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REVISED

Asymmetric Synthesis of (+)-1-Epiaustraline and Attempted Synthesis of
Australine

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Abstract: A diastereoselective synthesis of the pyrrolizidine alkaloid, (+)-1-epiaustraline has been achieved *via* a diastereoselective *syn*-dihydroxylation of a pyrrolo[1,2-*c*]oxazol-3-one precursor that was readily prepared by a RCM reaction. Attempts to extend this methodology to the synthesis of australine were not successful since the final pyrrolidine ring closure to produce the desired pyrrolizidine of the target molecule was not productive.

Alexine (**1**) was the first alkaloid to be isolated with the 3-hydroxymethyl-2,3,5,6,7,7a-hexahydro-1H-pyrrolizine-1,2,7-triol structure in 1988.¹ In the same year its 7a-epimer, australine (**2**), was isolated from the seeds of *Castanospermum australe*.² Later reports described the isolation of other epimers of **2** from these seeds, including 1-epiaustraline **3**.^{3,4} These alkaloids have been shown to have glycosidase inhibitory activities^{2,3c,4} and other biological studies have revealed the potential of these and related polyhydroxylated pyrrolizidines as antiviral and anti-retroviral agents.⁵ These interesting biological properties coupled with the polyfunctional and stereochemically rich nature of these compounds have attracted the attention of synthetic chemists resulting in the total synthesis of alexine,⁶ and its epimers,^{6,7} australine,⁸ and its epimers,⁷⁻¹¹ and casuarine.¹²

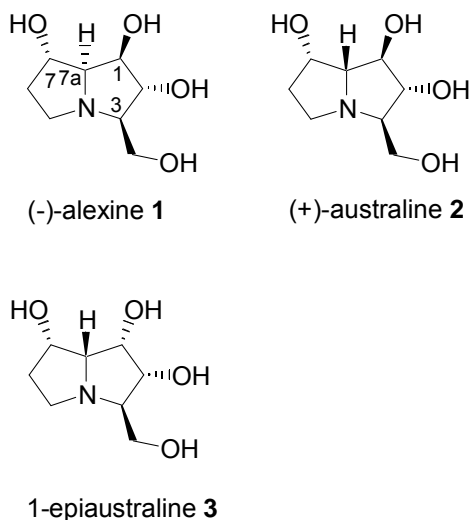
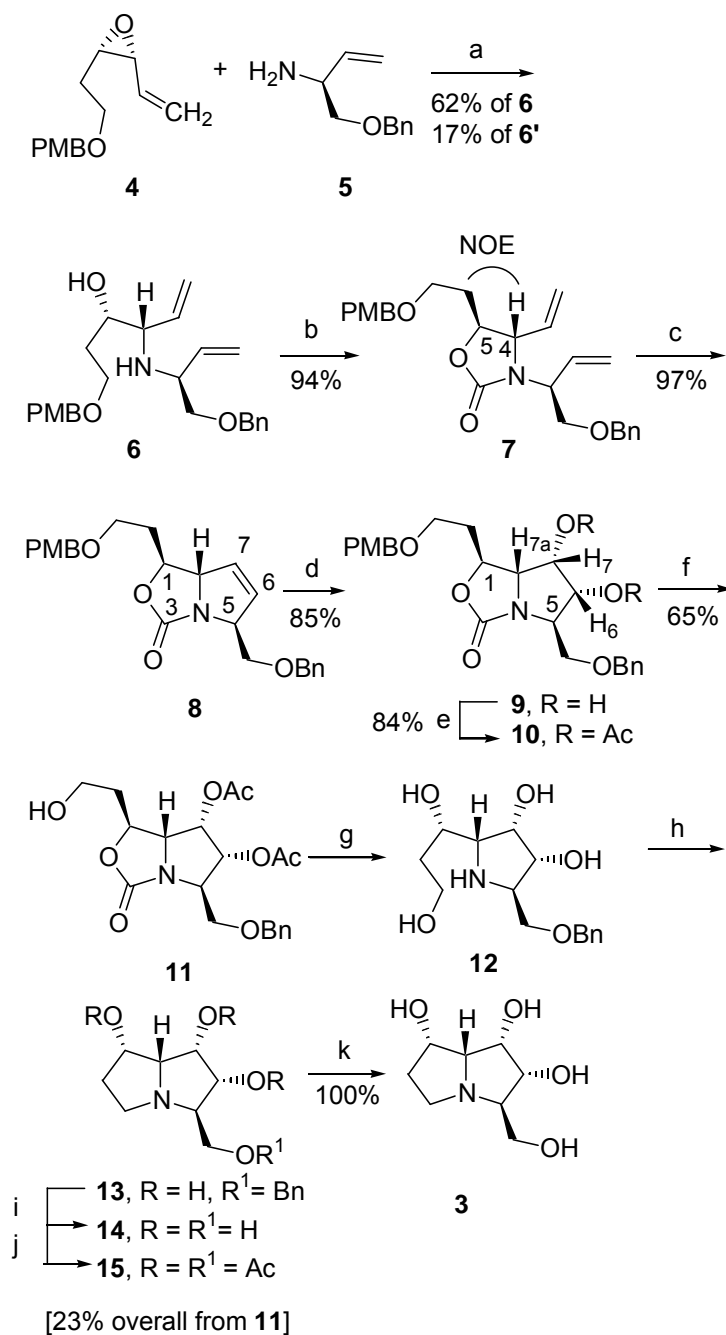


Figure 1. Structures of 3-hydroxymethyl pyrrolizidine

In 2003 we reported a new and potentially general synthetic methodology for the synthesis of australine and its epimers using aminolysis of a chiral vinyl epoxide and RCM as key reactions.¹¹ We demonstrated the viability of this synthetic methodology

with the asymmetric synthesis of (-)-7-epiaustaline and (+)-1,7-diepiaustraline.¹¹ We report here, as an extension of this work, the synthesis of (+)-1-epi-australine and our attempts to prepare australine. These target molecules required that the starting vinyl epoxide **4** had the *cis*-[(3*R*, 4*S*)] stereochemistry rather than the *trans*-[(3*R*, 4*R*)] stereochemistry used by us previously and it was of interest to examine the effect of this stereochemical difference on the diastereoselectivities of the reactions leading to our target molecules.

The starting vinyl epoxide (-)-(3*R*, 4*S*)-**4** was prepared from the corresponding Sharpless epoxy alcohol (82 % ee from ¹H NMR analysis of its Mosher ester, see experimental section) *via* Swern oxidation followed by a Wittig-olefination reaction.^{11,13} A solution of the vinyl epoxide (-)-**4** and the (*S*)-allylamine **5**¹⁴ (1.4 equiv, *ca* 99% ee) in acetonitrile was heated at 120 °C in a sealed tube using LiOTf (1.5 equiv) as a catalyst for 3 d. This gave a mixture of two diastereomeric products. Separation by PTLC gave the desired amino alcohol (+)-**6** in 62% yield and its diastereomer (structure not shown but referred to as compound **6'** in the experimental section) in 17% yield that arises from the reaction of *ent*-**4** with **5**. The amino-alcohol (+)-**6** was converted to the diastereomerically pure 2-oxazolidinone derivative (+)-**7** in 94% yield using triphosgene under basic conditions.^{11,15} The minor diastereomeric amino-alcohol was converted to its corresponding 2-oxazolidinone derivative in 69% yield. In their ¹H NMR spectra, *J*_{4,5} for both 2-oxazolidinones was 7.5 Hz, while the NOESY spectra of these compounds showed strong cross peaks between H-4 and the *exo*-cyclic methylenes at C-5 (see Scheme 1 for details). This was consistent with both 2-oxazolidinones having the C-4, C-5 *trans*-stereochemistry which would arise from an S_N2 ring opening of **4** or *ent*-**4** with **5**.



Scheme 1. *Reagents and conditions:* a) LiOTf, CH₃CN, 120 °C, sealed tube, 72 h; b) triphosgene, Et₃N, DCM, 0 °C, 2.5 h; c) Grubbs' catalyst I, DCM, reflux, 3 h; d) K₂OsO₄·2H₂O, NMO, acetone, H₂O, RT, 21 h; e) Ac₂O, pyridine, RT, 23 h; f) DDQ, DCM, H₂O, RT, 5.5 h; g) NaOH, EtOH, 70 °C, sealed tube, 37 h; h) DIAD, PPh₃, pyridine, 0 °C, 4 h then RT 3 h; i) PdCl₂, H₂, MeOH, RT, 1.5 h; j) Ac₂O, pyridine, RT, 22 h; k) Amberlyst A-26 (OH-form) resin, MeOH, RT, 2 h.

