



Cite this: *Org. Biomol. Chem.*, 2016, **14**, 10953

Cascade oxime formation, cyclization to a nitron, and intermolecular dipolar cycloaddition†

Rachel C. Furnival, Rungroj Saruengkhanphasit, Heather E. Holberry, Jonathan R. Shewring, Hélène D. S. Guerrand, Harry Adams and Iain Coldham*

Simple haloaldehydes, including enolisable aldehydes, were found to be suitable for the formation of cyclic products by cascade (domino) condensation, cyclisation, dipolar cycloaddition chemistry. This multi-component reaction approach to heterocyclic compounds was explored by using hydroxylamine, a selection of aldehydes, and a selection of activated dipolarophiles. Initial condensation gives intermediate oximes that undergo cyclisation with displacement of halide to give intermediate nitrones; these nitrones undergo *in situ* intermolecular dipolar cycloaddition reactions to give isoxazolidines. The cycloadducts from using dimethyl fumarate were treated with zinc/acetic acid to give lactam products and this provides an easy way to prepare pyrrolizinones, indolizinones, and pyrrolo[2,1-*a*]isoquinolinones. The chemistry is illustrated with a very short synthesis of the pyrrolizidine alkaloid macronecine and a formal synthesis of petasinecine.

Received 25th August 2016,
Accepted 30th October 2016

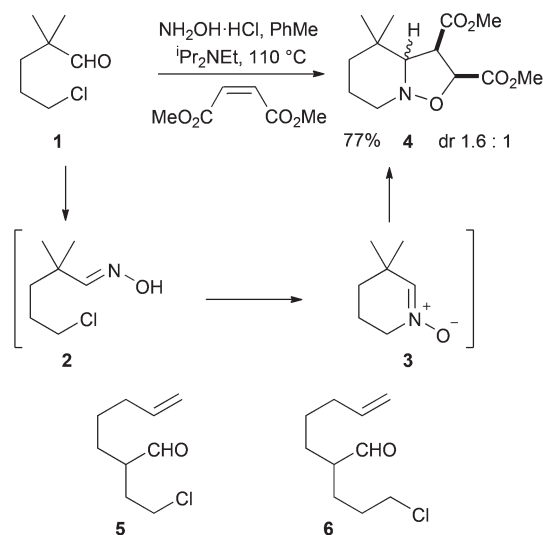
DOI: 10.1039/c6ob01871h

www.rsc.org/obc

Introduction

Cycloaddition reactions of nitrones have been known for over 50 years.¹ The majority of examples involve the condensation of an aldehyde with an *N*-alkyl-hydroxylamine or oxidation of an amine to form the nitron, followed by cycloaddition with an alkene dipolarophile.² An alternative approach makes use of the condensation of an aldehyde or ketone with hydroxylamine to give an oxime that undergoes subsequent *N*-alkylation to give the nitron. Various *N*-alkylating agents can be used and the most common are unsaturated systems that allow the nitrogen atom of the oxime to undergo conjugate addition.³ We have been exploring the *N*-alkylation of oximes by intramolecular substitution of an alkyl halide. This cyclization reaction provides the desired nitron that undergoes intramolecular dipolar cycloaddition with an alkene.^{4,5}

So far, we have reported only two examples of intermolecular cycloaddition using this strategy and these make use of a non-enolisable aldehyde as the substrate for reaction with hydroxylamine.^{6,7} For example, the aldehyde **1** reacts to give the intermediate oxime **2** that undergoes cyclization onto the alkyl chloride to give the nitron **3** that can be trapped intermolecularly with dimethyl maleate to give the product **4** as a mixture of diastereoisomers (Scheme 1).⁶ The enolisable



Scheme 1 Previous studies with related aldehydes.^{4,6}

aldehyde **5** failed to give the desired tricyclic product and led instead to 3-(pent-4-enyl)pyrrole.^{4f} However, the aldehyde **6** underwent successful condensation with hydroxylamine, followed by cyclization then intramolecular cycloaddition onto the internal unactivated alkene, and this was used in a synthesis of myrioxazine A.^{4c}

In this paper, we report successful reactions of aldehydes, including enolisable aldehydes, with hydroxylamine, followed by *in situ* cyclization and intermolecular dipolar cycloaddition.

Department of Chemistry, University of Sheffield, Brook Hill, Sheffield, S3 7HF, UK.
E-mail: i.coldham@sheffield.ac.uk

† Electronic supplementary information (ESI) available. CCDC 1006037–1006042, 1022997 and 1051097. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6ob01871h



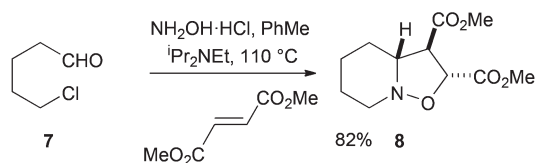
The ability to undergo such chemistry is likely due to the use of reactive, electron-poor alkene dipolarophiles. This chemistry allows the formation of a greater range of substituted products without the need to block enolisation.

Results and discussion

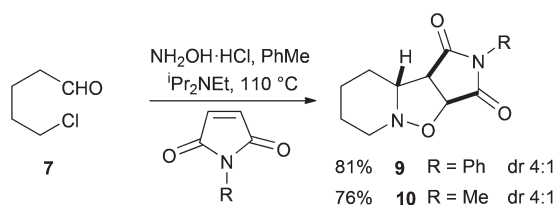
Our initial work in this area focused on the simple aldehyde substrate **7** (Scheme 2). This was prepared by Swern oxidation of commercially available 5-chloro-1-pentanol.⁸ Treatment of the aldehyde **7** with hydroxylamine hydrochloride salt, the base ⁱPr₂NEt, and the dipolarophile dimethyl fumarate gave the desired bicyclic product **8** in high yield as a single diastereoisomer. The stereochemistry could not be determined at this stage, although NMR spectroscopic analysis and later single crystal X-ray analysis of a derivative (see below), revealed the stereochemistry as shown. The ¹H NMR spectroscopic data for the product **8** match those reported from oxidation of *N*-hydroxypiperidine and cycloaddition of the resulting nitron with dimethyl fumarate.⁹

Changing the dipolarophile from dimethyl fumarate to *N*-phenylmaleimide gave the desired bicyclic product **9** in high yield as the major diastereoisomer (dr 4 : 1) (Scheme 3). The diastereoisomers were separable by column chromatography and the stereochemistry of the major isomer **9** was determined by single crystal X-ray analysis. In a similar way, the use of *N*-methylmaleimide gave the desired product **10** in high yield as the major diastereoisomer (dr 4 : 1). The coupling constants for the methine protons in the cycloadduct **10** matched those of the cycloadduct **9**, indicating the same relative stereochemistry for the major isomer.

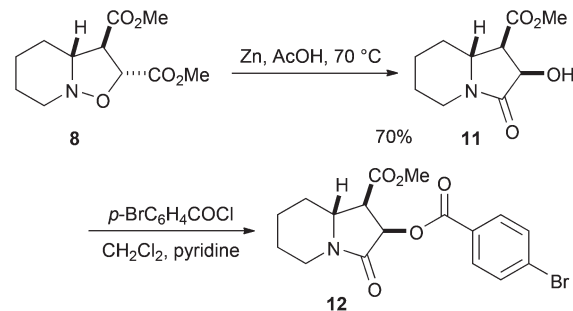
Treatment of the cycloadduct **8** with zinc in acetic acid resulted in reductive cleavage of the N–O bond and subsequent cyclization of the amine onto one of the ester groups to give the lactam **11** as a single diastereoisomer (Scheme 4). This



Scheme 2 Aldehyde substrate **7** with dimethyl fumarate.



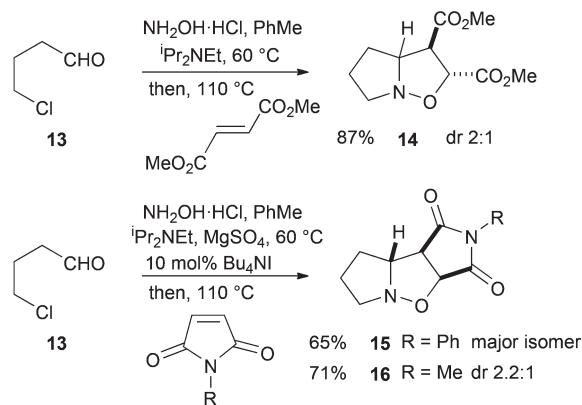
Scheme 3 Aldehyde substrate **7** with *N*-phenyl- or *N*-methylmaleimide (major diastereoisomer of product drawn).



Scheme 4 Preparation of lactam **11** and ester **12**.

product was crystalline but the needles were too fine for X-ray analysis. However, conversion of the alcohol **11** to the ester **12** using *p*-bromobenzoyl chloride gave crystals suitable for X-ray analysis and allowed the determination of the relative stereochemistry of **12** (and hence of the cycloadduct **8**).

