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Abstract

A diastereoselective and modular approach to the synthesis of the 3-hydroxymethyl-2,3,5,6,7,7*a*-hexahydro-1H-pyrrolizine-1,2,7-triol structure, characteristic of several natural pyrrolizidine natural products has been developed. This approach culminated in the synthesis of (-)-7-epiaustraline and (+)-1,7-diepiaustraline. The oxazolidinone group has been found to be a useful protecting group in the RCM reaction and, as part of a pyrrolo[1,2-*c*]oxazol-3-one ring system, has functioned as a stereo- and regio-directing group, in a key diastereoselective *cis*-dihydroxylation reaction and a regioselective nucleophilic ring-opening of a *S*,*S*-dioxo-dioxathiole.

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Asymmetric Synthesis of (-)-7-Epiaustraline and (+)-1,7-Diepiaustraline

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Abstract: A diastereoselective and modular approach to the synthesis of the 3-hydroxymethyl-2,3,5,6,7,7*a*-hexahydro-1H-pyrrolizine-1,2,7-triol structure, characteristic of several natural pyrrolizidine natural products has been developed. This approach culminated in the synthesis of (-)-7-epiaustraline and (+)-1,7-diepiaustraline. The oxazolidinone group has been found to be a useful protecting group in the RCM reaction and, as part of a pyrrolo[1,2-*c*]oxazol-3-one ring system, has functioned as a stereo- and regio-directing group, in a key diastereoselective *cis*-dihydroxylation reaction and a regioselective nucleophilic ring-opening of a *S*,*S*-dioxo-dioxathiole.

Dedicated to Prof. John Bremner on the occasion of his 60th birthday.

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 the Australian legume, *Castanospermum australe*.[2] Later reports described the isolation of other epimers of **2** from these seeds.[3] A recent re-investigation of these seed extracts confirmed the presence of the alkaloids **2**-**4** and revealed the isolation of three new alkaloids, the 2-*O*-β-D-glucopyranosyl derivative of **3** and the compounds **5** and **6**.[4] The latter two alkaloids were epimeric at C-7, with **6** having the same C-7, C-7a stereochemistry as casurine **7**.[5] Compound **6** is the first 7-epiaustraline alkaloid to be isolated. While this honor was originally claimed for 7-epiaustraline itself,[3c] synthetic studies by Denmark[6] established that 7-epiaustraline was not a natural product and that the original investigators had isolated australine. These alkaloids have been tested for their glycosidase inhibitory activities[2,3c] and recently on several α- and β-glucosidase enzymes and α-L-fucosidase.[4] Compounds **2**, **5** and **7** and the 2-*O*-β-D-glucopyranosyl derivative of **3** and the 6-*O*-α-D-glucopyranosyl derivative of **7**, were the most potent and specific enzyme inhibitors. Other biological studies[7] have revealed the potential of these and related polyhydroxylated pyrrolizidines as antiviral and anti-retroviral agents.[7b,c] 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,[8] and its epimers,[8,9] australine,[10] and its epimers,[6,9-11] and casuarine.[12]

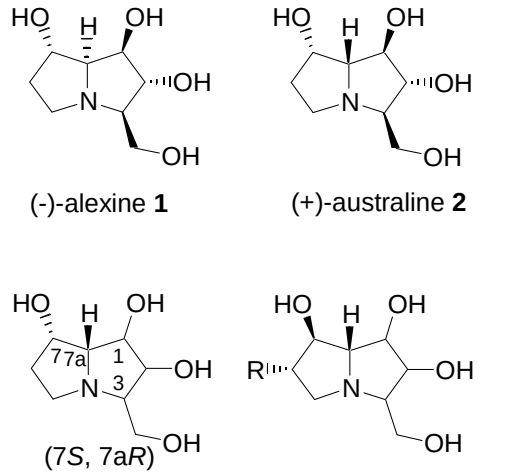


Figure 1. Structures of 3-hydroxymethyl pyrrolizidine

We report here a new synthetic strategy for the preparation of these natural products, and their various stereoisomers, as shown in Figure 1. This modular approach, which in principle allows access to all the stereoisomers of 3-hydroxymethyl-2,3,5,6,7,7a-hexahydro-1H-pyrrolizine-1,2,7-triol (**A**), is shown in Figure 2.

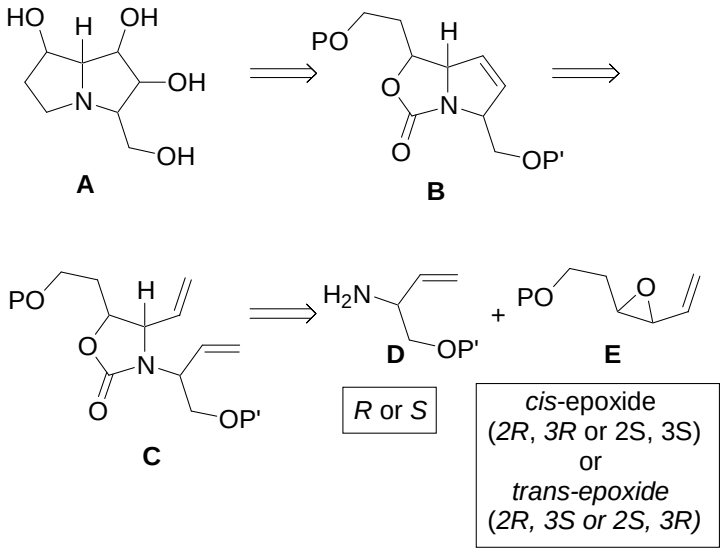


Figure 2. Retrosynthetic analysis

Aminolysis[13-15] of the enantiomerically enriched *cis*- or *trans*-vinyl epoxide **E**, that is readily available in all configurational forms using the Sharpless epoxidation,[15,16] with either *R* or *S* chiral allylic amine **D**,[17] could regio- and diastereoselectively provide the corresponding 1,2-amino alcohol with any stereochemistry desired. Protection of the amino alcohol functionality as the 2-oxazolidinone **C** followed by a ring-closing metathesis reaction[13,15,18-20] should provide the conformationally rigid pyrrolo[1,2-*c*]oxazol-3-one structure **B**. The bicyclic nature of **B** should allow for a stereochemically controlled *cis*-dihydroxylation of the 3,4-double bond of **B**, a problem that we[15] and others[18j,21] experienced in the synthesis of (-)-swainsonine. To test the feasibility of this approach we chose (+)-1,7-diepiaustraline **8** and (-)-7-epiaustaline **9** as our target molecules (Figure 3). These compounds have the 6,7-*cis* and 6,7-*trans* diol stereochemistry, respectively. It was anticipated that by employing a oxozolidinone protecting group then the conformationally rigid pyrrolo[1,2-*c*]oxazol-3-one structure (**F**, Figure 3) obtained would allow for the introduction of these functionalities in a diastereoselective manner.

