Asymmetric synthesis of (-)-7-epiaustraline and (+)-1,7-diepiaustraline

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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-2,3,5,6,7,7a-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. In the same year its 7a-epimer, australine (2), was isolated from the seeds of the Australian legume, Castanospermum australe. Later reports described the isolation of other epimers of 2 from these seeds. 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-\(O\)-\(\beta\)-D-glucopyranosyl derivative of 3 and the compounds 5 and 6. The latter two alkaloids were epimeric at C-7, with 6 having the same C-7, C-7a stereochemistry as casurine 7. Compound 6 is the first 7-epiaustraline alkaloid to be isolated. While this honor was originally claimed for 7-epiaustraline itself, synthetic studies by Denmark 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 and recently on several \(\alpha\)- and \(\beta\)-glucosidase enzymes and \(\alpha\)-L-fucosidase. Compounds 2, 5 and 7 and the 2-\(O\)-\(\beta\)-D-glucopyranosyl derivative of 3 and the 6-\(O\)-\(\alpha\)-D-glucopyranosyl derivative of 7, were the most potent and specific enzyme inhibitors. Other biological studies have revealed the potential of these and related polyhydroxylated pyrrolizidines as antiviral and anti-retroviral agents. 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, and its epimers, australine, and its epimers, and casuarine.
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.
Aminolysis\textsuperscript{13-15} of the enantiomerically enriched \textit{cis}- or \textit{trans}-vinyl epoxide \textbf{E}, that is readily available in all configurational forms using the Sharpless epoxidation,\textsuperscript{15,16} with either \textit{R} or \textit{S} chiral allylic amine \textbf{D},\textsuperscript{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 \textbf{C} followed by a ring-closing metathesis reaction\textsuperscript{13,15,18-20} should provide the conformationally rigid pyrrolo[1,2-\textit{c}]oxazol-3-one structure \textbf{B}. The bicyclic nature of \textbf{B} should allow for a stereochemically controlled \textit{cis}-dihydroxylation of the 3,4-double bond of \textbf{B}, a problem that we\textsuperscript{15} and others\textsuperscript{18j,21} experienced in the synthesis of (-)-swainsonine. To test the feasibility of this approach we chose (+)-1,7-diepiaustraline \textbf{8} and (-)-7-epiaustaline \textbf{9} as our target molecules (Figure 3). These compounds have the 6,7-\textit{cis} and 6,7-\textit{trans} diol stereochemistry, respectively. It was anticipated that by employing a oxazolidinone protecting group then the conformationally rigid pyrrolo[1,2-\textit{c}]oxazol-3-one structure (\textbf{F}, Figure 3) obtained would allow for the introduction of these functionalities in a diastereoselective manner.
Figure 3. Target molecules

The starting vinyl epoxide (+)-(2R, 3R)-10 was prepared from the corresponding Sharpless epoxy alcohol (94 % ee from 1H 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 (1.4 equiv) in acetonitrile was heated at 120 °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, CH₃CN, 120 °C, sealed tube, 72 h; b) triphosgene, Et₃N, DCM, RT, 2 h; c) Grubbs’ catalyst I, DCM, reflux, 44 h; d) K₂OsO₄·H₂O, NMO, acetone, H₂O, RT, 24 h; e) Ac₂O, pyridine, RT, 24 h; f) DDQ, DCM, H₂O, RT, 2 h; g) NaOH, EtOH, 70 °C, sealed
tube, 24 h; h) DIAD, PPh₃, pyridine, 0 °C, 2.5 h; i) Ac₂O, pyridine, RT, 24 h; j) PdCl₂, H₂, MeOH, RT, 1.5 h; k) Ac₂O, 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 CH₂Cl₂ 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 % K₂OsO₄·2H₂O 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 H7a 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).
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 °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\(_3\)P)\(^{15,27}\) 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 peracylation 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,\(^{8c}\) and its specific rotation ([\(\alpha\)]\(_D\))\(^{24}\).
+6.4 (c 0.7, MeOH), $[\alpha]_D^{24} +8.6$ (c 0.7, H$_2$O)) closely matched that previously reported (lit.9c ($[\alpha]_D^{20} + 4.7$ (c 0.5, H$_2$O)).

