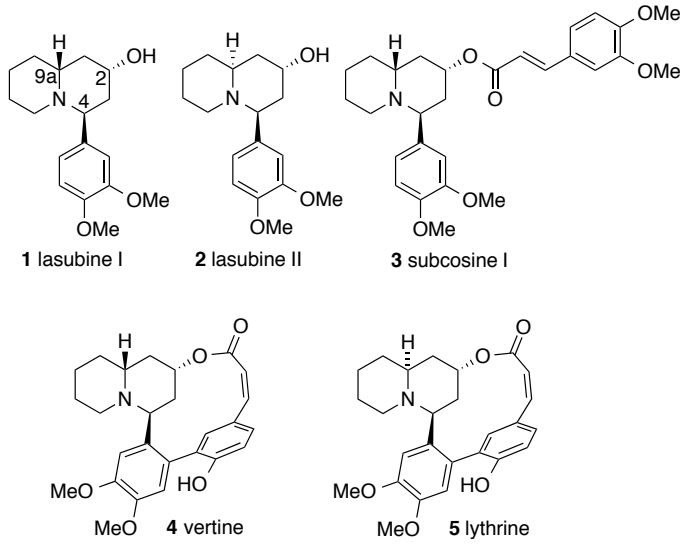

Figure 1. Selected quinolizidine alkaloids.

Thus, Lasubine I **1** might be available by addition of an aryl nucleophile to an N-acyl iminium ion **6** (Figure 1). This species, in turn, could arise from an isoxazolidine **7**, bearing a protected aldehyde and an ester in the appropriate positions. That this isoxazolidine has *trans*-stereochemistry indicates that it could be generated from a methoxy isoxazolidine **8**, with installation of the side chain and the ester group by allylation and cross metathesis respectively. Use of a variety of aryl nucleophiles in the late stage reaction with the iminium ion **6** would enable synthesis of a library of anaolgs.

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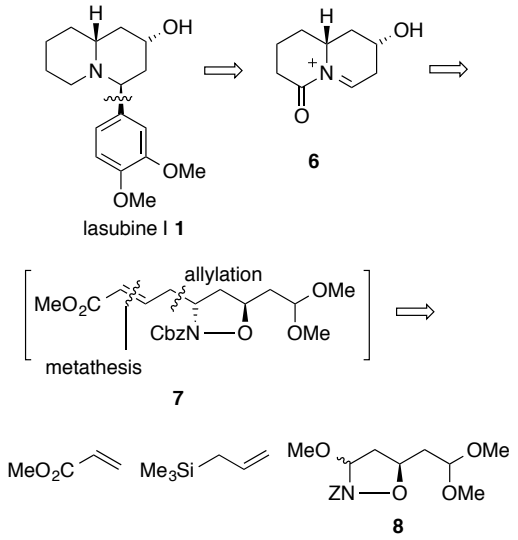
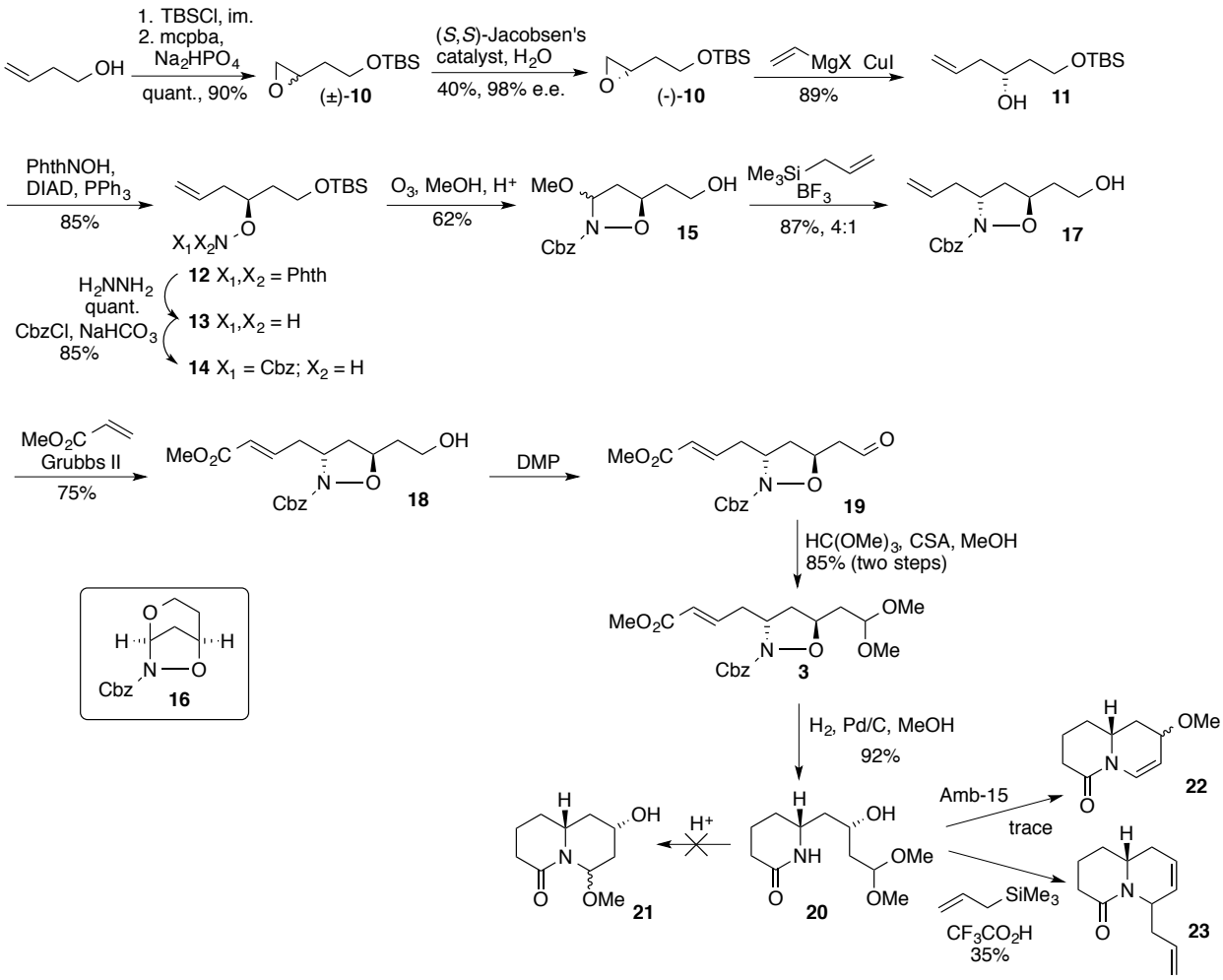


Figure 2. Retrosynthetic analysis for Lasubine I.