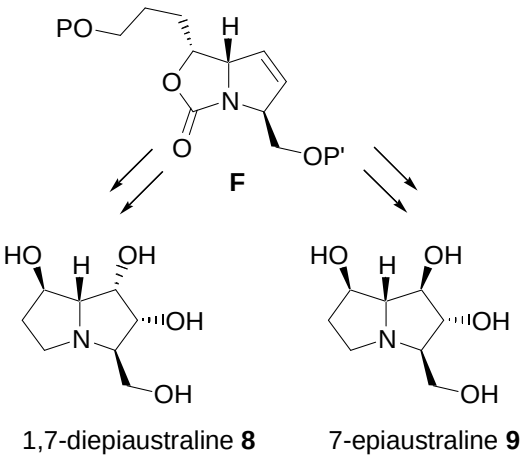
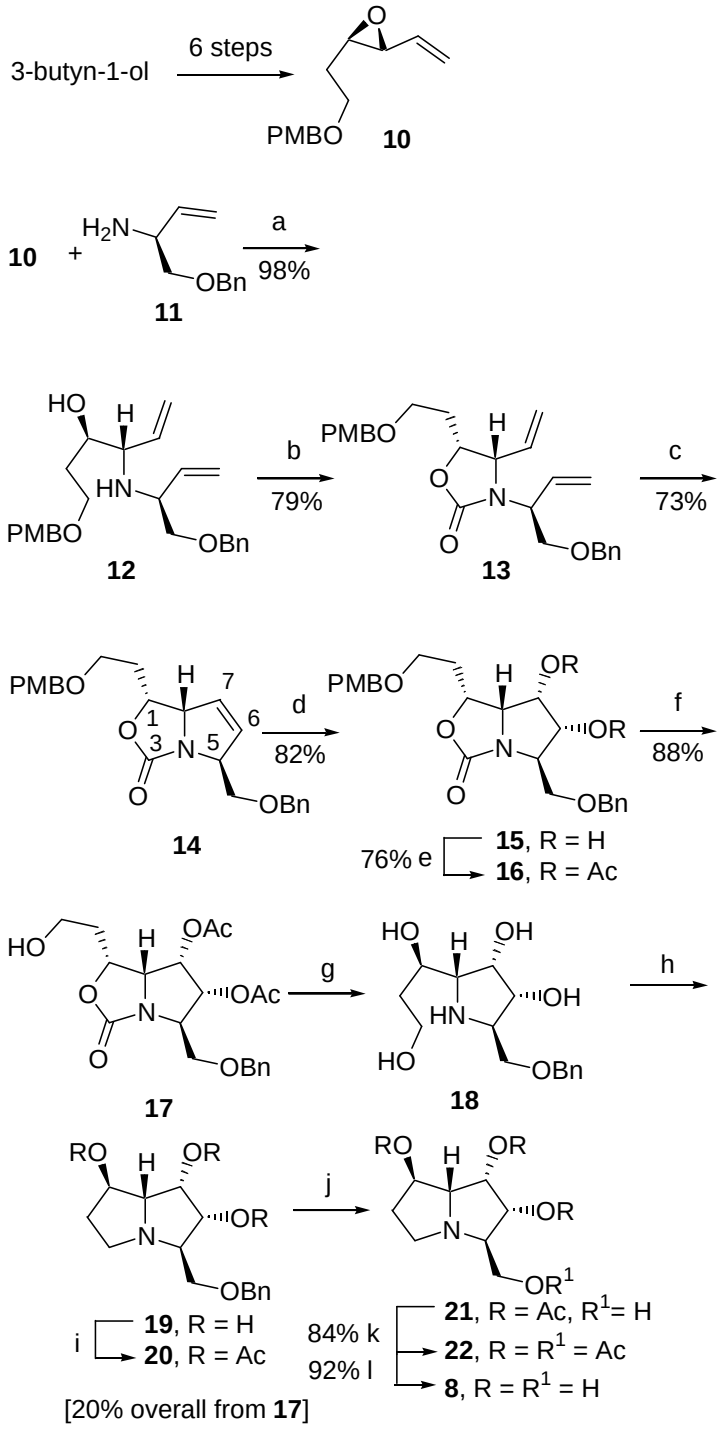


Figure 3. Target molecules

The starting vinyl epoxide (+)-(2*R*, 3*R*)-**10** was prepared from the corresponding Sharpless epoxy alcohol (94 % ee from ^{1}H NMR analysis of its Mosher ester) *via* Swern oxidation followed by a Wittig-olefination reaction.[13,15,22] A solution of the vinyl epoxide (+)-**10** and the (*S*)-allylamine **11**[17] (1.4 equiv) in acetonitrile was heated at 120 ^{o}C in a sealed tube using LiOTf (1.5 equiv) as a catalyst for 72 h. This gave the amino alcohol (+)-**12,** along with no more than 2-3% of another diastereomer, in 98% yield *via* an S_N2 ring opening. The amino-alcohol (+)-**12** was converted to the diastereomerically pure 2-oxazolidinone derivative (+)-**13** in 79% yield using triphosgene under basic conditions.[23]



Scheme 1. *Reagents and conditions*: a) LiOTf, CH_3CN, 120 ^{0}C, sealed tube, 72 h; b) triphosgene, Et_3N, DCM, RT, 2 h; c) Grubbs' catalyst I, DCM, reflux, 44 h; d) $K_2OsO_4{\cdot}H_2O$, NMO, acetone, H_2O, RT, 24 h; e) Ac_2O, pyridine, RT, 24 h; f) DDQ, DCM, H_2O, RT, 2 h; g) NaOH, EtOH, 70 ^{0}C, sealed

tube, 24 h; h) DIAD, PPh_3, pyridine, 0 ^{0}C, 2.5 h; i) Ac_2O, pyridine, RT, 24 h; j) $PdCl_2$, H_2, MeOH, RT, 1.5 h; k) Ac_2O, pyridine, RT, 24 h; l) NaOMe, MeOH, RT, 15 h.

We were then ready to try the ring-closing metathesis (RCM) of **13**. While 2-oxazolo[3,4-*a*]pyridin-3-ones [18g,19a,20a-d,24] and their seven and eight[18d,19b,e] membered-ring analogues have been successfully prepared *via* RCM, the RCM of 3-allyl-4-vinyl-2-oxazolidinone to give pyrrolo[1,2-*c*]oxazol-3-one has been reported not to proceed at RT.[18a] We found that the RCM of **13** using standard conditions, 5-10 mol % of Grubbs I catalyst (benzylidenebis(tricyclohexylphosphine)ruthenium dichloride) in refluxing CH_2Cl_2 at high dilution (~4 mM)[13,15] for 20 h, gave low conversion to the desired 2,5-dihydropyrrole **14**. However, by initiating the reaction using 25 mol% Grubbs I catalyst and then adding a further 25 mol% catalyst after 24 h, then **14** could be isolated in 73% yield after a total of 48 h of heating at reflux. Compound (-)-**14** was treated with 5 mol % $K_2OsO_4.2H_2O$ and NMO (2.1 equiv),[15] to effect *cis*-dihydroxylation (DH) of the double bond, giving diol (-)-**15** in good yield (82%). Only one diastereomeric product was isolated, which was expected to arise from delivery of the two hydroxyl groups to the least hindered face of the 6,7-double bond in (-)-**14**. Figure 4 shows a molecular model (PC Spartan Pro, AM1) of **14**, the β-face is more sterically demanding due to the pseudo-axial proton H7*a* and the β-C-5 benzyloxymethyl substituent, that hinder the β-face (convex face) to attack by the osmium reagent (Figure 4). A similar argument has been proposed for the facial selectivity of DH reactions on related indolizines.[15,18j,21] The absolute stereochemistry assigned to **14** was unequivocally confirmed by its conversion to (+)-1,7-di-epiaustraline (**8**).

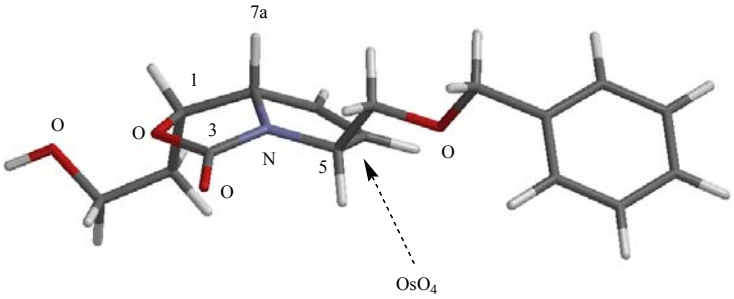
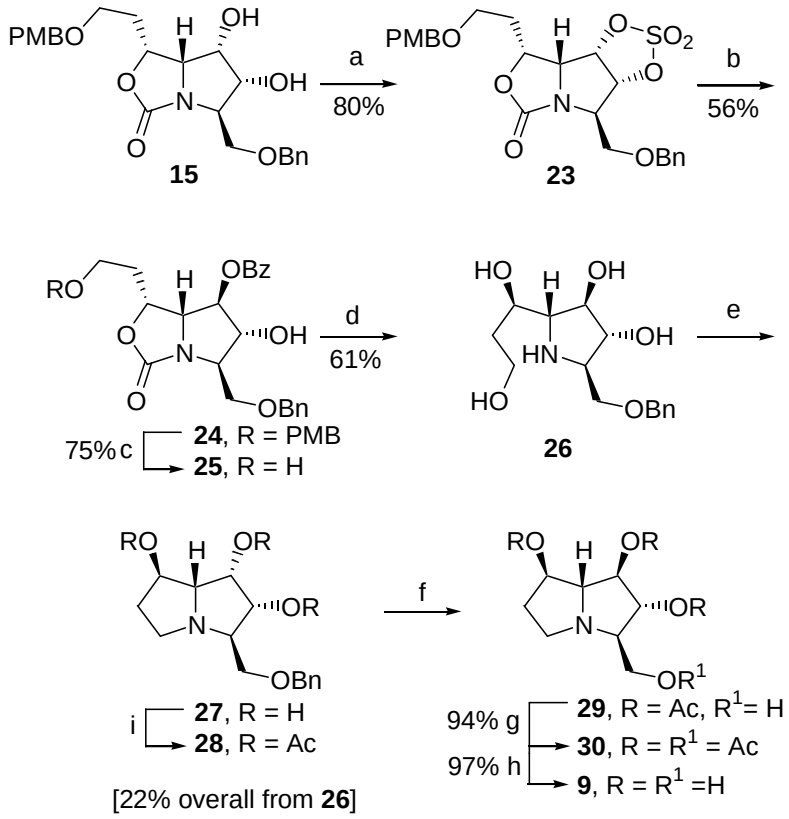


Figure 4. Molecular Model (PC Spartan Pro, AM1) of **14** (PMB group not shown).