Cyclization of the oxime derived from the aldehyde **7** gives a six-membered ring nitron. We had previously found that a six-membered ring nitron could be prepared and reacted intramolecularly (by using aldehyde **6**, see Scheme 1).^{4c} However, aldehyde **5** was unsuccessful and resulted in a pyrrole product. To test the feasibility of conducting the intermolecular chemistry with the homologous aldehyde containing one less methylene unit, we prepared the aldehyde **13**. We were pleased to find that treatment of aldehyde **13** with hydroxylamine hydrochloride salt, the base ⁱPr₂NEt, and the dipolarophile dimethyl fumarate gave the desired bicyclic product **14** (as a mixture of diastereoisomers) in high yield (Scheme 5). The reaction was best conducted by pre-forming the oxime at 60 °C, then heating to 110 °C in the presence of the dipolarophile. Product **14** has been reported to be formed as a mixture of isomers starting from oxidation of *N*-hydroxypyrrolidine and cycloaddition of the resulting 1-pyrroline-1-oxide.¹⁰ The dipolarophiles *N*-phenylmaleimide and *N*-methylmaleimide gave the desired cycloaddition products **15** and **16** in good yield. The reaction was cleaner on addition



Scheme 5 Aldehyde substrate **13** with dimethyl fumarate, *N*-phenyl- or *N*-methylmaleimide.

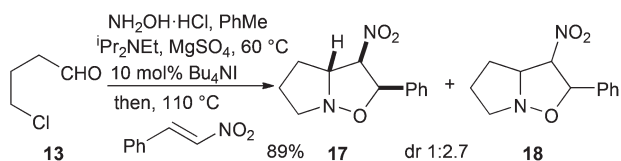


of some MgSO_4 and $n\text{-Bu}_4\text{NI}$. The diastereoisomers were separable by column chromatography, although the minor isomer of the *N*-phenyl adduct **15** was isolated together with the adduct of hydroxylamine and *N*-phenylmaleimide. The stereochemistry of the major isomer of **16** was determined by single crystal X-ray analysis. This has the same relative stereochemistry as that for the major isomer of the homolog **10**. We assume that the major isomer of **15** also has this relative stereochemistry.

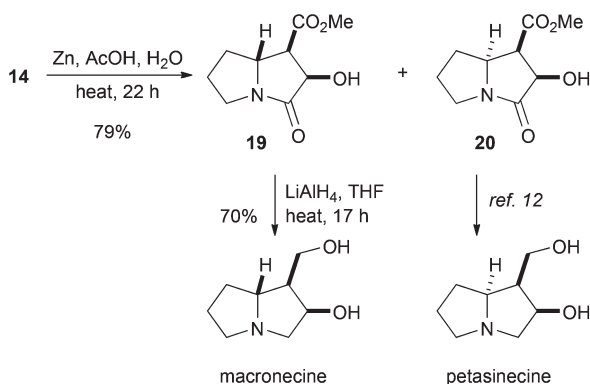
With the aldehyde substrate **13** we also tested the dipolarophile β -nitrostyrene. This resulted in two products, the minor one of which was amenable to single crystal X-ray analysis, revealing the unexpected isomer **17** (Scheme 6). We have not been able to determine the stereochemistry of the other isomer **18**, but on standing in CDCl_3 , this converts to a mixture of **17** and **18**. The isomer **17** could arise either from the isomer **18** (for example by epimerization or *via* retro-Mannich reaction) or from a stepwise rather than concerted cycloaddition process.¹¹

From the results above, it is clear that the aldehyde **13** is amenable to the desired cascade chemistry involving oxime formation, cyclization to give a nitron, followed by intermolecular cycloaddition. This requires an activated alkene to promote cycloaddition, otherwise (as found for compound **5**) the five-membered nitron is prone to conversion to a pyrrole ring.

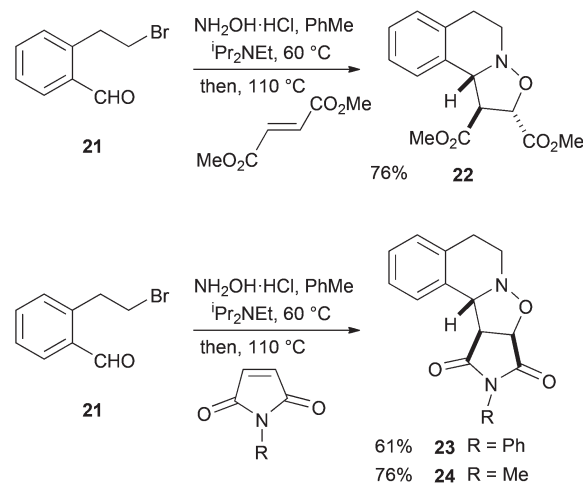
Treatment of the 2 : 1 mixture of cycloadducts **14** with Zn/AcOH gave the desired lactams **19** and **20** (ratio 2 : 1) that were separable by careful column chromatography (Scheme 7). The major product was stereoisomer **19** and the spectroscopic data matched the reported data.¹² The major isomer, lactam **19**,



Scheme 6 Aldehyde substrate **13** with β -nitrostyrene.



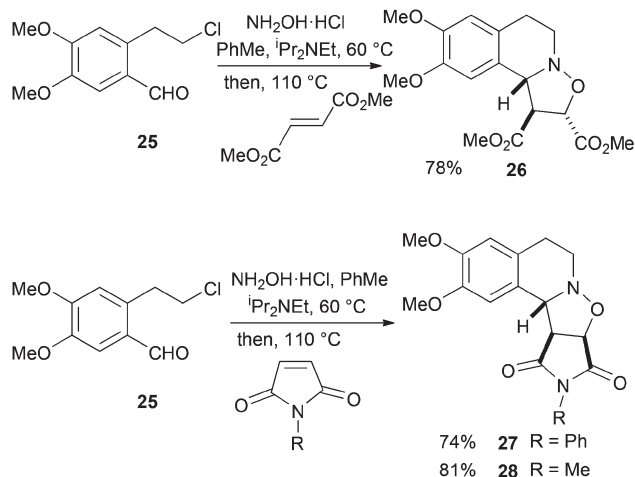
Scheme 7 Preparation of the alkaloid macronecine.



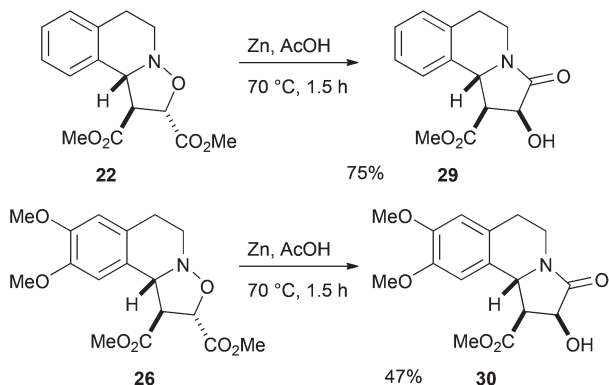
Scheme 8 Aldehyde substrate **21** with dimethyl fumarate, *N*-phenyl- or *N*-methylmaleimide.

was reduced with LiAlH_4 to give the pyrrolizidine alkaloid (\pm)-macronecine following a literature procedure (Scheme 7).¹² The ^1H NMR spectroscopic data matched that reported for the natural product.¹³ The chemistry also provides a formal synthesis of the alkaloid (\pm)-petasinecine by reduction.¹² Therefore the chemistry allows a rapid access to these natural products in just three steps from 4-chlorobutanal (**13**).

To complement the examples above, we studied the same cascade chemistry with the benzaldehyde substrate **21**. This was prepared in two steps from isochroman.^{6b,14} Condensation of aldehyde **21** with hydroxylamine at 60 °C followed by addition of dimethyl fumarate, *N*-phenylmaleimide or *N*-methylmaleimide gave the cycloadducts **22–24** (Scheme 8). These products were all formed as a single diastereoisomer. The relative stereochemistry for adducts **22** and **24** was confirmed by single crystal X-ray analysis. The preference for the



Scheme 9 Aldehyde substrate **25** with dimethyl fumarate, *N*-phenyl- or *N*-methylmaleimide.



Scheme 10 Preparation of lactams 29 and 30.

exo adducts matches that reported from reaction of the isolated nitrone.¹⁵

In a similar way, the aldehyde 25¹⁴ was treated with hydroxylamine at 60 °C followed by addition of dimethyl fumarate, *N*-phenylmaleimide or *N*-methylmaleimide to give the cycloadducts 26–28 (Scheme 9). The relative stereochemistries of the adducts 27 and 28 were confirmed by single crystal X-ray analysis.

The products 22 and 26 were treated with zinc in acetic acid to give the lactams 29 and 30 respectively as single isomers (Scheme 10).

Conclusions

In conclusion, cascade chemistry involving condensation of hydroxylamine, cyclization and intermolecular dipolar cycloaddition has been shown to be successful with a range of aldehydes, including enolisable aldehydes, together with electron-deficient dipolarophiles to give a variety of bicyclic, tricyclic and tetracyclic products. The isoxazolidine cycloadducts from using dimethyl fumarate as the dipolarophile were subjected to N–O bond cleavage to give, after cyclization, α -hydroxylactams. The chemistry provides a rapid entry to nitrogen-containing heterocycles of potential pharmaceutical interest and application to natural product synthesis, as demonstrated by a short synthesis of the alkaloid macronecine and a formal synthesis of petasinecine.

