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PAPER

Stereoselective synthesis of functionalised carbocyclic amides: construction of the *syn*-(4a*S*,10b*S*)-phenanthridone skeleton†

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A new synthetic approach has been developed for the preparation of 7-deoxypancratistatin analogues bearing a *syn*-(4a*S*,10b*S*)-phenanthridone ring junction. A one-pot tandem process involving a substrate-directed Overman rearrangement and ring closing metathesis reaction was developed for the stereoselective synthesis of a carbocyclic allylic trichloroacetamide. Conversion to a 6-bromopiperonyl amide, followed by a Heck reaction generated a homoallylic alcohol and completed the *syn*-(4a*S*,10b*S*)-phenanthridone carbon skeleton. Stereoselective epoxidation and dihydroxylation of the *syn*-(4a*S*,10b*S*)-phenanthridone framework was then investigated leading to the preparation of new analogues of 7-deoxypancratistatin.

Introduction

The Amaryllidaceae family of plants which are found throughout the tropics and warm temperate regions of the world consists of approximately 85 genera and 1100 species.[1] Since the 4th century BC, there has been considerable interest in these plants as sources for therapeutic agents.[2] For example, nearly 500 structurally diverse alkaloids have been isolated from these plants and found to have a wide range of biological properties, including antitumour, antifungal, antiviral, antibacterial and antimalarial activities.[3]

The Amaryllidaceae alkaloids, (+)-pancratistatin isolated by Pettit and co-workers[4] and (+)-7-deoxypancratistatin **1** (Fig. 1) isolated by the research group of Ghosal *et al.*,[5] exhibited strong *in vitro* antiproliferative activity against a series of human tumour cell lines as well as number of *in vivo* experimental cancer systems.[6,7] These highly hydroxylated phenanthridones are among only a few agents known to show chemotherapeutic efficacy in a Japanese encephalitis virus-infected mouse model.[7] Understanding the mode of action of these compounds has been restricted by their low natural abundance (*e.g.* pancratistatin was isolated in 0.039% yield from *Pancratium littorale* bulbs),[4] as well as their poor water solubility. (+)-7-Deoxypancratistatin **1**, although less potent than (+)-pancratistatin, exhibits a better therapeutic index in antiviral assays due to reduced toxicity. For this reason, there have been extensive synthetic studies undertaken to produce quantities of (+)-7-deoxypancratistatin **1** as well as structural analogues and prodrugs.[1,8,9] For example, Plumet and co-workers reported a total synthesis of (+)-7-deoxypancratistatin **1** in 19 steps and 8% overall yield from furan and *trans*-1,2-bis(phenylsulfonyl)ethylene,[10] while the research group of Hudlicky prepared 7-deoxypancratistatin-1-carboxaldehyde and carboxylic acid analogues *via* the intramolecular ring-opening of an epoxy aziridine intermediate with an aluminium acetylide.[9a]

The majority of synthetic studies of (+)-7-deoxypancratistatin **1** have focused on the preparation of analogues with the natural *anti*-(4a*R*,10b*S*)-phenanthridone ring junction. We were interested in developing a new synthetic approach that would allow the efficient preparation of an intermediate such as homoallylic

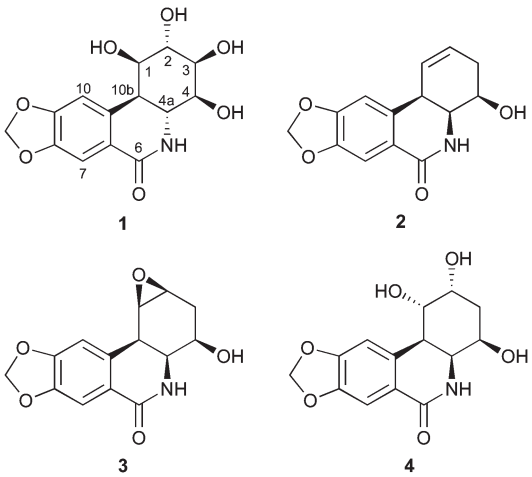

Fig. 1 (+)-7-Deoxypancratistatin **1** and analogues **2**, **3** and **4**.

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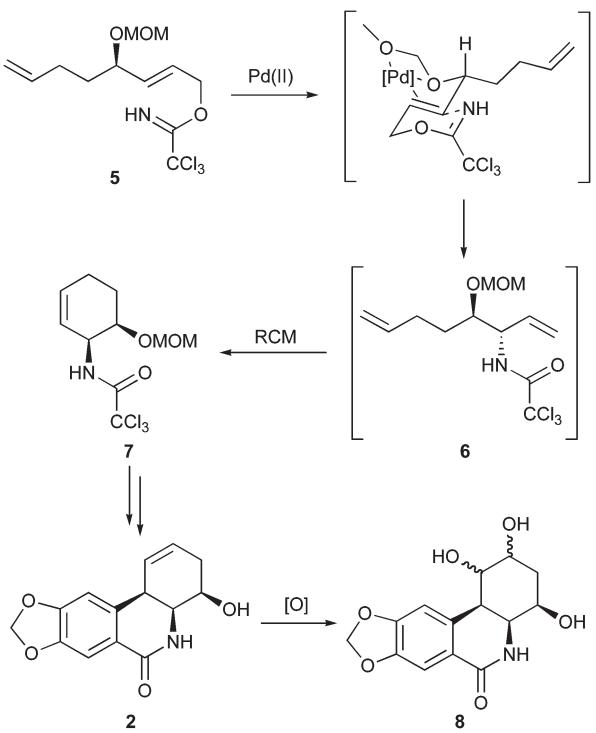
alcohol **2** bearing a *syn*-(4a*S*,10b*S*)-phenanthridone ring junction. It was proposed that the molecular shape of such an intermediate would allow the highly stereoselective functionalisation of the cyclohexene ring producing new oxygenated analogues for biological testing such as **3** and **4**. We now report the synthesis of homoallylic alcohol **2** using a one-pot, substrate-directed Overman rearrangement and ring closing metathesis (RCM) tandem process to effect the key steps. The stereoselective epoxidation and dihydroxylation of **2** for the preparation of novel 7-deoxypancratistatin analogues is also described.

Results and discussion

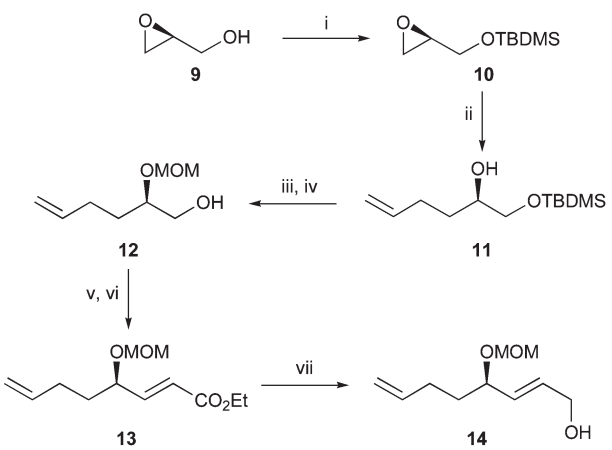
The proposed synthetic route to novel 7-deoxypancratistatin analogues bearing a *syn*-(4a*S*,10b*S*)-phenanthridone ring junction is shown in Scheme 1. The key transformation involved the conversion of allylic trichloroacetimidate **5** to carbocyclic amide **7** using a one-pot tandem process composed of an Overman rearrangement, followed by a RCM reaction.[11] In recent years, we have shown that MOM-ether directed palladium(II)-catalysed Overman rearrangements of allylic trichloroacetimidates allows the preparation of *erythro*-allylic trichloroacetamides in high diastereoselectivity.[12] We believed that palladium(II)-catalysed rearrangement of **5** would similarly yield the *erythro*-allylic trichloroacetamide **6** as the major product, ultimately leading to carbocyclic amide **7** after the RCM reaction. It was then proposed that formation of a 6-bromopiperonyl amide, followed by a modified Heck reaction would give homoallylic alcohol **2**. Finally, using this novel *syn*-(4a*S*,10b*S*)-phenanthridone skeleton, stereoselective oxidation of the alkene moiety would then provide new 7-deoxypancratistatin analogues **8**.