2. Results and Discussion

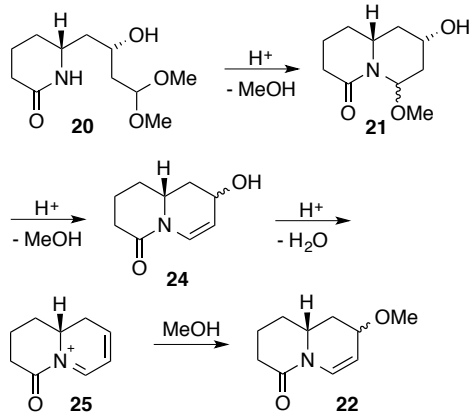
2.1. The First Approach

The TBS ether of racemic 3,4-epoxybutan-1-ol, (±)-**10**, readily available by oxidation of the TBS ether of 3-butenol **9**, was resolved by the method of Jacobsen (Scheme 1).[8] The (*S*)-epoxide **7** was then subjected to copper(I) catalysed ring opening with vinyl magnesium bromide to give the secondary alcohol **11** in good yield.[9] At this point, the enantiomeric excess was determined by the method of Mosher and found to be better than 98%. The secondary alcohol was then converted to the alkoxy phthalimide **12** by the Mitsunobu reaction.[10] Following our earlier procedure,[5,7] this was converted to the corresponding Cbz protected hydroxylamine **14**. The enantiomeric excess was confirmed to still be greater than 98% by chiral HPLC. Ozonolysis in methanol in the presence of an acid catalyst delivered the desired methoxyoxazolidine **15** with concomitant loss of the TBS group. Interestingly, on standing in unpurified $CDCl_3$, the methoxyoxazolidine **15** converted to the bicyclic oxazolidine **16**. On the other hand, exposure of the methoxyoxazolidine **15** to allyl trimethylsilane in the presence of BF_3•OEt_2 delivered the allylated oxazolidine **17** as a 4:1 mixture of diastereoisomers. The major isomer was assigned *trans* stereochemistry based upon our earlier work.[6,7] This assignment was borne out subsequently. Cross-metathesis of the *trans*-isoxazolidine **17** with methyl acrylate gave the anticipated ester **18**. The free alcohol group was then oxidised with the Dess-Martin periodinane to give the labile aldehyde **19**. This compound was found to undergo facile epimerisation (presumably at the position β- to the aldehyde) upon silica gel chromatography. We attribute this to an acid catalysed retro-Michael-Michael mechanism. As a consequence, aldehyde **19** was subjected to prompt conversion to acetal **3**. Camphorsulfonic acid was found to be a superior catalyst for this reaction compared to Amberlyst-15, especially on larger scale. Hydrogenation of acetal **3**, either in a flask or in flow, triggered a tandem process, resulting in N-O-bond cleavage, *N*-deprotection, alkene reduction and lactamistion. Lactam **20** was obtained in essentially quantitative yield as a single diastereoisomer.



Scheme 1. The first approach to the lasubine structure.

At this point, we attempted the acid catalysed formation of N,O-acetal **21** to allow late stage introduction of the aryl group through application of iminium ion chemistry.[11] To our dismay, a complex mixture of products was obtained. Using acetic acid, trifluoroacetic acid, *p*-tosic acid or Amberlyst-15, the only identifiable product was the methoxy enamide **22**, albeit in trace amounts. We postulate that this is formed by, first, condensation to give the desired N,O-acetal **20**. This intermediate, however, rapidly eliminates methanol to give the hydroxy enamide **24**. This intermediate, in turn, then undergoes substitution by methanol, presumably via the iminium ion **25**, giving **22** (Scheme 2). Evidence for the involvement of iminium ion **25** is that, when acetal **18** was treated with allyltrimethylsilane in the presence of trifluoroacetic acid, allylation product **23** could be isolated.[12] No reaction was observed when a series of Lewis acids (BF_3•OEt_2, $TiCl(O\textit{i}\text{-}Pr)_3$, BCl_3, $TiCl_4$) was employed.

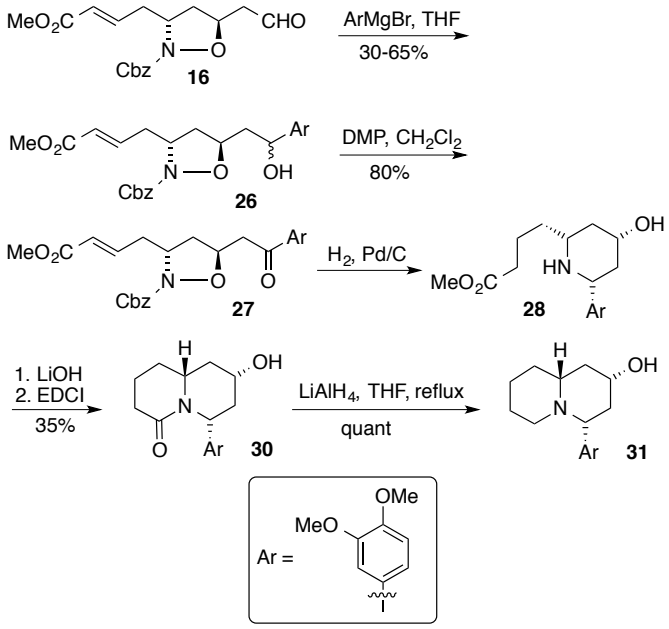


Scheme 2. Iminium ion mechanism.

2.2. Formal Syntheses of Lasubine II and Subcosine II

With our failure to prepare the required N,O-acetal **21** due to its facile onward reactions, we turned to a different strategy to access lasubine alkaloids, albeit with a different expected stereochemical outcome (Scheme 3). Returning to aldehyde **19**, treatment with 3,4-dimethoxyphenyl magnesium bromide gave the secondary alcohol **26** as a mixture of diastereoisomers in somewhat variable yield. Better yields were obtained in small scale reactions. Alcohols **26** were then oxidised to the corresponding ketone **27**. Once again, we employed a tandem process triggered by hydrogenation. In this case, the process was comprised of N,O-bond cleavage, alkene reduction and *N*-

deprotection, as before, but followed by reductive amination to yield piperidinol **28** as a single diastereoisomer. This was found to be the anticipated all-*cis* diastereoisomer.[13] As expected, once liberated from the isoxazolidine, the free amine exclusively reacted with the ketone carbonyl. Direct formation of lactam **30** from piperidinol **28** did not occur, even upon heating. We have noted the reluctance of δ-lactams to form previously.[14] In this instance, we employed the same solution as before: hydrolysis to the parent acid **29**, followed by ring closure using EDCI. This yielded the desired lactam **30** which, on treatment with lithium aluminium hydride in THF at reflux, was converted into (+)-*epi*-lasubine-II **31** in quantitative yield. Both the spectroscopic data and the optical rotation ($[\alpha]_D^{20}$ +65.0 (*c* 0.78, $CHCl_3$); lit.[15] $[\alpha]_D^{20}$ +57 (*c* 0.46, MeOH)) for the synthetic material were in good agreement with that reported earlier. As *epi*-lasubine II **31** has previously been converted into lasubine II **2** and into subcosine II **3**,[16] this work represents formal syntheses of these two alkaloids.



Scheme 3. Synthesis of (+)-*epi*-Lasubine II **29**.

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3. Conclusion

A strategy to synthesise the lasubine structure employing isoxazolidine chemistry has been achieved, resulting in formal syntheses of both lasubine II and subcosine II. The use of carefully planned tandem reactions triggered by hydrogenation contributes greatly to the step economy. The addition of other Grignard reagents to aldehyde **16** should enable the synthesis of a liubrary of analogs.

