A new procedure for the reduction of α,β-unsaturated pyrrolidinones to 2*H*-pyrroles and 1*H*-pyrroles based on initial activation by *N*-nitrosation

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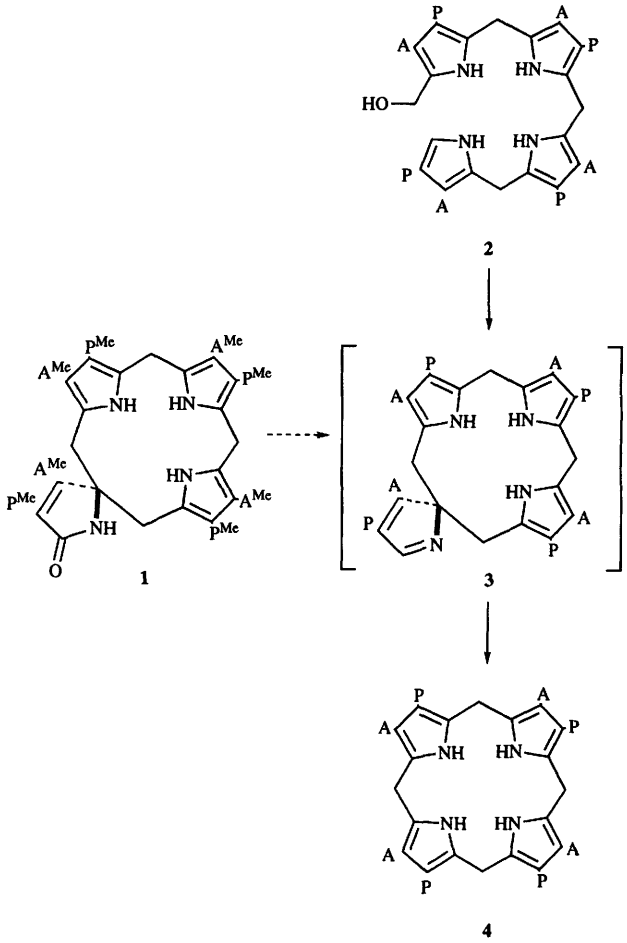
A new two step procedure is developed for the half-reduction of lactams to cyclic imines and enamines. *N*-Nitrosation using dinitrogen tetroxide furnishes *N*-nitroso lactams, which undergo chemoselective 1,2-reduction to *N*-nitroso carbinolamines‡ by one equivalent of hydride delivered from lithium triethylborohydride. The nitroso group is cleaved in a novel way using samarium(II) iodide and dehydration then generates the corresponding imine (which may tautomerise to the isomeric enamine). The reduction can be performed in the presence of esters and has proved efficient for the preparation of 2*H*-pyrroles (pyrrolenines) and 1*H*-pyrroles relevant to the study of tetrapyrrole biosynthesis.

Introduction

We have long been interested in effecting the half-reduction of secondary amides and lactams to imines. This interest arises because we wish to reduce the macrocyclic spiro lactam **1** in this way; lactam **1** has been prepared by total synthesis.[1] The expected product of such a reduction would yield, after methyl ester hydrolysis, the spiro pyrrolenine **3** which has been strongly supported[1,2] as an intermediate during the conversion of hydroxymethylbilane **2** into uropophyrinogen III **4** by uroporphyrinogen III synthase (EC 4.2.1.75, also called cosynthetase). This is a key step early in the biosynthesis of all natural tetrapyrroles[3] and their relatives such as vitamin B_{12} (Scheme 1).

The half-reduction of secondary amides and lactams to the corresponding imines is formally a two electron reduction process. The transformation is difficult to achieve since imines are reduced rapidly to amines by most metal hydride reagents. Indeed, the most frequently employed route for this overall transformation is over-reduction of the amide to the corresponding secondary amine followed by oxidation to the imine. Numerous metal hydrides can be employed for the reduction step[4] and several oxidants have been described[5–15] which generate an imine from an amine. This approach was used successfully[16] for conversion of the simple model system **5** into the pyrrolenine **6** (Scheme 2). However, the combined presence in lactam **1** of eight methyl ester groups and three pyrrole nuclei carrying no electron-withdrawing groups (*cf.* the system **5**) raises substantial problems for this approach. Accordingly, we aimed to devise a direct method for the controlled half-reduction of a lactam to a cyclic imine.