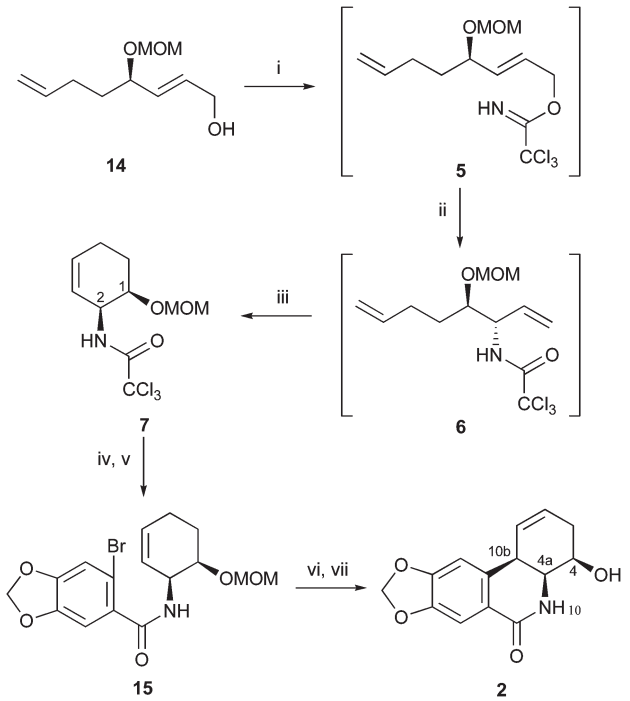
Scheme 1 Proposed route to novel 7-deoxypancratistatin analogues.

The first stage of the synthesis required the preparation of allylic alcohol **14**, the precursor for the one-pot tandem process (Scheme 2). Protection of (*S*)-glycidol **9** as a TBDMS-ether was followed by regioselective ring-opening of the epoxide using allylmagnesium bromide and copper(I) bromide-dimethyl sulfide. This gave secondary alcohol **11** in 90% yield. Protection of the secondary alcohol as the MOM-ether, followed by removal of the TBDMS-protecting group under standard conditions gave **12** in quantitative yield. A one-pot Swern oxidation and Horner–Wadsworth–Emmons reaction under Masamune–Roush conditions then gave *E*-α,β-unsaturated ethyl ester **13** in 99% yield.[13,14] DIBAL-H reduction of **13** then completed the 7-step synthesis of allylic alcohol **14** in 86% overall yield.

Allylic trichloroacetimidate **5** was prepared by the reaction of allylic alcohol **14** with trichloroacetonitrile and DBU (Scheme 3).[15] Initial attempts at preparing carbocyclic amide **7** involved the palladium(II)-catalysed Overman rearrangement[16] of **5** in dichloromethane at room temperature followed by a ring closing metathesis reaction with Grubbs 1st generation catalyst.[17] This gave **7** in 45% yield over the three steps and in a 5 : 1 ratio of (1*R*,2*S*)- and (1*R*,2*R*)-diastereomers, respectively. Previous work in our group has shown that the diastereoselective outcome of MOM-ether directed palladium(II)-catalysed Overman rearrangements can be enhanced by using non-coordinating solvents such as toluene.[12c] The use of such solvents minimises competition for the coordination of the MOM-ether oxygen atoms with the Pd(II)-catalyst. Therefore, the one-pot tandem process was repeated using toluene as a solvent. This gave the (1*R*,2*S*)- and (1*R*,2*R*)-diastereomers in a much improved 10 : 1 ratio, respectively. The desired (1*R*,2*S*)-diastereomer **7** was easily isolated in 60% yield (from **14**) by flash column chromatography. To access homo-allylic alcohol **2**, carbocyclic amide **7** was initially hydrolysed with sodium hydroxide. The resulting amine was then coupled with 6-bromopiperonylic acid[18] using EDCI and this gave the corresponding amide **15** in 79% yield over the two steps. Mori and co-workers during their synthesis of (+)-γ-lycorane showed that an intramolecular Heck reaction



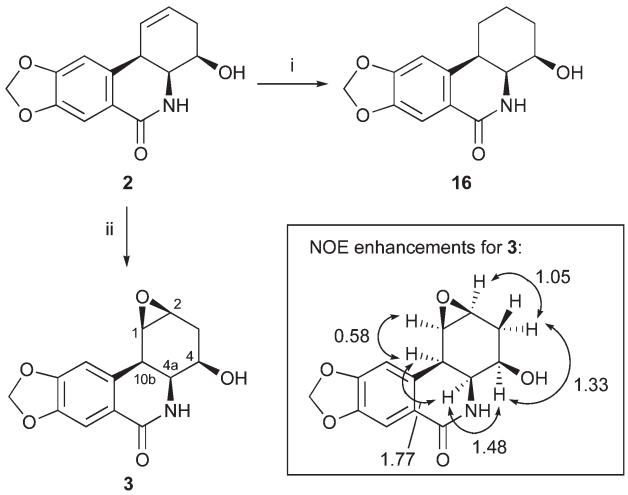
Scheme 2 *Reagents and conditions*: (i) TBDMSCl, imidazole, THF, rt, 98%; (ii) allylmagnesium bromide, CuBr.SMe_2, THF, −78 °C, 90%; (iii) MOMBr, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, 45 °C, 100%; (iv) TBAF, THF, 0 °C, 100%; (v) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (vi) $(EtO)_2P(O)CH_2CO_2Et$, DBU, LiCl, MeCN, rt, 99% over two steps; (vii) DIBAL-H, Et_2O, −78 °C, 98%.



Scheme 3 *Reagents and conditions*: (i) Cl_3CCN, DBU, CH_2Cl_2, rt; (ii) $PdCl_2(MeCN)_2$ (10 mol%), toluene, rt; (iii) Grubbs I (10 mol%), rt, 60%; (iv) 1 M NaOH, MeOH; (v) 6-bromopiperonylic acid, EDCI, DMAP (cat.), MeCN, 0 °C to rt, 79% over two steps; (vi) $Pd(OAc)_2$, Ph_3P, $EtN(i\text{-}Pr)_2$, DMF, 155 °C, 78%; (vii) 1.6 N HCl, MeOH, 40 °C, 97%.

between a 6-bromopiperonyl moiety and a tetrahydroindolin-2-one could be achieved to yield a tricyclic ring system with an all *cis*-ring junction where the alkene had migrated out of conjugation with the aromatic ring.[19] Hence, it was proposed that under similar reaction conditions, **15** would also yield an all *cis*-ring junction with a non-conjugated alkene. On reaction of **15** with palladium(II)-acetate in the presence of triphenylphosphine and Hünig's base, the desired (4*R*,4a*S*,10b*S*)-3,4,4a,5-tetrahydrophenanthridin-6-one was isolated as the sole product in 78% yield. The relative stereochemistry was confirmed by difference NOE experiments which clearly showed the *syn*-relationship of the 4-, 4a- and 10b-hydrogen atoms. Dilute HCl was then used to remove the MOM-protecting group to give **2** in 97% yield.