4. Experimental section

Unless otherwise indicated, all starting materials were obtained from commercial suppliers, and were used without further purification. Each reaction with air- and moisture-sensitive components was carried out under a nitrogen atmosphere unless otherwise indicated. Tetrahydrofuran was distilled from sodium/benzophenone, and dichloromethane was distilled from calcium hydride. Analytical thin-layer chromatography (TLC) was performed on Merck DC pre coated TLC plates with 0.25 mm Kieselgel 60 F_{254}. Visualization was performed with a 254 nm UV lamp, or stained with ammonium molybdate or potassium permanganate solution. Flash chromatography was performed using silica gel 60 (particle size 0.040-0.063 mm) purchased from Merck. All melting points were measured on a Stanford Research Systems OptiMelt apparatus and are uncorrected. Optical rotations were measured on a Jasco P-1030 polarimeter using a 100 mm path-length cell at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz or JEOL 396 MHz spectrometer in $CDCl_3$. Chemical shifts are expressed in parts per million (δ) using residual solvent protons as internal standards (δ 7.26 for ^1H, δ 77.0 for ^{13}C) where possible or alternatively to $SiMe_4$ (δ = 0.00 ppm) as internal standard. Coupling constants (J) are reported in Hertz (Hz). Coupling patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet) or m (multiplet). IR spectra were obtained on a Jasco FT/IR-4100 spectrometer or Shimadzu IR Prestige-21 spectrometer and are reported in frequency of absorption (cm^{-1}). Low resolution mass spectrometry was obtained on a Waters Acquity UPLC PDA with ZQ2000 system. High-resolution mass spectra (HRMS) were acquired on a Waters Q-ToF Premier mass spectrometer in positive ion mode.

(But-3-en-1-yloxy)(t-butyl)dimethylsilane (**9**)
To a solution of 3-buten-1-ol (25.0 mL, 290.5 mmol) in dichloromethane (300 mL) was added imidazole (21.76 g, 319.6 mmol) and *t*-butyldimethylsilyl chloride (48.16 g, 319.6 mmol). The reaction mixture was stirred at room temperature overnight. Saturated aqueous NH_4Cl (2 × 100 mL) was added to the reaction mixture and the organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by distillation under reduced pressure (1 mbar, 50 °C) to give the desired TBS protected alcohol **9** as a colourless oil (54.20 g, 99%). R_f 0.79 (10% Ethyl Acetate/Hexane); ν_{max} (neat) 3078, 2955, 2877, 2342, 1830, 1641, 1464, 1383, 1256, 1099 cm^{-1}; δ_H (400 MHz $CDCl_3$): 5.82 (1H, ddt, *J* 17.1, 10.2, 6.8 Hz), 5.14-4.94 (2H, m), 3.66 (2H, t, *J* 6.8 Hz), 2.29 (1H, dt, *J* 6.8, 1.3 Hz), 2.26 (1H, dt, *J* 6.8, 1.3 Hz), 0.89 (9H, s), 0.05 (6H, s); δ_C (101 MHz $CDCl_3$): 135.4, 116.2, 62.8, 37.5, 26.0, 18.4, -5.3; MS (ESI +ve) *m/z* 109.2 (90), 129.2 (M^+-*t*-Bu, 40), 156.3 (M^+-C2H6, 86); HRMS (ESI) *m/z* calculated for $C_{10}H_{23}OSi$ $[M+H]^+$ 187.1518, found 187.1517.

t-Butyldimethyl(2-(oxiran-2-yl)ethoxy)silane ((±)-**10**)
3-Chloroperbenzoic acid (77%, 51.95 g, 231.8 mmol) was added portionwise to a stirred solution of silyl alcohol **9** (36.00 g, 193.2 mmol) in dichloromethane (300 mL). The mixture was stirred at room temperature overnight. The white precipitate was first removed by filtration through a pad of Celite. The filtrate was washed with a 1:1 mixture of saturated aqueous $NaHCO_3$ and Na_2SO_3 (2 × 100 mL). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography eluting at 5% Ethyl Acetate/Hexane to give the desired epoxide (±)-**10** as a colourless oil (35.20 g, 92%). R_f 0.56 (10% Ethyl Acetate/Hexane); ν_{max} (neat) 2953, 2928, 2857, 1472, 1387, 1256, 1103 cm^{-1}; δ_H (400 MHz $CDCl_3$): 3.87-3.68 (2H, m), 3.05 (1H, dddd, *J* 6.6, 4.9, 4.0, 2.7 Hz), 2.78 (1H, app t, *J* 4.0 Hz), 2.52 (1H, dd, *J* 5.1, 2.8 Hz), 1.90 - 1.65 (2H, m), 0.90 (9H, s), 0.06 (6H, s); δ_C (101 MHz $CDCl_3$): 60.0, 50.0, 47.2, 35.9, 25.9, 18.3, -5.4; MS (ESI +ve) *m/z* 109.2 (90), 145.3 (M^+-*t*-Bu, 40); HRMS (ESI) *m/z* calculated for $C_{10}H_{23}O_2Si$ $[M+H]^+$ 203.1467, found 203.1460.

(S)-t-Butyldimethyl(2-(oxiran-2-yl)ethoxy)silane ((-)-**10**)

To a mixture of (*S,S*)-(+)-N,N'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexane-diamino-cobalt(II) (894 mg, 1.5 mmol), epoxide (±)-**10** (59.95 g, 296.2 mmol), acetic acid (339 µL, 5.9 mmol) and THF (2.9 mL) at 0 °C was added water (2.9 mL, 162.9 mmol) in one portion. The reaction was allowed to warm to room temperature and stirred for 24 h. The reaction mixture was purified by flash column chromatography (2 to 5% Ethyl Acetate/Hexane) to provide epoxide (-)-**10**[17] (24.02 g, 101 mmol, 40 %) as a yellowish oil. $[\alpha]_D^{20}$ -13.5 (*c* 1.05*,* $CHCl_3$) {lit. $[\alpha]_D^{20}$ -12.8 (c 2.11, $CHCl_3$).

(R)-1-((t-Butyldimethylsilyl)oxy)hex-5-en-3-ol (**11**)
To a solution of epoxide (-)-**10** (24.02 g, 118.7 mmol) and CuI (4.53 g, 23.8 mmol) in THF (200 mL) at –78 °C was added vinyl magnesium chloride (111.3 mL, 178.1 mmol of a 1.6M in THF solution) dropwise. After addition was complete, the reaction mixture was warmed slowly to room temperature and stirred until the reaction was shown to be complete by TLC analysis. The reaction was quenched by the addition of saturated aqueous NH_4Cl (200 mL) and the insoluble copper salts were removed by filtration. The phases were separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic extract was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% Ethyl Acetate/Hexane) to yield allylic alcohol **11** as a yellow oil (24.35 g, 89%). R_f 0.36 (10% Ethyl Acetate/Hexane); $[\alpha]_D^{20}$ +8.8 (*c* 1.07*,* $CHCl_3$); ν_{max} (neat) 3447, 2930, 2859, 1827, 1641, 1471, 1256, 1090 cm^{-1}; δ_H (400 MHz $CDCl_3$): 5.85 (1H, ddt, *J* 17.3, 10.2, 7.1 Hz), 5.19-5.00 (2H, m), 3.98-3.71 (3H, m), 3.35 (1H, d, *J* 2.4 Hz), 2.39-2.10 (2H, m), 1.76-1.63 (2H, m), 0.90 (9H, s), 0.08 (6H, s); δ_C (101 MHz $CDCl_3$): 135.0, 117.3, 71.2, 62.6, 42.0, 37.8, 25.9, 18.1, -5.5, - 5.6; MS (ESI +ve) *m/z* 130.1 (20), 156.1 (80), 213.2 (M^+-OH, 30), 231.2 (M^++H, 100); HRMS (ESI) *m/z* calculated for $C_{12}H_{27}O_2Si$ $[M+H]^+$ 231.1780, found 231.1770.