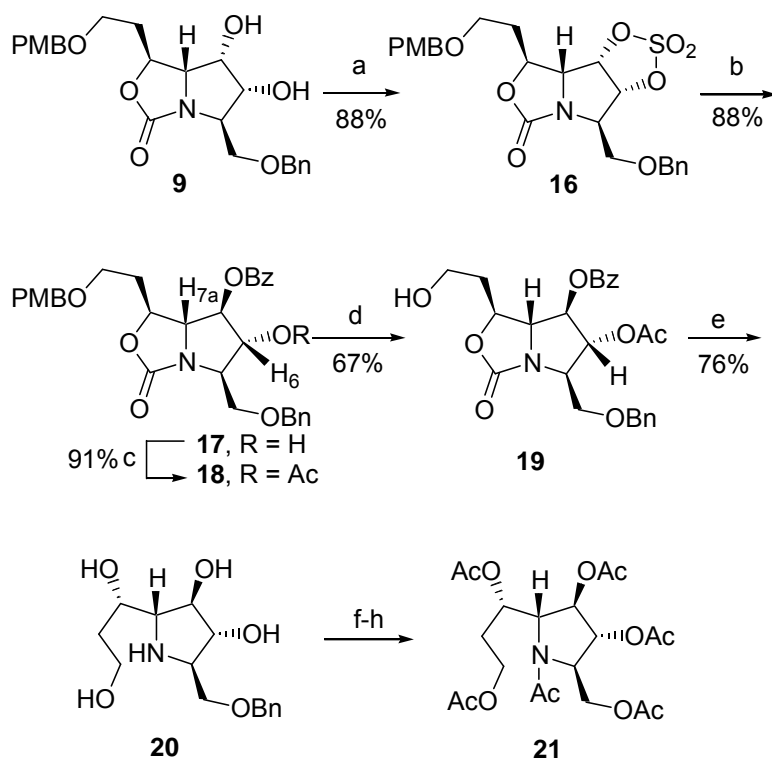
The RCM of **7** using standard conditions, 5-10 mol % of Grubbs I catalyst (benzylidenebis(tricyclohexylphosphine)ruthenium dichloride) in refluxing CH_2Cl_2 at high dilution (~4 mM) for 20 h, gave low conversion to the desired 2,5-dihydropyrrole (-)-**8**. However, by initiating the reaction using 22 mol% Grubbs I catalyst and then adding a further 9 mol% catalyst after 25 h, (-)-**8** could be isolated in 97% yield after a total of 42 h of heating at reflux.^{16,17} Compound (-)-**8** was treated with 5 mol % $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$ and NMO (2.1 equiv),^{11,13} to effect *syn*-dihydroxylation (DH) of the double bond, giving diol (-)-**9** in good yield (85%). A small amount (< 5%) of the C-6, C-7 di-epimeric diol was also formed but was readily separated by column chromatography. The stereochemistry of diol **9** was that expected from our previous studies with osmylation occurring from the concave face of the 2-oxazolidinone **8**.^{11,17} This stereochemistry was evident from NOESY studies on its acetate **10** that showed significant cross peaks between H-6 and the *exo*-cyclic methylene at C-5 and between H-6 and H-7a. The absolute stereochemistry assigned to **9** was unequivocally confirmed by its conversion to (-)-1-epiaustraline (**3**).

Attempts to deprotect the primary PMB ether in **9** under oxidative conditions with DDQ¹⁸ gave a poor yield of the desired primary alcohol due to the formation of several other products that could not be structurally identified. The diacetate derivative **10** however was smoothly converted to the primary alcohol **11** in 63% yield. Compound **11** was then converted to the pyrrolizidine-tetraacetate **15** in three synthetic steps. Base hydrolysis of **11** followed by ion-exchange chromatography gave **12** which was cyclized to the desired pyrrolizidine ring system under Mitsunobu conditions^{12,19} in pyridine at 0 °C. The crude reaction mixture was then treated under hydrogenolysis conditions^{12,13,20} and then peracetylation gave the pyrrolizidine-tetraacetate **15** in 23% over yield from **11**. Finally,

methoxide catalysed removal of the acetates of **15** gave (+)-1-epiaustraline (**3**) in quantitative yield. This sample had identical spectral characteristics to those reported in the literature for (+)-**3**,^{7c,10} and its specific rotation ($[\alpha]_{\text{D}}^{25} +14.3$ (*c* 1.1, H₂O)) closely matched that previously reported (lit.^{10a} ($[\alpha]_{\text{D}}^{25} +13.695$ (*c* 1.72, H₂O))).

Scheme 2 outlines our attempted synthesis of australine (**2**). This synthesis required inversion of the stereochemistry at C-7 in the pyrrolo[1,2-*c*]oxazol-3-one **9**. Thus **9** was converted to its cyclic-sulfate **16** using thionyl chloride followed by oxidation of the resulting cyclic sulfite with catalytic ruthenium tetroxide (88% yield for the two-step conversion).^{11,21} Nucleophilic ring opening of the *S,S*-dioxo-dioxathiole ring of **16** with cesium benzoate,^{11,21,22} followed by an acidic work up gave a 73 : 27 mixture of regioisomeric benzoates in 88% yield. The regioisomers were readily separated by column chromatography as their acetate derivatives. In this way the acetate **18** of the major regioisomer could be obtained in 66% yield while the acetate of the minor regioisomer was isolated in 25% yield. The structure of the major regioisomer **18** was established by NOESY experiments which showed significant cross peaks between H-6 the *exo*-cyclic methylene at C-5 and between H-6 and H-7a (See Scheme 2 for proton numbering). The modest regioselectivity found in the ring opening of **16** is in stark contrast to that of 1-epi-**16** which gave less than 5% of the other regioisomer resulting from attack of benzoate anion at C-6.¹¹ While, nucleophilic attack on **16** would be expected to occur preferentially at C-7, since backside attack at C-6 would be more sterically demanding due to the β-C-5 benzyloxymethyl substituent, the configuration at C-1 also clearly influences the regiochemistry of ring-opening. Thus the β-orientation of the C-1 substituent in **16** must be responsible for the reduced regioselectivity found in the ring opening of **16**. Oxidative removal of the primary PMB ether in **18** using DDQ gave the

corresponding primary alcohol **19** in 67% yield. Base hydrolysis of the esters and the oxazolidinone ring of **19** gave the amino tetrol **20** in 76% yield. Attempted cyclization of **20** under Mitsunobu conditions proved problematic and hydrogenolysis of the crude reaction mixture and then peracetylation gave a mixture from which only the hexaacetate **21** could be isolated in low yield [12%, MS (ES +ve) m/z 460 ($M+H^+$, 27%)]. None of the desired peracetylated pyrrolizidine product could be detected. While we have always had poor yields for this type of cyclization reaction,^{11,16} this is the first time it has not been successful.



Scheme 2. Reagents and conditions: a) (i) SOCl_2 , Et_3N , DCM, 0 °C, 30 min; (ii) $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$, NaIO_4 , $\text{CCl}_4:\text{CH}_3\text{CN}:\text{H}_2\text{O} = 2:2:3$, RT, 2 h; b) (i) PhCOOH , Cs_2CO_3 , DMF, 40 °C, 23 h; (ii) H_2SO_4 (conc.), THF, H_2O , RT, 18 h; c) Ac_2O , pyridine, RT, 23 h; d) DDQ, DCM, H_2O , RT, 2 h; e) NaOH , EtOH , 70 °C, 19 h; f) DIAD, PPh_3 , THF, 0 °C, 3 h then RT, 3 h; g) PdCl_2 , H_2 , MeOH, RT, 1 h; h) Ac_2O , pyridine, RT, 15 h.

In summary, we have developed diastereoselective synthesis of the pyrrolizidine alkaloid, (+)-1-epi-australine *via* a diastereoselective *syn*-dihydroxylation of a pyrrolo[1,2-*c*]oxazol-3-one precursor that was readily prepared by a RCM reaction. Attempts to extend this methodology to the synthesis of australine were not successful since the final pyrrolidine ring closure to produce the desired pyrrolizidine of the target molecule was not productive.

Experimental Section

List of Abbreviations: ArH: Aromatic protons of PMB, Ar*H: Aromatic protons of Bn or Ph, BzH: Aromatic protons of Bz, ArCH₂: CH₂ of PMB, Ar*CH₂: CH₂ of Bn, ArC: Quaternary aromatic carbons of PMB, Ar*C: Quaternary aromatic carbons of Bn, ArCH: Aromatic CH carbons of PMB, Ar*CH: Aromatic CH carbons of Bn, BzCH: Aromatic CH carbons of Bz

General Methods. All reactions were carried out under an atmosphere of nitrogen. All NMR spectra were obtained as a CDCl₃ solution at 300 MHz (¹H NMR) or 75 MHz (¹³C NMR) unless otherwise stated and were referenced to the relevant solvent peak. ¹³C NMR assignments were made from DEPT experiments. Silica gel chromatography was performed using Merck GF 254 flash silica gel packed by the slurry method. Small-scale separations (<2.0 g) were performed using either a 10 or 20 mm diameter column, and large-scale separations (>2.0 g) were performed using either a 30 or 50 mm diameter column, each with the stated solvent system. Specific rotations were measured using a 10 or a 50 mm cell, and the values quoted were an average of 5-10 measurements. They are reported by the following convention: optical rotation [$10^{-1} \cdot \text{deg} \cdot \text{cm}^3 \cdot \text{g}^{-1}$] (concentration, solvent). Acidic ion-exchange chromatography was performed using DOWEX 50WX8-50 acidic cation exchange resin, packed by the slurry method in 10 mm diameter column. In all cases the compounds were applied as their HCl salts dissolved in distilled water. The column was first eluted with water (100 mL) and then eluted with 14% ammonia solution (w/w). In all cases, HRMS (exact masses) were obtained on lieu of elemental analysis, and ¹H and ¹³C NMR spectroscopy were used as criteria for purity.

Synthesis of (-)-6-(4-Methoxyphenyl)methoxy-3*R*,4*S*-epoxy-1-hexene (4)

Step 1: 5-(4-Methoxyphenyl)methoxy-2*Z*-penten-1-ol. To the solution of 1-(4'-methoxy)benzyloxy-3-butyne (431 mg, 1.96 mmol) and quinoline (329 mg, 2.55 mmol) was added Pd/CaCO₃ (35.8 mg). The mixture was stirred at RT under a nitrogen atmosphere for 1.5 h. The mixture was then filtered through celite before the filtrate was washed with 1M HCl (3x). The organic portion was dried with MgSO₄, filtered and

evaporated to dryness *in vacuo*. Chromatography of the residue eluting with EtOAc/petrol (0%-50%) gave the title compound (396 mg, 91%). ^1H NMR δ 7.22 (d, 2H, J 8.4 Hz, ArH), 6.85 (d, 2H, J 8.7 Hz, ArH), 5.73 (dt, 1H, J 10.8, 7.2 Hz, H-2), 5.53 (dt, 1H, J 10.8, 8.1 Hz, H-3), 4.41 (s, 2H, ArCH₂), 4.06 (d, 2H, J 6.9 Hz, H-1), 3.75 (s, 3H, OMe), 3.43 (t, 2H, J 6.0 Hz, H-5), 3.08 (bs, 1H, OH), 2.35 (td, 2H, J 7.2, 6.6 Hz, H-4); ^{13}C NMR δ 158.9 (ArC), 130.7 (CH-2), 129.7 (ArC), 129.1 (ArCH), 128.7 (CH-3), 113.5 (ArCH), 72.4 (ArCH₂), 68.6 (CH₂-5), 57.4 (CH₂-1), 54.9 (OMe), 27.7 (CH₂-4); MS (CI +ve) m/z 222 (M^+); HRMS (CI +ve) Calcd for C₁₃H₁₈NO₃ (M^+) 222.1256, found: 222.1253.