Experimental

5-Chloropentanal 7

DMSO (3.4 mL, 48 mmol) in CH₂Cl₂ (10 mL) was added to freshly distilled oxalyl chloride (2.1 mL, 24 mmol) in CH₂Cl₂ (60 mL) at –78 °C. After 10 min, 5-chloropentan-1-ol (2.4 mL, 20 mmol) in CH₂Cl₂ (10 mL) was added slowly. After 30 min, triethylamine (13.9 mL, 100 mmol) was added. The mixture was allowed to warm to room temperature, then CH₂Cl₂ (20 mL) and water (20 mL) were added. The aqueous layer was washed with CH₂Cl₂ (3 × 50 mL). The combined organic layers

were dried (MgSO₄) and evaporated. Purification by column chromatography, eluting with CH₂Cl₂, gave aldehyde 7 (2.05 g, 85%) as an oil; *R*_f 0.8 (CH₂Cl₂); ν_{\max} (film)/cm^{–1} 2935, 2865, 2730, 1720; ¹H NMR (400 MHz, CDCl₃) δ = 9.80 (1H, t, *J* 1.5 Hz, CHO), 3.60–3.54 (2H, m, CH₂), 2.55–2.48 (2H, m, CH₂), 1.88–1.77 (4H, m, 2 × CH₂); ¹³C NMR (100 MHz, CDCl₃) δ = 201.8, 44.5, 43.0, 31.8, 19.4. Data consistent with the literature.⁸

(2*R**,3*R**,3*aR**)-Dimethyl hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-2,3-dicarboxylate 8

Hydroxylamine hydrochloride (142 mg, 2.04 mmol) and *N,N*-diisopropylethylamine (0.74 mL, 4.3 mmol) were added to aldehyde 7 (204 mg, 1.70 mmol) in PhMe (17 mL) and the mixture was heated to 110 °C. After 30 min, dimethyl fumarate (368 mg, 2.55 mmol) was added and heating was continued at 110 °C. After 3.5 h, the mixture was cooled to room temperature and the solvent was evaporated. Purification by column chromatography, eluting with CH₂Cl₂–MeOH (98 : 2), gave the product 8 (340 mg, 82%) as an oil; *R*_f 0.36 [CH₂Cl₂–MeOH (98 : 2)]; ν_{\max} (film)/cm^{–1} 2950, 2850, 1730; ¹H NMR (400 MHz, CDCl₃) δ = 4.84 (1H, d, *J* 5.5 Hz, CH), 3.81 (3H, s, CH₃), 3.79 (3H, s, CH₃), 3.60–3.52 (1H, m, CH), 3.42 (1H, dd, *J* 10, 5.5 Hz, CH), 2.54 (1H, ddd, *J* 12, 10, 3 Hz, CH), 2.41–2.32 (1H, m, CH), 2.19–2.10 (1H, m, CH), 1.72–1.65 (3H, m, 2 × CH), 1.50 (1H, qd, *J* 13, 4 Hz, CH), 1.31–1.17 (1H, m, 2 × CH); ¹³C NMR (100 MHz, CDCl₃) δ = 172.0, 171.2, 75.8, 70.5, 56.0, 55.2, 52.7, 52.5, 28.6, 24.3, 23.2; HRMS (ES) Found: MH⁺, 244.1186. C₁₁H₁₈NO₅ requires MH⁺, 244.1185.

(3*aR**,3*bS**,8*aS**)-2-Phenyl-hexahydro-8-oxa-2,7*a*-diazacyclopenta[*a*]indene-1,3-dione 9

Hydroxylamine hydrochloride (147 mg, 2.11 mmol) and *N,N*-diisopropylethylamine (0.77 mL, 4.4 mmol) were added to aldehyde 7 (211 mg, 1.76 mmol) in PhMe (17 mL) and the mixture was heated to 110 °C. After 30 min, *N*-phenylmaleimide (457 mg, 2.63 mmol) was added and heating was continued at 110 °C. After 2 h, the mixture was cooled to room temperature and the solvent was evaporated. Purification by column chromatography, eluting with CH₂Cl₂–MeOH (99 : 1), gave the product 9 (307 mg, 64%) as a solid and its diastereomer (83 mg, 17%) as a solid. The product 9 was recrystallized from CH₂Cl₂–hexanes (1 : 1) as needles; m.p. 157–159 °C; *R*_f 0.43 [CH₂Cl₂–MeOH (98 : 2)]; ν_{\max} (film)/cm^{–1} 2960, 2935, 1710; ¹H NMR (400 MHz, CDCl₃) δ = 7.52–7.47 (2H, m, 2 × CH), 7.45–7.39 (1H, m, CH), 7.36–7.31 (2H, m, 2 × CH), 4.93 (1H, d, *J* 7.5 Hz, CH), 3.74–3.68 (1H, m, CH), 3.56–3.48 (1H, m, CH), 3.39 (1H, dd, *J* 7.5, 1.5 Hz, CH), 3.08–2.98 (1H, m, CH), 1.89–1.60 (4H, m, 4 × CH), 1.55–1.31 (2H, m, 2 × CH); ¹³C NMR (100 MHz, CDCl₃) δ = 175.2, 174.5, 131.5, 129.2, 128.8, 126.4, 75.1, 63.4, 54.3, 50.3, 25.7, 22.5, 19.3; HRMS (ES) Found: MH⁺, 273.1250. C₁₅H₁₇N₂O₃ requires MH⁺, 273.1239.

Crystal data deposited at CCDC 1006040.

Unit cell parameters: *a* 12.9691(19), *b* 6.6225(11), *c* 15.583(3), *P*21/*n*.



Data for minor stereoisomer: m.p. 135–137 °C; R_f 0.27 [CH_2Cl_2 –MeOH (98 : 2)]; ν_{max} (film)/ cm^{-1} 2960, 2935, 1710; ^1H NMR (400 MHz, CDCl_3) δ = 7.52–7.45 (2H, m, 2 \times CH), 7.45–7.39 (1H, m, CH), 7.34–7.29 (2H, m, 2 \times CH), 4.91 (1H, d, J 7.5 Hz, CH), 3.64–3.55 (2H, m, 2 \times CH), 2.61–2.50 (2H, m, 2 \times CH), 2.28–2.18 (1H, m, CH), 1.85–1.79 (2H, m, 2 \times CH), 1.68–1.53 (1H, m, CH), 1.50–1.37 (1H, m, CH), 1.34–1.19 (1H, m, CH); ^{13}C NMR (100 MHz, CDCl_3) δ = 176.8, 175.6, 131.5, 129.2, 129.0, 126.4, 75.1, 55.1, 50.6, 26.9, 24.4, 23.5, 19.4; HRMS (ES) Found: MH^+ , 273.1239. $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}_3$ requires MH^+ , 273.1239.

(3aR*,3bS*,8aS*)-2-Methyl-hexahydro-8-oxa-2,7a-diaza-cyclopenta[*a*]indene-1,3-dione 10

Hydroxylamine hydrochloride (142 mg, 2.04 mmol) and *N,N*-diisopropylethylamine (0.74 mL, 4.3 mmol) were added to aldehyde 7 (204 mg, 1.70 mmol) in PhMe (17 mL) and the mixture was heated to 110 °C. After 30 min, *N*-methylmaleimide (283 mg, 2.55 mmol) was added and heating was continued at 110 °C. After 3.5 h, the mixture was cooled to room temperature and the solvent was evaporated. Purification by column chromatography, eluting with CH_2Cl_2 –MeOH (98 : 2), gave the product 10 (218 mg, 61%) as a solid and its diastereomer (54 mg, 15%) as a solid. Data for the major stereoisomer 10: m.p. 80–83 °C; R_f 0.44 [CH_2Cl_2 –MeOH (95 : 5)]; ν_{max} (film)/ cm^{-1} 2925, 2860, 1695; ^1H NMR (400 MHz, CDCl_3) δ = 4.78 (1H, d, J 7 Hz, CH), 3.60–3.54 (1H, m, CH), 3.51–3.47 (1H, m, CH), 3.22 (1H, dd, J 7, 1.5 Hz, CH), 3.05 (3H, s, CH_3), 3.01–2.90 (1H, m, CH), 1.84–1.74 (2H, m, 2 \times CH), 1.67–1.54 (2H, m, 2 \times CH), 1.51–1.38 (1H, m, CH), 1.37–1.20 (1H, m, CH); ^{13}C NMR (100 MHz, CDCl_3) δ = 176.0, 175.4, 75.1, 62.8, 54.4, 50.2, 25.7, 25.0, 22.5, 19.2; HRMS (ES) Found: MH^+ , 211.1084. $\text{C}_{10}\text{H}_{15}\text{N}_2\text{O}_3$ requires MH^+ , 211.1083.