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 $\beta$-C-5 benzyloxyxymethyl 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$_2$O)), almost identical to that reported in the literature (lit.6 $[\alpha]_D^{20} –13.04$ (c 0.55, H$_2$O, pH 8.37)).
Scheme 2. Reagents and conditions: a) (i) SOCl₂, Et₃N, DCM, 0 °C, 30 min; (ii) RuCl₃·3H₂O, NaIO₄, CCl₄:CH₃CN:H₂O = 2:2:3, RT, 2 h; b) (i) PhCOOH, Cs₂CO₃, DMF, 40 °C, 23 h; (ii) H₂SO₄ (conc.), THF, H₂O, RT, 18 h; c) DDQ, DCM, H₂O, RT, 2 h; d) NaOH, EtOH, 70 °C, 19 h; e) DIAD, PPh₃, THF, 0 °C, 3 h; f) Ac₂O, pyridine, RT, 21 h; g) PdCl₂, H₂, MeOH, RT, 1 h; h) Ac₂O, pyridine, RT, 15 h; i) K₂CO₃, MeOH, RT, 24 h.

In summary, we have developed a diastereoselective and modular approach to the synthesis of the 3-hydroxymethyl-2,3,5,6,7,7a-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-3R-[(1S-phenylmethoxymethyl)-2-propenyl]amino-1-hepten-4-ol (12). To a mixture of 10 (195 mg, 0.833 mmol) and 11 (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 °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. [α]D ^22 +3.8 (c 2.7, CHCl₃); ¹H 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 (dd, 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); ¹³C 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 (CH₂), 118.0 (CH₂), 113.7 (CH, Ar), 73.2 (CH₂), 73.0 (CH₂), 72.8 (CH₂), 72.0 (CH), 68.3 (CH₂), 62.4 (CH), 57.9 (CH), 55.3 (CH₃), 33.0 (CH₂); MS (Cl +ve) m/z 412 (M+1^+, 100%); HRMS (Cl +ve) Calcd for C₂₅H₃₄NO₄ (MH⁺) 412.2488. Found: 412.2478.

(+)-4S-Ethenyl-5R-[2-(4-Methoxyphenyl)methoxy]ethyl-3-(1S-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 °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 °C and was then added to the above amine solution at 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 (MgSO₄) 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 \(\delta\) 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 8.7, 10.2 Hz), 3.60-3.56 (m, 2H), 1.91-1.71 (m, 2H); \(^{13}\)C NMR \(\delta\) 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 (Cl +ve) m/z 438 (M$^+$); 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\(a\)\(R\))\)-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. \([\alpha]_D^{25} -90.3 (c 2.4, CHCl_3)\); \(^1\)H NMR \(\delta\) 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).
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 (ddddd, 1H, J 4.5, 6.9, 8.1, 14.4 Hz), 1.78 (ddddd, 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 (Cl +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$a^R$)-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 (Cl +ve) m/z 444 (M+1$^+$); HRMS (El +ve) Calcd for C$_{24}$H$_{29}$NO$_7$ (M$^+$) 443.1944. Found: 443.1926.
(-)-(1R,5R,6R,7S,7aR)-6,7-Diacetoxy-1-[2-(4-methoxyphenyl)methoxy]ethyl-5-(phenylmethoxy)methyl-5,6,7,7a-tetrahydro-1H,3H-pyrrolo[1,2-c]oxazol-3-one (16). Compound 15 (170 mg, 0.384 mmol) was dissolved in pyridine (2.0 mL) and then Ac₂O (2.0 mL) was added. The mixture was stirred at RT for 20 h, then diluted with DCM (40 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 an oil which was purified by column chromatography (30%-70% EtOAc/petrol) to give product 16 as a colorless oil (154 mg, 76%). [α]D₂₆ -4.3 (c 2.0, CHCl₃); ¹H 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); ¹³C 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 (CH₂), 72.8 (CH₂), 72.6 (CH), 69.0 (CH₂), 65.6 (CH₂), 63.2 (CH), 59.7 (CH), 55.1 (CH₃), 29.6 (CH₂), 20.7 (CH₃), 20.2 (CH₃); MS (Cl +ve) m/z 528 (M+1⁺); HRMS (ES +ve) Calcd for C₂₈H₃₄NO₉ (MH⁺) 528.2234. Found: 528.2238.