Attempts to deprotect the primary PMB ether in **14** under oxidative conditions with DDQ[25] 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 **16** however was smoothly converted to the primary alcohol **17** in 88% yield. Compound **17** was then converted to the pyrrolizidine-triacetate **20** in three synthetic steps. Base hydrolysis of **16** followed by ion-exchange chromatography gave **18** which was cyclized to the desired pyrrolizidine ring system under Mitsunobu conditions[26] in pyridine at 0 ^{o}C. This reaction resulted in a mixture of **19** and starting tetrol **18**, which were readily separated as their peracetylated derivatives. In this way the pyrrolizidine-triacetate **20** was obtained in 20% overall yield from **17**, over the three synthetic steps. The use of longer reaction times or other cyclization methods (e.g. CBr_4, Ph_3P)[15,27] did not result in improved yields of **20**. Compound **20** was then smoothly converted to the triacetate of (+)-1,7-diepiaustraline (**22**) by first hydrogenolysis of the primary benzyl ether group[15,28] and then peracetylation in 84% overall yield. Finally, methoxide catalysed removal of the secondary acetates of **22** gave (+)-1,7-diepiaustraline (**8**) in 92% yield. This sample had identical spectral characteristics to those reported in the literature for (+)-**8**,[9c] and its specific rotation ($[\alpha]_D^{24}$

+6.4 (*c* 0.7, MeOH), $[\alpha]_D^{24}$ +8.6 (*c* 0.7, H_2O)) closely matched that previously reported (lit.[9c] ($[\alpha]_D^{20}$ + 4.7 (*c* 0.5, H_2O)).

Scheme 2 outlines the synthesis of (-)-7-epiaustraline (**9**). This synthesis required inversion of the stereochemistry at C-7 in the pyrrolo[1,2-*c*]oxazol-3-one **15**. Thus **15** was converted to its cyclic-sulfate **23** using thionyl chloride followed by oxidation of the resulting cyclic sulfite with catalytic ruthenium tetroxide (80% yield for the two-step conversion).[29] Regioselective nucleophilic ring opening of the *S*,*S*-dioxo-dioxathiole ring of **15** with cesium benzoate,[29,30] followed by an acid catalysed-hydrolysis gave the benzoate **24** in 56% yield. A small amount (*ca* 5%) of the other regioisomer could be detected from ^{1}H NMR analysis of the crude reaction mixture, however this minor compound could not be isolated pure. Nucleophilic attack on **23** 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. Oxidative removal of the primary PMB ether in **24** using DDQ gave the corresponding primary alcohol **25** in 75% yield, without the need to protect the C-6 hydroxyl group. Base hydrolysis of the oxazolidinone ring gave the amino tetrol **26** in 61% yield. Cyclization of **26** under Mitsunobu conditions again proved problematic and after acetylation of the crude cyclization mixture, the desired triacetate **28** was isolated in 22% overall yield from **26**. This compound was readily converted to the known triacetate of (-)-7-epiaustraline (**30**) according to Scheme 2. This sample had identical spectral characteristics to those reported in the literature for (-)-**30**.[3b,7a] Base catalysed hydrolysis of **30** gave (-)-7-epiaustaline (**9**) that had spectral data and a specific rotation ($[\alpha]_D^{24}$ –14.1 (*c* 0.22, H_2O)), almost identical to that reported in the literature (lit.[6] $[\alpha]_D^{20}$ –13.04 (*c* 0.55, H_2O, pH 8.37)).



Scheme 2. *Reagents and conditions*: a) (i) $SOCl_2$, Et_3N, DCM, 0 ^{0}C, 30 min; (ii) $RuCl_3{\cdot}3H_2O$, $NaIO_4$, CCl_4:CH_3CN:H_2O = 2:2:3, RT, 2 h; b) (i) PhCOOH, Cs_2CO_3, DMF, 40 ^{0}C, 23 h; (ii) H_2SO_4 (conc.), THF, H_2O, RT, 18 h; c) DDQ, DCM, H_2O, RT, 2 h; d) NaOH, EtOH, 70 ^{0}C, 19 h; e) DIAD, PPh_3, THF, 0 ^{0}C, 3 h; f) Ac_2O, pyridine, RT, 21 h; g) $PdCl_2$, H_2, MeOH, RT, 1 h; h) Ac_2O, pyridine, RT, 15 h; i) K_2CO_3, MeOH, RT, 24 h.

In summary, we have developed a diastereoselective and modular approach to the synthesis of the 3-hydroxymethyl-2,3,5,6,7,7*a*-hexahydro-1H-pyrrolizine-1,2,7-triol structure, characteristic of several pyrrolizidine natural products. The oxazolidinone group has been found to be a useful protecting group in the RCM reaction and, as part of a pyrrolo[1,2-c]oxazol-3-one ring system, has functioned as a stereo- and regio-directing group, in a key diastereoselective *cis*-dihydroxylation reaction and a

regioselective nucleophilic ring-opening of a *S*,*S*-dioxo-dioxathiole. The application of this strategy to the synthesis of the alkaloids in the australine family (**2**-**6)** is currently in progress.

Experimental Section

(+)-6-(4-Methoxyphenyl)methoxy-3*R*-[(1*S*-phenylmethoxymethyl)-2-propenyl]amino-1-hepten-4-ol (12). To a mixture of **10** (195 mg, 0.833 mmol) and **11**[17] (202 mg, 1.144 mmol) in dry acetonitrile (1 mL), in a thick walled glass tube, was added lithium triflate (195 mg, 1.249 mmol). The vessel was flushed with nitrogen and sealed and then stirred and heated at 120 ^{0}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) to give compound **12** (334 mg, 98%) as a yellow oil. $[\alpha]_D^{22}$ +3.8 (*c* 2.7, $CHCl_3$); ^{1}H NMR δ 7.34-7.27 (m, 5H), 7.23 (d, 2H, *J* 8.7 Hz), 6.86 (d, 2H, *J* 8.7 Hz), 5.66 (ddd, 1H, *J* 8.4, 10.2, 17.1 Hz), 5.54 (dddd, 1H, *J* 1.8, 6.0, 9.9, 15.9 Hz), 5.25-5.09 (m, 4H, 2x =CH_2), 4.51 (s, 2H), 4.43 (s, 2H), 3.79 (s, 3H), 3.79 (m, 1H), 3.66-3.59 (m, 2H), 3.47-3.39 (m, 3H), 3.12 (dd, 1H, *J* 4.2, 8.1 Hz), 1.77-1.59 (m, 2H); ^{13}C NMR δ 159.0 (C, Ar), 137.9 (C, Ar), 137.4 (CH), 136.0 (CH), 130.1 (C, Ar), 129.2 (CH, Ar), 128.3 (CH, Ar), 127.5 (CH, Ar), 127.5 (CH, Ar), 118.1 (CH_2), 118.0 (CH_2), 113.7 (CH, Ar), 73.2 (CH_2), 73.0 (CH_2), 72.8 (CH_2), 72.0 (CH), 68.3 (CH_2), 62.4 (CH), 57.9 (CH), 55.3 (CH_3), 33.0 (CH_2); MS (CI +ve) *m/z* 412 ($M+1^+$, 100%); HRMS (CI +ve) Calcd for $C_{25}H_{34}NO_4$ (MH^+) 412.2488. Found: 412.2478.

