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

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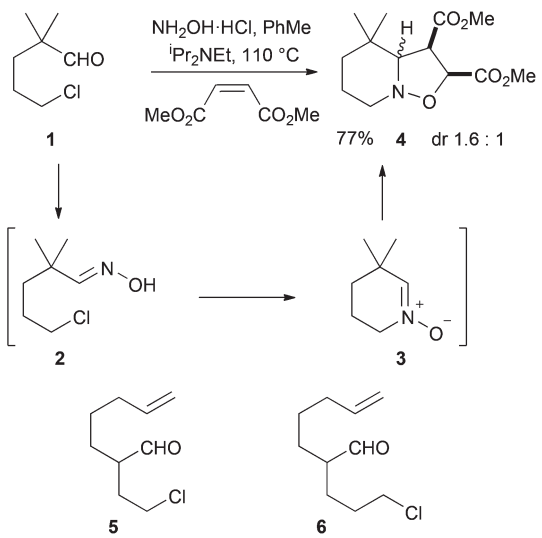
Simple haloaldehydes, including enolisable aldehydes, were found to be suitable for the formation of cyclic products by cascade (domino) condensation, cyclisation, dipolar cycloaddition chemistry. This multi-component reaction approach to heterocyclic compounds was explored by using hydroxylamine, a 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.

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 nitrone, 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 nitrone. 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 nitrone 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 nitrone **3** that can be trapped intermolecularly with dimethyl maleate to give the product **4** as a mixture of diastereoisomers (Scheme 1).[6] The enolisable 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]



Scheme 1 Previous studies with related aldehydes.[4,6]

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

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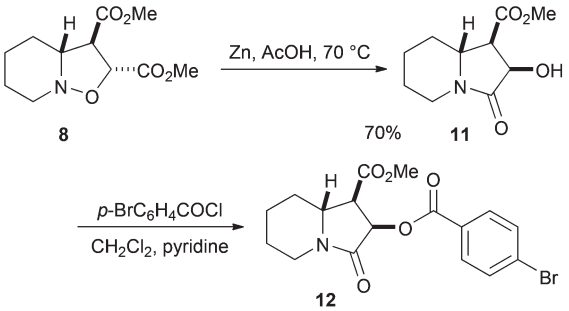
The ability to undergo such chemistry is likely due to the use of reactive, electron-poor alkene dipolarophiles. This chemistry allows the formation of a greater range of substituted products without the need to block enolisation.

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 $^{i}Pr_2NEt$, 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 ^{1}H NMR spectroscopic data for the product **8** match those reported from oxidation of *N*-hydroxypiperidine and cycloaddition of the resulting nitrone with dimethyl fumarate.[9]

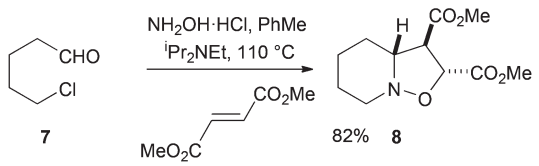
Changing the dipolarophile from dimethyl fumarate to *N*-phenylmaleimide gave the desired bicyclic product **9** in high yield as the major diastereoisomer (dr 4 : 1) (Scheme 3). The diastereoisomers were separable by column chromatography and the stereochemistry of the major isomer **9** was determined 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 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**).

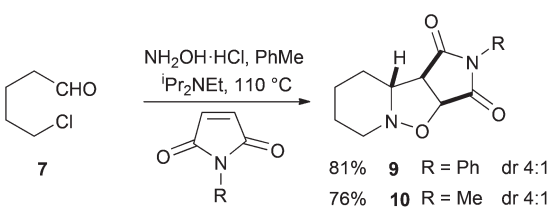


Scheme 4 Preparation of lactam **11** and ester **12**.

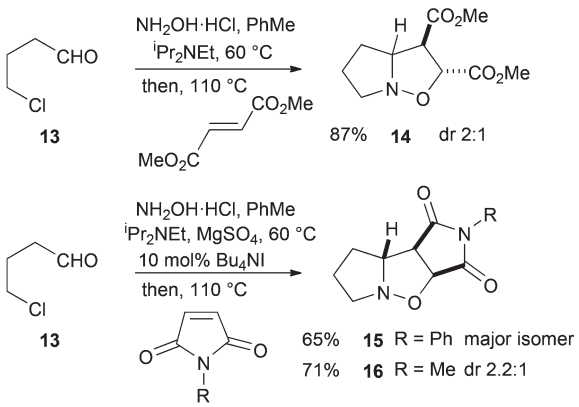
Cyclization of the oxime derived from the aldehyde **7** gives a six-membered ring nitrone. We had previously found that a six-membered ring nitrone could be prepared and reacted intramolecularly (by using aldehyde **6**, see Scheme 1).[4c] However, aldehyde **5** was unsuccessful and resulted in a pyrrole 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 $^{i}Pr_2NEt$, 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 2 Aldehyde substrate **7** with dimethyl fumarate.