Having developed a highly efficient approach for the stereoselective synthesis of the *syn*-(4a*S*,10b*S*)-phenanthridone skeleton, conversion to novel 7-deoxypancratistatin analogues was next investigated. Initially, cyclohexene **2** was subjected to hydrogenation using 10% palladium on carbon which gave cyclohexane **16** in 88% yield (Scheme 4). The stereoselective epoxidation of **2** was then investigated. A number of studies have shown that cyclic allylic alcohols[20] and amides[11e,21] can undergo highly stereoselective directed epoxidation according to Henbest's rule using *m*-CPBA.[22] However, cyclic homoallylic alcohols and amides in general, tend to give very modest levels of stereoselectivity with aryl peroxyacids and other epoxidising reagents.[23] Reaction of cyclohexene **2** with *m*-CPBA at room temperature gave epoxide **3** as a single diastereomer in 75% yield (Scheme 4). Difference NOE experiments clearly showed



Scheme 4 *Reagents and conditions*: (i) H_2, 10% Pd/C, MeOH, rt, 88%; (ii) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 75%.

correlation between the 1-, 2-, 3_{eq}-, 4-, 4a- and 10b-hydrogen atoms confirming the preparation of the (1*R*,2*S*,4*R*,4a*S*,10b*S*)-stereoisomer. To rationalise the stereochemical outcome of this reaction, the two possible partial chair conformers of **2** were modelled using density-functional theory.[24] The low energy conformer (conformer a, Fig. 2) places the C-4a amide substituent in a pseudo-axial position while the C-4 alcohol functional group is in a pseudo-equatorial position. The other possible partial chair conformer (conformer b, Fig. 2) which is 11.3 kJ mol^{-1} higher in energy, places the C-4a amide in a pseudo-equatorial position and the C-4 alcohol pseudo-axially. Thus, irrespective of which chair conformer is adopted during the epoxidation, a functional

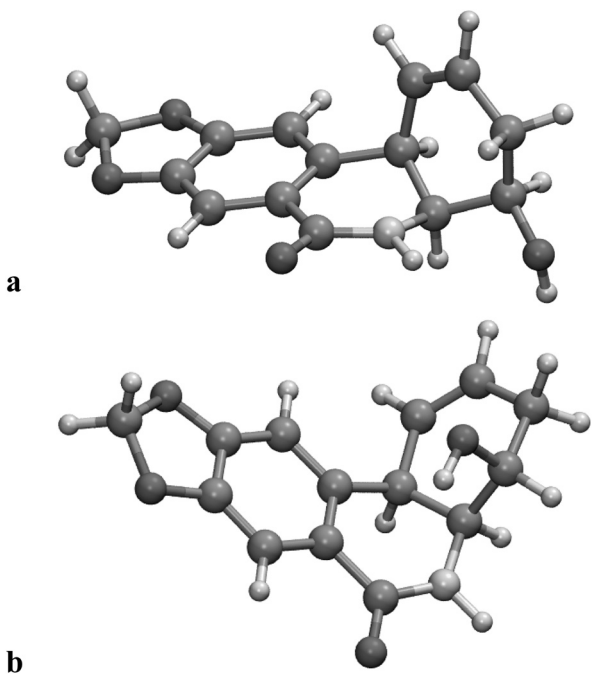
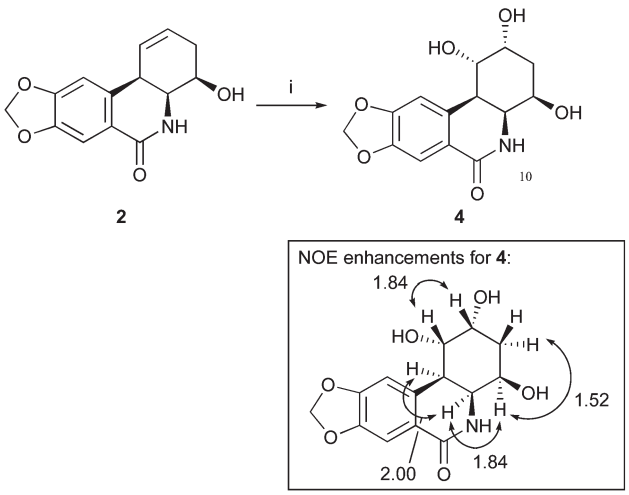


Fig. 2 DFT-optimised structures[24] of **2**. Partial chair conformer a (top structure) is the lowest energy conformer, while conformer b (bottom structure) is 11.3 kJ mol^{-1} higher in energy.



Scheme 5 *Reagents and conditions*: (i) OsO_4, TMEDA, CH_2Cl_2, −78 °C to rt, 90%.

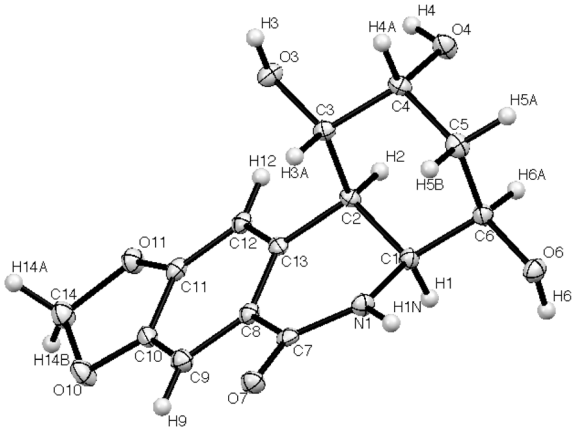


Fig. 3 Molecular structure of compound **4**. Displacement ellipsoids are drawn at 50% probability level and H-atoms are drawn with spheres of arbitrary radius.

group (the C-4a amide in conformer a and the C-4 hydroxyl group in conformer b) capable of H-bonding with *m*-CPBA is in close proximity with the alkene moiety, resulting in a directed epoxidation leading to the (1*R*,2*S*,4*R*,4a*S*,10b*S*)-stereoisomer.

The next stage of this project then investigated the dihydroxylation of **2** for the preparation of targets more similar in structure to 7-deoxypancratistatin. Following the epoxidation reaction described above, we were interested to discover whether the *syn*-(4a*S*,10b*S*)-phenanthridone ring junction of **2** would allow a directed dihydroxylation reaction. Donohoe and co-workers have shown that reaction of osmium tetroxide with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) generated a reagent that undergoes highly selective directed dihydroxylation with cyclic allylic alcohols and amides.[25] More importantly, this complex also undergoes selective directed dihydroxylation with cyclic homoallylic alcohols and amides.[26] Reaction of cyclohexene **2** with osmium tetroxide and TMEDA gave a dihydroxylated product as a single diastereomer in 90% yield (Scheme 5).

Initial analysis of this compound using coupling constants of the cyclohexane ring hydrogens from the ^{1}H NMR spectrum as well as difference NOE experiments (see Scheme 5) suggested that the (1*R*,2*S*)-stereoisomer **4** had been formed *via* a non-directed reaction mechanism. Confirmation of the (1*R*,2*S*)-stereoisomer was achieved by X-ray crystallography (Fig. 3, see also ESI†).[27] (1*R*,2*S*,4*R*,4a*S*,10b*S*)-1,2,3,4,4a,10b-Hexahydro-1,2,4-trihydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (**4**) crystallises in the orthorhombic space group $P2_12_12_1$ and the structure clearly shows that the C-1 and C-2 hydroxyl groups are in an *anti*-relationship with the substituents at C-4, C-4a and C-10b. While *m*-CPBA is small enough to coordinate to either the C-4 hydroxyl or the C-4a amide and undergo a directed epoxidation from the more hindered concave face of cyclohexene **2** (see molecular models of both possible partial chair conformers in Fig. 2), it appears that the complex formed from osmium tetroxide and TMEDA is too large to be directed by one of these functional groups and instead, effects a highly selective dihydroxylation of the C1-C2-alkene moiety from the least hindered convex face. Thus, the molecular shape of the *syn*-(4a*S*,10b*S*)-phenanthridone skeleton has a significant influence on the functionalisation of the alkene where the size of the reagent and its ability to undergo a directed reaction dictates the face of attack. It should be emphasised that unlike other cyclic homoallylic alcohols and amides, the two reactions studied so far with this novel phenanthridone framework gave the oxidised products as single stereoisomers.