(S)-2-((1-((t-Butyldimethylsilyl)oxy)hex-5-en-3-yl)oxy)isoindoline-1,3-dione (**12**)
A stirred mixture of allylic alcohol **11** (17.66 g, 76.6 mmol), PPh_3 (24.13 g, 92.0 mmol) and *N*-hydroxyphthalimide (15.00 g, 92.0 mmol) in anhydrous THF (400 mL) was cooled to 0 °C in an ice-water bath. Once cooled, di-*iso*-propyl azodicarboxylate (DIAD) (18.1 mL, 92.0 mmol) was added dropwise. The mixture was stirred at 0 °C for 1 hour and then left to stir at room temperature overnight. The mixture was concentrated *in vacuo* and the residue was absorbed onto silica and purified by flash chromatography with gradual elution (5-10% Ethyl Acetate/Hexane) to give *N*-hydroxyphthalimide **12** as a colourless oil (21.63 g, 75%). R_f 0.54 (10% Ethyl Acetate/Hexane); $[\alpha]_D^{20}$ +29.5 (*c* 1.15 ,$CHCl_3$); ν_{max} (neat) 3509, 2953, 2854, 1790, 1743, 1468, 1373, 1256, 1188, 1096 cm-1; δ_H (400 MHz, $CDCl_3$): 7.89-7.68 (4H, m), 5.93 (ddt, 1H, *J* 17.1, 10.2, 6.9 Hz), 5.20-5.03 (2H, m), 4.51-4.40 (1H, m), 3.94-3.75 (2H, m), 2.63-2.40 (2H, m), 2.06- 1.80 (2H, m), 0.87 (9H, s), 0.05 (6H, s); δ_C (101 MHz, $CDCl_3$): 164.2, 134.4, 133.4, 129.1, 123.4, 117.8, 84.9, 59.5, 37.6, 35.7, 25.9, 18.2, -5.4; MS (ESI +ve) *m/z* 164.0 (16), 244.3 (M^+-$C_8H_3O_2$, 30), 376.5 (M^++H, 100), 398.5 (M^++Na, 42); HRMS (ESI) *m/z* calculated for $C_{20}H_{30}NO_4Si$ $[M+H]^+$ 376.1944, found 376.1943.

(S)-O-(1-((t-Butyldimethylsilyl)oxy)hex-5-en-3-yl)hydroxylamine (**13**)
Hydrazine monohydrate (5.6 mL, 116.1 mmol) was added dropwise to a stirred solution of *N*-hydroxyphthalimide **12** (21.63 g, 57.6 mmol) in dichloromethane (400 mL) at room temperature. The mixture was stirred for 2 hours, and then filtered through a pad of Celite, washing with Et_2O (2 × 100 mL). The filtrate was concentrated *in vacuo* to give desired hydroxylamine **13** (12.10 g, 86%) as a clear oil that was used in the subsequent reaction without further purification. R_f 0.35 (50% Ethyl Acetate/Hexane); $[\alpha]_D^{20}$ +27.7 (c 1.21, $CHCl_3$); ν_{max} (neat) 3316, 3075, 2953, 2857, 1639, 1586, 1256, 1092 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 5.84 (1H, ddt, *J* 17.2, 10.2, 7.1 Hz), 5.22 (2H, br. s), 5.15-5.01 (2H, m), 3.82-3.62 (3H, m), 2.47-2.23 (2H, m), 1.86-1.62 (2H, m), 0.90 (9H, s), 0.06 (6H, s); δ_C (101 MHz, $CDCl_3$): 135.0, 116.8, 80.3, 60.0, 37.5, 35.7, 26.0., 18.3, -5.3; MS (ESI +ve) m/z 114.2 (100), 246.5 (M^++H, 70); HRMS (ESI) m/z calculated for $C_{12}H_{28}NO_2Si$ $[M+H]^+$ 246.1889, found 246.1881.

Benzyl (S)-((1-((t-butyldimethylsilyl)oxy)hex-5-en-3-yl)oxy)carbamate (**14**)
Anhydrous sodium carbonate (7.74 g, 73.7 mmol) and benzyl chloroformate (8.2 mL, 73.7 mmol) were added sequentially to a stirred solution of hydroxylamine **13** (12.00 g, 48.9 mmol) in dichloromethane (300 mL) and water (300 mL) at room temperature. The mixture was stirred overnight. The organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography with gradual elution (5-20% Ethyl Acetate/Hexane) to give desired *N*-benzyloxycarbonyl hydroxylamine **14** (15.00 g, 81%) as a clear oil. R_f 0.73 (50% Ethyl Acetate/Hexane); $[\alpha]_D^{20}$ +22.0 (*c* 1.16, $CHCl_3$); ν_{max} (neat) 3445, 3285, 2953, 2855, 1732, 1495, 1254, 1096 (neat) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 7.52 (1H, br. s), 7.39-7.29 (5H, m), 5.85 (1H, ddt, *J* 17.2, 10.3, 7.0 Hz), 5.23-4.98 (4H, m), 4.03-3.90 (1H, m), 3.81-3.67 (2H, m), 2.49-2.28 (2H, m), 1.86-1.71 (2H, m), 0.88 (9H, s), 0.04 (6H, s); δ_C (101 MHz, $CDCl_3$): 157.4, 135.7, 134.4, 128.5, 128.3, 128.3, 117.3, 82.9, 67.4, 59.9, 37.5, 35.4, 25.9, 18.2, -5.4; MS (ESI +ve) *m/z* 171.3 (40), 204.3 (90), 380.5 (M^++H, 100), 402.6 (M^++Na, 64) HRMS (ESI) m/z calculated for $C_{20}H_{34}NO_4Si$ $[M+H]^+$ 380.2257, found 380.2256.