(+)-4*S*-Ethenyl-5*R*-[2-(4-Methoxyphenyl)methoxy]ethyl-3-(1*S*-phenylmethoxymethyl-2-propenyl)-1,3-oxazolidin-2-one (13). A solution of **12** (618 mg, 1.503 mmol) in dry DCM (50 mL) was cooled to 0 ^{0}C and triethylamine (852 mg, 1.2 mL, 8.416 mmol) was added. A solution of triphosgene (268 mg, 0.902 mmol) in dry DCM (3 mL) was cooled to 0 ^{0}C and was then added to the above amine solution at 0 ^{0}C. TLC analysis (40% EtOAc/petrol) indicated complete disappearance of the compound **12** after 2 h. The reaction was quenched with water (50 mL). The aqueous portion was extracted with DCM (4x). The combined organic portions were dried ($MgSO_4$) and filtered and the

solvent was evaporated to give a yellow semi-solid. Chromatography of the residue eluting with (20%-40%) EtOAc/petrol gave compound **13** (520 mg, 79%) as a pale yellow oil. $[\alpha]_D^{25}$ +18.3 (*c* 2.5, $CHCl_3$); ^{1}H NMR δ 7.34-7.30 (m, 5H), 7.24 (d, 2H, *J* 8.7 Hz), 6.87 (d, 2H, *J* 8.7 Hz), 5.87-5.66 (m, 2H), 5.24 (dt, 1H, *J* 17.1, 1.2 Hz), 5.24 (dd, 1H, *J* 1.2, 10.8 Hz), 5.18 (dt, 1H, *J* 10.2, 1.2 Hz), 5.13 (dt, 1H, *J* 17.7, 1.2 Hz), 4.70 (ddd, 1H, *J* 3.9, 8.1, 9.3 Hz), 4.59 (d, 1H, *J* 12.0 Hz), 4.47 (d, 1H, *J* 11.7 Hz), 4.44 (d, 1H, *J* 11.4 Hz), 4.39 (d, 1H, *J* 11.4 Hz), 4.32 (dtt, 1H, *J* 5.4, 1.2, 9.0 Hz), 4.21 (t, 1H, *J* 8.7 Hz), 3.81 (dd, 1H, *J* 8.7, 10.2 Hz), 3.71 (s, 3H), 3.63 (dd, 1H, *J* 5.7, 10.2 Hz), 3.60-3.56 (m, 2H), 1.91-1.71 (m, 2H); ^{13}C NMR δ 159.2 (C, Ar), 157.3 (CO), 137.8 (C, Ar), 133.9 (CH), 133.5 (CH), 130.2 (C, Ar), 129.3 (CH, Ar), 128.4 (CH, Ar), 127.8 (CH, Ar), 127.7 (CH, Ar), 120.9 (CH_2), 118.5 (CH_2), 113.8 (CH, Ar), 74.4 (CH), 72.9 (CH_2), 72.9 (CH_2), 68.8 (CH_2), 65.8 (CH_2), 61.5 (CH), 56.2 (CH), 55.2 (CH_3), 31.0 (CH_2); MS (CI +ve) *m/z* 438 ($M+1^+$); HRMS (EI +ve) Calcd for $C_{26}H_{31}NO_5$ (M^+) 437.2202. Found: 437.2184.

(-)-(1*R*,5*R*,6*R*,7*S*,7*aR*)–1-[2-(4-Methoxyphenyl)methoxy]ethyl-5-(phenylmethoxy)methyl-5,7*a*-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one (14)

Grubbs' Catalyst I (245 mg, 0.298 mmol) was added to a solution of **13** (520 mg, 1.190 mmol) in dry DCM (600 mL) under nitrogen. The mixture was heated at reflux under nitrogen for 24 h. TLC analysis (35% EtOAc/petrol) indicated incomplete conversion of compound **13**. Additional Grubbs' Catalyst I (245 mg, 0.298 mmol) was added and the reaction was continued under the same conditions for another 24 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 (20%-70% EtOAc/petrol) to give **14** (358 mg, 73%) as a clear oil. $[\alpha]_D^{24}$ -90.3 (*c* 2.4, $CHCl_3$); ^{1}H NMR δ 7.36-7.21 (m, 7H), 6.87 (d, 1H, *J* 8.7 Hz), 6.02 (ddd, 1H, *J* 1.8, 1.8, 6.0 Hz), 5.91 (ddd, 1H, *J* 1.8, 1.8, 6.0 Hz), 4.92 (ddd, 1H, *J* 4.2, 8.4, 8.7

Hz), 4.83-4.78 (m, 2H), 4.56 (s, 2H), 4.45 (d, 1H, *J* 11.4 Hz), 4.41 (d, 1H, *J* 11.4 Hz), 3.79 (s, 3H), 3.62-3.53 (m, 4H), 1.92 (dddd, 1H, *J* 4.5, 6.9, 8.1, 14.4 Hz), 1.78 (dddd, 1H, *J* 4.5, 4.8, 8.7, 14.4 Hz); ^{13}C NMR δ 162.2 (CO), 159.2 (C, Ar), 137.9 (C, Ar), 132.9 (CH), 130.0 (C, Ar), 129.3 (CH, Ar), 128.3 (CH, Ar)**,** 128.1 (CH), 127.6 (CH, Ar), 127.5 (CH, Ar), 113.8 (CH, Ar), 76.4 (CH), 73.2 (CH_2), 73.0 (CH_2), 71.1 (CH_2), 68.2 (CH), 66.8 (CH), 65.8 (CH_2), 55.2 (CH_3), 32.5 (CH_2); MS (CI +ve) *m/z* 410 ($M+1^+$); HRMS (CI +ve) Calcd for $C_{24}H_{28}NO_5$ (MH^+) 410.1967. Found: 410.1958.

(-)-(1*R*,5*R*,6*R*,7*S*,7*aR*)–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 (15). To a solution of **14** (327 mg, 0.800 mmol) in acetone (6 mL) were added water (4 mL), 4-morpholine *N*-oxide (206 mg, 1.759 mmol) and potassium osmate dihydrate (14.7 mg, 0.040 mmol). The mixture was stirred at RT for 24 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 eluating with 2.5%-7.5% methanol/DCM affording compound **15** as a brown oil (191 mg, 82%). $[\alpha]_D^{24}$ -43.9 (*c* 2.2, $CHCl_3$); ^{1}H NMR δ 7.35-7.28 (m, 5H), 7.22 (d, 2H, *J* 8.4 Hz), 6.86 (d, 2H, *J* 8.7 Hz), 4.80 (dt, 1H, *J* 5.4, 7.8 Hz), 4.59 (d, 1H, *J* 12.0 Hz), 4.54 (d, 1H, *J* 12.0 Hz), 4.44 (d, 1H, *J* 12.3 Hz), 4.40 (d, 1H, *J* 12.0 Hz), 4.31 (dd, 1H, *J* 3.3, 6.3 Hz), 4.00 (t, 1H, *J* 2.7 Hz), 3.80-3.53 (m, 6H), 3.79 (s, 3H), 2.48-2.38 (m, 1H), 2.26-2.15 (m, 1H); ^{13}C NMR (one Ar C could not be observed) δ 162.6 (CO), 137.8 (C, Ar), 130.1 (C, Ar), 129.3 (CH, Ar), 128.5 (CH, Ar), 127.8 (CH, Ar), 127.6 (CH, Ar), 113.8 (CH, Ar), 76.4 (CH), 74.1 (CH), 73.5 (CH_2), 72.9 (CH_2), 72.3 (CH), 70.4 (CH_2), 66.4 (CH_2), 65.0 (CH), 62.3 (CH), 55.2 (CH_3), 30.8 (CH_2); MS (CI +ve) *m/z* 444 ($M+1^+$); HRMS (EI +ve) Calcd for $C_{24}H_{29}NO_7$ (M^+) 443.1944. Found: 443.1926.