Conclusions

In summary, a one-pot substrate directed Overman rearrangement and RCM reaction has been developed for the stereoselective synthesis of a highly functionalised carbocyclic amide. This flexible synthetic intermediate was converted using a modified Heck reaction to a novel *syn*-(4a*S*,10b*S*)-phenanthridone skeleton. Epoxidation of the *syn*-(4a*S*,10b*S*)-phenanthridone framework using a substrate directed method generated the predicted stereoisomer as the sole product in 75% yield. Despite this result, dihydroxylation of the phenathridone using a substrate directed method gave the non-directed product in 90% yield as a single stereoisomer. Together, these results show that with some understanding of the size and reactivity of potential reagents, this novel *syn*-(4a*S*,10b*S*)-phenanthridone skeleton can be used to prepare new analogues and stereoisomers of 7-deoxypancratistatin with excellent levels of stereoselectivity. Current studies are underway to fully explore the stereoselective functionalisation of the *syn*-(4a*S*,10b*S*)-phenanthridone skeleton for the preparation of wide range of new 7-deoxypancratistatin analogues. The results of these studies as well as biological evaluation of these novel compounds will be communicated in due course.

Experimental

All reagents and starting materials were obtained from commercial sources and used as received. All dry solvents were purified using a PureSolv 500 MD solvent purification system. All reactions were performed under an atmosphere of argon unless otherwise mentioned. Brine refers to a saturated solution of sodium chloride. Flash column chromatography was carried out using Fisher matrix silica 60. Macherey-Nagel aluminium-backed

plates pre-coated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualised by staining with potassium permanganate. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in ppm relative to tetramethylsilane as the standard. Assignment of ^1H and ^{13}C NMR signals are based on two-dimensional COSY and DEPT experiments, respectively. Infrared spectra were recorded using Golden Gate apparatus on a JASCO FTIR 410 spectrometer and mass spectra were obtained using a JEOL JMS-700 spectrometer. Melting points were determined on a Reichert platform melting point apparatus. Optical rotations were determined as solutions irradiating with the sodium D line (λ = 589 nm) using an Autopol V polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}.

(2*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,3-epoxypropane (10)[28]

A mixture of (*S*)-glycidol **9** (3.10 g, 0.04 mol), *tert*-butyldimethylsilyl chloride (9.40 g, 0.06 mol) and imidazole (4.20 g, 0.06 mol) in tetrahydrofuran (70 mL) were stirred overnight at room temperature. A white precipitate was removed by filtration and washed with diethyl ether (70 mL). The combined filtrate was concentrated and purified by flash column chromatography (elution with petroleum ether–diethyl ether, 10 : 1) to give (2*R*)-1-(*tert*-butyldimethylsilyloxy)-2,3-epoxypropane (**10**) (7.70 g, 98%) as a colourless oil. $[\alpha]_D^{24}$ +2.7 (*c* 1.0, $CHCl_3$), lit.[28] +2.9 (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} (Neat) 2930 (CH), 1253, 1161, 983, 835; δ_H (400 MHz, $CDCl_3$) 0.09 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$), 0.92 (9H, s, $SiC(CH_3)_3$), 2.66 (1H, dd, *J* 4.6, 2.4 Hz, 1-*H*H), 2.79 (1H, dd, *J* 5.2, 4.6 Hz, 1-H*H*), 3.10–3.14 (1H, m, 2-H), 3.68 (1H, dd, *J* 11.8, 4.8 Hz, 3-*H*H), 3.87 (1H, dd, *J* 11.8, 3.2 Hz, 3-H*H*); δ_C (100 MHz, $CDCl_3$) −5.4 (2 × CH_3), 18.4 (C), 26.0 (3 × CH_3), 45.0 (CH_2), 52.5 (CH) and 63.9 (CH_2); *m*/*z* (CI) 189.1309 (MH^+. $C_9H_{21}O_2Si$ requires 189.1311), 145 (35%), 131 (50), 89 (62), 73 (12).

(2*R*)-1-(*tert*-Butyldimethylsilyloxy)hex-5-en-2-ol (11)[29]

A solution of allyl magnesium bromide (1.0 M in diethyl ether) (100.0 mL, 100.0 mmol) was added dropwise to a solution of copper(I) bromide dimethylsulfide complex (0.69 g, 3.40 mmol) in tetrahydrofuran (150 mL) at −78 °C and the white suspension was stirred for 0.5 h. (2*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,3-epoxypropane (**10**) (12.70 g, 67.0 mmol) in tetrahydrofuran (60 mL) was then added and the reaction mixture was warmed to 0 °C and stirred for 2 h. The reaction was quenched by the addition of a saturated ammonium chloride solution (100 mL) and extracted with ethyl acetate (3 × 100 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (elution with petroleum ether–diethyl ether, 10 : 1) gave (2*R*)-1-(*tert*-butyldimethylsilyloxy)hex-5-en-2-ol (**11**) (13.90 g, 90%) as a colourless oil. Spectroscopic data as reported in literature.[29] ν_{max}/cm^{-1} (Neat) 3460 (OH), 2929 (CH), 1641 (C=C), 1472, 1252, 1088; $[\alpha]_D^{24}$ −6.7 (*c* 1.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.01 (6H, s, $Si(CH_3)_2$), 0.82 (9H, s, $SiC(CH_3)_3$), 1.35–1.55 (2H, m, 3-H_2), 2.00–2.22 (2H, m, 4-H_2), 2.35 (1H, br d, *J* 3.3 Hz, OH), 3.33 (1H, dd, *J* 9.9, 7.1 Hz, 1-*H*H), 3.53–3.62 (2H, m, 1-H*H* and 2-H), 4.88–4.92 (1H, m, 6-*H*H), 4.94–5.00 (1H, m, 6-H*H*), 5.76 (1H, ddt, *J* 17.1, 10.3, 6.6 Hz, 5-H); δ_C (100 MHz, $CDCl_3$) −5.4 (2 × CH_3), 18.3 (C), 25.9 (3 × CH_3), 29.8 (CH_2), 32.0 (CH_2), 67.2 (CH_2), 71.2 (CH), 114.8 (CH_2), 138.4 (CH); *m*/*z* (CI) 231.1776 (MH^+. $C_{12}H_{27}O_2Si$ requires 231.1780), 173 (8), 81 (15).