Benzyl (5R)-5-(2-hydroxyethyl)-3-methoxyisoxazolidine-2-carboxylate (**15**)
Amberlyst A-15 (866 mg) was added to a solution of *N*-benzyloxycarbonyl hydroxylamine **14** (38.17 g, 100.5. mmol) in MeOH (500 mL). The mixture was cooled to -78 °C and a stream of O_3/O_2 was passed through the mixture until the solution turned blue in colour. The flask was then purged with O_2 until the blue colour dissipated. Me_2S (8.9 mL, 121.2 mmol) was added and the mixture was warmed to room temperature and stirred for a further 24 h. The solvent was removed with a rotary evaporator and the residue was taken up in dichloromethane (300 mL) and washed with water (2 x 100 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography with gradual elution (25-50% Ethyl Acetate/Hexane) to give methoxy isoxazolidine **15** (22.08 g, 78%) as an inconsequential mixture of diastereomers (ratio = 1.5:1) and as a clear oil. R_f 0.23 (% Ethyl Acetate/Hexane); ν_{max} (neat) 3520, 2950, 1746, 1497, 1270, 1057 (neat) cm-1; MS (ESI +ve) *m/z* 206.1 (100), 304.1 (M^++Na, 40) HRMS (ESI) m/z calculated for $C_{14}H_{20}NO_5$ [M+H]+ 282.1341, found 282.1340.
Minor diastereomer: δ_H (400 MHz, $CDCl_3$): 7.44-7.27 (5H, m), 5.51-5.36 (1H, m), 5.33-5.10 (2H, m), 4.65-4.52 (1H, m), 3.89-3.63 (2H, m), 3.38 (3H, s), 2.43 (1H, ddd, *J* 13.1, 7.0, 1.7 Hz), 2.21-1.78 (3H, m); δ_C (101 MHz, $CDCl_3$): 156.6, 135.5, 128.6, 128.4, 128.0, 89.9, 79.5, 68.3, 60.0, 55.8, 41.1, 35.2;
Major diastereomer: δ_H (400 MHz, $CDCl_3$): 7.44 -7.27 (5H, m), 5.51-5.36 (1H, m), 5.33-5.10 (2H, m), 4.27-4.05 (1H, m), 3.89-3.63 (2H, m), 3.40 (3H, s), 2.64 (1H, dt, *J* 13.1, 7.1 Hz), 2.21 – 1.78 (3H, m); δC (101 MHz, $CDCl_3$): 157.4, 135.6, 135.5, 128.6, 128.4, 128.0, 91.8, 80.6, 68.2, 59.6, 56.2, 41.5, 35.2.

Benzyl (3R,5S)-3-allyl-5-(2-hydroxyethyl)isoxazolidine-2-carboxylate (*trans*-**17**) *and benzyl (3S,5S)-3-allyl-5-(2-hydroxyethyl)isoxazolidine-2-carboxylate* (*cis*-**17**)

$BF_3{\cdot}Et_2O$ (6.1 mL, 49.8 mmol) was added to a stirred solution of methoxy isoxazolidine **15** (7.00 g, 24.9 mmol) and allyltrimethylsilane (15.8 mL, 99.5 mmol) in anhydrous dichloromethane (100 mL) at -78 °C. Once addition was complete, the reaction mixture was gradually warmed to room temperature and left to stir until the reaction was shown to be complete by TLC analysis. The reaction mixture was cooled to -78 °C and quenched with Et_3N (3.5 mL, 25.0 mmol). The mixture was allowed to warm to room temperature and was diluted with water (100 mL). The organic phase was dried over (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (25 to 50% Ethyl Acetate/Hexane) to give *trans*-**17** (3.81 g, 52%) as a colourless oil, *cis*-**17** (725 mg, 10%) as a pale yellow oil and a remaining 1:1 mixture of both isomers (1.84 g, 25%) which was not separated. *Trans diastereomer* **17**: R_f 0.35 (50% Ethyl Acetate/Hexane); $[\alpha]_D^{20}$ -51.8 (*c* 1.40, $CHCl_3$); ν_{max} (neat) 3428, 2949, 2887, 1713, 1455, 1337, 1088 cm-1; δ_H (400 MHz $CDCl_3$): 7.49-7.30 (5H, m), 5.77 (1H, ddt, *J* 17.2, 10.2, 7.0 Hz), 5.38-4.96 (4H, m), 4.45 (1H, ddt, *J* 9.1, 7.2, 4.5 Hz), 4.36-4.24 (1H, m), 3.85-3.57 (2H, m), 2.48 (1H, dddt, *J* 14.1, 7.1, 5.8, 1.3 Hz), 2.34-2.14 (2H, m), 2.06 (1H, ddd, *J* 12.6, 8.3, 4.6 Hz), 1.72-1.51 (2H, m); δ_C (101 MHz $CDCl_3$): 157.4, 135.8, 133.8, 128.6, 128.4, 118.0, 79.4, 68.0, 60.2, 58.1, 39.1, 38.8, 36.2; MS (ESI +ve) *m/z* 248.4 (M^+-C_2H_5O, 100), 292.4 (M^++H, 30), 314.3 (M^++Na, 20); HRMS (ESI) *m/z* calculated for $C_{16}H_{22}NO_4$ $[M+H]^+$ 292.1549, found 292.1556.

Cis diastereomer **17**: R_f 0.35 (50% Ethyl Acetate/Hexane); $[\alpha]_D^{20}$ +66.2 (*c* 1.22, $CHCl_3$); ν_{max} (neat) 3416, 2945, 1730, 1454, 1337, 1074 cm^{-1}; δ_H (400 MHz $CDCl_3$): 7.43-7.28 (5H, m), 5.77 (1H, ddt, *J* 17.2, 10.2, 7.0 Hz), 5.23 (1H, d, *J* 12.3 Hz), 5.16 (1H, d, *J* 12.3 Hz), 5.14-5.02 (2H, m), 4.34-4.23 (1H, m), 4.03 (1H, app. dq, *J* 10.0, 6.2 Hz), 3.87-3.67 (2H, m), 2.54-2.41 (2H, m), 2.36-2.25 (1H, m), 1.92 (2H, app. q, *J* 6.0 Hz), 1.76-1.56 (1H, m); δ_C (101 MHz $CDCl_3$): 158.4, 135.9, 134.0, 128.6, 128.3, 127.9, 117.8, 80.3, 67.8, 59.9, 59.7, 40.0, 39.9, 35.3; MS (ESI +ve) *m/z* 248.4 (M^+-C_2H_5O, 100), 292.4 (M^++H, 32), 314.3 (M^++Na, 16); HRMS (ESI) *m/z* calculated for $C_{16}H_{22}NO_4$ $[M+H]^+$ 292.1549, found 292.1548.

Benzyl (3R,5S)-5-(2-hydroxyethyl)-3-((E)-4-methoxy-4-oxobut-2-en-1-yl)isoxazolidine-2- carboxylate (**18**)

To a stirred solution of allyl isoxazolidine *trans*-**17** (5.50 g, 18.9 mmol) and methyl acrylate (5.1 mL, 57.0 mmol) in dichloromethane (250 mL) heated at reflux was added a solution of Grubbs' II catalyst (242 mg, 285 µmol) in dichloromethane (5 mL) dropwise over a period of 3 hours. The mixture was then left to stir at the same temperature overnight. The reaction mixture was allowed to cool to room temperature and the volatiles were removed *in vacuo*. The residue was absorbed onto silica gel and purified by flash column chromatography with gradual elution (50 to 70% Ethyl Acetate/Hexane) to give α, β-unsaturated ester **18** (4.99 g, 75%) as a clear oil. R_f 0.22 (50% Ethyl Acetate/Hexane); $[\alpha]_D^{20}$ -44.3 (*c* 2.38, $CHCl_3$); ν_{max} (neat) 3443, 2951, 2889, 1715, 1454, 1337, 1215, 1086 cm^{-1}; δ_H (400 MHz $CDCl_3$): 7.43-7.29 (5H, m), 6.90 (1H, dt, *J* 15.7, 7.3 Hz), 5.90 (1H, dt, *J* 15.8, 1.5 Hz), 5.23 (1H, d, *J* 12.0 Hz), 5.15 (1H, d, *J* 12.1 Hz), 4.46 (1H, ddt, *J* 9.1, 7.0, 4.6 Hz), 4.41-4.32 (1H, m),3.83-3.59 (5H, m), 2.62 (1H, dddd, *J* 14.8, 7.4, 6.1, 1.6 Hz), 2.44 (1H, dtd, *J* 14.5, 7.2, 1.5 Hz), 2.26-1.97 (2H, m), 1.77-1.53 (2H, m).; δ_C (101 MHz $CDCl_3$): 166.5, 157.4, 143.8, 135.6, 128.6, 128.5, 128.4, 123.9, 79.3, 68.1, 60.1, 57.5, 51.5, 39.1, 37.4, 36.1; MS (ESI +ve) *m/z* 306.4 (M^+-C_2H_5O, 100), 350.5 (M^++H, 10); HRMS (ESI) *m/z* calculated for $C_{18}H_{24}NO_6$ [M+H]+ 350.1604, found 350.1602.