Step 2: (-)-5-(4-Methoxyphenyl)methoxy-2R,3S-epoxy-1-pentanol. To a mixture of titanium tetra-isopropoxide (1.6 mL, 5.35 mmol), 4Å molecular sieves (1.93 g) in dry DCM (100 mL) were added D-(-)-diisopropyltartrate (1.4 mL, 6.42 mmol) and anhydrous *tert*-butyl hydroperoxide (5.3 mL, 26.2 mmol, 5.0 M) under N₂ at -40 °C. After 10 min, a solution of **1** (2.37 g, 10.7 mmol) in dry DCM (10 mL) was added. The resulting yellow mixture was stirred at -20 °C for 18 h. After this time, 10% aqueous tartaric acid (50 mL) was added dropwise and the mixture was allowed to warm to RT over 1 h until the solution was transparent. Then the organic layer was separated, washed with brine and dried (MgSO₄). The solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel. Elution with 30%-100% EtOAc/petrol afforded the title compound (2.41 g, 95%) as a yellow oil. $[\alpha]_{\text{D}}^{24}$ -10.5 (c 2.3, CHCl₃); ^1H NMR δ 7.25 (d, 2H, J 8.7 Hz, ArH), 6.89 (d, 2H, J 8.7 Hz, ArH), 4.47 (s, 2H, ArCH₂), 3.86 (ddd, 1H, J 12.0, 10.2, 5.1 Hz, H-1a), 3.80 (s, 3H, OMe), 3.68-3.54 (m, 2H, H-5), 3.46 (ddd, 1H, J 12.3, 8.7, 3.6 Hz, H-1b), 3.17 (dt, 1H, J 9.0, 4.5 Hz, H-2), 3.10 (dd, 1H, J 10.5, 3.3 Hz, OH), 3.02 (dt, 1H, J 9.6, 4.2 Hz, H-3), 2.09 (ddd, 1H, J 14.7, 3.9, 2.7 Hz, H-4a), 1.74 (dddd, 1H, J 14.4, 10.8, 9.3, 4.8 Hz, H-4b); ^{13}C NMR δ 159.4 (ArC), 129.6 (ArCH), 129.0 (ArC), 113.8 (ArCH), 73.1 (ArCH₂), 66.3 (CH₂-5), 59.8 (CH₂-1), 55.2 (CH-2), 55.1 (OMe), 54.8 (CH-3), 27.9 (CH₂-4); MS (CI +ve) m/z 238 (M^+); HRMS (CI +ve) Calcd for C₁₃H₁₈NO₄ (M^+) 238.1205, found: 238.1197.

Mosher Ester Analysis: (-)-5-(4-Methoxyphenyl)methoxy-2*S*,3*S*-epoxy-1-pentyl-(*R*)- α -methoxy- α -(trifluoromethyl)phenyl acetate. 5-(4-Methoxy)benzyloxy-2*R*,3*S*-epoxy-1-pentanol (25 mg, 0.103 mmol) was dissolved in dry DCM (0.9 mL), then triethylamine (90 μ L), 4-dimethylaminopyridine (13 mg, 0.108 mmol) and *R*-(-)- α -methoxy- α -(trifluoromethyl)phenylacetyl chloride (21 μ L, 0.113 mmol) were added. The mixture was stirred at RT for 15 min. All the volatiles were removed *in vacuo* to give a dark semi-solid which was purified by column chromatography (15%-30% EtOAc/petrol) to give a pale yellow oil (42 mg, 90%, 82% ee). $[\alpha]_D^{24}$ -31.0 (c 2.1, CHCl₃); ¹H NMR (major diastereomer) δ 7.55-7.51 (m, 2H, Ar*H), 7.43-7.39 (m, 3H, Ar*H), 7.25 (d, 2H, *J* 8.4 Hz, ArH), 6.88 (d, 2H, *J* 8.7 Hz, ArH), 4.48 (dd, 1H, *J* 12.0, 3.9 Hz, H-1a), 4.44 (s, 2H, ArCH₂), 4.36 (dd, 1H, *J* 12.0, 7.2 Hz, H-1b), 3.79 (s, 3H, MeOAr), 3.60-3.56 (m, 2H, H-5), 3.57 (s, 3H, MeOC), 3.26-3.15 (m, 2H, H-2, H-3), 1.84 (apparent q, 2H, *J* 6.0 Hz, H-4); ¹H NMR (minor diastereomer, in part) δ 4.54 (dd, 1H, *J* 12.0, 3.9 Hz, H-1a), 4.31 (dd, 1H, *J* 12.3, 7.2 Hz, H-1b); ¹³C NMR δ 166.4 (CO), 159.2 (ArC), 132.0 (Ar*C), 130.1 (ArC), 129.7 (Ar*CH), 129.2 (ArCH), 128.4 (Ar*CH), 127.2 (Ar*CH), 123.1 (q, *J*_{C,F} 287.1 Hz, CF₃), 113.7 (ArCH), 84.6 (q, *J*_{C,F} 27.6 Hz, CCF₃), 72.8 (ArCH₂), 66.5 (CH₂-5), 64.77 (CH₂-1), 55.5 (q, *J*_{C,F} 1.5 Hz, COMe), 55.2 (MeOAr), 54.3 (CH-3), 53.0 (CH-2), 28.7 (CH₂-4); MS (CI +ve) *m/z* 453 (M-1⁺); HRMS (CI +ve) Calcd for C₂₃H₂₅O₆F₃ (M⁺) 454.1603, found: 454.1596.

Steps 4 and 5: 5-(4-Methoxyphenyl)methoxy-2*S*,3*S*-epoxypentanal and (-)-6-(4-Methoxyphenyl)methoxy-3*R*,4*S*-epoxy-1-hexene (4). To a stirred solution oxalyl chloride (0.5 mL, 5.72 mmol) in dry DCM (7 mL) was added slowly dimethyl sulfoxide (0.68 mL, 9.53 mmol) at -50 °C to -60 °C under N₂. The mixture was stirred for 5 min and 5-(4-methoxy)benzyloxy-2*R*,3*S*-epoxy-1-pentanol (907 mg, 3.81 mmol) in DCM (3 mL) was added within 5 min *via* cannula. Stirring was continued for an additional 40 min. Triethylamine (2.7 mL, 19.1 mmol) was then added and the mixture was stirred for 5 min and then allowed to warm to RT. After 20 min, the reaction was quenched by water (25 mL). The aqueous layer was re-extracted with additional DCM (3x). The combined organic portions were washed with saturated NaCl solution, HCl (1M), water, aqueous Na₂CO₃ (sat.), water and dried (MgSO₄). The filtered solution was evaporated to

give a yellow oil. The crude aldehyde product was used in the next step without further purification. A solution of potassium bis(trimethylsilyl)amide (22.1 mL, 11.1 mmol, 0.5 M in toluene) was cooled to $-10\text{ }^{\circ}\text{C}$ and transferred *via* cannula to a stirred suspension of methyltriphenylphosphonium bromide (4.09 g, 11.4 mmol) in dry THF (25 mL) at $-10\text{ }^{\circ}\text{C}$ under N_2 . The bright yellow suspension was stirred at RT for 20 min, re-cooled to $-10\text{ }^{\circ}\text{C}$ and the above crude aldehyde in THF (8 mL) was added *via* cannula. TLC analysis (30% EtOAc/petrol) indicated complete disappearance of the crude 5-(4-methoxy)benzyloxy-2*S*,3*S*-epoxypentanal after 2.5 h. The reaction mixture was poured into brine and extracted with diethyl ether (3x). The combined organic extract was dried (MgSO_4). The solvent was evaporated under reduced pressure to give a semi-solid which was purified by column chromatography (10%-35% EtOAc/petrol) to give the title compound **5** as a pale yellow oil (685 mg, 77% overall for 2 steps). $[\alpha]_{\text{D}}^{23} -14.2$ (*c* 2.1, CHCl_3); ^1H NMR δ 7.26 (dt, 2H, *J* 8.7, 2.7 Hz, ArH), 6.88 (dt, 2H, *J* 8.7, 3.0 Hz, ArH), 5.71 (ddd, 1H, *J* 17.4, 10.5, 6.9 Hz, H-2), 5.47 (ddd, 1H, *J* 17.4, 1.8, 0.6 Hz, H-1a), 5.35 (ddd, 1H, *J* 10.8, 1.8, 0.6 Hz, H-1b), 4.46 (s, 2H, ArCH_2), 3.80 (s, 3H, OMe), 3.60 (td, 2H, *J* 6.3, 0.9 Hz, H-6), 3.43 (dd, 1H, *J* 7.2, 4.5 Hz, H-3), 3.24 (ddd, 1H, *J* 6.9, 5.7, 4.5 Hz, H-4), 1.92-1.75 (m, 2H, H-5); ^{13}C NMR δ 159.1 (ArC), 132.3 (CH_2 -2), 130.3 (ArC), 129.2 (ArCH), 120.5 (CH_2 -1), 113.7 (ArCH), 72.7 (ArCH_2), 67.0 (CH_2 -6), 56.9 (CH-3), 56.3 (CH-4), 55.2 (OMe), 28.4 (CH_2 -5); MS (CI +ve) *m/z* 234 (M^+); HRMS (CI +ve) Calcd for $\text{C}_{14}\text{H}_{18}\text{NO}_3$ (M^+) 234.1256, found: 234.1254.