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



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

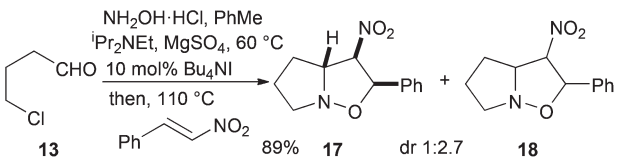
of some $MgSO_4$ and *n*-Bu_4NI. The diastereoisomers were separable by column chromatography, although the minor isomer of the *N*-phenyl adduct **15** was isolated together with the adduct of hydroxylamine and *N*-phenylmaleimide. The stereochemistry of the major isomer of **16** was determined by 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]

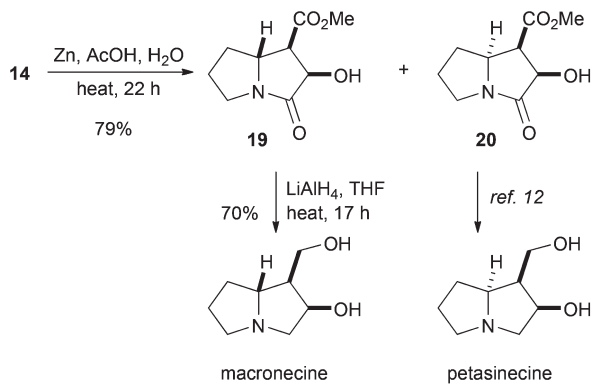
From the results above, it is clear that the aldehyde **13** is amenable to the desired cascade chemistry involving oxime formation, cyclization to give a nitrone, followed by intermolecular cycloaddition. This requires an activated alkene to promote cycloaddition, otherwise (as found for compound **5**) the five-membered nitrone 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**, was reduced with $LiAlH_4$ to give the pyrrolizidine alkaloid (±)-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 (±)-petasinecine by reduction.[12] Therefore the chemistry allows a rapid access to these natural products in just three steps from 4-chlorobutanal (**13**).

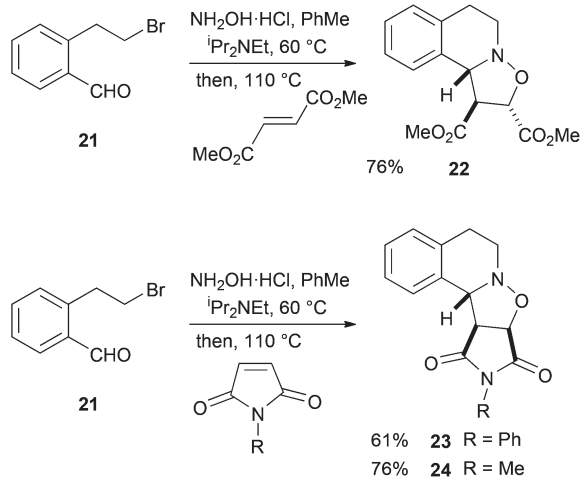
To complement the examples above, we studied the same cascade chemistry with the benzaldehyde substrate **21**. This was prepared in two steps from isochroman.[6b,14] Condensation of aldehyde **21** with hydroxylamine at 60 °C followed by addition of dimethyl fumarate, *N*-phenylmaleimide or *N*-methylmaleimide 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



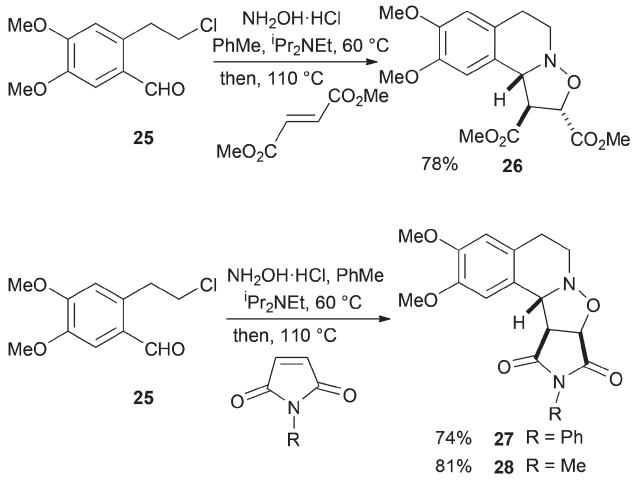
Scheme 6 Aldehyde substrate **13** with β-nitrostyrene.