Benzyl (3R,5S)-3-((E)-4-methoxy-4-oxobut-2-en-1-yl)-5-(2-oxoethyl)isoxazolidine-2 carboxylate (**19**)

Dess-Martin periodinane (DMP) (3.71 g, 8.8 mmol) was added in one portion at room temperature to a solution of alcohol **18** (2.04 g, 5.8 mmol, 1.0 eq) in dichloromethane (30 mL). The reaction was stirred for 4 hours and a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ (30 mL) was added. The slurry was stirred until all solids were dissolved to form a clear biphasic solution. The aqueous layer was extracted three times with Et_2O (3 x 15 mL) and the combined organic layers were washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give aldehyde **19** as a clear oil (99%) which was used in the subsequent reaction without further purification. R_f 0.38 (50% Ethyl Acetate/Hexane); $[\alpha]_D^{20}$ -43.8 (*c* 1.48, $CHCl_3$); ν_{max} (neat) 3507, 2951, 1715, 1697, 1454, 1337, 1074 cm^{-1}; δ_H (400 MHz $CDCl_3$): 9.65 (1H, t, *J* 1.3 Hz), 7.42-7.31 (5H, m), 6.90 (1H, dt, *J* 15.7, 7.2 Hz), 5.91 (1H, dt, *J* 15.7, 1.5 Hz), 5.24 (1H, d, *J* 12.1 Hz), 5.16 (1H, d, *J* 12.1 Hz), 4.78-4.66 (1H, m), 4.45-4.34 (1H, m), 3.73 (3H, s), 2.74 (1H, ddd, *J* 17.5, 7.1, 1.3 Hz), 2.62 (1H, dddd, *J* 14.8, 7.1, 6.1, 1.5 Hz), 2.51-2.37 (2H, m), 2.27 (1H, ddd, *J* 12.7, 7.1, 4.2 Hz), 2.09 (1H, ddd, *J* 12.9, 8.3, 5.0 Hz); δ_C (101 MHz $CDCl_3$): 198.9, 166.4, 157.5, 143.6, 135.6, 128.6, 128.5, 128.4, 124.0, 75.3, 68.2, 57.7, 51.6, 47.2, 38.8, 37.3; MS (ESI +ve) *m/z* 304.2 (M^+-C_2H_5O, 100), 370.1 (M^++Na, 5); HRMS (ESI) *m/z* calculated for $C_{18}H_{22}NO_6$ $[M+H]^+$ 348.1447, found 348.1451.

Benzyl (3R,5S)-5-(2,2-dimethoxyethyl)-3-((E)-4-methoxy-4-oxobut-2-en-1- yl)isoxazolidine-2-carboxylate (**3**)

(±)-Camphorsulfonic acid (6.7 mg, 28.7 µmol) was added to a solution of aldehyde **19** (200 mg, 576 µmol) and trimethyl orthoformate (9.4 µL, 86.3 µmol) in dry MeOH (5 mL). The mixture was stirred at room temperature overnight. The mixture was neutralised with Et_3N (0.1 mL) and the solvents removed under reduced pressure. The residue was redissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ (2 x 5 mL) The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography with gradual elution (40 to 60% Ethyl Acetate/Hexane) to give acetal **3** as a colourless oil (190 mg, 85%). R_f 0.45 (50% Ethyl Acetate/Hexane); $[\alpha]_D^{20}$ -26.9 (*c* 0.67, $CHCl_3$); ν_{max} (neat) 2953, 1738, 1722, 1697, 1454, 1337, 1275, 1125 cm^{-1}; δ_H (400 MHz $CDCl_3$): 7.44-7.30 (5H, m), 6.90 (1H, dt, *J* 15.7, 7.3 Hz), 5.90 (1H, dt, *J* 15.7, 1.5 Hz), 5.21 (1H, d, *J* 12.1 Hz), 5.17 (1H, d, *J* 12.4 Hz), 4.52 (1H, dd, *J* 7.8, 3.6 Hz), 4.46-4.29 (2H, m), 3.73 (3H, s), 3.34 (3H, s), 3.21 (3H, s), 2.62 (1H, dddd, *J* 14.7, 7.4, 6.0, 1.6 Hz), 2.43 (1H, dtd, *J* 14.6, 7.3, 1.5 Hz), 2.19-2.10 (2H, m), 1.77 (1H, ddd, *J* 14.2, 8.9, 3.6 Hz), 1.59 (1H, m).; δ_C (101 MHz $CDCl_3$): 166.5, 157.4, 143.9, 135.8, 128.6, 128.3, 128.2, 123.9, 102.3, 68.0, 57.5, 54.2, 53.1, 51.5, 38.9, 37.4, 37.0; MS (ESI +ve) *m/z* 318.2 (M^+-$C_3H_7O_2$, 100), 416.2 (M^++Na, 10); HRMS (ESI) *m/z* calculated for $C_{20}H_{28}NO_7$ $[M+H]^+$ 394.1866, found 394.1885.

(R)-6-((S)-2-Hydroxy-4,4-dimethoxybutyl)piperidin-2-one (**20**)