(1R*,2R*,8aR*)-Methyl 2-hydroxy-3-oxo-octahydroindolizine-1-carboxylate 11

Zinc powder (186 mg, 2.85 mmol) was added to cycloadduct 8 (165 mg, 0.678 mmol) in AcOH/ H_2O (14 mL, 5 : 9). The mixture was heated to 70 °C for 2 h before being cooled to room temperature. The zinc salts were filtered, washed with CH_2Cl_2 and the solvent was evaporated. The solute was partitioned between aqueous ammonia (5 mL) and CH_2Cl_2 (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 \times 15 mL). The organic fractions were dried (MgSO_4), filtered and evaporated to give the lactam 11 (102 mg, 70%) as a solid, which was recrystallized from CH_2Cl_2 –hexanes (1 : 1) as needles; m.p. 124–127 °C; R_f 0.10 [CH_2Cl_2 –MeOH (99 : 1)]; ν_{max} (film)/ cm^{-1} 3220, 2950, 2920, 2895, 2865, 1740, 1680; ^1H NMR (400 MHz, CDCl_3) δ = 4.50 (1H, d, J 7.5 Hz, CH), 4.13 (1H, dt, J 13, 5 Hz, CH), 3.95–3.87 (1H, m, CH), 3.80 (3H, s, CH_3), 2.93 (1H, t, J 7.5 Hz, CH), 2.78 (2H, dt, J 13, 3.5 Hz, 2 \times CH), 2.14–2.06 (1H, m, CH), 1.96–1.87 (1H, m, CH), 1.81–1.72 (1H, m, CH), 1.50 (1H, qt, J 13, 3.5 Hz, CH), 1.40–1.24 (1H, m, CH), 1.11 (1H, qd, J 13, 3.5 Hz, CH); ^{13}C NMR (100 MHz, CDCl_3) δ = 170.4, 169.8, 70.2, 56.8, 52.2, 50.4, 40.5, 32.4, 24.1, 23.4; HRMS

(ES) Found: MH^+ , 214.1070. $\text{C}_{10}\text{H}_{16}\text{NO}_4$ requires MH^+ , 214.1079.

(1R*,2R*,8aR*)-Methyl 2-(4-bromobenzoyloxy)-3-oxo-octahydroindolizine-1-carboxylate 12

p-Bromobenzoyl chloride (875 mg, 5.0 mmol) and DMAP (60 mg, 0.5 mmol) were added to the lactam 11 (425 mg, 2.0 mmol) in pyridine (2 mL) at room temperature. After 16 h, the solvent was evaporated. Purification by column chromatography, eluting with CH_2Cl_2 –MeOH (99 : 1), gave ester 12 (687 mg, 87%) as fine needles; m.p. 90–92 °C; R_f 0.2 [CH_2Cl_2 –MeOH (99 : 1)]; ν_{max} (film)/ cm^{-1} 2940, 2855, 1735, 1695; ^1H NMR (400 MHz, CDCl_3) δ = 7.92 (2H, d, J 8.5 Hz, 2 \times CH), 7.60 (2H, d, J 8.5 Hz, 2 \times CH), 5.76 (1H, d, J 6.5 Hz, CH), 4.23 (1H, d, J 14 Hz, CH), 3.75–3.66 (2H, m, 2 \times CH), 2.75 (1H, t, J 14 Hz, CH), 2.04–1.97 (1H, m, CH), 1.92–1.85 (1H, m, CH), 1.83–1.76 (1H, m, CH), 1.55–1.38 (3H, m, 3 \times CH); ^{13}C NMR (100 MHz, CDCl_3) δ = 169.0, 166.1, 164.5, 131.8, 131.4, 129.7, 128.6, 70.2, 56.9, 52.4, 48.7, 40.8, 32.4, 24.0, 23.4; HRMS (ES) Found: MH^+ , 396.0444. $\text{C}_{17}\text{H}_{19}\text{NO}_5$ requires MH^+ , 396.0447.

Crystal data deposited at CCDC 1022997.

Unit cell parameters: *a* 11.0353(7), *b* 21.5973(13), *c* 15.0726(9), *P*21/*c*.

4-Chlorobutanol 13

DMSO (2.9 mL, 40.6 mmol) in CH_2Cl_2 (10 mL) was added dropwise to oxalyl chloride (1.8 mL, 20.3 mmol) in CH_2Cl_2 (60 mL) at –78 °C. After 10 min, 4-chlorobutanol (1.8 mL, 16.9 mmol) in CH_2Cl_2 (10 mL) was added dropwise. After 30 min, Et_3N (11.8 mL, 84.5 mmol) was added. After 30 min, the mixture was allowed to warm to room temperature then water (20 mL) and CH_2Cl_2 (20 mL) were added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 \times 50 mL). The combined organic layers were dried (MgSO_4), filtered and evaporated. Purification by column chromatography, eluting with CH_2Cl_2 , gave aldehyde 13 (1.09 g, 61%) as an oil; R_f 0.9 (CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) 9.84 (1H, s, CHO), 3.62 (2H, t, J 6.5 Hz, CH_2), 2.70 (2H, t, J 6.5 Hz, CH_2), 2.13 (2H, pent., J 6.5 Hz, CH_2). Data consistent with the literature.¹⁶

(2S*,3S*,3aS*)-2,3-Dimethyl hexahydropyrrolo[1,2-*b*][1,2]oxazole-2,3-dicarboxylate 14a and (2S*,3S*,3aR*)-2,3-dimethyl hexahydropyrrolo[1,2-*b*][1,2]oxazole-2,3-dicarboxylate 14b

To aldehyde 13 (106 mg, 1 mmol) in PhMe (10 mL) was added hydroxylamine hydrochloride (85 mg, 1.2 mmol) and $^i\text{Pr}_2\text{NET}$ (0.41 mL, 2.4 mmol) and the mixture was warmed to 60 °C. After 30 min, dimethylfumarate (217 mg, 1.5 mmol) was added and the mixture was heated under reflux. After 3.5 h, the mixture was allowed to cool to room temperature and the solvent was evaporated. Purification by column chromatography, eluting with CH_2Cl_2 –MeOH (99 : 1) gave cycloadducts 14a and 14b (200 mg, 0.87 mmol, 87%) as an oil, as an inseparable mixture of diastereoisomers (dr 2 : 1); alternatively, aldehyde 13 (500 mg, 4.7 mmol) in PhMe (50 mL), hydroxylamine hydrochloride (390 mg, 5.6 mmol), $^i\text{Pr}_2\text{NET}$ (2.0 mL, 11 mmol) and dimethylfumarate (1.0 g, 7.0 mmol) gave, after



heating for 17 h then purification as above, the cycloadducts **14a** and **14b** (770 mg, 3.4 mmol, 72%) as an oil (dr 2 : 1); R_f 0.5 [CH_2Cl_2 -MeOH (98 : 2)]; ν_{max} (film)/ cm^{-1} 2955, 1735; ^1H NMR (500 MHz, CDCl_3) δ = 4.98 (0.35H, d, J 5.5 Hz, CH), 4.85 (0.65H, d, J 7.5 Hz, CH), 4.13–4.08 (0.35H, dd, J 7.5, 5.0 Hz, CH), 3.93–3.85 (1H, m, CH), 3.81 (3H, s, 2 \times Me), 3.79 (3H, s, 2 \times Me), 3.57–3.49 (0.35H, ddd, J 14.0, 8.0, 3.5 Hz, CH), 3.39 (0.65H, dd, J 7.5, 5.0 Hz, CH), 3.39–3.43 (0.35H, m, CH), 3.13–3.02 (1.3H, m, 2 \times CH), 2.13–1.99 (1.65H, m, 3 \times CH), 1.86–1.72 (2H, m, 2 \times CH), 1.63–1.53 (0.35H, m, CH); ^{13}C (125.7 MHz, CDCl_3) δ = 171.7, 170.9, 170.5, 169.9, 78.9, 76.0, 69.7, 68.3, 57.4, 56.3, 56.2, 55.1, 52.7, 52.65, 52.6, 52.4, 29.8, 26.6, 24.3, 23.2; HRMS (ES) Found: MH^+ , 230.1022. $\text{C}_{10}\text{H}_{16}\text{NO}_5$ requires MH^+ 230.1028. ^1H NMR data consistent with the literature.⁹

(1S*,2S*,6R*)-4-Phenyl-7-oxa-4,8-diazatricyclo[6.3.0.0¹]undecane-3,5-dione 15

To aldehyde **13** (106 mg, 1 mmol) in PhMe (10 mL) was added hydroxylamine hydrochloride (76 mg, 1.1 mmol), $^i\text{Pr}_2\text{NEt}$ (0.41 mL, 2.4 mL), dry MgSO_4 (~200 mg) and Bu_4NI (37 mg, 0.1 mmol) and the mixture was warmed to 60 °C. After 30 min, *N*-phenylmaleimide (260 mg, 1.5 mmol) was added and the mixture was heated under reflux. After 3.5 h, the mixture was allowed to cool to room temperature and the solvent was evaporated. Purification by column chromatography, eluting with CH_2Cl_2 -MeOH (99 : 1), gave cycloadduct **15** (168 mg, 65%) as an oil; R_f 0.4 [CH_2Cl_2 -MeOH (99 : 1)]; ν_{max} (film)/ cm^{-1} 2960, 1710, 1498; ^1H NMR (400 MHz, CDCl_3) δ = 7.55–7.33 (5H, m, Ph), 4.97 (1H, d, J 7.5 Hz, CH), 3.90 (1H, t, J 8.0 Hz, CH), 3.73 (1H, d, J 7.5 Hz, CH), 3.66–3.58 (2H, m, 2 \times CH), 3.07 (1H, dt, J 14.5, 8.5 Hz, CH), 2.07–1.98 (1H, m, CH), 1.93–1.73 (2H, m, 2 \times CH); ^{13}C NMR (101 MHz, CDCl_3) δ = 174.8, 174.4, 131.4, 129.2, 128.9, 126.4, 75.9, 70.8, 55.9, 54.2, 30.0, 24.3; HRMS (ES) Found: MH^+ , 259.1074. $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}_3$ requires MH^+ , 259.1083.