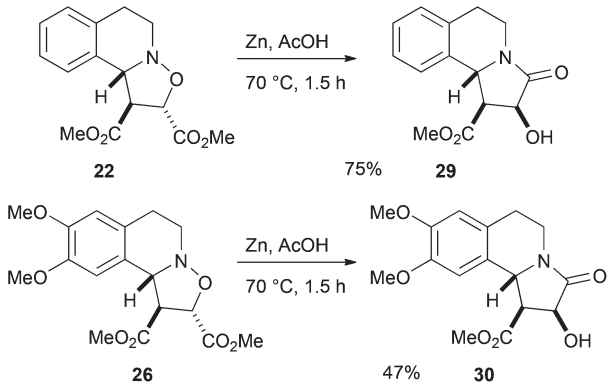
Scheme 7 Preparation of the alkaloid macronecine.



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



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 **25**[14] 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 CH_2Cl_2 (10 mL) was added to freshly distilled oxalyl chloride (2.1 mL, 24 mmol) in CH_2Cl_2 (60 mL) at −78 °C. After 10 min, 5-chloropentan-1-ol (2.4 mL, 20 mmol) in CH_2Cl_2 (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 CH_2Cl_2 (20 mL) and water (20 mL) were added. The aqueous layer was washed with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with CH_2Cl_2, gave aldehyde **7** (2.05 g, 85%) as an oil; R_f 0.8 (CH_2Cl_2); ν_{max} (film)/cm^{-1} 2935, 2865, 2730, 1720; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.80 (1H, t, *J* 1.5 Hz, CHO), 3.60–3.54 (2H, m, CH_2), 2.55–2.48 (2H, m, CH_2), 1.88–1.77 (4H, m, 2 × CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 201.8, 44.5, 43.0, 31.8, 19.4. Data consistent with the literature.[8]

(2*R,3*R**,3a*R**)-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 CH_2Cl_2–MeOH (98 : 2), gave the product **8** (340 mg, 82%) as an oil; R_f 0.36 [CH_2Cl_2–MeOH (98 : 2)]; ν_{max} (film)/cm^{-1} 2950, 2850, 1730; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.84 (1H, d, *J* 5.5 Hz, CH), 3.81 (3H, s, CH_3), 3.79 (3H, s, CH_3), 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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. $C_{11}H_{18}NO_5$ requires MH$^+$, 244.1185.

(3a*R,3b*S**,8a*S**)-2-Phenyl-hexahydro-8-oxa-2,7a-diaza-cyclopenta[*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 CH_2Cl_2–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 CH_2Cl_2–hexanes (1 : 1) as needles; m.p. 157–159 °C; R_f 0.43 [CH_2Cl_2–MeOH (98 : 2)]; ν_{max} (film)/cm^{-1} 2960, 2935, 1710; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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. $C_{15}H_{17}N_2O_3$ 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52–7.45 (2H, m, 2 × CH), 7.45–7.39 (1H, m, CH), 7.34–7.29 (2H, m, 2 × CH), 4.91 (1H, d, *J* 7.5 Hz, CH), 3.64–3.55 (2H, m, 2 × CH), 2.61–2.50 (2H, m, 2 × CH), 2.28–2.18 (1H, m, CH), 1.85–1.79 (2H, m, 2 × 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. $C_{15}H_{17}N_2O_3$ requires MH^+, 273.1239.

(3a*R**,3b*S**,8a*S**)-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; ^{1}H 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 × CH), 1.67–1.54 (2H, m, 2 × 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. $C_{10}H_{15}N_2O_3$ requires MH^+, 211.1083.

(1*R**,2*R**,8a*R**)-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 × 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; ^{1}H 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 × 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. $C_{10}H_{16}NO_4$ requires MH^+, 214.1079.