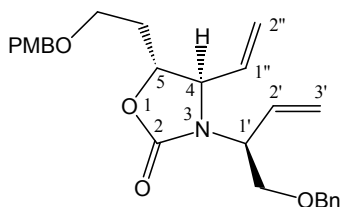
(+)-1-(4-Methoxyphenyl)methoxy-4*S*-[1*S*-phenylmethoxymethyl)-2-propenyl]amino-5-hepten-3*S*-ol (6) and its diastereomer (-)-1-(4-Methoxyphenyl)methoxy-4*R*-[1*S*-phenylmethoxymethyl)-2-propenyl]amino-5-hepten-3*R*-ol (6'). To a mixture of **4** (860 mg, 3.68 mmol) and (2*S*)-1-(phenylmethoxymethyl)but-3-enyl amine **5** (761 mg, 4.30 mmol) in dry acetonitrile (2 mL), in a thick walled glass tube, was added lithium triflate (860 mg, 5.51 mmol). The vessel was flushed with nitrogen and sealed and then stirred and heated at $120\text{ }^{\circ}\text{C}$ for 3 days. The mixture was then cooled to RT and all volatiles were removed *in vacuo* to give a dark sticky oil which was purified by column chromatography (0%-10% methanol/DCM) and semi-preparative TLC (6% MeOH/DCM) to give compound **6** (943

mg, 62%) and the diastereomer **6'** (262 mg, 17%) as yellow oils. Spectral data for **6**: $[\alpha]_D^{24} +3.4$ (*c* 3.2, CHCl₃); ¹H NMR δ 7.38-7.28 (m, 5H, Ar*H), 7.25 (d, 2H, *J* 8.7 Hz, ArH), 6.86 (d, 2H, *J* 8.7 Hz, ArH), 5.56-5.42 (m, 2H, H-5, H-2'), 5.21 (dd, 1H, *J* 10.5, 2.1 Hz, x =CH₂(Z)), 5.19 (dd, 1H, *J* 17.4, 2.1 Hz, =CH₂(E)), 5.16 (dd, 1H, *J* 9.9, 2.1 Hz, =CH₂(Z)), 5.10 (dd, 1H, *J* 17.4, 1.8 Hz, =CH₂(E)), 4.53 (d, 1H, *J* 12.0 Hz, Ar*CH_aCH_b), 4.48 (d, 1H, *J* 12.0 Hz, Ar*CH_aCH_b), 4.44 (s, 2H, ArCH₂), 3.79 (s, 3H, OMe), 3.63 (dd, 2H, *J* 6.6, 6.0 Hz, H-1), 3.50-3.35 (m, 4H, H-3, H-1', CH₂OBn), 2.88 (t, 1H, *J* 8.4 Hz, H-4), 1.86 (dddd, 1H, *J* 14.1, 7.2, 6.9, 2.7 Hz, H-2a), 1.62 (dddd, 1H, *J* 14.4, 9.3, 6.3, 6.0 Hz, H-2b); ¹³C NMR δ 159.0 (ArC), 137.9 (Ar*C), 137.4, 136.8 (CH-5, CH-2'), 130.4 (ArC), 129.2 (ArCH), 128.3, 127.6, 127.5 (3x Ar*CH), 118.3, 118.3 (CH₂-6, CH₂-3'), 113.6 (ArCH), 73.2 (CH₂OBn), 72.8 (Ar*CH₂), 72.6 (ArCH₂), 70.7 (CH-3), 67.5 (CH₂-1), 63.5 (CH-4), 57.3 (CH-1'), 55.1 (OMe), 33.4 (CH₂-2); MS (CI +ve) *m/z* 412 (M+1⁺, 100%); HRMS (CI +ve) Calcd for C₂₅H₃₄NO₄ (MH⁺) 412.2488, found: 412.2505. Spectral data for **6'**: $[\alpha]_D^{25} -5.6$ (*c* 2.3, CHCl₃); ¹H NMR δ 7.34-7.27 (m, 5H, Ar*H), 7.24 (d, 2H, *J* 8.7 Hz, ArH), 6.86 (d, 2H, *J* 8.4 Hz, ArH), 5.80 (ddd, 1H, *J* 17.4, 10.2, 6.6 Hz, H-2'), 5.61 (ddd, 1H, *J* 17.1, 10.5, 8.1 Hz, H-5), 5.22-5.08 (m, 4H, H-6, H-3'), 4.52 (s, 2H, ArCH₂ or Ar*CH₂), 4.43 (s, 2H, ArCH₂ or Ar*CH₂), 3.79 (s, 3H, OMe), 3.67-3.60 (m, 2H, H-1), 3.56-3.36 (m, 4H, H-2, H-1', CH₂OBn), 2.99 (t, 1H, *J* 8.1 Hz, H-4), 1.86 (dtd, 1H, *J* 14.1, 6.3, 2.7 Hz, H-2a), 1.63 (ddt, 1H, *J* 14.1, 9.3, 6.3 Hz, H-2b); ¹³C NMR δ 159.1 (ArC), 138.8 (CH-2'), 138.2 (Ar*C), 137.9 (CH-5), 130.3 (ArC), 129.2 (ArCH), 128.3, 127.6, 127.5 (3x Ar*CH), 117.8 (CH₂-6), 116.1 (CH₂-3'), 113.7 (ArCH), 73.1, 72.7 (Ar*CH₂ and ArCH₂), 72.9 (CH₂OBn), 71.6 (CH-3), 67.9 (CH₂-1), 65.0 (CH-4), 58.4 (CH-1'), 55.2 (OMe), 33.3 (CH₂-2); MS (CI +ve) *m/z* 412 (M+1⁺, 100%); HRMS (CI +ve) Calcd for C₂₅H₃₄NO₄ (MH⁺) 412.2488, found: 412.2474.

(+)-4S-Ethenyl-5S-[2-(4-methoxyphenyl)methoxy]ethyl-3-(1S-phenylmethoxymethyl-2-propenyl)-1,3-oxazolidin-2-one (7). A solution of **6** (226 mg, 0.549 mmol) in dry DCM (15 mL) was cooled to 0 °C and triethylamine (311 mg, 0.43 mL, 3.075 mmol) was added. A solution of triphosgene (82 mg, 0.275 mmol) in dry DCM (1 mL) was cooled to 0 °C and was then added to the above amine solution at 0 °C. TLC analysis (34% EtOAc/petrol) indicated complete disappearance of the compound **6**

after 2.5 h. The reaction was quenched with water (30 mL). The aqueous portion was extracted with DCM (4x). The combined organic portions were dried (MgSO₄) and filtered and the solvent was evaporated to give a yellow semi-solid. Chromatography of the residue eluting with (15%-40%) EtOAc/petrol gave diastereomerically pure compound **7** (226 mg, 94%) as a pale yellow oil. $[\alpha]_D^{28} +29.1$ (*c* 3.6, CHCl₃); ¹H NMR (500 MHz) δ 7.35-7.26 (m, 5H, Ar*H), 7.22 (d, 2H, *J* 8.5 Hz, ArH), 6.86 (d, 2H, *J* 8.5 Hz, ArH), 5.81 (ddd, 1H, *J* 17.5, 10.5, 7.5 Hz, H-2'), 5.69 (ddd, 1H, *J* 17.0, 10.0, 9.0 Hz, H-1''), 5.22 (dt, 1H, *J* 17.5, 1.0 Hz, H-3'a (*E*)), 5.19 (dt, 1H, *J* 10.5, 1.0 Hz, H-2''a), 5.18 (dt, 1H, *J* 10.5, 1.0 Hz, H-3'b), 5.11 (dt, 1H, *J* 17.0, 1.0 Hz, H-2''b), 4.59 (d, 1H, *J* 12.0 Hz, Ar*CH_aCH_b), 4.44 (d, 1H, *J* 12.0 Hz, Ar*CH_aCH_b), 4.40 (d, 1H, *J* 11.0 Hz, ArCH_aCH_b), 4.36 (d, 1H, *J* 11.5 Hz, ArCH_aCH_b), 4.36-4.32 (m, 1H, H-1'), 4.24 (td, 1H, *J* 7.5, 4.5 Hz, H-5), 3.90 (dd, 1H, *J* 9.0 7.5 Hz, H-4), 3.81 (dd, 1H, *J* 10.5, 9.5 Hz, CH_aCH_bOBn), 3.77 (s, 3H, OMe), 3.61 (dd, 1H, *J* 10.0, 5.5 Hz, CH_aCH_bOBn), 3.57-3.54 (m, 2H, CH₂CH₂O), 1.95-1.84 (m, 2H, CH₂CH₂O); ¹³C NMR δ 159.0 (ArC), 157.3 (CO), 137.6 (Ar*C), 135.9 (CH-2'), 133.3 (CH-1''), 123.0 (ArC), 129.2 (ArCH), 128.2, 127.8, 127.6 (3x Ar*CH), 120.3 (CH₂-2''), 118.4 (CH₂-3'), 113.6 (ArCH), 76.2 (CH-5), 72.7 (Ar*CH₂ and ArCH₂), 68.3 (CH₂OBn), 65.2 (CH₂CH₂O), 64.3 (CH-4), 56.0 (CH-1'), 55.1 (OMe), 33.4 (CH₂CH₂O); MS (CI +ve) *m/z* 438 (M+1⁺); HRMS (CI +ve) Calcd for C₂₆H₃₂NO₅ (MH⁺) 438.2280, found: 438.2262.