At the outset, the only reported method for the controlled half-reduction of amides was that devised by Eschenmoser in connection with his elegant studies on the total synthesis of corrins.[17] This involved conversion of lactam **7** into amidrazone **8** which on irradiation with UV light in methanol gave the half reduced product **9**; molecular nitrogen and stilbene were extruded [Scheme 3(*a*)]. More recently, Ganem has described a procedure which utilises Schwartz's zirconium reagent $[(C_5H_5)_2ZrHCl]$ to effect reductive de-oxygenation of simple secondary amides and lactams to their corresponding imines[18] [*e.g.* Scheme 3(*c*)]. An alternative approach was developed in Cambridge[19,20] involving conversion of a lactam such as **10** into the corresponding thiolactam **11** followed by controlled reductive desulfurisation with nickel boride to afford the pyrrolenine **12** [Scheme 3(*b*)]. This approach has been used for most of our recent work on the chemistry of pyrrolomethylpyrrolenines.[19] However, we have not yet been able to prepare the thiolactam analogue of lactam **1** and so our



Scheme 1 $A^{Me} = CH_2CO_2Me$, $P^{Me} = CH_2CH_2CO_2Me$, A = CH_2CO_2H, P = $CH_2CH_2CO_2H$

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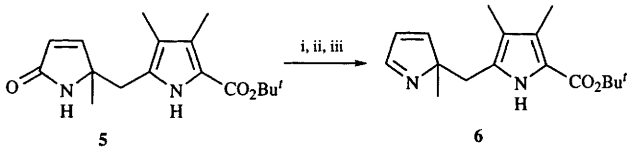
‡ IUPAC prefer the term hemiaminal.



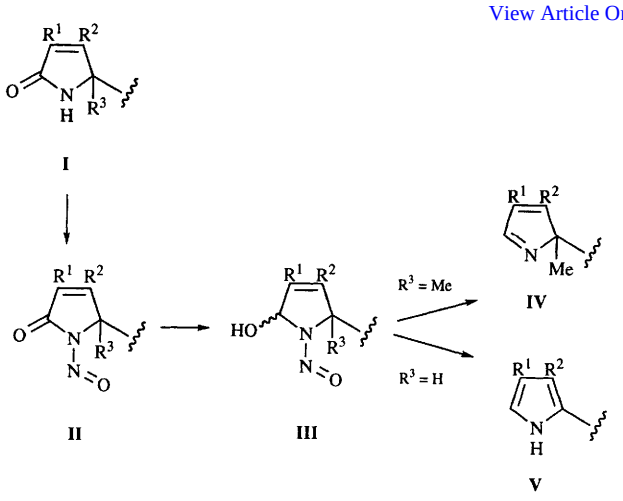
5 6

Scheme 2 *Reagents:* i, $Et_3O^+BF_4^-$, 1,8-$(Me_2N)_2$-naphthalene, CH_2Cl_2; ii, DIBAL, PhMe; iii, Bu^{t}OCl, CH_2Cl_2, then 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)

search for alternative strategies for the half-reduction of lactams has continued.

This paper describes a novel and efficient procedure for accomplishing this transformation on lactams of general structure **I** (Scheme 4). The method involves formation of the corresponding *N*-nitroso amide **II**, chemoselective half-reduction using lithium triethylborohydride ($LiEt_3BH$) at −78 °C to give an *N*-nitroso carbinolamine intermediate **III** (which need not be isolated or handled) followed by reductive cleavage *in situ* of the N–N bond with samarium(II) iodide. Elimination of water then occurs to give either pyrrolenine **IV** or α-free pyrrole **V** depending on the substituents present.

The enhanced electrophilicity of the carbonyl group in *N*-nitroso amides relative to their parent amides has received very little attention [21] despite the fact that the activation imparted by *N*-nitrosation appears to be similar to that afforded by formation of carbamate and sulfonamide derivatives. These derivatives have been used to promote attack of Wittig [22] and other nucleophilic reagents at amide carbonyls.[23,24] Indeed, recently it has been shown that diisobutylaluminium hydride (DIBAL) [24] and $LiEt_3BH$ [25] will deliver hydride selectively to the lactam carbonyl in certain derivatives of *N*-carbamoyl pyroglutamate to give the corresponding *N*-carbamoyl carbinolamines [*e.g.* **15** ⟶ **16**, Scheme 3(*d*)]. However, it has not been possible to prepare *N*-carbamoyl derivatives of lactams **1** or **10**, presumably due to steric crowding. In contrast