(+)-(1R,5R,6R,7S,7aR)-6,7-Diacetoxy-1-(2-hydroxy)ethyl-5-(phenylmethoxy) methyl-5,6,7,7a-tetrahydro-1H,3H-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 (MgSO₄) 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%). \([\alpha]_D^{25} +15.9 (c 1.4, \text{CHCl}_3); \) \(^1\text{H NMR} \delta 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), 4.51 (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); \(^{13}\text{C NMR} \delta 169.9 (\text{CO}), 169.7 (\text{CO}), 161.4 (\text{CO}), 137.7 (\text{C, Ar}), 128.4 (\text{CH, Ar}), 127.7 (\text{CH, Ar}), 127.5 (\text{CH, Ar}), 73.9 (\text{CH}), 73.8 (\text{CH}), 73.4 (\text{CH}_2), 72.7 (\text{CH}), 69.0 (\text{CH}_2), 63.4 (\text{CH}), 59.9 (\text{CH}), 59.1 (\text{CH}_2), 31.8 (\text{CH}_2), 20.8 (\text{CH}_3), 20.4 (\text{CH}_3); \) 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 \((-\)-(1S,2R,3R,7R,7aR)-1,2,7-Triacetoxy-3-(phenylmethoxy)methylhexahydro-1H-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 \(^0\text{C}\) in a sealed tube for 24 h. The volatiles were then removed \textit{in vacuo} to give a yellow-green solid, and the residue was treated with 2M hydrochloric acid (3 mL). All the volatiles were removed \textit{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\text{H NMR} (\text{CD}_3\text{OD}) \delta 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$_3$OD) $\delta$ 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 (Cl +ve) $m/z$ 298 (M$^+$, 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°C was added dropwise diisopropyl azodicarboxylate (83.5 µL, 0.424 mmol) under nitrogen. The mixture was stirred at 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$_2$O (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 $\delta$ 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 (dd, 1H, $J$ 6.6, 6.9, 10.8 Hz), 3.04 (dd, 1H, $J$ 4.2, 5.7, 9.6 Hz), 2.89 (dd, 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 $\delta$ 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 (Cl +ve) $m/z$ 406 (M$^+$, 100%); HRMS (ES +ve) Calcd for C$_{21}$H$_{28}$NO$_9$ (MH$^+$) 406.1866. Found: 406.1860.
(+)-(1S,2R,3R,7R,7aR)–1,2,7-Triacetoxy-3-(acetoxymethyl)hexahydro-1H-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 Ac₂O (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 NaHCO₃ solution. 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 (30%-70% EtOAc/petrol) to give compound 22 as a pale yellow oil (14.4 mg, 84% overall for 2 steps). [α]D⁰ +10.5 (c 1.4, CHCl₃); ¹H 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 3.9, 6.6, 10.5 Hz), 2.83 (ddd, 1H, J 3.9, 6.6, 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); ¹³C 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 (CH₂), 64.6 (CH), 53.0 (CH₂), 32.4 (CH₂), 20.9 (CH₃), 20.80 (CH₃), 20.7 (CH₃), 20.4 (CH₃); MS (Cl +ve) m/z 358 (M+1⁺, 100%); HRMS (ES +ve) Calcd for C₁₆H₂₄NO₈ (MH⁺) 358.1502. Found: 358.1507.