(+)-4*R*-Ethenyl-5*R*-[2-(4-methoxyphenyl)methoxy]ethyl-3-(1*S*-phenylmethoxymethyl-2-propenyl)-1,3-oxazolidin-2-one (7')



The same procedure described above for the preparation of **7** was used starting with **6'** (49 mg, 0.118 mmol) in dry DCM (5 mL), triethylamine (92 μ L, 0.66 mmol) and triphosgene (18 mg, 0.059 mmol) in dry DCM (1 mL). Compound **7'** (36 mg, 69%) was obtained as a pale yellow oil. $[\alpha]_D^{27} +12.7$ (*c* 1.8, CHCl₃); ¹H NMR δ 7.36-7.29 (m, 5H, Ar*H), 7.23 (d, 2H, *J* 8.7 Hz, ArH), 6.87 (d, 2H, *J* 8.7 Hz, ArH), 5.95 (ddd, 1H, *J* 17.7, 9.9, 6.6 Hz, H-2'), 5.69 (ddd, 1H, *J* 17.4, 9.6, 8.7 Hz, H-1''), 5.29-5.20 (m, 4H, H-3', H-2''), 4.54 (d, 1H, *J* 12.6 Hz, Ar*CH_aCH_b), 4.50 (d, 1H, *J* 12.3 Hz,

Ar*CH_aCH_b), 4.42 (d, 1H, *J* 11.4 Hz, ArCH_aCH_b), 4.37 (d, 1H, *J* 11.1 Hz, ArCH_aCH_b), 4.27 (ddd, 1H, *J* 7.8, 7.5, 4.8 Hz, H-5), 4.25-4.17 (m, 1H, H-1'), 3.98 (dd, 1H, *J* 8.7, 7.5 Hz, H-4), 3.91 (t, 1H, *J* 9.0 Hz, CH_aCH_bOBn), 3.80 (s, 3H, OMe), 3.59-3.53 (m, 3H, CH_aCH_bOBn, CH₂CH₂O), 1.98-1.81 (m, 2H, CH₂CH₂O); ¹³C NMR (one Ar*CH could not be observed) δ 159.2 (ArC), 156.9 (CO), 137.9 (Ar*C), 135.7 (CH-1''), 132.6 (CH-2'), 130.1 (ArC), 129.3 (ArCH), 128.3, 127.6 (2x Ar*CH), 120.5 (CH₂-2''), 118.8 (CH₂-3'), 113.7 (ArCH), 76.5 (CH-5), 73.0 (Ar*CH₂), 72.8 (ArCH₂), 69.8 (CH₂OBn), 66.2 (CH-4), 65.3 (CH₂CH₂O), 56.1 (CH-1'), 55.2 (OMe), 33.8 (CH₂CH₂O); MS (CI +ve) *m/z* 438 (M+1⁺); HRMS (EI +ve) Calcd for C₂₆H₃₁NO₅ (M⁺) 437.2202, found: 437.2202.

(-)-(1*S*,5*S*,7*aS*)-1-[2-(4-Methoxyphenyl)methoxy]ethyl-5-(phenylmethoxy)methyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one (8). Grubbs' Catalyst I (212 mg, 0.258 mmol) was added to a solution of **7** (520 mg, 1.19 mmol) in dry DCM (200 mL) under nitrogen. The mixture was heated at reflux under nitrogen for 25 h. TLC analysis (35% EtOAc/petrol) indicated incomplete conversion of compound **7**. Additional Grubbs' Catalyst I (85.0 mg, 0.103 mmol) was added and the reaction was continued under the same conditions for another 17 h. The reaction mixture was cooled and then the solvent was removed *in vacuo* to give a brown oil which was purified by column chromatography (25%-85% EtOAc/petrol) to give **8** (204 mg, 97%) as a light brown oil. [α]_D²⁶ -134.9 (c 2.1, CHCl₃); ¹H NMR (500 MHz) δ 7.34-7.26 (m, 5H, Ar*H), 7.23 (d, 2H, *J* 8.5 Hz, ArH), 6.87 (d, 2H, *J* 8.5 Hz, ArH), 5.96 (dt, 1H, *J* 5.5, 2.0 Hz, H-7), 5.87 (bd, 1H, *J* 6.0 Hz, H-6), 4.74-4.72 (m, 1H, H-5), 4.56 (d, 1H, *J* 12.0 Hz, Ar*CH_aCH_b), 4.53 (d, 1H, *J* 12.0 Hz, Ar*CH_aCH_b), 4.54-4.52 (m, 1H, H-1), 4.44 (d, 1H, *J* 11.5 Hz, ArCH_aCH_b), 4.44-4.43 (m, 1H, H-7a), 4.40 (d, 1H, *J* 11.5 Hz, ArCH_aCH_b), 3.77 (s, 3H, OMe), 3.61 (apparent dd, 2H, *J* 7.0, 5.0 Hz, CH₂CH₂O), 3.53 (dd, 1H, *J* 10.0, 5.0 Hz, CH_aCH_bOBn), 3.50 (dd, 1H, *J* 10.0, 5.5 Hz, CH_aCH_bOBn), 2.14-2.02 (m, 2H, CH₂CH₂O); ¹³C NMR one ArC could not be observed δ 161.7 (CO), 158.8 (ArC), 137.5 (Ar*C), 131.4 (CH-7), 129.5 (CH-6), 128.9 (ArCH), 127.9, 127.2, 127.1 (3x Ar*CH), 113.3 (ArCH), 79.4 (CH-1), 72.8 (Ar*CH₂), 72.5 (ArCH₂), 70.9 (CH₂OBn), 70.0 (CH-7a), 66.0 (CH-5), 65.2

(CH₂CH₂O), 54.8 (OMe), 35.1 (CH₂CH₂O); MS (CI +ve) *m/z* 410 (M+1⁺); HRMS (CI +ve) Calcd for C₂₄H₂₈NO₅ (M⁺) 410.1967, found: 410.1929.

(-)-(1*S*,5*S*,6*R*,7*S*,7*aS*)-1-[2-(4-Methoxyphenyl)methoxy]ethyl-5-

(phenylmethoxy)methyl-5,6,7,7*a*-tetrahydro-6,7-dihydroxy-1*H*,3*H*-pyrrolo[1,2-

c]oxazol-3-one (9). To a solution of **8** (170 mg, 0.416 mmol) in acetone (3 mL) were added water (2 mL), 4-morpholine *N*-oxide (107 mg, 0.916 mmol) and potassium osmate dihydrate (15 mg, 0.042 mmol). The mixture was stirred at RT for 21 h. Then all volatiles were removed *in vacuo*. The residue was dissolved in toluene and evaporated to dryness *in vacuo* to give a dark, semi-solid which was chromatographed on silica gel (eluting with 0%-7.5% methanol/DCM) to afford compound **9** as a brown oil (156 mg, 85%). [α]_D²⁴ -84.0 (*c* 1.3, CHCl₃); ¹H NMR (500 MHz) δ 7.26-7.17 (m, 5H, Ar*H), 7.14 (d, 2H, *J* 8.0 Hz, ArH), 6.78 (d, 2H, *J* 9.0 Hz, ArH), 4.79 (ddd, 1H, *J* 7.5, 5.5, 2.5 Hz, H-1), 4.48 (d, 1H, *J* 12.0 Hz, Ar*CH_aCH_b), 4.45 (d, 1H, *J* 12.0 Hz, Ar*CH_aCH_b), 4.34 (d, 1H, *J* 11.5 Hz, ArCH_aCH_b), 4.30 (d, 1H, *J* 11.5 Hz, ArCH_aCH_b), 4.26 (dd, 1H, *J* 5.0, 4.0 Hz, H-6), 3.82 (bs, 1H, H-7), 3.70 (s, 3H, OMe), 3.64-3.62 (m, 2H, H-5, CH_aCH_bOBn), 3.57-3.54 (m, 2H, H-7a, CH_aCH_bOBn), 3.52-3.49 (m, 2H, CH₂CH₂O), 1.99-1.92 (m, 1H, CH_aCH_bCH₂O), 1.91-1.84 (m, 1H, CH_aCH_bCH₂O); ¹³C NMR δ 161.8 (CO), 159.2 (ArC), 137.8 (Ar*C), 129.9 (ArC), 129.4 (ArCH), 128.4, 127.8, 127.6 (3x Ar*CH), 113.8 (ArCH), 76.9 (CH-6), 73.5 (Ar*CH₂), 73.1 (CH-1), 73.0 (ArCH₂), 71.5 (CH-7), 70.2 (CH₂OBn), 66.6 (CH-7a), 65.7 (CH₂CH₂O), 62.0 (CH-5), 55.3 (OMe), 35.3 (CH₂CH₂O); MS (CI +ve) *m/z* 444 (M+1⁺); HRMS (EI +ve) Calcd for C₂₄H₂₉NO₇ (M⁺) 443.1944, found: 443.1943.

(-)-(1*S*,5*R*,6*R*,7*S*,7*aS*)-6,7-Diacetoxy-1-[2-(4-methoxyphenyl)methoxy]ethyl-5-

(phenylmethoxy)methyl-5,6,7,7*a*-tetrahydro-1*H*,3*H*-pyrrolo[1,2-c]oxazol-3-one (10).

Compound **9** (174 mg, 0.394 mmol) was dissolved in anhydrous pyridine (2.0 mL) and then Ac₂O (2.0 mL) was added. The mixture was stirred at RT for 23 h, then diluted with DCM (30 mL) and washed with saturated aqueous NaHCO₃ solution at 0 °C. The aqueous portion was extracted with DCM (4x). The combined organic portions were

dried (MgSO₄), filtered and evaporated *in vacuo* to give an oil which was purified by column chromatography (30%-50% EtOAc/petrol) to give product **10** as a pale yellow oil (174 mg, 84%). $[\alpha]_D^{26}$ -13.9 (*c* 2.3, CHCl₃); ¹H NMR δ 7.33-7.27 (m, 5H, Ar*H), 7.21 (d, 2H, *J* 8.7 Hz, ArH), 6.87 (d, 2H, *J* 8.4 Hz, ArH), 5.56 (dd, 1H, *J* 6.6, 3.6 Hz, H-6), 5.37 (t, 1H, *J* 3.6 Hz, H-7), 4.60 (ddd, 1H, *J* 7.5, 6.0, 3.9 Hz, H-1), 4.58 (d, 1H, *J* 11.7 Hz, Ar*CH_aCH_b), 4.52 (d, 1H, *J* 12.0 Hz, Ar*CH_aCH_b), 4.43 (d, 1H, *J* 11.4 Hz, ArCH_aCH_b), 4.38 (d, 1H, *J* 11.7 Hz, ArCH_aCH_b), 3.96-3.91 (m, 2H, H-5, H-7a), 3.79 (s, 3H, OMe), 3.70 (dd, 1H, *J* 10.2, 3.6 Hz, CH_aCH_bOBn), 3.63 (dd, 1H, *J* 10.2, 3.0 Hz, CH_aCH_bOBn), 3.56 (dd, 2H, *J* 6.6, 5.4 Hz, OCH₂CH₂), 2.15-1.94 (m, 2H, OCH₂CH₂), 2.10 (s, 3H, Ac), 1.99 (s, 3H, Ac); ¹³C NMR δ 169.8 (CO, Ac), 169.6 (CO, Ac), 160.7 (CO-3), 159.2 (ArC), 137.6 (Ar*C), 129.8 (ArC), 129.2 (ArCH), 128.3, 127.6, 127.4 (3x Ar*CH), 113.7 (ArCH), 74.3 (CH-6), 73.3 (Ar*CH₂), 72.9 (CH-1), 72.8 (ArCH₂), 72.1 (CH-7), 68.9 (CH₂OBn), 65.1 (OCH₂CH₂), 64.7 (CH-7a), 59.9 (CH-5), 55.1 (OMe), 35.0 (OCH₂CH₂), 20.5 (CH₃, Ac), 20.3 (CH₃, Ac); MS (CI +ve) *m/z* 528 (M+1⁺); HRMS (CI +ve) Calcd for C₂₈H₃₄NO₉ (MH⁺) 528.2234, found: 528.2257.