(-)-(1*R*,5*R*,6*R*,7*S*,7*aR*)–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 (16). Compound **15** (170 mg, 0.384 mmol) was dissolved in pyridine (2.0 mL) and then Ac_2O (2.0 mL) was added. The mixture was stirred at RT for 20 h, then diluted with DCM (40 mL) and washed with saturated $NaHCO_3$ solution at 0 ^{0}C. The aqueous portion was extracted with DCM (3x). The combined organic portions were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give an oil which was purified by column chromatography (30%-70% EtOAc/petrol) to give product **16** as a colorless oil (154 mg, 76%). $[\alpha]_D^{26}$ -4.3 (*c* 2.0, $CHCl_3$); ^{1}H NMR (500 MHz) δ 7.35-7.26 (m, 5H), 7.22 (d, 2H, *J* 8.5 Hz), 6.87 (d, 2H, *J* 8.5 Hz), 5.53 (dd, 1H, *J* 3.0, 7.5 Hz), 5.46-5.45 (m, 1H), 4.82 (ddd, 1H, *J* 7.0, 7.0, 14.0 Hz), 4.60 (d, 1H, *J* 12.0 Hz), 4.54 (d, 1H, *J* 12.0 Hz), 4.42 (s, 2H), 3.96 (dt, 1H, *J* 7.0, 3.5 Hz), 3.92 (dd, 1H, *J* 2.0, 7.5 Hz), 3.71 (dd, 1H, *J* 3.5, 10.5 Hz), 3.61 (dd, 1H, *J* 3.0, 10.5 Hz), 3.58-3.51 (m, 2H), 2.10 (s, 3H), 2.07-2.01 (m, 1H), 1.99-1.89 (m, 1H), 1.97 (s, 3H); ^{13}C NMR δ 169.6 (CO), 169.4 (CO), 161.2 (CO), 159.2 (C, Ar), 137.6 (C, Ar), 129.7 (C, Ar), 129.2 (CH, Ar), 128.3 (CH, Ar), 127.6 (CH, Ar), 127.4 (CH, Ar), 113.7 (CH, Ar), 73.8 (CH), 73.4 (CH), 73.3 (CH_2), 72.8 (CH_2), 72.6 (CH), 69.0 (CH_2), 65.6 (CH_2), 63.2 (CH), 59.7 (CH), 55.1 (CH_3), 29.6 (CH_2), 20.7 (CH_3), 20.2 (CH_3); MS (CI +ve) *m/z* 528 ($M+1^+$); HRMS (ES +ve) Calcd for $C_{28}H_{34}NO_9$ (MH^+) 528.2234. Found: 528.2238.

(+)-(1*R*,5*R*,6*R*,7*S*,7*aR*)–6,7-Diacetoxy-1-(2-hydroxy)ethyl-5-(phenylmethoxy) methyl-5,6,7,7*a*-tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one (17). To a solution of **16** (150 mg, 0.285 mmol) in dichloromethane (25 mL) and water (2 mL) was added 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (90.5 mg, 0.399 mmol). After the mixture had stirred at RT for 3 h, TLC analysis (70% EtOAc/petrol) indicated the presence of compound **16**. Additional DDQ (38.8 mg, 0.171 mmol) was then added to the mixture. The reaction was continued for another 2 h. The mixture was diluted with water (50 mL)

and extracted with DCM (3x). The combined organics were dried ($MgSO_4$) and filtered and the solvent was removed under reduced pressure to give a red semi-solid that was purified by column chromatography (30%-80% EtOAc/petrol) to give the product **17** as a colorless oil (102 mg, 88%). $[\alpha]_D^{25}$ +15.9 (*c* 1.4, $CHCl_3$); ^{1}H NMR δ 7.38-7.26 (m, 5H), 5.57 (dd, 1H, *J* 3.6, 7.5 Hz), 5.52-5.50 (m, 1H), 4.86 (ddd, 1H, *J* 6.0, 7.8, 7.8 Hz), 4.61 (d, 1H, *J* 12.0 Hz), 4.55 (d, 1H, *J* 12.0 Hz), 4.04 (dd, 1H, *J* 2.1, 7.5 Hz), 3.98 (dt, 1H, *J* 7.2, 3.3 Hz), 3.86-3.77 (m, 2H), 3.73 (dd, 1H, *J* 3.3, 10.2 Hz), 3.63 (dd, 1H, *J* 3.3, 10.2 Hz), 2.12 (s, 3H), 2.08-1.98 (m, 1H), 1.98 (s, 3H), 1.93-1.82 (m, 1H); ^{13}C NMR δ 169.9 (CO), 169.7 (CO), 161.4 (CO), 137.7 (C, Ar), 128.4 (CH, Ar), 127.7 (CH, Ar), 127.5 (CH, Ar), 73.9 (CH), 73.8 (CH), 73.4 (CH_2), 72.7 (CH), 69.0 (CH_2), 63.4 (CH), 59.9 (CH), 59.1 (CH_2), 31.8 (CH_2), 20.8 (CH_3), 20.4 (CH_3); MS (CI +ve) *m/z* 408 ($M+1^+$, 100%); HRMS (ES +ve) Calcd for $C_{20}H_{26}NO_8$ (MH^+) 408.1658. Found: 408.1657.

Three Step Synthesis of (-)-(1*S*,2*R*,3*R*,7*R*,7*aR*)–1,2,7-Triacetoxy-3-(phenylmethoxy)methylhexahydro-1*H*-pyrrolizine (20) from 17. To a solution of **17** (101 mg, 0.248 mmol) in ethanol (4 mL) was added sodium hydroxide (99.3 mg, 2.482 mmol). The reaction was heated at 70 ^{0}C in a sealed tube for 24 h. The volatiles were then removed *in vacuo* to give a yellow-green solid, and the residue was treated with 2M hydrochloric acid (3 mL). All the volatiles were removed *in vacuo* to give a yellow solid that was purified by acidic ion-exchange chromatography to give the desired compound **18** (*ca* 100 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 **18**: ^{1}H NMR (CD_3OD) δ 7.43-7.26 (m, 5H), 5.07 (bs, 1H, OH), 4.67 (d, 1H, *J* 11.7 Hz), 4.62 (d, 1H, *J* 11.7 Hz), 4.38 (t, 1H, *J* 3.3 Hz), 4.25 (dd, 1H, *J* 3.3, 8.7 Hz), 4.22-4.17 (m, 1H), 3.88 (dd, 1H, *J* 3.3, 10.8 Hz), 3.84-3.71 (m, 4H), 3.55 (dd, 1H, *J* 2.7, 7.5 Hz), 1.96-1.75 (m,

2H); ^{13}C NMR (CD_3OD) δ 138.8 (C, Ar), 129.4 (CH, Ar), 129.0 (CH, Ar), 128.9 (CH, Ar), 74.3 (CH), 73.1 (CH), 71.9 (CH), 67.9 (CH_2), 66.0 (CH), 65.5 (CH), 62.6 (CH), 59.1 (CH_2), 37.5 (CH_2); $[\alpha]_D^{26}$ +18.1 (*c* 1.8, MeOH); MS (CI +ve) *m/z* 298 ($M+1^+$, 100%); HRMS (ES +ve) Calcd for $C_{15}H_{24}NO_5$ (MH^+) 298.1654. Found: 298.1645. To a stirred mixture of **18** obtained above, triphenylphosphine (111 mg, 0.424 mmol) and anhydrous pyridine (4 mL) at 0 ^{0}C was added dropwise diisopropyl azodicarboxylate (83.5 μL, 0.424 mmol) under nitrogen. The mixture was stirred at 0 ^{0}C for 2.5 h. The volatiles were removed *in vacuo* then 1M hydrochloric acid (15 mL) was added. The solution was concentrated *in vacuo* to give a yellow solid, which was purified by acidic ion-exchange chromatography to give compound **19**. This material was dissolved in pyridine (2.0 mL) and then Ac_2O (2.0 mL) was added. The mixture was stirred at RT for 24 h, and then diluted with DCM (25 mL) and washed with saturated $NaHCO_3$ solution. The aqueous portion was extracted with DCM (3x) and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a solid. Purification by column chromatography (30%-70% EtOAc/petrol) gave product **20** (19.4 mg, 20% overall for 3 steps) as a colorless oil. $[\alpha]_D^{27}$ -5.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.36-7.27 (m, 5H), 5.48 (t, 1H, *J* 4.5 Hz), 5.20-5.15 (m, 2H), 4.58 (d, 1H, *J* 12.0 Hz), 4.51 (d, 1H, *J* 12.0 Hz), 3.66 (dd, 1H, *J* 3.6, 4.5 Hz), 3.55 (dd, 1H, *J* 4.2, 9.6 Hz), 3.47 (dd, 1H, *J* 5.7, 9.9 Hz), 3.29 (ddd, 1H, *J* 6.6, 6.9, 10.8 Hz), 3.04 (ddd, 1H, *J* 4.2, 5.7, 9.6 Hz), 2.89 (ddd, 1H, *J* 6.3, 6.6, 10.8 Hz), 2.26-1.88 (m, 2H), 2.10 (s, 3H), 2.02 (s, 3H), 1.95 (s, 3H); ^{13}C NMR δ 170.6 (CO), 169.7 (CO), 169.5 (CO), 138.1 (C, Ar), 128.3 (CH, Ar), 127.6 (CH, Ar), 127.5 (CH, Ar), 74.0 (CH), 73.9 (CH), 73.4 (CH_2), 71.5 (CH), 71.4 (CH_2), 69.5 (CH), 65.8 (CH), 53.2 (CH_2), 32.3 (CH_2), 21.0 (CH_3), 20.8 (CH_3), 20.5 (CH_3); MS (CI +ve) *m/z* 406 ($M+1^+$, 100%); HRMS (ES +ve) Calcd for $C_{21}H_{28}NO_9$ (MH^+) 406.1866. Found: 406.1860.