In a round bottomed flask, acetal **3** was dissolved (180 mg, 458 µmol) in MeOH (100 mL). The sample inlet line and outlet line were both placed in the reaction solution. A 30 mm column of 10% Pd/C was inserted into the H-Cube reactor. The pressure was set to 1 bar, the flow rate of the HPLC pump was set to 1.0 mL/min, and the temperature to 25 °C using the touch screen control. The "Full Hydrogen" mode was selected. The reaction

was started by pressing the "start" button on the touch screen control. The reaction mixture was continuously passed through the instrument, until the starting material was shown to be completely consumed by TLC analysis. The column was washed with MeOH (10 mL in 10 min) to remove any substrate still adsorbed to the catalyst. The reaction mixture was then evaporated *in vacuo* and the resulting residue was purified by flash column chromatography (10% Methanol/Ethyl Acetate) to give the desired lactam **20** as a colourless oil (105 mg, 99%). R_f 0.25 (10% Methanol/Ethyl Acetate); $[\alpha]_D^{20}$ -33.8 (*c* 0.51, $CHCl_3$); ν_{max} (neat) 3443, 2951, 1632, 1126, 1053 cm^{-1}; δ_H (400 MHz $CDCl_3$): 6.52 (1H, br. s), 4.55 (1H, dd, *J* 6.7, 3.9 Hz), 4.10- 3.90 (1H, m), 3.75-3.61 (1H, m), 3.44 (1H, br. s), 3.40 (3H, s), 3.36 (3H, s), 2.42-2.22 (2H, m), 1.93-1.81 (3H, m), 1.79-1.51 (m, 4H), 1.47-1.35 (m, 1H); δ_C (101 MHz $CDCl_3$): 172.1, 104.4, 65.4, 54.5, 53.2, 49.3, 43.1, 39.1, 31.2, 29.3, 19.6; MS (ESI +ve) *m/z* 168.2 (M^+-$C_2H_7O_2$, 100), 200.3 (M^+-OCH_3, 26), 232.40 (M^++H, 34), 254.3 (M^++Na, 10); HRMS (ESI) *m/z* calculated for $C_{11}H_{22}NO_4$ $[M+H]^+$ 232.1549, found 232.1547.

Benzyl (3R,5S)-5-((R)-2-(3,4-dimethoxyphenyl)-2-hydroxyethyl)-3-((E)-4-methoxy-4- oxobut-2-en-1-yl)isoxazolidine-2-carboxylate and benzyl (3R,5S)-5-((S)-2-(3,4- dimethoxyphenyl)-2-hydroxyethyl)-3-((E)-4-methoxy-4-oxobut-2-en-1-yl)isoxazolidine-2- carboxylate (**26**)

To a solution of aldehyde **19** (80.0 mg, 230 µmol) in anhydrous THF (5 mL) cooled to -78 °C was added the Grignard reagent, 3, 4-dimethoxyphenyl magnesium bromide (1.4 mL, 690 µmol of a 0.5 M in THF solution) dropwise. The reaction mixture was allowed to stir at the same temperature for a further 1 hour and then allowed to warm slowly to room temperature. Progress of the reaction was monitored closely by TLC analysis based on the disappearance of the starting material The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc (2 ×10 mL) The organic layer was separated, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was then purified by flash column chromatography to give alcohol **26** as a 2:1 mixture of diastereomers (73 mg, 65%). R_f 0.35 (50% Ethyl Acetate/Hexane); ν_{max} (neat) 3520, 2952, 2837, 1732, 1714, 1514, 1444, 1337, 1028 cm^{-1}; MS (ESI +ve) *m/z* 424.2 (100), 508.2 (M^++Na, 14); HRMS (ESI) *m/z* calculated for $C_{26}H_{32}NO_8$ $[M+H]^+$ 486.2128, found 486.2111.

Major diastereomer:

δ_H (400 MHz $CDCl_3$): 7.48 -7.29 (5H, m), 6.96-6.71 (4H, m), 5.89 (1H, dt, *J* 15.7, 1.4 Hz), 5.27 (1H, d, *J* 12.1 Hz), 5.20 (1H, d, *J* 12.0 Hz), 4.79 (1H, dd, *J* 7.8, 5.5 Hz), 4.45-4.27 (2H, m), 3.87 (6H, s), 3.72 (3H, s), 2.59 (1H, dddd, *J* 14.9, 7.4, 6.3, 1.5 Hz), 2.42 (1H, dtd, *J* 14.4, 7.1, 1.5 Hz), 2.24-2.03 (2H, m), 1.90 (1H, ddd, *J* 14.5, 10.1, 7.8 Hz), 1.66 (1H, ddd, *J* 14.5, 5.7, 3.8 Hz); δ_C (101 MHz $CDCl_3$): 166.4, 157.7, 149.1, 148.5, 143.7, 136.7, 135.6, 128.6, 128.5, 128.4, 123.9, 118.1, 111.1, 109.1, 79.7, 72.4, 68.3, 57.5, 56.0, 55.9, 51.5, 43.2, 39.2, 37.4.

Minor diastereomer:

δ_H (400 MHz $CDCl_3$): 7.47 -7.27 (5H, m), 7.02-6.61 (4H, m), 5.88 (1H, dd, *J* 15.7, 1.6 Hz), 5.32-5.10 (2H, m), 4.95 (1H, dd, *J* 8.6, 3.3 Hz), 4.64-4.50 (1H, m), 4.47- 4.24 (1H, m), 3.85 (s, 6H), 3.71 (s, 3H), 2.68-2.53 (m, 1H), 2.51-2.33 (m, 1H), 2.20-2.05 (m, 1H), 1.83-1.71 (m, 2H); δ_C (101 MHz $CDCl_3$): 166.5, 157.4, 149.1, 148.4, 143.8, 136.9, 135.7, 128.6, 128.4, 128.1, 123.9, 117.6, 111.1, 108.9, 77.9, 70.8, 68.1, 57.6, 56.0, 55.9, 51.6, 42.5, 39.1, 37.5.

Benzyl (3R,5S)-5-(2-(3,4-dimethoxyphenyl)-2-oxoethyl)-3-((E)-4-methoxy-4-oxobut-2-en- 1-yl)isoxazolidine-2-carboxylate (**27**)

Dess-Martin periodinane (DMP) (288 mg, 679 µmol) was added in one portion at room temperature to a solution of alcohols **26** (220 mg, 453 µmol) in dichloromethane (10 mL). The mixture was stirred for 4 hours and a 1:1 mixture of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ (10 mL) was added. The slurry was stirred until all solids were dissolved to form a clear biphasic solution. The aqueous layer was extracted three times with Et_2O (2 x 10 mL) and the combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (50 to 70% Ethyl Acetate/Hexane) to give ketone **27** as a yellow oil (140 mg, 64%). R_f 0.56 (50% Ethyl Acetate/Hexane); $[\alpha]_D^{20}$ -38.9 (*c* 0.27, $CHCl_3$); ν_{max} (neat) 3362, 2931, 2855, 1732, 1643, 1514, 1261 cm^{-1}; δ_H (400 MHz $CDCl_3$): 7.44 (1H, d, *J* 2.0 Hz), 7.40-7.28 (6H, m), 6.92 (1H, dt, *J* 15.7, 7.2 Hz), 6.82 (1H, d, *J* 8.4 Hz), 5.92 (1H, dt, *J* 15.7, 1.5 Hz), 5.21 (1H, d, *J* 12.2 Hz, 1H), 5.15 (1H, d, *J* 12.1 Hz), 4.91-4.78 (1H, m), 4.48-4.33 (1H, m), 3.95 (3H, s), 3.90 (3H, s), 3.73 (3H, s), 3.45 (1H, dd, *J* 16.9, 4.9 Hz), 2.87 (1H, dd, *J* 17.0, 8.5 Hz), 2.73-2.59 (1H, m), 2.47 (1H, dtd, *J* 14.6, 7.3, 1.5 Hz), 2.37 (1H, ddd, *J* 12.8, 7.0, 4.0 Hz), 2.17 (1H, ddd, *J* 12.8, 8.3, 5.2 Hz); δ_C (101 MHz $CDCl_3$): 195.3, 166.5, 157.4, 153.7, 149.2, 143.8, 135.8, 129.7, 128.6, 128.3, 128.2, 123.9, 122.9, 110.0, 109.9, 68.0, 57.8, 56.1, 56.0, 51.5, 41.8, 39.0, 37.3; MS (ESI +ve) *m/z* 440.2 (40), 484.2 (M^++H, 100), 506.1 (M^++Na, 10); HRMS (ESI) *m/z* calculated for $C_{26}H_{30}NO_8$ $[M+H]^+$ 484.1971, found 484.1977.