(-)-(1S,5R,6R,7S,7aS)-6,7-Diacetoxy-1-(2-hydroxy)ethyl-5-(phenylmethoxy) methyl-5,6,7,7a-tetrahydro-1H,3H-pyrrolo[1,2-c]oxazol-3-one (11). To a solution of **10** (227 mg, 0.432 mmol) in dichloromethane (30 mL) and water (2.5 mL) was added 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (137 mg, 0.604 mmol). After the mixture was stirred at RT for 2.5 h, TLC analysis (70% EtOAc/petrol) indicated the presence of compound **10**. Additional DDQ (59 mg, 0.259 mmol) was then added to the mixture. The reaction was continued for another 3 h. The mixture was diluted with water (25 mL) and extracted with DCM (4x). The combined organics were dried (MgSO₄) and filtered and the solvent was removed under reduced pressure to give a red, semi-solid that was purified by column chromatography (40%-90% EtOAc/petrol) to give the product **11** as a pale yellow oil (114 mg, 65%). $[\alpha]_D^{25}$ -4.6 (*c* 2.0, CHCl₃); ¹H NMR δ 7.36-7.24 (m, 5H, Ar*H), 5.56 (dd, 1H, *J* 6.6, 3.6 Hz, H-6), 5.41 (t, 1H, *J* 3.6 Hz, H-7), 4.62 (ddd, 1H, *J* 7.8, 5.7, 3.6 Hz, H-1), 4.58 (d, 1H, *J* 12.0 Hz, Ar*CH_aCH_b), 4.52 (d, 1H, *J* 12.3 Hz, Ar*CH_aCH_b), 3.96-3.91 (m, 2H, H-7a, H-5), 3.78 (bt, 2H, *J* 5.7 Hz, CH₂CH₂OH), 3.71 (dd, 1H, *J* 10.2, 3.6 Hz, CH_aCH_bOBn), 3.62 (dd, 1H, *J* 10.2, 3.0 Hz, CH_aCH_bOBn), 2.22

(bs, 1H, OH), 2.13-1.85 (m, 2H, $\underline{\text{CH}_2\text{CH}_2\text{OH}}$), 2.11 (s, 3H, Ac), 1.99 (s, 3H, Ac); ^{13}C NMR δ 170.1, 169.8 (2x CO, Ac), 160.7 (CO-3), 137.6 (Ar*C), 128.4, 127.7, 127.5 (3x Ar*CH), 74.3 (CH-6), 73.4 (Ar*CH₂), 73.0 (CH-1), 72.2 (CH-7), 68.9 ($\underline{\text{CH}_2\text{OBn}}$), 64.9 (CH-7a), 59.9 (CH-5), 58.2 ($\underline{\text{CH}_2\text{CH}_2\text{OH}}$), 37.3 ($\underline{\text{CH}_2\text{CH}_2\text{OH}}$), 20.6, 20.4 (2x CH₃, Ac); MS (CI +ve) m/z 408 (M+1⁺, 100%); HRMS (CI +ve) Calcd for C₂₀H₂₆NO₈ (MH⁺) 408.1658, found: 408.1666.

Four Step Synthesis of (-)-(1S,2R,3R,7S,7aR)-1,2,7-Triacetoxy-3-(acetoxymethyl)hexahydro-1H-pyrrolizine (15) from 13.

(+)-(2S,3R,4S,5R)-5-[(1S)-1,3-Dihydroxypropyl]-2-[(phenylmethoxy)methyl]pyrrolizine-3,4-diol (13). To a solution of **12** (174 mg, 0.429 mmol) in ethanol (6 mL) was added sodium hydroxide (171 mg, 4.285 mmol). The reaction was heated at 70 °C in a sealed tube for 37 h. The volatiles were then removed *in vacuo* to give a yellow solid, and the residue was treated with 1M hydrochloric acid (6 mL). The volatiles were removed *in vacuo* to give a yellow solid that was purified by acidic ion-exchange chromatography to give the desired compound **12** (ca 168 mg) as a yellow solid. This compound appeared pure by NMR analysis but from the mass recovery (>100%) this material was believed to contain salts. Spectral data for **12**: ^1H NMR (CD₃OD) δ 7.42-7.26 (m, 5H, Ar*H), 4.66 (d, 1H, J 11.7Hz, Ar*CH_aCH_b), 4.60 (d, 1H, J 11.7 Hz, Ar*CH_aCH_b), 4.24 (dd, 1H, J 8.7, 3.9 Hz, H-3), 4.22-4.16 (m, 2H, H-4, CHOH), 3.86 (dd, 1H, J 10.5, 3.3 Hz, CH_aCH_bOBn), 3.82-3.76 (m, 3H, CH_aCH_bOBn, CH₂CH₂OH), 3.69 (ddd, 1H, J 8.7, 6.0, 3.0 Hz, H-2), 3.53 (dd, 1H, J 9.0, 3.0 Hz, H-5), 1.92 (dtd, 1H, J 14.1, 7.2, 3.0 Hz, CH_aCH_bCH₂OH), 1.67 (ddt, 1H, J 14.4, 9.0, 5.7 Hz, CH_aCH_bCH₂OH); ^{13}C NMR (CD₃OD) δ 138.9 (Ar*C), 129.4, 129.0, 128.9 (3x Ar*CH), 74.3 (Ar*CH₂), 73.5 (CH-3), 71.6 (CH-4), 67.9 ($\underline{\text{CH}_2\text{OBn}}$), 67.6 (CH-5), 66.8 (CHOH), 61.7 (CH-2), 59.1 ($\underline{\text{CH}_2\text{CH}_2\text{OH}}$), 37.5 ($\underline{\text{CH}_2\text{CH}_2\text{OH}}$); MS (CI +ve) m/z 298 (M+1⁺, 100%); HRMS (CI +ve) Calcd for C₁₅H₂₄NO₅ (MH⁺) 298.1654, found: 298.1658.

(-)-(1S,2R,3R,7S,7aR)-1,2,7-Triacetoxy-3-(acetoxymethyl)hexahydro-1H-pyrrolizine (15). To a stirred mixture of **12** obtained above, triphenylphosphine (157 mg, 0.600

mmol) and anhydrous pyridine (5 mL) at 0 °C was added dropwise diisopropyl azodicarboxylate (0.12 mL, 0.60 mmol) under nitrogen. The mixture was stirred at 0 °C for 4 h and then warm up to RT for 3 h. The volatiles were removed *in vacuo* then 1M hydrochloric acid (15 mL) and DCM (15 mL) were added. The aqueous layer was washed with DCM (15 mL) and then concentrated *in vacuo* to give a yellow solid, which was purified by acidic ion-exchange chromatography to give **13**. This material was dissolved in methanol (2 mL) and palladium chloride (21 mg, 0.118 mmol) was added. The mixture was stirred under one atmosphere of hydrogen (H₂ balloon) at RT for 1.5 h. The mixture was then filtered through a plug of cotton wool and the solvent was removed under reduced pressure to give **14** as a pale yellow oil. This oil was then dissolved in anhydrous pyridine (1mL) and Ac₂O (1 mL) was added to the solution. The mixture was stirred at RT for 22 h, then diluted with DCM (20 mL) and washed with saturated NaHCO₃ solution at 0°C. The aqueous portion was extracted with DCM (3x). The combined organic portions were dried (MgSO₄), filtered and evaporated *in vacuo* to give a solid which was purified by column chromatography (35%-90% EtOAc/petrol) to give **15** as a pale yellow oil (21 mg, 23% overall for 4 steps). $[\alpha]_D^{26}$ -19.0 (*c* 2.1, CHCl₃); ¹H NMR δ 5.44 (t, 1H, *J* 3.9 Hz, H-1), 5.31 (dd, 1H, *J* 15.3, 7.8 Hz, H-7), 5.10 (dd, 1H, *J* 9.3, 4.2 Hz, H-2), 4.20 (dd, 1H, *J* 11.4, 4.2 Hz, CH_aCH_bOAc), 4.04 (dd, 1H, *J* 11.4, 5.4 Hz, CH_aCH_bOAc), 3.87 (dd, 1H, *J* 7.5, 3.9 Hz, H-7a), 3.32 (ddd, 1H, *J* 9.6, 5.7, 4.2 Hz, H-3), 3.18 (dt, 1H, *J* 11.1, 7.8 Hz, H-5a), 2.95 (ddd, 1H, *J* 11.1, 7.2, 5.4 Hz, H-5b), 2.14-1.92 (m, 2H, H-6), 2.11 (s, 3H, Ac), 2.09 (s, 3H, Ac), 2.03 (s, 3H, Ac), 2.01 (s, 3H, Ac); ¹³C NMR δ 170.8, 170.4, 169.6, 169.4 (4x CO), 74.4 (CH-7), 73.7 (CH-2), 71.7 (CH-1), 66.7 (CH-3), 65.0 (CH₂OAc), 64.7 (CH-7a), 52.3 (CH₂-5), 30.9 (CH₂-6), 21.0, 20.8, 20.7, 20.4 (4x CH₃, Ac); MS (CI +ve) *m/z* 358 (M+1⁺, 100%); HRMS (CI +ve) Calcd for C₁₆H₂₄NO₈ (MH⁺) 358.1502, found: 358.1485.