(1*R**,2*R**,8a*R**)-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; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 (2H, d, *J* 8.5 Hz, 2 × CH), 7.60 (2H, d, *J* 8.5 Hz, 2 × 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 × 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 × 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. $C_{17}H_{19}NO_5{}^{79}Br$ 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-Chlorobutanal 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 × 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); ^{1}H 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]

(2*S**,3*S**,3a*S**)-2,3-Dimethyl hexahydropyrrolo[1,2-*b*][1,2]oxazole-2,3-dicarboxylate 14a and (2*S**,3*S**,3a*R**)-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}Pr$_2$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}Pr$_2$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; ^{1}H 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 × Me), 3.79 (3H, s, 2 × 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 × CH), 2.13–1.99 (1.65H, m, 3 × CH), 1.86–1.72 (2H, m, 2 × 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. $C_{10}H_{16}NO_5$ requires MH$^+$ 230.1028. ^{1}H NMR data consistent with the literature.[9]

(1*S**,2*S**,6*R**)-4-Phenyl-7-oxa-4,8-diazatricyclo[6.3.0.0^1]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}Pr$_2$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; ^{1}H 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 × 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 × 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. $C_{14}H_{15}N_2O_3$ requires MH$^+$, 259.1083.

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

(1*S**,2*S**,6*R**)-4-Methyl-7-oxa-4,8-diazatricyclo[6.3.0.0^1]undecane-3,5-dione 16a and (1*R**,2*S**,6*R**)-4-methyl-7-oxa-4,8-diazatricyclo[6.3.0.0^1]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}Pr$_2$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; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.86 (1H, d, *J* 7.0 Hz, CH), 4.00–3.91 (2H, m, 2 × 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 × 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. $C_9H_{13}N_2O_3$ 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), *Pna*21.

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; ^{1}H 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 × CH), 3.06 (3H, s, CH_3), 3.04–2.96 (1H, m, CH), 2.23–2.12 (2H, m, 2 × 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. $C_9H_{13}N_2O_3$ requires MH$^+$, 197.0926.

(2*R**,3*R**,3a*R**)-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}Pr$_2$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; ^{1}H 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 × 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. $C_{12}H_{15}N_2O_3$ requires MH$^+$, 235.1083; Anal. Calcd for $C_{12}H_{14}N_2O_3$: 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), *P*21/*c*.

Data for adduct **18**: R_f 0.6 [petrol–EtOAc (4 : 1)]; ν_{max} (film)/cm^{-1} 2980, 1545, 1500; ^{1}H 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 × 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. $C_{12}H_{15}N_2O_3$ requires MH$^+$, 235.1083.

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

To a 2 : 1 mixture of cycloadducts **14** (215 mg, 0.9 mmol) in H_2O (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 CH_2Cl_2 (50 mL) and aqueous NH_3 (5 mL, 35%), the layers separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography, eluting with CH_2Cl_2–^{i}PrOH (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), H_2O (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 [CH_2Cl_2–^{i}PrOH–NH_3 (90 : 9 : 1)]; ^{1}H NMR (400 MHz, $CDCl_3$) 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, CH_3), 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 [CH_2Cl_2–^{i}PrOH–NH_3 (90 : 9 : 1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.76 (1H, br s, CH), 3.98 (1H, dt, *J* 8.0, 6.5 Hz, NCH), 3.74 (3H, s, CH_3), 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 $LiAlH_4$ (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 CH_2Cl_2–MeOH–NH_3 (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 [CH_2Cl_2–MeOH–NH_3 (10 : 5 : 1)]; ^{1}H NMR (400 MHz, $CDCl_3$) 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]

(1*S,2*S**,10b*R**)-1,2-Dimethyl 2,5,6,10b-tetrahydro-1*H*-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 CH_2Cl_2–MeOH (99.7 : 0.3), gave the product **22** (150 mg, 76%), which was recrystallised from CH_2Cl_2–hexanes as needles; m.p. 83–85 °C, lit.[13] m.p. 89–90 °C; R_f 0.5 [CH_2Cl_2–MeOH (99.5 : 0.5)]; ν_{max} (film)/cm^{-1} 2955, 1735; ^{1}H NMR (400 MHz, $CDCl_3$) 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, CH_3), 3.80–3.76 (1H, m, CH), 3.77 (3H, s, CH_3), 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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, $C_{15}H_{18}NO_5$ 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*.

(8a*R,11a*S**,11b*R**)-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 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 CH_2Cl_2–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 [CH_2Cl_2–MeOH (99.5 : 0.5)]; ν_{max} (film)/cm^{-1} 2935, 1715; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (101 MHz, $CDCl_3$) 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. $C_{19}H_{17}N_2O_3$ requires MH^+, 321.1239.