(+)-(1S,2R,3R,7R,7aR)–Hexahydro–3-hydroxymethyl–1H-pyrrolizine-1,2,7-triol, [(+)-1,7-Diepiustraline] (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%). [α]D²⁴ +6.4 (c 0.7, MeOH), [α]D²⁴ +8.6 (c 0.7, H₂O) [lit⁹c [α]D²⁰ +4.7 (c
0.5, H₂O)]; ¹H NMR (500MHz, CD₃OD) 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); ¹³C NMR (CD₃OD) δ 76.1 (CH), 74.7 (CH), 71.9 (CH), 71.8 (CH), 70.7 (CH), 64.2 (CH₂), 54.2 (CH₂), 36.1 (CH₂); MS (CI +ve) m/z 190 (M⁺, 100%); HRMS (ES +ve) Calcd for C₉H₁₆NO₄ (MH⁺) 190.1079. Found: 190.1099.

(-)-(3aS,3bR,4R,8R,8aR)-4-[2-(4-Methoxyphenyl)methoxy]ethyl-8-phenylmethoxymethyltetrahydro-3aH-[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 Et₃N (24.8 μL, 0.178 mmol) followed by thionyl chloride (7.1 μL, 0.097 mmol) at 0 °C. The mixture was stirred for 20 min at 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 (MgSO₄), 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. [α]D²⁵ –21.3 (c 0.3, CHCl₃); ¹H 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 (bddd, 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); ¹³C 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 (CH₂), 73.1 (CH₂), 71.1 (CH₂), 66.2 (CH₂), 65.5 (CH), 63.7 (CH), 55.3 (CH₃), 29.5 (CH₂); MS (CI +ve) m/z 370 (M-PMB+2⁺); HRMS (ES +ve) Calcd for C₂₄H₂₈NO₈ (MH⁺) 490.1536. Found: 490.1531. The crude cyclic sulfite obtained above was
dissolved in 1.75 mL of a solution of CCl₄: CH₃CN: H₂O (2: 2: 3, v/v/v) and RuCl₃·3H₂O (1.1 mg, 0.0042 mmol) was added followed by NaIO₄ (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 (MgSO₄). 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. [α]D²⁶ -14.6 (c 1.5, CHCl₃); ¹H 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); ¹³C 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 (CH₂), 73.2 (CH₂), 70.8 (CH₂), 66.1 (CH₂), 65.8 (CH), 62.7 (CH), 55.2 (CH₃), 29.3 (CH₂); [α]D²⁶ -14.6 (c 1.5, CHCl₃); MS (Cl +ve) m/z 386 (M-PMB+2⁺); HRMS (ES +ve) Calcd for C₂₄H₂₆NO₉S (MH⁺) 506.1485. Found: 506.1505; Calcd for C₂₄H₂₇NO₉NaS (M+Na⁺) 528.1304. Found: 528.1318.

(+)-(1R,5R,6R,7R,7aR)-6-Hydroxyl-1-[2-(4-methoxyphenyl)methoxy]ethyl-7-phenylcarbonyloxy-5-phenylmethoxymethyltetrahydro-1H-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 °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 \textit{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. \([\alpha]_D^{25} +40.0 (c 1.8, \text{CHCl}_3)\); \(^1\)H NMR \(\delta\) 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) \(\delta\) 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), 113.5 (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\(_8\)Na (M+Na\(^+\)) 570.2104. Found: 570.2164.

\((+)-(1R,5R,6R,7R,7aR)-6$\text{Hydroxyl-1-(2-hydroxy)ethyl-7-phenylcarbonyloxy-5-(phenylmethoxy)methyl-tetrahydro-1H-pyrrolo[1,2-c][1,3]oxazol-3-one}$ (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. \([\alpha]_D^{28} +56.9 (c 1.5, \text{CHCl}_3)\); \(^1\)H NMR \(\delta\) 7.98 (ddd, 2H, \(J\ 1.5, 7.5\) Hz), 7.62 (tt, 1H, \(J\ 1.5, 7.8\) Hz), 7.52 (t, 2H, \(J\ 7.8\) Hz), 7.32-7.29 (m, 5H), 5.14 (dd, 1H, \(J\ 4.8, 7.8\) Hz), 4.97 (ddd, 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 (dd, 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 \(\delta\) 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 (CH2), 73.3 (CH), 70.1 (CH2), 64.8 (CH), 64.7 (CH), 59.0 (CH2), 33.0 (CH2); MS (CI +ve) m/z 428 (M+1+, 100%); HRMS (EI +ve) Calcd for C23H25NO7 (M-1+) 426.1553. Found: 426.1514.