(+)-(1S,2R,3R,7S,7aR)-Hexahydro-3-hydroxymethyl-1H-pyrrolizine-1,2,7-triol, [(+)-1-Epiaustraline] (1). To a solution of **15** (21 mg, 0.109 mmol) in methanol (2 mL) was added Amberlyst A-26 resin (50 mg). The reaction mixture was stirred for 2 h at RT. The TLC analysis indicated the complete conversion. The mixture was then filtered

through a sintered glass frit and rinsed with methanol. The filtrate was concentrated to give the title compound (11 mg) as a colorless oil. $[\alpha]_D^{25} +14.3$ (c 1.1, H_2O) [lit.^{10a} $[\alpha]_D^{25} +13.695$ (c 1.72, H_2O)]; The 1H and ^{13}C NMR spectral data for this compound were essentially identical to that reported in the literature.¹⁰ 1H NMR (500 MHz, D_2O) δ 4.57 (dt, 1H, J 5.0, 4.5 Hz, H-7), 4.40 (t, 1H, J 5.0 Hz, H-1), 3.91 (dd, 1H, J 9.0, 4.5 Hz, H-2), 3.80 (dd, 1H, J 11.5, 4.0 Hz, CH_aCH_bOH), 3.63 (dd, 1H, J 11.5, 7.0 Hz, CH_aCH_bOH), 3.46 (t, 1H, J 5.0 Hz, H-7a), 3.17 (ddd, 1H, J 10.5, 7.0, 4.0 Hz, H-5a), 3.02 (ddd, 1H, J 9.0, 6.5, 4.0 Hz, H-3), 2.93 (ddd, 1H, J 10.5, 9.5, 6.5 Hz, H-5b), 2.04 (ddt, 1H, J 13.5, 6.5, 4.0 Hz, H-6a), 1.96 (dddd, 1H, J 13.5, 9.5, 7.0, 5.0 Hz, H-6b); ^{13}C NMR (D_2O) δ 75.2 (CH-2), 73.7 (CH-7), 72.7 (CH-1), 70.6 (CH-3), 66.6 (CH-7a), 63.6 (CH_2OH), 52.7 (CH_2 -5), 35.9 (CH_2 -6); MS (CI +ve) m/z 190 ($M+1^+$, 100%); HRMS (EI +ve) Calcd for $C_8H_{15}NO_4$ (M^+) 189.1001, found: 189.0995.

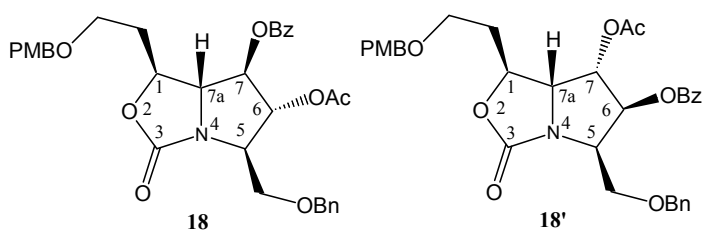
(-)-(3a*S*,3b*R*,4*S*,8*R*,8a*R*)-4-[2-(4-Methoxyphenyl)methoxy]ethyl-8-phenylmethoxymethyltetrahydro-3a*H*-[1,3,2]dioxathio[4',5':3,4]pyrrolo[1,2-*c*][1,3]oxazol-6-one 2,2-dioxide (16). To a solution of **9** (190 mg, 0.430 mmol) in DCM (5 mL) was added Et_3N (0.14 mL, 0.988 mmol) followed by thionyl chloride (39.2 μ L, 0.537 mmol) at 0 °C. The mixture was stirred for 30 min at 0 °C and water (15 mL) was added to the mixture. The aqueous layer was extracted with DCM (4x). The combined organic phases were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a brown oil. The crude cyclic sulfite was used in the next step without further purification. The crude cyclic sulfite obtained above was dissolved in 7 mL of a solution of CCl_4 : CH_3CN : H_2O (2: 2: 3, v/v/v) and $RuCl_3 \cdot 3H_2O$ (6 mg, 0.024 mmol) was added followed by $NaIO_4$ (175 mg, 0.816 mmol). The mixture was stirred at RT for 2.5 h and then diluted with diethyl ether (20 mL) and water (20 mL). The organic layer was washed with saturated aqueous sodium bicarbonate solution followed by brine and then dried ($MgSO_4$). The solvent was evaporated and then purification of the residue by column chromatography (35%-50% EtOAc/petrol) gave compound **16** (191 mg, 88%) as a pale yellow oil. $[\alpha]_D^{24} -52.9$ (c 2.0, $CHCl_3$); 1H NMR δ 7.37-7.34 (m, 5H, Ar*H), 7.22-7.19 (m, 2H, Ar*H), 7.20 (d, 2H, J 8.7 Hz, ArH), 6.86 (d, 2H, J 8.7 Hz, ArH), 5.35 (dd, 1H, J

5.4, 0.9 Hz, H-8a), 5.04 (t, 1H, J 5.4 Hz, H-3a), 4.78 (td, 1H, J 6.6, 3.9 Hz, H-4), 4.49 (d, 1H, J 12.0 Hz, ArCH_aCH_b or Ar*CH_aCH_b), 4.43-4.39 (m, 2H, ArCH_aCH_b or Ar*CH_aCH_b and H-8), 4.39 (s, 2H, ArCH₂ or Ar*CH₂), 4.25 (dd, 1H, J 4.8, 3.9 Hz, H-3b), 3.78 (s, 3H, OMe), 3.73-3.57 (m, 4H, CH₂OBn and CH₂CH₂O), 2.14-2.07 (m, 2H, CH₂CH₂O); ¹³C NMR δ 159.3 (ArC), 158.7 (CO-6), 136.6 (Ar*C), 129.7 (ArC), 129.4, 128.7, 128.3, 127.7 (3x Ar*CH and 1x ArCH), 113.8 (ArCH), 87.6 (CH-8a), 84.4 (CH-3a), 73.8 (ArCH₂ or Ar*CH₂), 73.7 (CH-4), 73.1 (Ar*CH₂ or ArCH₂), 70.9 (CH₂OBn), 67.1 (CH-3b), 65.7 (CH₂CH₂O), 62.3 (CH-8), 55.2 (OMe), 34.9 (CH₂CH₂O); MS (CI +ve) m/z 506 (M+1⁺); HRMS (EI +ve) Calcd for C₂₄H₂₇NO₉S (M⁺) 505.1407, found: 505.1426.

(-)-(1S,5S,6R,7R,7aS)-6-Hydroxyl-1-[2-(4-methoxyphenyl)methoxy]ethyl-7-phenylcarbonyloxy-5-phenylmethoxymethyltetrahydro-1H-pyrrolo[1,2-c][1,3]oxazol-3-one (17). To a solution of **16** (192 mg, 0.381 mmol) in DMF (8 mL) was added benzoic acid (79 mg, 0.65 mmol) followed by cesium carbonate (186 mg, 0.572 mmol). The mixture was stirred under nitrogen at 40 °C for 3 h. DMF was removed under reduced pressure and the residue was suspended in THF (8 mL). Water (20 drops) followed by concentrated sulfuric acid (4 drops) was added and the suspension became a clear solution. The solution was stirred at RT for 9.5 h. The volatiles were removed *in vacuo* to give a semi-solid which was purified by column chromatography (20%-60% EtOAc/petrol) to give **18** (184 mg, 88%) as a mixture (73:27) of regioisomers as a colourless oil. Spectral data for the major isomer: ¹H NMR δ 7.96 (d, 2H, J 7.8 Hz, BzH), 7.60 (td, 1H, J 7.5, 0.6 Hz, BzH), 7.43 (t, 2H, J 7.8 Hz, BzH), 7.32-7.26 (m, 5H, Ar*H), 7.18 (d, 2H, J 8.4 Hz, ArH), 6.81 (d, 2H, J 7.8 Hz, ArH), 5.01 (dd, 1H, J 6.3, 4.2 Hz, H-7), 4.97 (dt, 1H, J 7.2, 5.1 Hz, H-1), 4.61 (t, 1H, J 3.6 Hz, H-6), 4.58 (s, 2H, Ar*CH₂), 4.36 (s, 2H, ArCH₂), 4.10 (bdd, 1H, J 9.0, 5.1 Hz, H-5), 3.88 (dd, 1H, J 6.3, 5.1 Hz, H-7a), 3.76 (s, 3H, OMe), 3.75-3.58 (m, 4H, CH₂OBn, CH₂CH₂O), 2.11-2.00 (m, 2H, CH₂CH₂O); ¹³C NMR δ 166.6 (CO, Bz), 160.6 (CO-3), 159.0 (ArC), 137.7 (Ar*C), 133.6 (CH, Bz), 123.0 (ArC), 129.7, 129.2, 128.5, 128.4, 127.7, 127.5 (1x ArCH, 3x Ar*CH and 2x BzCH), 128.7 (C, Bz), 113.7 (ArCH), 84.3 (CH-7), 79.0 (CH-6), 78.3 (CH-1), 73.3 (Ar*CH₂), 72.7 (ArCH₂), 69.6 (CH₂OBn), 67.7 (CH-7a), 65.4 (CH₂CH₂O), 64.4 (CH-5), 55.2 (OMe), 35.2 (CH₂CH₂O), 20.8 (CH₃, Ac); MS (ES +ve) m/z 548 (M+1⁺,

25%), 570 ($M+Na^+$, 100%); HRMS (ES +ve) Calcd for $C_{31}H_{34}NO_8$ (MH^+) 548.2284, found: 548.2284.