(2*R*)-1-(*tert*-Butyldimethylsilyloxy)-2-(methoxymethoxy)hex-5-ene

(2*R*)-1-(*tert*-Butyldimethylsilyloxy)hex-5-en-2-ol (**11**) (4.0 g, 17.0 mmol) was dissolved in dichloromethane (80 mL) and cooled to 0 °C. Diisopropylethylamine (8.9 mL, 51.0 mmol) was added followed by bromomethyl methyl ether (2.8 mL, 34.8 mmol). The solution was stirred at 0 °C for 0.5 h then heated under reflux overnight. The reaction mixture was cooled to room temperature, acidified with 1 M hydrochloric acid solution (50 mL) and then extracted with dichloromethane (3 × 100 mL). The organic extracts were combined, dried ($MgSO_4$) and the filtrate concentrated *in vacuo*. Flash column chromatography (diethyl ether–petroleum ether, 1 : 20) yielded (2*R*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)hex-5-ene as a colourless oil (4.7 g, 100%). (Found: C, 61.4; H, 11.0. $C_{14}H_{30}O_3Si$ requires C, 61.3; H, 11.0%); ν_{max}/cm^{-1} (NaCl) 2929 (CH), 1642 (C=C), 1472, 1255, 1110, 1040; $[\alpha]_D^{24}$ +28.8 (*c* 1.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.01 (6H, s, $Si(CH_3)_2$), 0.82 (9H, s, $SiC(CH_3)_3$), 1.35–1.54 (2H, m, 3-H_2), 2.00–2.21 (2H, m, 4-H_2), 3.34 (3H, s, OCH_3), 3.50–3.62 (3H, m, 1-H_2 and 2-H), 4.60 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.72 (1H, d, *J* 6.8 Hz, OCH*H*O), 4.89–4.94 (1H, m, 6-*H*H), 4.95–5.01 (1H, m, 6-H*H*), 5.77 (1H, ddt, *J* 17.1, 10.3, 6.6 Hz, 5-H); δ_C (100 MHz, $CDCl_3$) −5.4 (2 × CH_3), 18.3 (C), 25.9 (3 × CH_3), 29.6 (CH_2), 31.0 (CH_2), 55.5 (CH_3), 65.7 (CH_2), 77.7 (CH), 96.4 (CH_2), 114.6 (CH_2), 138.5 (CH); *m*/*z* (CI) 243.1775 (MH^+−MeOH. $C_{13}H_{27}O_2Si$ requires 243.1780), 231 (8%), 133 (11), 81 (18).

(2*R*)-2-(Methoxymethoxy)hex-5-en-1-ol (12)

A solution of tetrabutylammonium fluoride (1 M in tetrahydrofuran) (57.10 mL, 57.10 mmol) was added to a solution of (2*R*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)hex-5-ene (13.09 g, 47.70 mmol) in tetrahydrofuran (100 mL) at 0 °C. The reaction was warmed to room temperature and stirred overnight. The reaction mixture was then concentrated and the resulting residue was re-suspended in diethyl ether (50 mL). The solution was washed with water (50 mL) and the aqueous layer was then extracted with diethyl ether (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), concentrated and then purified by flash column chromatography (elution with petroleum ether–diethyl ether, 5 : 2) to give (2*R*)-2-(methoxymethoxy)hex-5-en-1-ol (**12**) (7.63 g, 100%) as a colourless oil. (Found: C, 59.9; H, 10.2. $C_8H_{16}O_3$ requires C, 60.0; H, 10.0%); ν_{max}/cm^{-1} (NaCl) 3432 (OH), 2947 (CH), 1641 (C=C), 1450, 1212, 1028; $[\alpha]_D^{24}$ −66.8 (*c* 0.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.49–1.70 (2H, m, 3-H_2), 2.07–2.24 (2H, m, 4-H_2), 3.14 (1H, br s, 3.4 Hz, 1-OH), 3.44 (3H, s, OCH_3), 3.47–3.64 (3H, m, 1-H_2 and 2-H), 4.69 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.75 (1H, d, *J* 6.9 Hz, OCH*H*O), 4.96–5.07 (2H, m, 6-H_2), 5.80 (1H, ddt, *J* 17.1, 10.3,

6.6 Hz, 5-H); δ_C (100 MHz, $CDCl_3$) 29.7 (CH_2), 30.8 (CH_2), 55.7 (CH_3), 66.7 (CH_2), 81.9 (CH), 97.1 (CH_2), 115.1 (CH_2), 138.0 (CH); *m*/*z* (CI) 129.0922 (MH^+–MeOH. $C_7H_{13}O_2$ requires 129.0916), 99 (14%), 81 (40), 69 (38).

Ethyl (2*E*,4*R*)-4-(methoxymethoxy)octa-2,7-dienoate (13)

Dimethyl sulfoxide (1.22 g, 15.6 mmol) was added to a stirred solution of oxalyl chloride (1.27 g, 10 mmol) in dichloromethane (100 mL) at −78 °C. The mixture was stirred for 0.3 h before (2*R*)-2-(methoxymethoxy)hex-5-en-1-ol (**12**) (1.0 g, 6.25 mmol) in dichloromethane (25 mL) was slowly added. The mixture was stirred for a further 0.3 h before triethylamine (3.16 g, 31.3 mmol) was added. This reaction mixture was stirred for 0.5 h at −78 °C and then allowed to warm to room temperature and stirred for a further 2 h. A solution of lithium chloride (0.39 g, 9.38 mmol), triethyl phosphonoacetate (2.10 g, 9.38 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (1.43 g, 9.38 mmol) in acetonitrile (50 mL) was then prepared and stirred for 1.0 h. The Swern solution was concentrated *in vacuo*, then the Horner Wadsworth Emmons solution was added and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with a saturated solution of ammonium chloride (50 mL) and concentrated to give an orange residue, which was then extracted with diethyl ether (4 × 75 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated to give an orange oil. Purification by flash column chromatography (diethyl ether–petroleum ether, 1 : 5) yielded ethyl (2*E*,4*R*)-4-(methoxymethoxy)octa-2,7-dienoate (**13**) (1.41 g, 98% yield) as a yellow oil. (Found: C, 63.2; H, 8.9. $C_{12}H_{20}O_4$ requires C, 63.2; H, 8.8%); ν_{max}/cm^{-1} (NaCl) 2941 (CH), 1720 (CO), 1658 (C=C), 1446, 1369, 1269, 1154; $[\alpha]_D^{24}$ +79.2 (*c* 1.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.59–1.80 (2H, m, 5-H_2), 2.09–2.21 (2H, m, 6-H_2), 3.39 (3H, s, OCH_3), 4.18–4.25 (3H, m, 4-H and OCH_2CH_3), 4.59 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.64 (1H, d, *J* 6.9 Hz, OCH*H*O), 4.97–5.08 (2H, m, 8-H_2), 5.81 (1H, ddt, *J* 17.1, 10.3, 6.6 Hz, 7-H), 5.99 (1H, dd, *J* 15.7, 1.2 Hz, 2-H), 6.82 (1H, dd, *J* 15.7, 6.5 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 29.3 (CH_2), 34.0 (CH_2), 55.7 (CH_3), 60.5 (CH_2), 74.6 (CH), 94.7 (CH_2), 115.2 (CH_2), 122.1 (CH), 137.7 (CH), 147.6 (CH), 166.2 (C); *m*/*z* (CI) 229.1435 (MH^+. $C_{12}H_{21}O_4$ requires 229.1440), 199 (33%), 197 (37), 167 (100), 81 (16), 69 (24).

(2*E*,4*R*)-4-(Methoxymethoxy)octa-2,7-dien-1-ol (14)

Ethyl (2*E*,4*R*)-4-(methoxymethoxy)octa-2,7-dienoate (**13**) (1.30 g, 5.7 mmol) was dissolved in diethyl ether (50 mL) and cooled to −78 °C. DIBAL-H (1 M in hexane) (12.5 mL, 12.5 mmol) was added dropwise and the reaction mixture was stirred at −78 °C for 3 h, before warming to room temperature overnight. The solution was cooled to 0 °C and quenched by the addition of a saturated solution of ammonium chloride (10 mL) and warmed to room temperature with vigorous stirring over 1 h, producing a white precipitate. The precipitate was filtered through a pad of Celite® and washed with diethyl ether (3 × 50 mL). The filtrate was then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (diethyl ether–petroleum ether, 3 : 2) yielded (2*E*,4*R*)-4-(methoxymethoxy)octa-2,7-dien-1-ol (**14**) (1.00 g, 98% yield) as a colourless oil. (Found: C, 64.5; H, 9.7. $C_{10}H_{18}O_3$ requires C, 64.5; H, 9.7%); ν_{max}/cm^{-1} (NaCl) 3408 (OH), 2937 (CH), 1641 (C=C), 1442, 1373, 1153, 1096, 1036; $[\alpha]_D^{24}$ +126.8 (*c* 1.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.54–1.64 (2H, m, 5-*H*H and OH), 1.68–1.78 (1H, m, 5-H*H*), 2.06–2.22 (2H, m, 6-H_2), 3.38 (3H, s, OCH_3), 4.02–4.09 (1H, m, 4-H), 4.17 (2H, dd, *J* 5.2, 1.4 Hz, 1-H_2), 4.54 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.70 (1H, d, *J* 6.9 Hz, OCH*H*O), 4.95–5.06 (2H, m, 8-H_2), 5.58 (1H, ddt, *J* 15.6, 7.8, 1.4 Hz, 3-H), 5.79–5.87 (2H, m, 2-H and 7-H); δ_C (100 MHz, $CDCl_3$) 29.6 (CH_2), 34.7 (CH_2), 55.5 (CH_3), 62.9 (CH_2), 75.7 (CH), 93.7 (CH_2), 114.9 (CH_2), 131.2 (CH), 132.3 (CH), 138.2 (CH); *m*/*z* (CI) 204 (MNH_4^+, 100%), 174 (31), 142 (29), 125 (14), 58 (16).