(+)-(2R,3R,4R,5R)-5-[(1R)-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, \text{MeOH}); ^{1}\text{H NMR (D}_2\text{O}) \delta 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}\text{C NMR (CD}_3\text{OD}) \delta 139.1 (C, Ar), 129.5 (CH, Ar), 129.0 (CH, Ar), 128.9 (CH, Ar), 78.5 (CH), 76.9 (CH), 74.4 (CH2), 69.3 (CH2), 69.0 (CH), 66.5 (CH), 63.1 (CH), 59.5 (CH2), 37.1 (CH2); MS (CI +ve) m/z 298 (M+1+, 100%); HRMS (ES +ve) Calcd for C15H24NO5 (MH+) 298.1654. Found: 298.1661.

(+)-(1R,2R,3R,7R,7aR)-1,2,7-Triacetoxy-3-(phenylmethoxy)methylhexahydro-1H-pyrrolizine \((28)\). The same procedure described above for the preparation of \(19\) was used using DIAD (16.3 \(\mu\text{L}, 0.083 \text{ 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, \text{CHCl}_3); ^{1}\text{H NMR} \delta 7.36-7.27 (m, 5H), 5.29 (dd, 1H, \(J\ 6.3, 6.9\ Hz), 5.21 \text{(dt, 1H, } J 6.0, 3.0 \text{ Hz)}, 5.11 \text{(dd, 1H, } J 6.0, 6.3 \text{ Hz}), 3.56-3.47 \text{(m, 2H), 3.38 \text{(dd, 1H, } J 3.0, 6.0Hz), 3.19 \text{(ddd, 1H, } J 6.0, 9.3, 11.7 \text{ Hz)}, 3.01-2.94 \text{(m, 2H), 2.19-2.04 \text{(m, 1H), 2.05 \text{(s, 3H),}})}\)
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 (Cl +ve) m/z 406 (M+1+, 100%); HRMS (ES +ve) Calcd for C$_{21}$H$_{28}$NO$_7$ (MH$^+$) 406.1866. Found: 406.1858.

(1R,2R,3R,7R,7aR)-1,2,7-Triacetoxy-3-acetoxymethylhexahydro-1H-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$_2$O (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 (Cl +ve) m/z 358 (M+1+, 100%); HRMS (EI +ve) Calcd for C$_{16}$H$_{24}$NO$_8$ (MH$^+$) 358.1502. Found: 358.1505.

(-)-(1R,2R,3R,7R,7aR)-Hexahydro-3-hydroxymethyl-1H-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 CHCl₃-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. [α]D²⁴ -14.1 (c 0.22, H₂O) [lit⁶ [α]D²³ -13.04 (c 0.55, H₂O, pH 8.37)]; ¹H NMR (500 MHz, D₂O) 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); ¹³C NMR (D₂O) δ 77.5 (CH), 76.0 (CH), 74.4 (CH), 73.3 (CH), 67.7 (CH), 62.2 (CH₂), 50.9 (CH₂), 30.7 (CH₂); MS (CI +ve) m/z 190 (M+1⁺); HRMS (ES +ve) Calcd for C₈H₁₆NO₄ (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-butyne-1-ol. Copies of the ¹H and ¹³C NMR spectra of compounds 8-23 and 25-29. ¹H NMR spectrum of 30 and the ¹³C NMR spectrum of 24. This material is available free of charge via the Internet at http://pubs.acs.org.
References


GRAPHICAL ABSTRACT

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

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