(-)-(1*S*,5*R*,6*R*,7*R*,7*aS*)-6-Acetoxy-1-[2-(4-methoxyphenyl)methoxy]ethyl-7-phenylcarbonyloxy-5-phenylmethoxymethyltetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (18) and (1*S*,5*R*,6*S*,7*S*,7*aS*)-7-Acetoxy-1-[2-(4-methoxyphenyl)methoxy]ethyl-6-phenylcarbonyloxy-5-phenylmethoxymethyltetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (18')



The same procedure described above for the preparation of **10** was used starting with **17** (224 mg, 0.409 mmol), Ac_2O (2.0 mL) in anhydrous pyridine (2

mL). Compounds **18** (160 mg, 66%) and its regioisomer **18'** (61 mg, 25%) were obtained respectively, as pale yellow oils. Spectral data for **18**: $[\alpha]_D^{23}$ -30.1 (c 1.1, $CHCl_3$); 1H NMR δ 7.94 (dt, 2H, J 8.4, 1.2 Hz, BzH), 7.60 (tt, 1H, J 7.8, 1.2 Hz, BzH), 7.43 (t, 2H, J 8.1 Hz, BzH), 7.33-7.28 (m, 2H, Ar*H), 7.26-7.23 (m, 3H, Ar*H), 7.18 (d, 2H, J 9.0 Hz, ArH), 6.81 (d, 2H, J 9.0 Hz, ArH), 5.60 (t, 1H, J 3.6 Hz, H-6), 5.15 (dd, 1H, J 6.0, 3.3 Hz, H-7), 5.06 (ddd, 1H, J 7.8, 4.8, 3.9 Hz, H-1), 4.59 (s, 2H, Ar*CH₂), 4.36 (s, 2H, ArCH₂), 4.15 (dd, 1H, J 6.6, 3.9 Hz, H-5), 3.93 (dd, 1H, J 6.3, 4.2 Hz, H-7a), 3.86 (dd, 1H, J 9.6, 3.6 Hz, CH_aCH_bOBn), 3.78 (s, 3H, OMe), 3.72 (dd, 1H, J 9.6, 4.2 Hz, CH_aCH_bOBn), 3.64-3.57 (m, 2H, CH₂CH₂O), 2.19-1.98 (m, 2H, CH₂CH₂O), 2.09 (s, 3H, Ac); ^{13}C NMR δ 170.3 (CO, Ac), 166.0 (CO, Bz), 160.0 (CO-3), 159.1 (ArC), 137.7 (Ar*C), 133.6 (CH, Bz), 130.1 (ArC), 129.7, 129.2, 128.5, 128.4, 127.7, 127.3 (1x ArCH, 3x Ar*CH and 2x BzCH), 128.6 (C, Bz), 113.7 (ArCH), 82.7 (CH-7), 81.0 (CH-6), 78.3 (CH-1), 73.4 (Ar*CH₂), 72.7 (ArCH₂), 70.4 (CH₂OBn), 69.0 (CH-7a), 65.4 (CH₂CH₂O), 63.4 (CH-5), 55.2 (OMe), 35.3 (CH₂CH₂O), 20.8 (CH₃, Ac); MS (ES +ve) m/z 590 ($M+1^+$, 12%), 612 ($M+Na^+$, 100%); HRMS (ES +ve) Calcd for $C_{33}H_{36}NO_9$ (MH^+) 590.2390, found: 590.2379. HRMS (EI +ve) Calcd for $C_{33}H_{35}NO_9$ (M^+) 589.2312, found: 589.2300. Spectral data for **18'**: 1H NMR (500 MHz) δ 7.91 (dd, 2H, J 8.0, 1.5 Hz, BzH),

7.60 (tt, 1H, *J* 7.5, 1.5 Hz, BzH), 7.43 (t, 2H, *J* 8.5 Hz, BzH), 7.20-7.13 (m, 7H, 2x ArH, 5x Ar*H), 6.76 (d, 2H, *J* 9.0 Hz, ArH), 5.74 (dd, 1H, *J* 6.0, 2.0 Hz, H-6), 5.26 (dd, 1H, *J* 4.0, 2.0 Hz, H-7), 4.53 (td, 1H, *J* 6.5, 4.0 Hz, H-1), 4.45-4.35 (m, 5H, ArCH₂, Ar*CH₂, H-5), 4.19 (t, 1H, *J* 4.0 Hz, H-7a), 3.71 (s, 3H, OMe), 3.80-3.57 (m, 4H, CH₂OBn, CH₂CH₂O), 2.11 (s, 3H, Ac), 2.17-2.04 (m, 2H, CH₂CH₂O); ¹³C NMR (125 MHz) δ 169.6 (CO, Ac), 164.5 (CO, Bz), 160.9 (CO-3), 159.2 (ArC), 137.4 (Ar*C), 133.5 (CH, Bz), 131.5 (ArC), 129.7 (CH, Bz), 129.2, 128.5, 128.3, 127.6, 127.6 (1x ArCH, 3x Ar*CH, 1x BzCH), 129.0 (C, Bz), 113.7 (ArCH), 76.9 (CH-6), 75.8 (CH-7), 73.5, 73.0 (ArCH₂, Ar*CH₂), 73.5 (CH-1), 67.3 (CH₂OBn), 65.6 (CH₂CH₂O), 65.5 (CH-7a), 59.2 (CH-5), 55.1 (OMe), 35.2 (CH₂CH₂O), 20.7 (CH₃, Ac); MS (ES +ve) *m/z* 590 (M+1⁺, 13%), 612 (M+Na⁺, 100%); HRMS (ES +ve) Calcd for C₃₃H₃₆NO₉ (MH⁺) 590.2390, found: 590.2374.

(-)-(1*S*,5*R*,6*R*,7*R*,7*aS*)-6-Acetoxy-1-(2-hydroxy)ethyl-7-phenylcarbonyloxy-5-(phenylmethoxy)methyl-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (19). The same procedure described above for the preparation of **11** was used starting with **18** (61 mg, 0.104 mmol) and DDQ (33 mg, 0.146 mmol) in a solution of DCM (10 mL) containing water (0.5 mL). After the mixture had stirred at RT for 3 h, TLC analysis (60% EtOAc/petrol) indicated the presence of compound **18**. Additional DDQ (14 mg, 0.062 mmol) was then added to the mixture. The reaction was continued for another 1 h. Compound **19** (33 mg, 67%) was obtained as a pale yellow oil. [α]_D²⁴ -54.7 (*c* 1.6, CHCl₃); ¹H NMR δ 7.96 (dt, 2H, *J* 8.4, 1.5 Hz, BzH), 7.62 (tt, 1H, *J* 7.5, 1.5 Hz, BzH), 7.45 (t, 2H, *J* 7.8 Hz, BzH), 7.33-7.29 (m, 2H, Ar*H), 7.27-7.21 (m, 3H, Ar*H), 5.63 (dd, 1H, *J* 3.0, 2.4 Hz, H-6), 5.15-5.09 (m, 2H, H-1, H-7), 4.61 (s, 2H, Ar*CH₂), 4.16 (td, 1H, *J* 3.9, 2.4 Hz, H-5), 3.90-3.85 (m, 2H, H-7a, CH₂CH₂OBn), 3.82-3.80 (m, 2H, CH₂CH₂OH), 3.74 (dd, 1H, *J* 9.6, 4.2 Hz, CH₂CH₂OBn), 2.16-1.95 (m, 2H, CH₂CH₂OH), 2.09 (s, 3H, Ac); ¹³C NMR δ 170.3 (CO, Ac), 166.5 (CO, Bz), 159.8 (CO-3), 137.6 (Ar*C), 133.8, 129.8 (2x CH, Bz), 128.4 (C, Bz), 128.6, 128.4, 127.7, 127.3 (3x Ar*CH, 1x BzCH), 83.3 (CH-7), 81.1 (CH-6), 78.5 (CH-1), 73.4 (Ar*CH₂), 70.4 (CH₂OBn), 69.2 (CH-7a), 63.4 (CH-5), 58.5 (CH₂CH₂OH), 37.8 (CH₂CH₂OH), 20.8 (CH₃, Ac); MS (ES

+ve) m/z 470 ($M+1^+$, 8%), 492 ($M+Na^+$, 100%); HRMS (ES +ve) Calcd for $C_{25}H_{28}NO_8$ (MH^+) 470.1815, found: 470.1797.

(+)-(2*S*,3*R*,4*R*,5*R*)-5-[(1*S*)-1,3-Dihydroxypropyl]-2-(phenylmethoxy)methyl pyrrolizine-3,4-diol (20). The same procedure described above for the preparation of **12** was used starting with **19** (32 mg, 0.067 mmol) and sodium hydroxide (427 mg, 0.674 mmol) in a solution of ethanol (1 mL). Compound **20** (15 mg, 76%) was obtained as a pale yellow oil. $[\alpha]_D^{25} +21.4$ (c 1.5, MeOH); 1H NMR (CD_3OD) δ 7.38-7.23 (m, 5H, Ar*H), 4.55 (s, 2H, Ar*CH₂), 3.84-3.69 (m, 5H, H-3, H-4, CHOH, CH₂CH₂OH), 3.64 (dd, 1H, J 9.6, 3.9 Hz, CH_aCH_bOBn), 3.51 (dd, 1H, J 9.6, 6.9 Hz, CH_aCH_bOBn), 3.10 (dt, 1H, J 6.9, 3.6 Hz, H-2), 2.80 (dd, 1H, J 6.9, 5.4 Hz, H-5), 1.78 (dtd, 1H, J 14.1, 6.9, 3.6 Hz, CH_aCH_bCH₂OH), 1.65 (ddt, 1H, J 14.7, 9.0, 5.7 Hz, CH_aCH_bCH₂OH); ^{13}C NMR (CD_3OD) δ 139.6 (Ar*C), 129.4, 128.9, 128.7 (3x Ar*CH), 80.1, 80.0 (CH-3, CH-4), 74.3 (Ar*CH₂), 72.5 (CH₂OBn), 69.7 (CHOH), 67.1 (CH-5), 62.3 (CH-2), 60.0 (CH₂CH₂OH), 38.0 (CH₂CH₂OH); MS (ES +ve) m/z 298 ($M+1^+$, 100%); HRMS (ES +ve) Calcd for $C_{15}H_{24}NO_5$ (MH^+) 298.1654, found: 298.1654.

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GRAPHICAL ABSTRACT

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