The minor diastereomer was isolated as a mixture with the adduct formed from conjugate addition of hydroxylamine with the maleimide.

(1S*,2S*,6R*)-4-Methyl-7-oxa-4,8-diazatricyclo[6.3.0.0¹]undecane-3,5-dione 16a and (1R*,2S*,6R*)-4-methyl-7-oxa-4,8-diazatricyclo[6.3.0.0¹]undecane-3,5-dione 16b

To aldehyde **13** (106 mg, 1 mmol) in PhMe (10 mL) was added hydroxylamine hydrochloride (76 mg, 1.1 mmol), $^i\text{Pr}_2\text{NEt}$ (0.41 mL, 2.4 mL), dry MgSO_4 (~200 mg) and Bu_4NI (37 mg, 0.1 mmol) and the mixture was warmed to 60 °C. After 30 min, *N*-methylmaleimide (260 mg, 1.5 mmol) was added and the mixture was heated under reflux. After 3.5 h, the mixture was allowed to cool to room temperature and the solvent was evaporated. Purification by column chromatography, eluting with CH_2Cl_2 -MeOH (99 : 1), gave cycloadduct **16a** (96 mg, 49%) as an oil and the cycloadduct **16b** (43 mg, 22%) as an oil, both of which recrystallised from EtOAc as cubes.

Data for adduct **16a**: m.p. 91–93 °C; R_f 0.4 [CH_2Cl_2 -MeOH (95 : 5)]; ν_{max} (film)/ cm^{-1} 2955, 1705; ^1H NMR (400 MHz,

CDCl_3) δ = 4.86 (1H, d, J 7.0 Hz, CH), 4.00–3.91 (2H, m, 2 \times CH), 3.38–3.30 (1H, m, CH), 3.18–3.06 (1H, m, CH), 3.04 (3H, s, CH_3), 2.07–1.94 (2H, m, 2 \times CH), 1.90–1.80 (1H, m, CH), 1.75–1.64 (1H, m, CH); ^{13}C NMR (101 MHz, CDCl_3) δ = 174.8, 172.0, 77.6, 67.9, 55.8, 53.6, 29.7, 25.0, 24.1; HRMS (ES) Found: MH^+ , 197.0922. $\text{C}_9\text{H}_{13}\text{N}_2\text{O}_3$ requires MH^+ , 197.0926.

Crystal data deposited at CCDC 1051097.

Unit cell parameters: a 7.9208(3), b 16.5681(9), c 6.7713(3), $Pna21$.

Data for adduct **16b**: m.p. 88–91 °C; R_f 0.3 [CH_2Cl_2 -MeOH (95 : 5)]; ν_{max} (film)/ cm^{-1} 2955, 1700; ^1H NMR (400 MHz, CDCl_3) δ = 4.83 (1H, d, J 7.0 Hz, CH), 3.77 (1H, t, J 8.5 Hz, CH), 3.61–3.52 (2H, m, 2 \times CH), 3.06 (3H, s, CH_3), 3.04–2.96 (1H, m, CH), 2.23–2.12 (2H, m, 2 \times CH), 1.88–1.80 (1H, m, CH), 1.75–1.68 (1H, m, CH); ^{13}C NMR (101 MHz, CDCl_3) δ = 174.8, 172.1, 77.6, 67.9, 55.8, 53.6, 25.7, 25.0, 24.1; HRMS (ES) Found: MH^+ , 197.0917. $\text{C}_9\text{H}_{13}\text{N}_2\text{O}_3$ requires MH^+ , 197.0926.

(2R*,3R*,3aR*)-3-Nitro-2-phenyl-hexahydropyrrolo[1,2-*b*][1,2]oxazole 17 and another isomer of 3-nitro-2-phenyl-hexahydropyrrolo[1,2-*b*][1,2]oxazole 18

To aldehyde **1** (106 mg, 1 mmol) in PhMe (10 mL) was added hydroxylamine hydrochloride (76 mg, 1.1 mmol), $^i\text{Pr}_2\text{NEt}$ (0.41 mL, 2.4 mL), MgSO_4 (~200 mg) and Bu_4NI (37 mg, 0.1 mmol) and the mixture was warmed to 60 °C. After 30 min, *trans*- β -nitrostyrene (224 mg, 1.5 mmol) was added and the mixture was heated under reflux. After 3.5 h, the mixture was allowed to cool to room temperature and the solvent was evaporated. Purification by column chromatography, eluting with petrol-EtOAc (8 : 2 to 1 : 1), gave cycloadducts **17** (56 mg, 24%) as a solid and **18** (152 mg, 65%) as an oil.

Data for adduct **17**: m.p. 89–92 °C; R_f 0.4 [petrol-EtOAc (1 : 1)]; ν_{max} (film)/ cm^{-1} 2980, 1550, 1455; ^1H NMR (400 MHz, CDCl_3) δ = 7.41–7.34 (5H, m, Ph), 5.50 (1H, d, J 5.5 Hz, CH), 5.24 (1H, dd, J 5.5, 1.5 Hz, CH), 4.51 (1H, broad t, J 7.5 Hz, CH), 3.50 (1H, dt, J 11.5, 5.5 Hz, CH), 3.21 (1H, dt, J 11.5, 7.5 Hz, CH), 2.35–2.25 (1H, m, CH), 2.08–1.99 (1H, m, CH), 1.94–1.77 (2H, m, 2 \times CH); ^{13}C NMR (101 MHz, CDCl_3) δ = 132.0, 129.3, 128.6, 126.5, 98.4, 80.8, 68.7, 56.4, 29.9, 24.0; HRMS (ES) Found: MH^+ , 235.1073. $\text{C}_{12}\text{H}_{15}\text{N}_2\text{O}_3$ requires MH^+ , 235.1083; Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_3$: C, 61.5; H, 6.0; N, 12.0. Found: C, 61.9; H, 6.0; N, 11.7.

Crystal data deposited at CCDC 1006037.

Unit cell parameters: a 9.0398(3), b 7.2748(3), c 17.0449(6), $P21/c$.

Data for adduct **18**: R_f 0.6 [petrol-EtOAc (4 : 1)]; ν_{max} (film)/ cm^{-1} 2980, 1545, 1500; ^1H NMR (400 MHz, CDCl_3) δ = 7.49–7.35 (5H, m, Ph), 5.75 (1H, d, J 6.0 Hz, CH), 5.43 (1H, dd, J 8.5, 6.0 Hz, CH), 4.29 (1H, br q, J 7.5 Hz, CH), 3.50 (1H, dt, J 12.5, 6.5 Hz, CH), 3.32 (1H, dt, J 12.5, 7.0 Hz, CH), 2.08–1.97 (4H, m, 4 \times CH); ^{13}C NMR (101 MHz, CDCl_3) δ = 132.3, 128.9, 128.8, 126.3, 96.4, 79.4, 68.1, 56.7, 26.4, 23.9; HRMS (ES) Found: MH^+ , 235.1088. $\text{C}_{12}\text{H}_{15}\text{N}_2\text{O}_3$ requires MH^+ , 235.1083.



(1S*,2S*,6aR*)-Methyl 2-hydroxy-3-oxo-hexahydro-1H-pyrrolizine-1-carboxylate 19 and (1S*,2S*,6aS*)-methyl 2-hydroxy-3-oxo-hexahydro-1H-pyrrolizine-1-carboxylate 20

To a 2 : 1 mixture of cycloadducts **14** (215 mg, 0.9 mmol) in H₂O (3.5 mL) and AcOH (2.5 mL) was added zinc (280 mg, 4.3 mmol) and the mixture was heated under reflux. After 22 h, the mixture was cooled to room temperature. The mixture was diluted with CH₂Cl₂ (50 mL) and aqueous NH₃ (5 mL, 35%), the layers separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated under reduced pressure. Purification by column chromatography, eluting with CH₂Cl₂-iPrOH (97 : 3), gave the lactams **19** and **20** (combined yield of 142 mg, 79%). The pure lactams were isolated after careful chromatography: **19** (72 mg, 40%), **20** (32 mg, 18%) and both were recrystallized from hot EtOAc as needles.

Alternatively, a 2 : 1 mixture of cycloadducts **14** (500 mg, 2.2 mmol), H₂O (11 mL), AcOH (5.5 mL) and zinc (600 mg, 9.2 mmol) gave, after heating for 22 h then purification as above, the lactams **19** (129 mg, 30%) and **20** (70 mg, 16%).