Methyl 4-((2R,4S,6R)-6-(3,4-dimethoxyphenyl)-4-hydroxypiperidin-2-yl)butanoate (**28**)

In a round bottomed flask, ketone **27** was dissolved (240 mg, 496 µmol) in MeOH (100 mL). The sample inlet line and outlet line were both placed in the reaction solution. A 30 mm column of 10% Pd/C was inserted into the HCube reactor. The pressure was set to 1 bar, the flow rate of the HPLC pump was set to 1.0 mL/min, and the temperature to 25 °C using the touch screen control. The "Full Hydrogen" mode was selected. The reaction was started by pressing the "start" button on the touch screen control. The reaction mixture was continuously passed through the instrument, until the starting material was shown to be completely consumed by TLC analysis. The column was washed with MeOH (10 mL in 10 min) to remove any substrate still adsorbed to the catalyst. The reaction mixture was then evaporated *in vacuo* and the resulting residue was purified by flash column chromatography (10% MeOH/dichloromethane) to give the desired piperidine **28** as a brown oil (155 mg, 92%). R_f 0.20 (10% MeOH/dichloromethane); $[\alpha]_D^{20}$ +28.1 (*c* 1.03, $CHCl_3$); ν_{max} (neat) 3420, 2943, 1730, 1518, 1264, 1026 cm^{-1}; δ_H (400 MHz $CDCl_3$): 6.94 (1H, d, *J* 2.0 Hz), 6.89 (1H, dd, *J* 8.2, 2.0 Hz), 6.81 (1H, d, *J* 8.2 Hz), 3.88 (3H, s), 3.86 (3H, s), 3.78 (1H, tt, *J* 11.0, 4.5 Hz), 3.66 (3H, s), 3.61 (1H, dd, *J* 11.5, 2.4 Hz), 2.72 (1H, dtd, *J* 11.1, 6.3, 2.3 Hz), 2.33 (2H, app. t, *J* 7.4 Hz), 2.17-1.99 (2H, m), 1.76-1.61 (2H, m), 1.59-1.38 (3H, m), 1.16 (1H, app. q, *J* 11.3 Hz).; δ_C (101 MHz $CDCl_3$): 174.0, 149.0, 148.5, 135.2, 119.1, 111.1, 110.4, 69.1, 59.6, 56.0, 55.9, 55.2, 51.6, 42.8, 40.6, 35.4, 33.8, 21.1; MS (ESI +ve) *m/z* 338.2 (M^++H 100); HRMS (ESI) *m/z* calculated for $C_{18}H_{28}NO_5$ $[M+H]^+$ 338.1967, found 338.1980.

(6R,8S,9aR)-6-(3,4-Dimethoxyphenyl)-8-hydroxyoctahydro-4H-quinolizin-4-one (**30**)

LiOH (6.1 mg, 255 µmol) and water (5.0 µL, 277 µmol) were added to a solution of ester **28** (78.0 mg, 231 µmol) in MeOH (5 mL). The mixture was heated at reflux overnight. The mixture was then cooled to room temperature and the volatiles were removed *in vacuo* to give the acid **29**. The residue was re-dissolved in DMF (3 mL) and EDCI·HCl (66.5 mg, 347 µmol) was added to crude acid **29**. The reaction mixture stirred at room temperature overnight. The reaction mixture was diluted with

EtOAc and washed with water. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography with silica (10% MeOH/dichloromethane) to give quinolizidinone **30** as a yellow oil (52.0 mg, 74%). R_f 0.10 (10% MeOH/dichloromethane); $[\alpha]_D^{20}$ +56.5 (*c* 0.34, $CHCl_3$); ν_{max} (neat) 3443, 2930, 1614, 1516, 1445, 1254, 1142, 1024 cm^{-1}; δ_H (400 MHz $CDCl_3$): 6.88-6.70 (3H, m), 5.30 (1H, t, *J* 4.6 Hz), 4.15-3.98 (1H, m), 3.85 (3H, s), 3.83 (3H, s), 3.45 (1H, ddt, *J* 13.2, 10.6, 2.8 Hz), 2.57-2.27 (4H, m), 2.21 (1H, ddd, *J* 13.9, 8.3, 2.4 Hz), 2.03-1.92 (2H, m), 1.88-1.73 (1H, m), 1.72-1.51 (2H, m).; δ_C (101 MHz $CDCl_3$): 170.7, 149.1, 147.7, 135.2, 117.4, 111.4, 109.4, 65.4, 55.9, 55.8, 53.1, 52.9, 39.9, 37.7, 32.5, 31.0, 20.4; MS (ESI +ve) *m/z* 150.1 (10), 168.1 (40), 306.1 (M^++H, 100); HRMS (ESI) *m/z* calculated for $C_{17}H_{24}NO_4$ $[M+H]^+$ 306.1705, found 306.1700.

(+)-2-epi-Lasubine II (**31**)

To a solution of quinolizidinone **30** (25.0 mg, 81.9 µmol) in anhydrous THF (5 mL) was added 1.0 M solution of $LiAlH_4$ in THF (0.2 mL, 205 µmol). The mixture was heated at reflux and stirred for 6 hours under an inert atmosphere. The reaction was quenched by adding water (0.5 mL). The resulting mixture was stirred vigorously for 10 min and the precipitate was removed by filtration. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (10% MeOH/dichloromethane) to give piperidine **31** as a pale yellow oil (21.5 mg, 90%). R_f 0.20 (10% MeOH/dichloromethane $[\alpha]_D^{20}$ +65.0 (*c* 0.78, $CHCl_3$) {lit.[15] $[\alpha]_D^{20}$ +57 (*c* 0.46, MeOH)}; ν_{max} (neat) 3345, 2932, 2853, 1514, 1454, 1263, 1030 cm^{-1}; δ_H (400 MHz $CDCl_3$): 7.10-6.44 (3H, m), 3.88 (3H, s), 3.86 (3H, s), 3.78-3.66 (1H, m), 2.92 (1H, dd, *J* 11.6, 2.7 Hz), 2.72-2.65 (1H, m), 2.13-1.76 (3H, m), 1.76- 1.33 (7H, m), 1.33-1.15 (2H, m); δ_C (101 MHz $CDCl_3$): 148.0, 136.5, 120.5-119.0 (br., 2C), 112.0-109.0 (br., 2C), 68.4, 68.3, 61.0, 56.0, 55.9, 52.9, 45.1, 42.7, 33.6, 26.0, 24.6; MS (ESI +ve) *m/z* 292.1 (M^++H, 100); HRMS (ESI) *m/z* calculated for $C_{17}H_{26}NO_3$ $[M+H]^+$ 292.1913, found 292.1914.

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Supplementary Material

^1H and ^{13}C NMR spectra of compounds **3, 10-15**, **17-23**, **27**, **28**, **30** and **31**.