(+)-(1*S*,2*R*,3*R*,7*R*,7*aR*)–1,2,7-Triacetoxy-3-(acetoxymethyl)hexahydro-1*H*-pyrrolizine (22). To a solution of **20** (19.4 mg, 0.048 mmol) in methanol (1 mL) was added palladium chloride (7.3 mg, 0.041 mmol). The mixture was stirred under an atmosphere of hydrogen at RT for 1 h. The mixture was then filtered through a plug of cotton wool and the solvent was removed under reduced pressure to give the title product **21** as a pale yellow oil. This oil was then dissolved in pyridine (0.5 mL) and Ac_2O (0.5 mL) was added to the solution. The mixture was stirred at RT for 18 h, then diluted with DCM (25 mL) and washed with saturated $NaHCO_3$ solution. The aqueous portion was extracted with DCM (3x). The combined organic portions were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a solid which was purified by column chromatography (30%-70% EtOAc/petrol) to give compound **22** as a pale yellow oil (14.4 mg, 84% overall for 2 steps). $[\alpha]_D^{25}$ +10.5 (*c* 1.4, $CHCl_3$); ^{1}H NMR δ 5.48 (dd, 1H, *J* 3.9, 4.2 Hz), 5.18 (ddd, 1H, *J* 3.9, 5.4, 9.6 Hz), 5.12 (dd, 1H, *J* 3.9, 9.3 Hz), 4.18 (dd, 1H, *J* 4.2, 11.4 Hz), 4.03 (dd, 1H, *J* 5.7, 11.4 Hz), 3.64 (dd, 1H, *J* 3.9, 4.2 Hz), 3.26 (ddd, 1H, *J* 6.6, 6.6, 10.5 Hz), 3.08 (ddd, 1H, *J* 4.2, 5.4, 9.3 Hz), 2.83 (ddd, 1H, *J* 6.6, 6.9, 10.5 Hz), 2.28-1.92 (m, 2H), 2.12 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H); ^{13}C NMR δ 170.7 (CO), 170.6 (CO), 169.6 (CO), 169.4 (CO), 73.9 (CH), 73.7 (CH), 71.3 (CH), 69.5 (CH), 64.9 (CH_2), 64.6 (CH), 53.0 (CH_2), 32.4 (CH_2), 20.9 (CH_3), 20.80 (CH_3), 20.7 (CH_3), 20.4 (CH_3); MS (CI +ve) *m/z* 358 (M+1$^+$, 100%); HRMS (ES +ve) Calcd for $C_{16}H_{24}NO_8$ (MH^+) 358.1502. Found: 358.1507.

(+)-*(*1*S*,2*R*,3*R*,7*R*,7*aR*)–Hexahydro–3-hydroxymethyl–1*H*-pyrrolizine-1,2,7-triol, [(+)-1,7-Diepiaustraline] (8). To a solution of **22** (14.4 mg, 0.040 mmol) in dry methanol (1 mL) was added the solution of sodium methoxide (0.087M, 46 μL, 0.004 mmol). The mixture was stirred under nitrogen at RT for 20 h. Then all the volatiles were removed *in vacuo* to give compound **8** as a colorless oil (7.0 mg, 92%). $[\alpha]_D^{24}$ +6.4 (*c* 0.7, MeOH), $[\alpha]_D^{24}$ +8.6 (*c* 0.7, H_2O) [lit[9c] $[\alpha]_D^{20}$ +4.7 (*c*

0.5, H_2O)]; ^{1}H NMR (500MHz, CD_3OD) δ 4.55 (dt, 1H, *J* 3.5, 5.5 Hz), 4.02 (t, 1H, *J* 4.0 Hz), 3.80 (dd, 1H, *J* 4.0, 9.5 Hz), 3.76 (dd, 1H, *J* 3.5, 11.0 Hz), 3.56 (dd, 1H, *J* 6.5, 11.5 Hz), 3.26 (t, 1H, *J* 4.0 Hz), 3.18 (ddd, 1H, *J* 6.5, 6.5, 11.0 Hz), 2.79-2.71(m, 2H), 2.12-2.06 (m, 1H), 1.79-1.73(m, 1H); ^{13}C NMR (CD_3OD) δ 76.1 (CH), 74.7 (CH), 71.9 (CH), 71.8 (CH), 70.7 (CH), 64.2 (CH_2), 54.2 (CH_2), 36.1 (CH_2); MS (CI +ve) *m/z* 190 ($M+1^+$, 100%); HRMS (ES +ve) Calcd for $C_8H_{16}NO_4$ (MH^+) 190.1079. Found: 190.1099.

(-)-(3*aS*,3*bR*,4*R*,8*R*,8*aR*)-4-[2-(4-Methoxyphenyl)methoxy]ethyl-8-phenylmethoxylmethyltetrahydro-3*aH*-[1,3,2]dioxathiolo[4',5':3,4]pyrrolo[1,2-*c*][1,3]oxazol-6-one 2,2-dioxide (23). To a solution of **22** (34.2 mg, 0.077 mmol) in DCM (1 mL) was added Et_3N (24.8 μL, 0.178 mmol) followed by thionyl chloride (7.1 μL, 0.097 mmol) at 0 ^{0}C. The mixture was stirred for 20 min at 0 ^{0}C and water (2 mL) was added to the mixture. The aqueous layer was extracted with DCM (3x). 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 the further purification. $[\alpha]_D^{25}$ –21.3 (*c* 0.3, $CHCl_3$); ^{1}H NMR δ 7.40-7.32 (m, 3H), 7.26 (dd, 2H, *J* 2.1, 8.1 Hz), 7.20 (d, 2H, *J* 8.7 Hz), 6.85 (d, 2H, *J* 9.0 Hz), 5.50 (dd, 1H, *J* 2.1, 5.1 Hz), 5.38 (dd, 1H, *J* 3.3, 5.1 Hz), 4.90 (dd, 1H, *J* 7.2, 14.1 Hz), 4.58 (d, 1H, *J* 12.0 Hz), 4.48 (d, 1H, *J* 12.0 Hz), 4.43 (s, 2H), 4.28 (dd, 1H, *J* 3.0, 6.9 Hz), 4.19 (bdd, 1H, *J* 3.0, 5.1 Hz), 3.79 (s, 3H), 3.73 (dd, 1H, *J* 2.7, 9.6 Hz), 3.69-3.55 (m, 3H), 2.42-2.24 (m, 2H); ^{13}C NMR (CO could not be observed) δ 159.3 (C, Ar), 137.1 (C, Ar), 129.8 (C, Ar), 129.4 (CH, Ar), 128.7 (CH, Ar), 128.2 (CH, Ar), 127.7 (CH, Ar), 113.9 (CH, Ar), 88.4 (CH), 85.2 (CH), 74.6 (CH), 73.7 (CH_2), 73.1 (CH_2), 71.1 (CH_2), 66.2 (CH_2), 65.5 (CH), 63.7 (CH), 55.3 (CH_3), 29.5 (CH_2); MS (CI +ve) *m/z* 370 (M-PMB+2^+); HRMS (ES +ve) Calcd for $C_{24}H_{28}NO_8$ (MH^+) 490.1536. Found: 490.1531. The crude cyclic sulfite obtained above was