Data for lactam **19**: m.p. 138–141 °C, lit.¹² m.p. for (+)-**19**: 191–192 °C; *R*_f 0.6 [CH₂Cl₂-iPrOH-NH₃ (90 : 9 : 1)]; ¹H NMR (400 MHz, CDCl₃) δ = 4.63 (1H, dd, *J* 6.0, 4.0 Hz, CH), 4.42 (1H, ddd, *J* 9.0, 8.0, 5.5 Hz, NCH), 3.85 (1H, d, *J* 4.0 Hz, OH), 3.80 (3H, s, CH₃), 3.52 (1H, dt, *J* 12.0, 8.0 Hz, NCH), 3.22 (1H, ddd, *J* 12.0, 8.5, 3.5 Hz, NCH), 2.95 (1H, dd, *J* 8.0, 6.0 Hz, CH), 2.28–2.13 (3H, m, 3 × CH), 1.44–1.32 (1H, m, CH). Data correspond to the literature.¹²

Data for lactam **20**: m.p. 182–185 °C, lit.¹² m.p. for **20** was not reported; *R*_f 0.5 [CH₂Cl₂-iPrOH-NH₃ (90 : 9 : 1)]; ¹H NMR (400 MHz, CDCl₃) δ = 4.76 (1H, br s, CH), 3.98 (1H, dt, *J* 8.0, 6.5 Hz, NCH), 3.74 (3H, s, CH₃), 3.67 (1H, t, *J* 6.5 Hz, CH), 3.63 (1H, dt, *J* 11.5, 7.0 Hz, NCH), 3.10–3.22 (2H, m, NCH and OH), 2.13–1.97 (3H, m, 3 × CH), 1.59–1.47 (1H, m, CH). Data correspond to the literature.¹²

Macronecine

The lactam **19** (126 mg, 0.63 mmol) in THF (9 mL) was added to a solution of LiAlH₄ (148 mg, 3.91 mmol) in THF (4 mL). The grey suspension was then heated under reflux. After 17 h, the mixture was cooled to room temperature and aqueous NaOH (0.3 mL, 2 M) was added. After 1 h, the suspension was filtered and was washed with MeOH (60 mL). The filtrate was concentrated to give a white solid which was purified by column chromatography on silica with a plug of Celite, eluting with CH₂Cl₂-MeOH-NH₃ (10 : 5 : 1), to give macronecine (70 mg, 70%) as an amorphous solid; m.p. 106–108 °C, lit.^{13g} m.p. 107–108 °C; *R*_f 0.1 [CH₂Cl₂-MeOH-NH₃ (10 : 5 : 1)]; ¹H NMR (400 MHz, CDCl₃) δ = 4.50 (1H, t, *J* 4.0 Hz, CH), 4.34 (2H, br s, 2 × OH), 3.89–3.82 (2H, m, 2 × CH), 3.56–3.50 (1H, m, CH), 3.17 (1H, d, *J* 11.0 Hz, CH), 2.97 (1H, td, *J* 11.0, 6.5 Hz, CH), 2.67 (1H, dd, *J* 11.0, 3.5 Hz, CH), 2.59–2.54 (1H, m, CH), 2.00–1.92 (1H, m, CH), 1.87–1.76 (3H, m, 3 × CH), 1.57–1.50 (1H, m, CH). Data corresponds to the literature.^{12,13}

(1S*,2S*,10bR*)-1,2-Dimethyl 2,5,6,10b-tetrahydro-1H-isoxazolo[3,2-*a*]isoquinoline-1,2-dicarboxylate 22

Hydroxylamine hydrochloride (56 mg, 0.81 mmol) and *N,N*-diisopropylethylamine (0.28 mL, 1.62 mmol) were added to aldehyde **21**¹⁴ (154 mg, 0.67 mmol) in PhMe (7 mL) and the mixture was heated to 60 °C. Dimethyl fumarate (117 mg, 0.81 mmol) was added and the mixture was heated under reflux. After 1 h, the mixture was cooled to room temperature and the solvent evaporated. Purification by column chromatography, eluting with CH₂Cl₂-MeOH (99.7 : 0.3), gave the product **22** (150 mg, 76%), which was recrystallised from CH₂Cl₂-hexanes as needles; m.p. 83–85 °C, lit.¹³ m.p. 89–90 °C; *R*_f 0.5 [CH₂Cl₂-MeOH (99.5 : 0.5)]; *ν*_{max} (film)/cm⁻¹ 2955, 1735; ¹H NMR (400 MHz, CDCl₃) δ = 7.26–7.19 (2H, m, 2 × CH), 7.16–7.13 (1H, m, CH), 7.07 (1H, d, *J* 7.0 Hz, CH), 4.95 (1H, d, *J* 7.5 Hz, CH), 4.89 (1H, d, *J* 8.5 Hz, CH), 3.88 (3H, s, CH₃), 3.80–3.76 (1H, m, CH), 3.77 (3H, s, CH₃), 3.42–3.38 (1H, m, CH), 3.23–3.15 (1H, m, CH), 3.08–3.00 (1H, m, CH), 2.96–2.92 (1H, m, CH); ¹³C NMR (100 MHz, CDCl₃) δ = 171.5, 171.1, 133.2, 132.5, 128.9, 127.6, 127.1, 126.5, 80.9, 67.4, 57.7, 52.8, 52.7, 49.7, 27.9; HRMS (ES) Found MH⁺, 292.1172, C₁₅H₁₈NO₅ requires MH⁺, 292.1185.

Crystal data deposited at CCDC 1006038.

Unit cell parameters: *a* 9.1248(8), *b* 32.242(3), *c* 9.4579(9), *P*21/*c*.

(8aR*,11aS*,11bR*)-10-Phenyl-5,8a,11a,11b-tetrahydropyrrolo [3',4':4,5][1,2]oxazolo[3,2-*a*]isoquinoline-9,11(6H,10H)-dione 23

Hydroxylamine hydrochloride (124 mg, 1.78 mmol) and *N,N*-diisopropylethylamine (0.62 mL, 3.55 mmol) were added to aldehyde **21**¹⁴ (339 mg, 1.48 mmol) in PhMe (15 mL) and the mixture was heated to 60 °C. After 2 h, *N*-phenylmaleimide (308 mg, 1.78 mmol) was added and the mixture was heated under reflux. After 1 h, the mixture was allowed to cool to room temperature and the solvent was evaporated. Purification by column chromatography, eluting with CH₂Cl₂-MeOH (99.8 : 0.2), gave cycloadduct **23** (291 mg, 61%) as an amorphous solid; m.p. 172–174 °C, lit.¹⁵ m.p. 178–179 °C; *R*_f 0.8 [CH₂Cl₂-MeOH (99.5 : 0.5)]; *ν*_{max} (film)/cm⁻¹ 2935, 1715; ¹H NMR (400 MHz, CDCl₃) δ = 7.55–7.51 (2H, m, 2 × CH), 7.47–7.44 (2H, m, 2 × CH), 7.41–7.39 (1H, m, CH), 7.35–7.31 (1H, m, CH), 7.28–7.25 (1H, m, CH), 7.16 (1H, d, *J* 7.5, CH), 4.98–4.95 (2H, m, 2 × CH), 3.93 (1H, dd, 7.5, 2.0 Hz, CH), 3.74–3.66 (1H, m, CH), 3.33–3.21 (2H, m, CH), 2.69–2.62 (1H, m, CH); ¹³C NMR (101 MHz, CDCl₃) δ = 174.7, 173.8, 133.9, 132.9, 131.4, 129.2, 128.9, 128.8, 127.3 (2 × CH), 127.2, 126.4, 75.7, 65.8, 56.8, 47.8, 22.9; HRMS (ES) Found MH⁺, 321.1232, C₁₉H₁₇N₂O₃ requires MH⁺, 321.1239.

(8aR*,11aS*,11bR*)-10-Methyl-5,8a,11a,11b-tetrahydropyrrolo [3',4':4,5][1,2]oxazolo[3,2-*a*]isoquinoline-9,11(6H,10H)-dione 24

Hydroxylamine hydrochloride (120 mg, 1.73 mmol) and *N,N*-diisopropylethylamine (0.60 mL, 3.47 mmol) were added to aldehyde **21**¹⁴ (327 mg, 1.43 mmol) in PhMe (15 mL) and the mixture was heated to 60 °C. *N*-Methylmaleimide (192 mg,



1.73 mmol) was added and the mixture was heated under reflux. After 1 h, the mixture was allowed to cool to room temperature and the solvent was evaporated. Purification by column chromatography, eluting with CH₂Cl₂-MeOH (99.7:0.3), gave the product **24** (280 mg, 76%), which was recrystallised from CH₂Cl₂-hexanes as needles; m.p. 162–164 °C, lit.¹¹ m.p. 164–166 °C; *R*_f 0.5 [CH₂Cl₂-MeOH (99.5:0.5)]; ν_{\max} (film)/cm⁻¹ 2915, 2825, 1700; ¹H NMR (400 MHz, CDCl₃) δ = 7.40 (1H, d, *J* 7.5, CH), 7.31 (1H, t, *J* 7.5, CH), 7.24 (1H, t, *J* 7.5, CH), 7.14 (1H, d, *J* 7.5, CH), 4.82–4.80 (2H, m, 2 × CH), 3.76 (1H, dd, *J* 7.5, 2.0 Hz, CH), 3.76–3.66 (1H, m, CH), 3.26–3.20 (2H, m, 2 × CH), 3.12 (3H, s, CH₃), 2.64–2.56 (1H, m, CH); ¹³C NMR (100 MHz, CDCl₃) δ = 175.6, 174.9, 133.8, 132.9, 128.8, 127.3, 127.2, 127.1, 75.7, 65.2, 56.7, 47.7, 25.2, 22.9; HRMS (ES) Found MH⁺, 259.1084. C₁₄H₁₅N₂O₃ requires MH⁺, 259.1083.