(1*R*,2*S*)-1-(Methoxymethoxy)-2-(2′,2′,2′-trichloromethylcarbonylamino)cyclohexa-3-ene (7)

(2*E*,4*R*)-4-(Methoxymethoxy)octa-2,7-dien-1-ol (**14**) (1.1 g, 5.9 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.22 g, 1.5 mmol) was added to the solution followed by trichloroacetonitrile (1.28 g, 8.8 mmol). The solution was then warmed to room temperature and stirred for 2 h. The reaction mixture was filtered through a short pad of silica gel and washed with diethyl ether (100 mL). The resulting filtrate was then concentrated to give allylic trichloroacetimidate **5**, which was used without further purification. Allylic trichloroacetimidate **5** (1.95 g, 5.9 mmol) was then dissolved in dichloromethane (10 mL) under an argon atmosphere. Bis(acetonitrile)palladium(II) chloride (0.15 g, 0.59 mmol) was added to the solution and the reaction mixture was stirred at room temperature overnight. Grubbs' catalyst (1st Generation) (0.49 g, 0.59 mmol) was then added and the reaction mixture was heated under reflux overnight. The mixture was cooled to room temperature, filtered through a short pad of Celite®, washed with diethyl ether (100 mL) and concentrated *in vacuo* to give a dark coloured solid. Purification by flash column chromatography (diethyl ether–petroleum ether, 1 : 7) gave (1*R*,2*S*)-1-(methoxymethoxy)-2-(2′,2′,2′-trichloromethylcarbonylamino)cyclohexa-3-ene (**7**) as a yellow oil (0.46 g, 45% yield over 3 steps). ν_{max}/cm^{-1} (NaCl) 3421 (NH), 2930 (CH), 1709 (CO), 1654 (C=C), 1500, 1148, 1102, 1036; $[\alpha]_D^{20}$ +79.1 (*c* 1.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.73–1.82 (1H, m, 6-*H*H), 2.00–2.13 (2H, m, 5-*H*H and 6-H*H*), 2.17–2.28 (1H, m, 5-H*H*), 3.42 (3H, s, OCH_3), 4.05 (1H, td, *J* 5.6, 1.3 Hz, 1-H), 4.60–4.66 (1H, m, 2-H), 4.72 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.76 (1H, d, *J* 6.9 Hz, OCH*H*O), 5.51–5.56 (1H, m, 3-H), 5.91–5.97 (1H, m, 4-H), 7.31 (1H, br d, *J* 7.0 Hz, NH); δ_C (100 MHz, $CDCl_3$) 20.2 (CH_2), 24.2 (CH_2), 48.6 (CH), 55.0 (CH_3), 70.9 (CH), 91.9 (C), 94.5 (CH_2), 123.4 (CH), 129.9 (CH), 160.7 (C); *m*/*z* (CI) 306.0056 (MH^+. $C_{10}H_{15}{}^{35}Cl^{37}Cl_2NO_3$ requires 306.0062), 268 (100%), 234 (45), 208 (7), 137 (9), 69 (22).

(1*R*,2*S*)-1-(Methoxymethoxy)-2-(2′,2′,2′-trichloromethylcarbonylamino)cyclohexa-3-ene (7) using toluene as the solvent

The reaction was performed as described above using (2*E*,4*R*)-4-(methoxymethoxy)-octa-2,7-dien-1-ol (**14**) (0.10 g, 0.54 mmol).

Bis(acetonitrile)palladium(II) chloride (0.014 g, 0.05 mmol) was used to catalyse the Overman rearrangement, which was stirred in toluene (10 mL) initially at 0 °C and slowly warmed to room temperature over 24 h before addition of Grubbs first generation catalyst (0.04 g, 0.05 mmol). Purification by flash column chromatography (elution with petroleum ether–diethyl ether, 7 : 1) gave (1*R*,2*S*)-1-(methoxymethoxy)-2-(2′,2′,2′-trichloromethylcarbonylamino)cyclohexa-3-ene (**7**) as a yellow oil (0.11 g, 60% yield over 3 steps). Spectroscopic data as described above.

(1*R*,2*S*)-1-(Methoxymethoxy)-2-aminocyclohex-3-ene

(1*R*,2*S*)-1-(Methoxymethoxy)-2-(2′,2′,2′-trichloromethylcarbonylamino)cyclohexa-3-ene (**7**) (0.53 g, 1.74 mmol) was dissolved in 1 : 1 mixture of 1.0 M NaOH–methanol (10 mL) and stirred overnight at room temperature. The reaction mixture was concentrated *in vacuo* and diluted with ethyl acetate (5 mL). The organic layer was washed with brine solution (2 × 10 mL), dried ($MgSO_4$) and concentrated to give (1*R*,2*S*)-1-(methoxymethoxy)-2-aminocyclohex-3-ene (0.26 g, 100%) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 3422 (NH_2), 2934 (CH), 1572, 1458, 1217, 1038; $[\alpha]_D^{24}$ +110.8 (*c* 0.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.50 (2H, br s, NH_2), 1.65–1.75 (1H, m, 6-*H*H), 1.76–1.87 (1H, m, 6-H*H*), 2.00–2.22 (2H, m, 5-H_2), 3.39–3.45 (4H, m, 2-H and OCH_3), 3.76 (1H, ddd, *J* 9.7, 4.2, 3.1 Hz, 1-H), 4.72 (1H, d, *J* 7.0 Hz, OC*H*HO), 4.77 (1H, d, *J* 7.0 Hz, OCH*H*O), 5.65–5.71 (1H, m, 3-H), 5.71–5.77 (1H, m, 4-H); δ_C (100 MHz, $CDCl_3$) 23.4 (CH_2), 23.8 (CH_2), 49.0 (CH), 55.5 (CH_3), 75.5 (CH), 95.3 (CH_2), 128.6 (CH), 129.4 (CH); *m*/*z* (CI) 158.1184 (MH^+. $C_8H_{16}NO_2$ requires 158.1181), 126 (30%), 85 (8), 69 (18).