dissolved in 1.75 mL of a solution of CCl_4: CH_3CN: H_2O (2: 2: 3, v/v/v) and $RuCl_3{\cdot}3H_2O$ (1.1 mg, 0.0042 mmol) was added followed by $NaIO_4$ (31.4 mg, 0.1467 mmol). The mixture was stirred at RT for 1.5 h and then diluted with ethyl ether (5 mL). The organic layer was filtered through a pad of celite. The filtrate was washed with water and saturated sodium bicarbonate solution followed by brine and then dried ($MgSO_4$). The solvent was evaporated and then chromatography of the residue, eluting with EtOAc/petrol (40%-70%), gave compound **23** (31.1 mg, 80%) as a pale yellow oil. $[\alpha]_D^{26}$ -14.6 (*c* 1.5, $CHCl_3$); ^{1}H NMR δ 7.40-7.33 (m, 3H), 7.24 (dd, 2H, *J* 1.5, 8.1 Hz), 7.17 (d, 2H, *J* 8.4 Hz), 6.84 (d, 2H, *J* 8.7 Hz), 5.36 (dd, 1H, *J* 1.8, 5.4 Hz), 5.21 (dd, 1H, *J* 3.0, 5.1 Hz), 4.88 (dt, 1H, *J* 6.6, 7.8 Hz), 4.56 (d, 1H, *J* 11.7 Hz), 4.46 (d, 1H, *J* 11.7 Hz), 4.45-4.40 (m, 3H), 4.19 (dd, 1H, *J* 3.0, 7.2 Hz), 3.78 (s, 3H), 3.74 (dd, 1H, *J* 3.0, 9.9 Hz), 3.67 (dd, 1H, *J* 3.0, 9.9 Hz), 3.70-3.64 (m, 1H), 3.57 (dt, 1H, *J* 3.3, 10.2 Hz), 2.40-2.17 (m, 2H); ^{13}C NMR (CO could not be observed) δ 159.4 (C, Ar), 136.8 (C, Ar), 129.6 (C, Ar), 129.5 (CH, Ar), 128.7 (CH, Ar), 128.3 (CH, Ar), 127.7 (CH, Ar), 113.9 (CH, Ar), 87.3 (CH), 85.4 (CH), 74.8 (CH), 73.8 (CH_2), 73.2 (CH_2), 70.8 (CH_2), 66.1 (CH_2), 65.8 (CH), 62.7 (CH), 55.2 (CH_3), 29.3 (CH_2); $[\alpha]_D^{26}$ -14.6 (*c* 1.5, $CHCl_3$); MS (CI +ve) *m/z* 386 (M-PMB+2$^+$); HRMS (ES +ve) Calcd for $C_{24}H_{28}NO_9S$ (MH^+) 506.1485. Found: 506.1505; Calcd for $C_{24}H_{27}NO_9NaS$ ($M+Na^+$) 528.1304. Found: 528.1318.

(+)-(1*R*,5*R*,6*R*,7*R*,7*aR*)-6-Hydroxyl-1-[2-(4-methoxyphenyl)methoxy]ethyl-7-phenylcarbonyloxy-5-phenylmethoxymethyltetrahydro-1*H*-pyrrolo[1,2-*c*][1, 3]oxazol-3-one (24). To a solution of **23** (158 mg, 0.312 mmol) in DMF (5 mL) was added benzoic acid (64.7 mg, 0.530 mmol) followed by cesium carbonate (152 mg, 0.468 mmol). The mixture was stirred under nitrogen at 40 ^{0}C for 4 h. DMF was removed under reduced pressure and the residue was suspended in THF (6 mL). Water (6 drops) followed by concentrated sulfuric acid (3 drops) was added and the suspension became a clear

solution. The solution was stirred at RT for 22 h. The volatiles were removed *in vacuo* to give a semi-solid which was purified by column chromatography (20%-60% EtOAc/petrol) to give **24** (95.3 mg, 56%) as a colourless oil. $[\alpha]_D^{25}$ +40.0 (*c* 1.8, $CHCl_3$); ^{1}H NMR δ 7.95 (dd, 2H, *J* 1.2, 8.4 Hz), 7.63-7.56 (m, 1H), 7.48-7.41 (m, 2H), 7.35-7.25 (m, 5H), 7.21 (d, 2H, *J* 8.7 Hz), 6.84 (d, 2H, *J* 8.7 Hz), 5.16 (dd, 1H, *J* 4.8, 7.8 Hz), 4.98 (ddd, 1H, *J* 3.9, 7.8, 11.7 Hz), 4.63-4.52 (m, 1H), 4.61 (d, 1H, *J* 12.0 Hz), 4.54 (d, 1H, *J* 12.6 Hz), 4.42 (d, 1H, *J* 11.4 Hz), 4.37 (d, 1H, *J* 11.4 Hz), 4.26 (t, 1H, J 7.8 Hz), 4.14 (apparent q, 1H, *J* 4.2 Hz), 3.79-3.74 (m, 1H), 3.77 (s, 3H), 3.71 (dd, 1H, *J* 2.4, 4.2 Hz), 3.62-3.58 (m, 2H), 2.10-1.88 (m, 2H); ^{13}C NMR (one Ar C could not be observed) δ 166.8 (CO), 160.5 (CO), 159.2 (C, Ar), 137.7 (C, Ar), 133.8 (CH, Ar), 129.9 (C, Ar), 129.7 (CH, Ar), 129.4 (CH, Ar), 128.6 (CH, Ar), 128.3 (CH, Ar), 127.7 (CH, Ar), 127.5 (CH, Ar), 113.8 (CH, Ar), 79.8 (CH), 79.3 (CH), 73.3 (CH_2), 72.9 (CH_2), 70.0 (CH_2), 65.6 (CH_2), 64.6 (CH), 64.5 (CH), 55.2 (CH_3), 30.8 (CH_2); MS (ES +ve) *m/z* 570 ($M+Na^+$, 100%); HRMS (ES +ve) Calcd for $C_{31}H_{34}NO_8$ (MH^+) 548.2284. Found: 548.2350; Calcd for $C_{31}H_{33}NO_8Na$ ($M+Na^+$) 570.2104. Found: 570.2164.

(+)-(1*R*,5*R*,6*R*,7*R*,7*aR*)-6-Hydroxyl-1-(2-hydroxy)ethyl-7-phenylcarbonyloxy-5-(phenylmethoxy)methyl-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (25). The same procedure described above for the preparation of **17** was used starting with **24** (30.6 mg, 0.056 mmol) and DDQ (15.2 mg, 0.067 mmol) in a solution of DCM (5 mL) containing water (0.5 mL). Compound **25** (17.9 mg, 75%) was obtained as a pale yellow oil. $[\alpha]_D^{28}$ +56.9 (*c* 1.5, $CHCl_3$); ^{1}H NMR δ 7.98 (ddd, 2H, *J* 0.6, 1.2, 7.8 Hz), 7.62 (tt, 1H, *J* 1.5, 7.5 Hz), 7.46 (t, 2H, *J* 7.8 Hz), 7.32-7.29 (m, 5H), 5.14 (dd, 1H, *J* 4.8, 7.8 Hz), 4.97 (bdd, 1H, *J* 7.5, 13.8 Hz), 4.62 (d, 1H, *J* 11.7 Hz), 4.56 (d, 1H, *J* 12.0 Hz), 4.64-4.54 (m, 1H), 4.29 (t, 1H, *J* 8.1 Hz), 4.13 (bdd, 1H, *J* 4.2, 8.1 Hz), 3.87-3.78 (m, 2H), 3.74 (dd, 1H, *J* 4.2, 9.9 Hz), 3.69 (dd, 1H, *J* 4.5, 9.9 Hz), 2.04-1.96 (m, 2H); ^{13}C NMR δ 167.1 (CO), 160.4 (CO), 137.7

(C, Ar), 134.0 (CH, Ar), 129.8 (CH, Ar), 128.7 (CH, Ar), 128.6 (C, Ar), 128.4 (CH, Ar), 127.8 (CH, Ar), 127.6 (CH, Ar), 80.1 (CH), 79.4 (CH), 73.4 (CH_2), 73.3 (CH), 70.1 (CH_2), 64.8 (CH), 64.7 (CH), 59.0 (CH_2), 33.0 (CH_2); MS (CI +ve) *m/z* 428 ($M+1^+$, 100%); HRMS (EI +ve) Calcd for $C_{23}H_{25}NO_7$ ($M-1^+$) 426.1553. Found: 426.1514.