Crystal data deposited at CCDC 1006039.

Unit cell parameters: *a* 6.8159(2), *b* 26.7835(7), *c* 7.0628(2), *P*21/*c*.

(1S*,2S*,10bR*)-1,2-Dimethyl 8,9-dimethoxy-2,5,6,10b-tetrahydro-1H-isoxazolo[3,2-*a*]isoquinoline-1,2-dicarboxylate 26

Hydroxylamine hydrochloride (56 mg, 0.81 mmol) and *N,N*-diisopropylethylamine (0.28 mL, 1.62 mmol) were added to aldehyde **25**¹⁴ (154 mg, 0.67 mmol) in PhMe (7 mL) and the mixture was heated to 60 °C. After 2.5 h, dimethyl fumarate (126 mg, 0.88 mmol) was added and the mixture was heated under reflux. After 1 h, the mixture was cooled to room temperature and the solvent was evaporated. Purification by column chromatography, eluting with CH₂Cl₂-MeOH (99.5:0.5), gave the cycloadduct **26** (182 mg, 78%) as an amorphous solid; m.p. 96–99 °C; *R*_f 0.5 [CH₂Cl₂-MeOH (98:2)]; ν_{\max} (film)/cm⁻¹ 2940, 1730, 1610; ¹H NMR (400 MHz, CDCl₃) δ = 6.61 (1H, s, CH), 6.58 (1H, s, CH), 4.96 (1H, d, *J* 7.5 Hz, CH), 4.80 (1H, d, *J* 8.5 Hz, CH), 3.87 (6H, s, 2 × CH₃), 3.84 (3H, s, CH₃), 3.78 (3H, s, CH₃), 3.78–3.74 (1H, m, CH), 3.40–3.37 (1H, m, CH), 3.17–3.13 (1H, m, CH), 3.01–2.94 (1H, m, CH), 2.85–2.80 (1H, m, CH); ¹³C NMR (101 MHz, CDCl₃) δ = 171.7, 171.2, 148.5, 147.7, 125.5, 124.0, 110.8, 109.7, 80.9, 67.2, 57.6, 55.9 (2 × CH₃), 52.8 (2 × CH₃), 49.9, 27.7; HRMS (ES) Found: MH⁺, 352.1381. C₁₇H₂₂N₂O₇ requires MH⁺, 352.1396.

(8aR*,11aS*,11bR*)-2,3-Dimethoxy-10-phenyl-5,8a,11a,11b-tetrahydropyrrolo[3',4':4,5][1,2]oxazolo[3,2-*a*]isoquinoline-9,11(6*H*,10*H*)-dione 27

Hydroxylamine hydrochloride (150 mg, 2.1 mmol) and *N,N*-diisopropylethylamine (0.75 mL, 4.3 mmol) were added to aldehyde **25**¹⁴ (410 mg, 1.8 mmol) in PhMe (18 mL) and the mixture was heated to 60 °C. After 2.5 h, *N*-phenylmaleimide (370 mg, 2.1 mmol) was added and the mixture was heated under reflux. After 1 h, the mixture was cooled to room temperature and the solvent was evaporated. Purification by column chromatography, eluting with CH₂Cl₂-MeOH (99.5:0.5), gave the cycloadduct **27** (500 mg, 74%) as an amorphous solid; m.p. 185–187 °C (decomposed); *R*_f 0.7 [CH₂Cl₂-MeOH (98:2)];

ν_{\max} (film)/cm⁻¹ 2985, 1710, 1615; ¹H NMR (400 MHz, CDCl₃) δ = 7.55–7.51 (2H, m, 2 × CH), 7.47–7.44 (1H, m, CH), 7.40–7.38 (2H, m, 2 × CH), 6.90 (1H, s, CH), 6.63 (1H, s, CH), 5.03 (1H, d, *J* 7.5 Hz, CH), 4.90 (1H, br, CH), 3.93 (3H, s, CH₃), 3.90 (3H, s, CH₃), 3.91–3.89 (1H, m, CH), 3.63–3.57 (1H, m, CH), 3.31–3.25 (1H, m, CH), 3.15–3.08 (1H, m, CH), 2.67–2.60 (1H, m, CH); ¹³C NMR (101 MHz, CDCl₃) δ = 174.9, 173.5, 148.4, 148.3, 131.4, 129.3, 129.0, 126.4, 125.8, 124.3, 111.0, 109.6, 76.0, 65.9, 56.5, 56.2, 56.0, 48.0, 23.4; HRMS (ES) Found: MH⁺, 381.1447. C₂₁H₂₁N₂O₅ requires MH⁺, 381.1450; Anal. Calcd for C₂₁H₂₀N₂O₅: C, 66.3; H, 5.3; N, 7.4. Found: C, 66.6; H, 5.1; N, 7.4.

Crystal data deposited at CCDC 1006041.

Unit cell parameters: *a* 10.6709(10), *b* 7.6760(7), *c* 22.1886(18), *P*21/*c*.

(8aR*,11aS*,11bR*)-2,3-Dimethoxy-10-methyl-5,8a,11a,11b-tetrahydropyrrolo[3',4':4,5][1,2]oxazolo[3,2-*a*]isoquinoline-9,11(6*H*,10*H*)-dione 28

Hydroxylamine hydrochloride (91 mg, 1.3 mmol) and *N,N*-diisopropylethylamine (0.45 mL, 2.6 mmol) were added to aldehyde **25**¹⁴ (250 mg, 1.1 mmol) in PhMe (11 mL) and the mixture was heated to 60 °C. After 2.5 h, *N*-methylmaleimide (150 mg, 1.3 mmol) was added and the mixture was heated under reflux. After 1 h, the mixture was cooled to room temperature and the solvent was evaporated. Purification by column chromatography, eluting with CH₂Cl₂-MeOH (99.5:0.5), gave the cycloadduct **28** (280 mg, 81%) as an amorphous solid; m.p. 154–156 °C (decomposed); *R*_f 0.7 [CH₂Cl₂-MeOH (98:2)]; ν_{\max} (film)/cm⁻¹ 2940, 1700, 1610; ¹H NMR (400 MHz, CDCl₃) δ = 6.84 (1H, s, CH), 6.60 (1H, s, CH), 4.86 (1H, d, *J* 7.5 Hz, CH), 4.75 (1H, br, CH), 3.93 (3H, s, CH₃), 3.89 (3H, s, CH₃), 3.73 (1H, dd, *J* 7.5, 2.5 Hz, CH), 3.60–3.57 (1H, m, CH), 3.24–3.17 (1H, m, CH), 3.12 (3H, s, CH₃), 3.13–3.06 (1H, m, CH), 2.58–2.52 (1H, m, CH); ¹³C NMR (101 MHz, CDCl₃) δ = 175.7, 174.7, 148.3, 148.2, 125.8, 124.3, 111.0, 109.5, 75.8, 65.2, 56.2, 55.9, 55.5, 47.9, 25.2, 23.0; HRMS (ES) Found: MH⁺, 319.1308. C₁₆H₁₉N₂O₅ requires MH⁺, 319.1294.

Crystal data deposited at CCDC 1006042.

Unit cell parameters: *a* 9.8243(10), *b* 8.6128(8), *c* 17.8328(18), *P*21/*c*.

(1S*,2S*,10bR*)-Methyl 2-hydroxy-3-oxo-1,2,3,4,5,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate 29

Zinc powder (56 mg, 0.85 mmol) was added to cycloadduct **22** (59 mg, 0.20 mmol) in AcOH/H₂O (1.5 mL, 1:2). The mixture was heated to 70 °C for 1.5 h before being cooled to room temperature. The zinc salts were filtered, washed with CH₂Cl₂ (8 mL) and the solvent was evaporated. The solute was partitioned between aqueous ammonia (4 mL, 18 M) and CH₂Cl₂ (8 mL), and the aqueous layer was extracted with CH₂Cl₂ (2 × 10 mL). The organic fractions were dried (MgSO₄), filtered and evaporated to give the lactam **29** (39 mg, 75%) as needles; m.p. 181–184 °C, lit.¹⁵ m.p. 190–192 °C; *R*_f 0.4 [CH₂Cl₂-MeOH (95:5)]; ν_{\max} (film)/cm⁻¹ 3250, 2950, 1730, 1680; ¹H NMR (400 MHz, CDCl₃) δ = 7.27–7.15 (4H, m, 4 × CH), 5.66 (1H, br,



OH), 5.48 (1H, d, *J* 8.0 Hz, CH), 4.61 (1H, d, *J* 7.5, CH), 4.26 (1H, ddd, *J* 13.0, 6.0, 3.0, CH), 3.90 (3H, s, CH₃), 3.25–3.18 (2H, m, 2 × CH), 3.00–2.92 (1H, m, CH), 2.87–2.81 (1H, m, CH); ¹³C NMR (100 MHz, CDCl₃) δ = 170.8, 170.1, 135.6, 133.4, 129.2, 127.4, 127.2, 125.2, 71.5, 56.5, 52.6, 52.1, 37.4, 28.5; HRMS (ES) Found MH⁺, 262.1075. C₁₄H₁₆NO₄ requires MH⁺, 262.1079.