(1*R*,2*S*)-1-(Methoxymethoxy)-2-(3,4-methylenedioxy-6-bromobenzamide)cyclohexa-3-ene (15)

In a stirred solution of (1*R*,2*S*)-1-(methoxymethoxy)-2-aminocyclohex-3-ene (0.05 g, 0.35 mmol) in acetonitrile (5 mL) at 0 °C was added 4-dimethylaminopyridine (0.01 g, 0.07 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.08 g, 0.53 mmol). To this reaction mixture, 6-bromopiperonylic acid (0.08 g, 0.35 mmol) was added and stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo*. The residue was diluted with 1.0 M hydrochloric acid (5 mL) and extracted with ethyl acetate (3 × 20 mL). Purification by flash column chromatography (elution with petroleum ether–diethyl ether, 2 : 8) gave (1*R*,2*S*)-1-(methoxymethoxy)-2-(3,4-methylenedioxy-6-bromobenzamide)cyclohexa-3-ene (**15**) (0.10 g, 79%) as a white solid. Mp 100–102 °C; ν_{max}/cm^{-1} (NaCl) 3297 (NH), 2912 (CH), 1649 (CO), 1478, 1239, 1033; $[\alpha]_D^{24}$ +101.2 (*c* 1.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.73–1.85 (1H, m, 6-*H*H), 1.97–2.12 (2H, m, 5-*H*H and 6-H*H*), 2.17–2.28 (1H, m, 5-H*H*), 3.37 (3H, s, OCH_3), 4.01–4.07 (1H, m, 1-H), 4.72 (1H, d, *J* 6.5 Hz, OC*H*HO), 4.76 (1H, d, *J* 6.5 Hz, OCH*H*O), 4.81–4.89 (1H, m, 2-H), 5.62–5.66 (1H, m, 4-H), 5.86–5.92 (1H, m, 3-H), 6.02 (2H, s, OCH_2O), 6.50 (1H, d, *J* 9.1 Hz, NH), 7.00 (1H, s, Ph), 7.05 (1H, s, Ph); δ_C (100 MHz, $CDCl_3$) 21.5 (CH_2), 25.5 (CH_2), 47.9 (CH), 55.8 (CH_3), 72.7 (CH), 95.8 (CH_2), 102.3 (CH_2), 109.5 (CH), 110.7 (C), 113.2 (CH), 125.7 (CH), 129.8 (CH), 131.1 (C), 147.4 (C), 149.6 (C), 166.6 (C); *m*/*z* (FAB) 384.0457 (MH^+. $C_{16}H_{19}{}^{79}BrNO_5$ requires 384.0447), 216 (26%), 135 (74), 89 (100), 46.9 (22).

(4*R*,4a*S*,10b*S*)-3,4,4a,10b-Tetrahydro-4-(methoxymethoxy)-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one

(1*R*,2*S*)-1-(Methoxymethoxy)-2-(3,4-methylenedioxy-6-bromobenzamide)cyclohexa-3-ene (**15**) (0.16 g, 0.42 mmol) was dissolved in *N*,*N*′-dimethylformamide (12 mL) and degassed for 1 h. Triphenylphosphine (0.04 g, 0.18 mmol), palladium(II) acetate, (0.02 g, 0.08 mmol) and diisopropylethylamine (0.14 mL, 0.84 mmol) were then added and the reaction mixture was heated at 155 °C in a sealed tube for 48 h. The reaction mixture was then concentrated *in vacuo* and purified by flash column chromatography (elution with ethyl acetate) to give (4*R*,4a*S*,10b*S*)-3,4,4a,10b-tetrahydro-4-(methoxymethoxy)-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one as a white solid (0.09 g, 78%). Mp 140–142 °C; ν_{max}/cm^{-1} (NaCl) 3397 (NH), 2894 (CH), 1660 (CO), 1460, 1258, 1145; $[\alpha]_D^{25}$ +136.9 (*c* 1.5, MeOH); δ_H (400 MHz, $CDCl_3$) 2.24–2.45 (2H, m, 3-H_2), 3.40 (3H, s, OCH_3), 3.50–3.56 (1H, m, 10b-H), 4.03 (1H, ddd, *J* 9.9, 6.5, 3.0 Hz, 4-H), 4.25 (1H, t, *J* 3.0 Hz, 4a-H), 4.72 (1H, d, *J* 7.0 Hz, OC*H*HO), 4.74 (1H, d, *J* 7.0 Hz, OCH*H*O), 5.27–5.32 (1H, m, 2-H), 5.63 (1H, ddt, *J* 10.0, 5.1, 2.6 Hz, 1-H), 5.89 (1H, br s, NH), 6.01 (1H, d, *J* 1.3 Hz, OC*H*′H′O), 6.02 (1H, d, *J* 1.3 Hz, OCH′*H*′O), 6.67 (1H, s, 10-H), 7.52 (1H, s, 7-H); δ_C (100 MHz, $CDCl_3$) 26.9 (CH_2), 39.9 (CH), 51.3 (CH), 55.8 (CH_3), 72.5 (CH), 95.0 (CH_2), 101.7 (CH_2), 107.0 (CH), 108.0 (CH), 122.2 (C), 124.1 (CH), 126.9 (CH), 135.8 (C), 147.3 (C), 151.3 (C), 165.2 (C); *m*/*z* (CI) 304.1181 (MH^+. $C_{16}H_{18}NO_5$ requires 304.1185), 262 (18%), 244 (6), 166 (3), 81 (8).

(4*R*,4a*S*,10b*S*)-3,4,4a,10b-Tetrahydro-4-hydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (2)

(4*R*,4a*S*,10b*S*)-3,4,4a,10b-Tetrahydro-4-(methoxymethoxy)-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (0.07 g, 0.22 mmol) was dissolved in 1 : 1 ratio of methanol and 1.6 N hydrochloric acid solution (5.0 mL). The reaction mixture was heated to 40 °C and stirred for 12 h, then cooled and neutralised with a 6 M solution of potassium hydrogencarbonate (5.0 mL). The two layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic layers were then dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography (elution with ethyl acetate) to give (4*R*,4a*S*,10b*S*)-3,4,4a,10b-tetrahydro-4-hydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (**2**) as a white solid (0.06 g, 97%). Mp 237–239 °C; ν_{max}/cm^{-1} (NaCl) 3356 (OH), 2951 (CH), 1651 (CO), 1462, 1246, 1018; $[\alpha]_D^{28}$ +159.0 (*c* 0.2, MeOH); δ_H (400 MHz, CD_3OD) 2.04–2.17 (1H, m, 3-*H*H), 2.20–2.29 (1H, m, 3-H*H*), 3.49–3.56 (1H, m, 10b-H), 3.94–4.03 (2H, m, 4a-H and 4-H), 5.17–5.22 (1H, m, 2-H), 5.54 (1H, ddt, *J* 10.1, 5.3, 2.6 Hz, 1-H), 5.92 (1H, d, *J* 1.0 Hz, OC*H*HO), 5.93 (1H, d, *J* 1.0 Hz, OCH*H*O), 6.73 (1H, s, 10-H), 7.23 (1H, s, 7-H); δ_C (100 MHz, CD_3OD) 29.6 (CH_2), 40.9 (CH), 54.7 (CH), 68.0 (CH), 103.3 (CH_2), 108.0 (CH), 108.4 (CH), 122.7 (C), 125.3 (CH), 128.0 (CH), 138.4 (C), 148.7 (C), 153.2 (C), 167.7

(C); *m/z* (CI) 260.0924 (MH^+. $C_{14}H_{14}NO_4$ requires 260.0923), 195 (3%), 113 (3), 81 (12).