(+)-(2*R*,3*R*,4*R*,5*R*)-5-[(1*R*)-1,3-Dihydroxypropyl]-2-(phenylmethoxy)methyl pyrrolizine-3,4-diol (26). The same procedure described above for the preparation of **18** was used starting with **25** (48.6 mg, 0.114 mmol) and sodium hydroxide (45.5 mg, 1.138 mmol) in a solution of ethanol (1 mL). Compound **26** (20.5 mg, 61%) was obtained as a pale yellow oil. $[\alpha]_D^{29}$ +14.0 (*c* 2.1, MeOH); ^{1}H NMR (D_2O) δ 7.57-7.44 (m, 5H), 4.66 (bs, 2H), 4.13 (t, 1H, *J* 6.9 Hz), 3.98-3.93 (m, 2H), 3.81-3.66 (m, 4H), 3.34 (bs, 1H), 3.12 (bs, 1H), 1.87-1.75 (m, 2H); ^{13}C NMR (CD_3OD) δ 139.1 (C, Ar), 129.5 (CH, Ar), 129.0 (CH, Ar), 128.9 (CH, Ar), 78.5 (CH), 76.9 (CH), 74.4 (CH_2), 69.3 (CH_2), 69.0 (CH), 66.5 (CH), 63.1 (CH), 59.5 (CH_2), 37.1 (CH_2); MS (CI +ve) *m/z* 298 ($M+1^+$, 100%); HRMS (ES +ve) Calcd for $C_{15}H_{24}NO_5$ (MH^+) 298.1654. Found: 298.1661.

(+)-(1*R*,2*R*,3*R*,7*R*,7*aR*)–1,2,7-Triacetoxy-3-(phenylmethoxy)methylhexahydro-1*H*-pyrrolizine (28). The same procedure described above for the preparation of **19** was used using DIAD (16.3 μL, 0.083 mmol) and Ph_3P (21.7 mg, 0.083 mmol) and **26** (20.5 mg, 0.069 mmol) in dry THF (1 mL). Compound **27** was obtained as a pale yellow oil. Acetylation of **27**, using the same procedure described above for the preparation of **20** gave the title compound **28** (6.3 mg, 22% overall for 2 steps) as a pale yellow oil. $[\alpha]_D^{29}$ +18.5 (*c* 0.6, $CHCl_3$); ^{1}H NMR δ 7.36-7.27 (m, 5H), 5.29 (dd, 1H, *J* 6.3, 6.9 Hz), 5.21 (dt, 1H, *J* 6.0, 3.0 Hz), 5.11 (dd, 1H, *J* 6.0, 6.3 Hz), 3.56-3.47 (m, 2H), 3.38 (dd, 1H, *J* 3.0, 6.0Hz), 3.19 (ddd, 1H, *J* 6.0, 9.3, 11.7 Hz), 3.01-2.94 (m, 2H), 2.19-2.04 (m, 1H), 2.05 (s, 3H),

2.02 (s, 3H), 1.99 (s, 3H), 1.89-1.80 (m, 2H); ^{13}C NMR (one Ar C could not be observed) δ 170.2 (CO), 170.1 (CO), 169.6 (CO), 127.9 (CH, Ar), 127.2 (CH, Ar), 127.2 (CH, Ar), 77.3 (CH), 76.8 (CH), 76.1 (CH), 73.0 (CH_2), 72.5 (CH), 71.4 (CH_2), 66.7 (CH), 52.2 (CH_2), 29.7 (CH_2), 20.6 (CH_3), 20.5 (CH_3), 20.4 (CH_3); MS (CI +ve) *m/z* 406 ($M+1^+$, 100%); HRMS (ES +ve) Calcd for $C_{21}H_{28}NO_7$ (MH^+) 406.1866. Found: 406.1858.

(1*R*,2*R*,3*R*,7*R*,7*aR*)–1,2,7-Triacetoxy-3-acetoxymethylhexahydro-1*H*-pyrrolizine (30). A solution of compound **28** (5.2 mg, 0.013 mmol) in MeOH (0.5 mL) was treated with palladium chloride (2.0 mg, 0.011 mmol) as described above for the preparation of **20**. The product **29** was acetylated using pyridine (0.5 mL) and Ac_2O (0.5 mL) as described above for the synthesis of **21**. Compound **30** (4.3 mg, 94% overall for 2 steps) was obtained as a pale yellow oil. ^{1}H NMR δ 5.22 (t, 1H, *J* 5.4 Hz), 5.22-5.19 (m, 1H), 5.16 (t, 1H, *J* 5.4 Hz), 4.11 (bd, 1H, *J* 1.2 Hz), 4.09 (bd, 1H, *J* 1.2 Hz), 3.39 (dd, 1H, *J* 3.0, 5.7 Hz), 3.20 (ddd, 1H, *J* 6.3, 9.0, 11.4 Hz), 3.03 (dd, 1H, *J* 5.4, 11.7 Hz), 2.91 (ddd, 1H, *J* 4.2, 7.5, 11.4 Hz), 2.17-2.09 (m, 1H), 2.09 (s, 6H), 2.06 (s, 3H), 2.04 (s, 3H), 1.91-1.84 (m, 1H); ^{13}C NMR δ 170.8 (CO), 170.6 (CO), 170.3 (CO), 169.8 (CO), 77.8 (CH), 77.5 (CH), 77.1 (CH), 73.1 (CH), 66.7 (CH), 64.9 (CH_2), 52.7 (CH_2), 30.3 (CH_2), 21.0 (CH_3), 20.9 (CH_3), 20.8 (CH_3); MS (CI +ve) *m/z* 358 ($M+1^+$, 100%.); HRMS (EI +ve) Calcd for $C_{16}H_{24}NO_8$ (MH^+) 358.1502. Found: 358.1505.

(-)-*(*1*R*,2*R*,3*R*,7*R*,7*aR*)–Hexahydro–3-hydroxymethyl–1*H*-pyrrolizine-1,2,7-triol, [(-)-7-Epiaustraline] (9). To a solution of **30** (4.3 mg, 0.012 mmol) in methanol (0.5 mL) was added potassium carbonate (2.0 mg). The mixture was stirred at RT for 24 h and then concentrated under

reduced pressure. The residue was dissolved in $CHCl_3$-MeOH (5:1, 6 mL) and filtered though a small pad of celite to give the title product **9** (2.2 mg, 97%) as a pale yellow oil. $[\alpha]_D^{24}$ -14.1 (*c* 0.22, H_2O) [lit[6] $[\alpha]_D^{23}$ –13.04 (*c* 0.55, H_2O, pH 8.37)]; ^1H NMR (500 MHz, D_2O) δ 4.18 (dt, 1H, *J* 5.0, 2.5 Hz), 3.62 (dd, 1H, *J* 4.0, 11.5 Hz), 3.55 (t, 1H, *J* 8.0 Hz), 3.52 (t, 1H, *J* 8.0 Hz), 3.47 (dd, 1H, *J* 6.5, 11.5 Hz), 2.92 (ddd, 1H, *J* 6.0, 10.0, 11.5 Hz), 2.82 (dd, 1H, *J* 2.0, 7.5 Hz), 2.70 (ddd, 1H, *J* 4.0, 7.5, 11.5 Hz), 2.49 (ddd, 1H, *J* 4.0, 6.5, 10.0 Hz), 1.91 (dddd, 1H, *J* 5.5, 7.5, 10.5, 13.0 Hz), 1.63-1.58 (m, 1 H); ^{13}C NMR (D_2O) δ 77.5 (CH), 76.0 (CH), 74.4 (CH), 73.3 (CH), 67.7 (CH), 62.2 (CH_2), 50.9 (CH_2), 30.7 (CH_2); MS (CI +ve) *m/z* 190 ($M+1^+$); HRMS (ES +ve) Calcd for $C_8H_{16}NO_4$ (MH^+) 190.1079. Found: 190.1073.

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Supporting Information Available. Full experimental details and characterization data for the synthesis of **10** from 3-butyn-1-ol. Copies of the ^1H and ^{13}C NMR spectra of compounds **8-23** and **25-29**, ^1H NMR spectrum of **30** and the ^{13}C NMR spectrum of **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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GRAPHICAL ABSTRACT

Asymmetric Synthesis of (-)-7-Epiaustraline and (+)-1,7-Diepiaustraline

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