(8a*R,11a*S**,11b*R**)-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 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 CH_2Cl_2–MeOH (99.7 : 0.3), gave the product **24** (280 mg, 76%), which was recrystallised from CH_2Cl_2–hexanes as needles; m.p. 162–164 °C, lit.[11] m.p. 164–166 °C; R_f 0.5 [CH_2Cl_2–MeOH (99.5 : 0.5)]; ν_{max} (film)/cm^{-1} 2915, 2825, 1700; ^{1}H NMR (400 MHz, $CDCl_3$) 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, CH_3), 2.64–2.56 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) 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. $C_{14}H_{15}N_2O_3$ 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*.

(1*S**,2*S**,10b*R**)-1,2-Dimethyl 8,9-dimethoxy-2,5,6,10b-tetrahydro-1*H*-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 CH_2Cl_2–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 [CH_2Cl_2–MeOH (98 : 2)]; ν_{max} (film)/cm^{-1} 2940, 1730, 1610; ^{1}H NMR (400 MHz, $CDCl_3$) 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 × CH_3), 3.84 (3H, s, CH_3), 3.78 (3H, s, CH_3), 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); ^{13}C NMR (101 MHz, $CDCl_3$) 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 × CH_3), 52.8 (2 × CH_3), 49.9, 27.7; HRMS (ES) Found: MH^+, 352.1381. $C_{17}H_{22}NO_7$ requires MH^+, 352.1396.

(8a*R**,11a*S**,11b*R**)-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 CH_2Cl_2–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 [CH_2Cl_2–MeOH (98 : 2)]; ν_{max} (film)/cm^{-1} 2985, 1710, 1615; ^{1}H NMR (400 MHz, $CDCl_3$) 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, CH_3), 3.90 (3H, s, CH_3), 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); ^{13}C NMR (101 MHz, $CDCl_3$) 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. $C_{21}H_{21}N_2O_5$ requires MH^+, 381.1450; Anal. Calcd for $C_{21}H_{20}N_2O_5$: 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*.

(8a*R**,11a*S**,11b*R**)-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 CH_2Cl_2–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 [CH_2Cl_2–MeOH (98 : 2)]; ν_{max} (film)/cm^{-1} 2940, 1700, 1610; ^{1}H NMR (400 MHz, $CDCl_3$) 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, CH_3), 3.89 (3H, s, CH_3), 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, CH_3), 3.13–3.06 (1H, m, CH), 2.58–2.52 (1H, m, CH); ^{13}C NMR (101 MHz, $CDCl_3$) 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. $C_{16}H_{19}N_2O_5$ 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*.

(1*S**,2*S**,10b*R**)-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/H_2O (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 CH_2Cl_2 (8 mL) and the solvent was evaporated. The solute was partitioned between aqueous ammonia (4 mL, 18 M) and CH_2Cl_2 (8 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The organic fractions were dried ($MgSO_4$), 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 [CH_2Cl_2–MeOH (95 : 5)]; ν_{max} (film)/cm^{-1} 3250, 2950, 1730, 1680; ^{1}H NMR (400 MHz, $CDCl_3$) 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, CH_3), 3.25–3.18 (2H, m, 2 × CH), 3.00–2.92 (1H, m, CH), 2.87–2.81 (1H, m, CH); ^{13}C NMR (100 MHz, $CDCl_3$) 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. $C_{14}H_{16}NO_4$ requires MH^+, 262.1079.

(1*S,2*S**,10b*R**)-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/H_2O (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 CH_2Cl_2 (15 mL) 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 × 15 mL). The organic fractions were dried ($MgSO_4$), 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 [CH_2Cl_2–MeOH (97 : 3)]; ν_{max} (film)/cm^{-1} 3300, 2990, 1730, 1665; ^{1}H 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, CH_3), 3.72 (3H, s, CH_3), 3.66 (3H, s, CH_3), 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); ^{13}C 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. $C_{16}H_{20}NO_6$ requires MH^+, 322.1291; Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.8; H, 6.0; N, 4.4. Found: C, 60.1; H, 5.8; N, 4.3.

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Notes and references

1 (*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.

2 For some reviews on nitrone 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.

3 (*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.

4 (*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.

5 For recent examples of cascade nitrone 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.

6 (*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.

7 For a related cascade nitrone 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.

8 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.

9 (*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.

10 (*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.

11 M. Burdisso, A. Gamba, R. Gandolfi and P. Pevarello, *Tetrahedron*, 1987, **43**, 1835.

12 S. E. Denmark and A. R. Hurd, *J. Org. Chem.*, 1998, **63**, 3045.

13 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.