(4*R*,4a*S*,10b*S*)-1,2,3,4,4a,10b-Hexahydro-4-hydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (16)

To a solution of (4*R*,4a*S*,10b*S*)-3,4,4a,10b-tetrahydro-4-hydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (**2**) (0.0027 g, 0.01 mmol) in methanol (5 mL) was added 10% palladium on carbon (0.001 g). The reaction mixture was allowed to stir under an atmosphere of hydrogen at room temperature for 12 h. The reaction mixture was filtered through a short pad of Celite®, which was washed with methanol (10 mL) and concentrated *in vacuo* to give (4*R*,4a*S*,10b*S*)-1,2,3,4,4a,10b-hexahydro-4-hydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (**16**) (0.0023 g, 88% yield) as a white solid. Mp 179–181 °C; ν_{max}/cm^{-1} (NaCl) 3363 (OH), 2944 (CH), 1646 (CO), 1448, 1410, 1111, 1021; $[\alpha]_D^{21}$ −37.7 (*c* 0.2, MeOH); δ_H (400 MHz, CD_3OD) 1.20–1.53 (4H, m, 1-*H*H, 2-H_2 and 3-*H*H), 1.63–1.73 (2H, m, 1-H*H* and 3-H*H*), 2.69 (1H, dt, *J* 12.1, 4.2 Hz, 10b-H), 3.74 (1H, dt, *J* 11.2, 4.2 Hz, 4-H), 3.80 (1H, t, *J* 4.2 Hz, 4a-H), 5.90 (1H, d, *J* 1.1 Hz, OC*H*HO), 5.92 (1H, d, *J* 1.1 Hz, OCH*H*O), 6.68 (1H, s, 10-H), 7.25 (1H, s, 7-H); δ_C (125 MHz, CD_3OD) 23.8 (CH_2), 29.1 (CH_2), 29.9 (CH_2), 41.1 (CH), 55.9 (CH), 70.4 (CH), 103.2 (CH_2), 108.1 (CH), 108.2 (CH), 122.6 (C), 141.6 (C), 148.5 (C), 152.9 (C), 168.2 (C); *m/z* (CI) 262.1075 (MH^+. $C_{14}H_{16}NO_4$ requires 262.1079), 244 (12%), 206 (22), 180 (8), 136 (4), 85 (21), 69 (40).

(1*R*,2*S*,4*R*,4a*S*,10b*S*)-1,2-Oxiraryl-1,2,3,4,4a,10b-hexahydro-4-hydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (3)

(4*R*,4a*S*,10b*S*)-3,4,4a,10b-Tetrahydro-4-hydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (**2**) (0.07 g, 0.27 mmol) was dissolved in dichloromethane (10 mL) along with sodium hydrogencarbonate (0.05 g, 0.55 mmol). To the stirred suspension was added *meta*-chloroperoxybenzoic acid (0.09 g, 0.55 mmol) at room temperature. The resulting suspension was stirred vigorously for 24 h. A 20% solution of sodium sulfite (10 mL) was added and the resulting two-phase mixture was stirred vigorously for 0.25 h. The two layers were separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with a 20% solution of sodium sulfite (10 mL) and a 5% solution of sodium hydrogencarbonate (2 × 20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (petroleum ether–diethyl ether, 2 : 5) gave (1*R*,2*S*,4*R*,4a*S*,10b*S*)-1,2-oxiraryl-1,2,3,4,4a,10b-hexahydro-4-hydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (**3**) (0.057 g, 75%) as a white solid. Mp 160–162 °C; ν_{max}/cm^{-1} (NaCl) 3350 (OH), 2851 (CH), 1654 (CO), 1466, 1249, 1035; $[\alpha]_D^{24}$ −61.2 (*c* 0.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.08 (1H, ddd, *J* 14.6, 10.7, 1.8 Hz, 3-*H*H), 2.15 (1H, d, *J* 4.2 Hz, 4-OH), 2.45 (1H, ddd, *J* 14.6, 5.6, 1.8 Hz, 3-H*H*), 2.84 (1H, dd, *J* 3.6, 1.1 Hz, 1-H), 3.27–3.33 (2H, m, 2-H and 10b-H), 3.88–3.92 (1H, m, 4a-H) 4.05–4.12 (1H, m, 4-H), 6.02 (1H, d, *J* 1.3 Hz, OC*H*HO), 6.03 (1H, d, *J* 1.3 Hz, OCH*H*O), 7.51 (1H, br s, NH), 6.82 (1H, s, 10-H), 7.55 (1H, s, 7-H); δ_C (125 MHz, $CDCl_3$) 27.4 (CH_2), 39.1 (CH), 52.2 (CH), 53.4 (CH), 54.4 (CH), 65.3 (CH), 101.9 (CH_2), 107.7 (CH), 107.8 (CH), 122.5 (C), 133.4 (C), 147.9 (C), 151.8 (C), 165.6 (C); *m/z* (CI) 276.0871 (MH^+. $C_{14}H_{14}NO_5$ requires 276.0872), 260 (34%), 206 (6), 113 (5), 85 (33), 69 (48).

(1*R*,2*S*,4*R*,4a*S*,10b*S*)-1,2,3,4,4a,10b-Hexahydro-1,2,4-trihydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (4)

(4*R*,4a*S*,10b*S*)-3,4,4a,10b-Tetrahydro-4-hydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (**2**) (0.018 g, 0.06 mmol) was dissolved in dichloromethane (4 mL) at −78 °C. Tetramethylethylenediamine (9 μL, 0.61 mmol) was added and the reaction mixture stirred for 0.1 h before the addition of osmium tetroxide (0.017 g 0.64 mmol). The dark coloured solution was stirred for 4 h at −78 °C before warming to room temperature and stirred for 1 h. The solvent was removed *in vacuo* and the dark coloured solid was dissolved in methanol (10 mL). Concentrated hydrochloric acid (5 drops) was added and the reaction stirred for 2 h. The solvent was removed *in vacuo* to afford a dark solid. Flash column chromatography (elution with ethyl acetate–methanol, 1 : 8) afforded (1*R*,2*S*,4*R*,4a*S*,10b*S*)-1,2,3,4,4a,10b-hexahydro-1,2,4-trihydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (**4**) (0.016 g, 90%) as a white solid. Mp 240 °C (decomposition); ν_{max}/cm^{-1} (NaCl) 3350 (NH–OH), 2914 (CH), 1643 (CO), 1465, 1253, 1034; $[\alpha]_D^{24}$ −50.9 (*c* 0.7, MeOH); δ_H (400 MHz, CD_3OD) 1.87 (1H, ddd, *J* 14.1, 12.2, 3.6 Hz, 3-*H*H), 2.00–2.07 (1H, m, 3-H*H*), 2.99 (1H, dd, *J* 10.5, 3.6 Hz, 10b-H), 3.51 (1H, dd, *J* 10.5, 3.6 Hz, 1-H), 3.95 (1H, td, *J* 3.6, 1.3 Hz, 4a-H), 4.00 (1H, q, *J* 3.6 Hz, 2-H), 4.30 (1H, dt, *J* 12.2, 3.6 Hz, 4-H), 6.01 (1H, d, *J* 1.1 Hz, OC*H*HO), 6.02 (1H, d, *J* 1.1 Hz, OCH*H*O), 6.84 (1H, s, 10-H), 7.84 (1H, s, 7-H); δ_C (100 MHz, CD_3OD) 35.4 (CH_2), 41.4 (CH), 56.6 (CH), 65.2 (CH), 70.5 (CH), 72.0 (CH), 103.2 (CH_2), 108.0 (CH), 111.0 (CH), 123.0 (C), 138.9 (C), 148.8 (C), 152.3 (C), 168.4 (C); *m/z* (EI) 293.0898 (M^+. $C_{14}H_{15}NO_6$ requires 293.0899), 207 (8%), 190 (30), 114 (100), 70 (76), 96 (14), 44 (42).

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27 Crystallographic data for (1*R*,2*S*,4*R*,4a*S*,10b*S*)-1,2,3,4,4a,10b-hexahydro-1,2,4-trihydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (**4**): $C_{14}H_{15}NO_6$, M = 293.27, orthorhombic, a = 6.5782(4), b = 8.7302(5), c = 21.2398(12) Å, V = 1219.78(12) Å^3, T = 100 K, space group $P2_12_12_1$, Z = 4, 16 471 reflections measured, 1603 unique (R_{int} = 0.064) which were used in all calculations. The final $R_1(F)$ = 0.0372, w$R_2(F^2)$ = 0.0857 (all data). The absolute configuration was not determined by this analysis. The structure has been deposited with the Cambridge Crystallographic Data Centre, with code CCDC 865745.

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