(1S*,2S*,10bR*)-Methyl 2-hydroxy-8,9-dimethoxy-3-oxo-1,2,3,4,5,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-1-carboxylate 30

Zinc powder (145 mg, 2.2 mmol) was added to cycloadduct **26** (185 mg, 0.53 mmol) in AcOH/H₂O (5 mL, 1:2) and the mixture was heated to 70 °C. After 1.5 h, the zinc salts were filtered, washing the filtrate with CH₂Cl₂ (15 mL) and the solvent was evaporated. The solute was partitioned between aqueous ammonia (5 mL) and CH₂Cl₂ (10 mL), and the aqueous layer was extracted with CH₂Cl₂ (3 × 15 mL). The organic fractions were dried (MgSO₄), filtered and evaporated. The residue was recrystallized with hot MeOH to give the lactam **30** (81 mg, 47%) as an amorphous solid; m.p. 190–192 °C; *R*_f 0.29 [CH₂Cl₂–MeOH (97:3)]; ν_{\max} (film)/cm^{−1} 3300, 2990, 1730, 1665; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 6.76 (1H, s, CH), 6.66 (1H, s, CH), 6.30 (1H, d, *J* 6.0 Hz, OH), 5.12 (1H, d, *J* 8.0 Hz, CH), 4.26 (1H, dd, *J* 7.0, 6.0 Hz, CH), 4.06–4.00 (1H, m, CH), 3.75 (3H, s, CH₃), 3.72 (3H, s, CH₃), 3.66 (3H, s, CH₃), 3.17 (1H, dd, *J* 8.0, 7.0 Hz, CH), 3.07–2.98 (1H, m, CH), 2.70–2.68 (2H, m, 2 × CH); ¹³C NMR (101 MHz, DMSO-*d*₆) δ = 171.0, 169.9, 148.2, 148.1, 128.2, 126.4, 112.8, 108.7, 71.5, 55.95, 55.9, 55.5, 53.0, 52.4, 36.9, 28.1; HRMS (ES) Found: MH⁺, 322.1301. C₁₆H₂₀NO₆ requires MH⁺, 322.1291; Anal. Calcd for C₁₆H₁₉NO₆: C, 59.8; H, 6.0; N, 4.4. Found: C, 60.1; H, 5.8; N, 4.3.

Acknowledgements

We acknowledge support from the University of Sheffield, the EPSRC, and the Thai Government. We are grateful to Alexandra Kirchner for related studies.

Notes and references

- (a) R. Grashey, R. Huisgen and H. Leitermann, *Tetrahedron Lett.*, 1960, **1**, 9; (b) N. A. LeBel, M. E. Post and J. J. Whang, *J. Am. Chem. Soc.*, 1964, **86**, 3759.
- For some reviews on nitron cycloadditions, see: (a) J. Revuelta, S. Cicchi, A. Goti and A. Brandi, *Synthesis*, 2007, 485; (b) A. J. M. Burrell and I. Coldham, *Curr. Org. Synth.*, 2010, **7**, 312.
- (a) R. Grigg, J. Markandu, S. Surendrakumar, M. Thornton-Pett and W. J. Warnock, *Tetrahedron*, 1992, **48**, 10399; (b) E. C. Davison, M. E. Fow, A. B. Holmes, S. D. Roughley, C. J. Smith, G. M. Williams, J. E. Davies, P. R. Raithby, J. P. Adams, I. T. Forbes, N. J. Press and M. J. Thompson, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1494; (c) R. A. Stockman, A. Sinclair, L. G. Arini, P. Szeto and D. L. Hughes, *J. Org. Chem.*, 2004, **69**, 1598; (d) M. S. Wilson and A. Padwa, *J. Org. Chem.*, 2008, **73**, 9601; (e) A. C. Flick, M. J. A. Caballero and A. Padwa, *Tetrahedron*, 2010, **66**, 3643.
- (a) I. Coldham, A. J. M. Burrell, L. E. White, H. Adams and N. Oram, *Angew. Chem., Int. Ed.*, 2007, **46**, 6159; (b) A. J. M. Burrell, I. Coldham, L. Watson, N. Oram, C. D. Pilgram and N. G. Martin, *J. Org. Chem.*, 2009, **74**, 2290; (c) A. J. M. Burrell, I. Coldham and N. Oram, *Org. Lett.*, 2009, **11**, 1515; (d) A. J. M. Burrell, L. Watson, N. G. Martin, N. Oram and I. Coldham, *Org. Biomol. Chem.*, 2010, **8**, 4530; (e) I. Coldham, A. J. M. Burrell, H. D. S. Guerrand and N. Oram, *Org. Lett.*, 2011, **13**, 1267; (f) I. Coldham, L. Watson, H. Adams and N. G. Martin, *J. Org. Chem.*, 2011, **76**, 2360; (g) I. Coldham, A. J. M. Burrell, L. Watson, N. Oram and N. G. Martin, *Heterocycles*, 2012, **84**, 597.
- For recent examples of cascade nitron formation by cyclization then intramolecular cycloaddition, see: (a) X. Peng, B. M. K. Tong, H. Hirao and S. Chiba, *Angew. Chem., Int. Ed.*, 2014, **53**, 1959; (b) C. V. Suneel Kumar and C. V. Ramana, *Org. Lett.*, 2014, **16**, 4766.
- (a) I. Coldham, S. Jana, L. Watson and C. D. Pilgram, *Tetrahedron Lett.*, 2008, **49**, 5408; (b) I. Coldham, S. Jana, L. Watson and N. G. Martin, *Org. Biomol. Chem.*, 2009, **7**, 1674.
- For a related cascade nitron formation by cyclization then intermolecular cycloaddition, see: A. Siriwardena, D. P. Sonawane, O. P. Bande, P. R. Markad, S. Yonekawa, M. B. Tropak, S. Ghosh, B. A. Chopade, D. J. Mahuran and D. D. Dhavale, *J. Org. Chem.*, 2014, **79**, 4398.
- For an alternative method, see: N. C. Deno, K. A. Eisenhardt, D. G. Pohl, H. J. Spinnelli and R. C. White, *J. Org. Chem.*, 1974, **39**, 520.
- (a) T. Shono, Y. Matsumura and K. Inoue, *J. Org. Chem.*, 1986, **51**, 549; (b) S. A. Ali and M. I. M. Wazeer, *J. Chem. Soc., Perkin Trans. 1*, 1988, 597.
- (a) J. J. Tufariello and J. P. Tette, *J. Org. Chem.*, 1975, **40**, 3866; (b) G. Pandey, G. Kumaraswamy and A. Krishna, *Tetrahedron Lett.*, 1987, **28**, 2649; (c) S. A. Ali, J. H. Khan, M. I. M. Wazeer and H. P. Perzanowski, *Tetrahedron*, 1989, **45**, 5979.
- M. Burdisso, A. Gamba, R. Gandolfi and P. Pevarello, *Tetrahedron*, 1987, **43**, 1835.
- S. E. Denmark and A. R. Hurd, *J. Org. Chem.*, 1998, **63**, 3045.
- For other syntheses of macronecine and petasinecine, see: (a) A. J. Aasen and C. C. J. Culvenor, *J. Org. Chem.*, 1969, **34**, 4143; (b) H. Rüeger and M. Benn, *Heterocycles*, 1983, **20**, 235; (c) J. Mulzer and M. Shanyoor, *Tetrahedron Lett.*, 1993, **35**, 6545; (d) H. Ito, Y. Ikeuchi, T. Taguchi and Y. Hanzawa, *J. Am. Chem. Soc.*, 1994, **116**, 5469; (e) D.-C. Ha, J.-B. Ahn and Y.-E. Kwon, *Bull. Korean Chem. Soc.*, 1998, **19**, 514; (f) D. Ma and J. Zhang, *J. Chem. Soc., Perkin Trans. 1*, 1999,



- 1703; (g) T. K. Sarkar, A. Hazra, P. Gangopadhyay, N. Panda, Z. Slanina, C.-C. Lin and H.-T. Chen, *Tetrahedron*, 2005, **61**, 1155; (h) T. Sengoku, T. Suzuki, T. Kakimoto, M. Takahashi and H. Yoda, *Tetrahedron*, 2009, **65**, 2415.
- 14 (a) M. Yamato, K. Hashigaki, N. Qais and S. Ishikawa, *Tetrahedron*, 1990, **46**, 5909; (b) P. C. B. Page, G. A. Rassias, D. Barros, A. Ardakani, B. Buckley, D. Bethell, T. A. D. Smith and A. M. Z. Slawin, *J. Org. Chem.*, 2001, **66**, 6926.
- 15 (a) M. Burdisso, A. Gamba and R. Gandolfi, *Tetrahedron*, 1988, **44**, 3735. See also: (b) R. Huisgen, H. Hauck, R. Grashey and H. Seidl, *Chem. Ber.*, 1969, **102**, 736.
- 16 K. M. Laemmerhold and B. Breit, *Angew. Chem., Int. Ed.*, 2010, **49**, 2367.