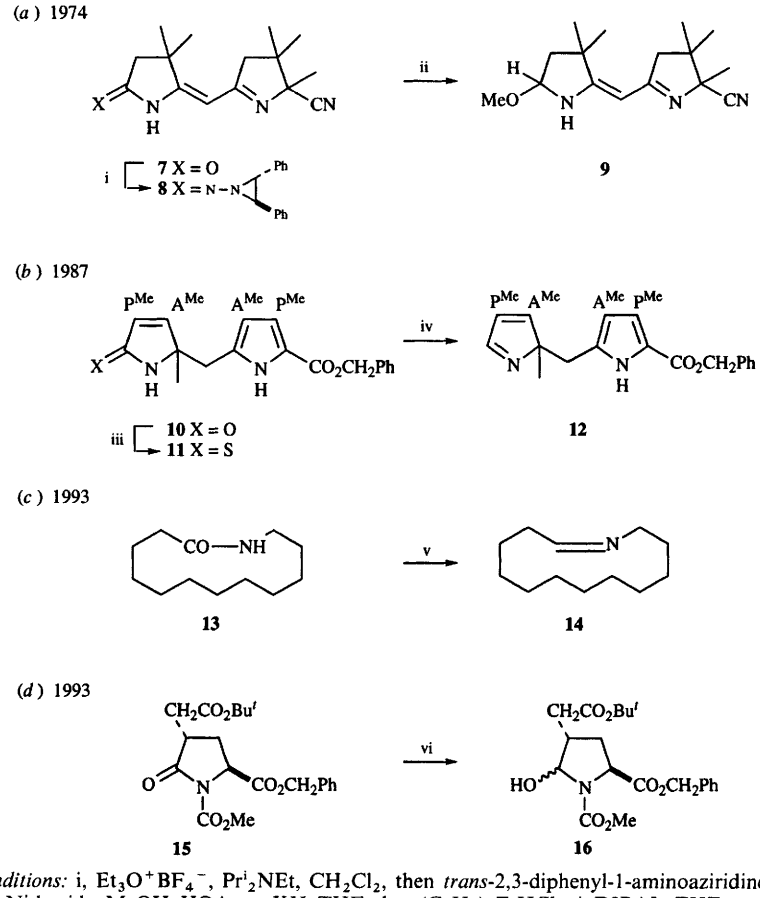


Scheme 4

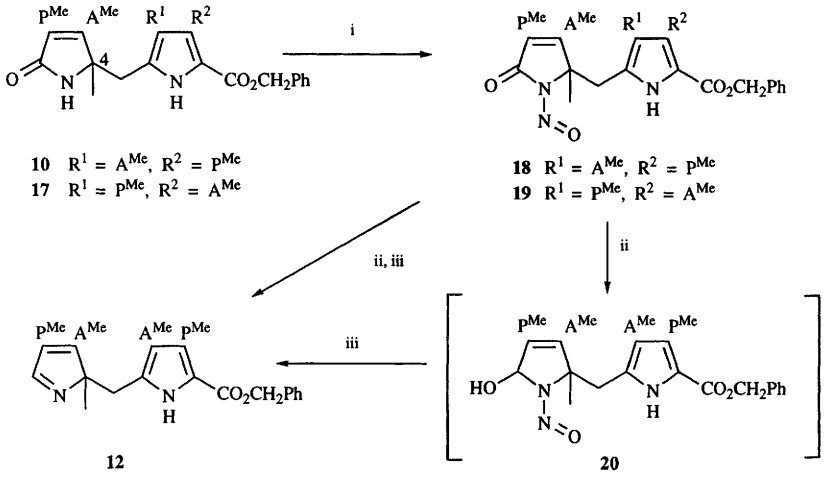
the nitroso group is small, is readily introduced and is now shown to be removed efficiently by reductive cleavage using samarium(II) iodide at low temperature. To the best of our knowledge, N–N bond cleavage of *N*-nitroso compounds in this way has not previously been reported, although samarium(II) iodide is known to reduce nitro groups to amines.[26]

Results and discussion

Pyrrolomethyl lactam **10**, prepared and used previously for related work in this area,[27] was chosen as the model system on which to develop a reduction procedure because **10** carries the main functionalities present in the more complex molecule of interest, the spiro lactam **1**. Aqueous nitrous acid has been commonly used for *N*-nitrosation of amides, however, several other sources of NO^+, compatible with organic solvents, are



Scheme 3 *Reagents and conditions:* i, $Et_3O^+BF_4^-$, Pr^i_2NEt, CH_2Cl_2, then *trans*-2,3-diphenyl-1-aminoaziridine; ii, *hν* (Hg, Pyrex), MeOH; iii, Lawesson's reagent, THF; iv, Ni-boride, MeOH–HOAc; v, KH, THF, then $(C_5H_5)_2ZrHCl$; vi, DIBAL, THF



Scheme 5 *Reagents and conditions:* i, N_2O_4, NaOAc, CH_2Cl_2; ii, $LiEt_3BH$, THF, −78 °C; iii, SmI_2, THF, then aq. NH_4Cl

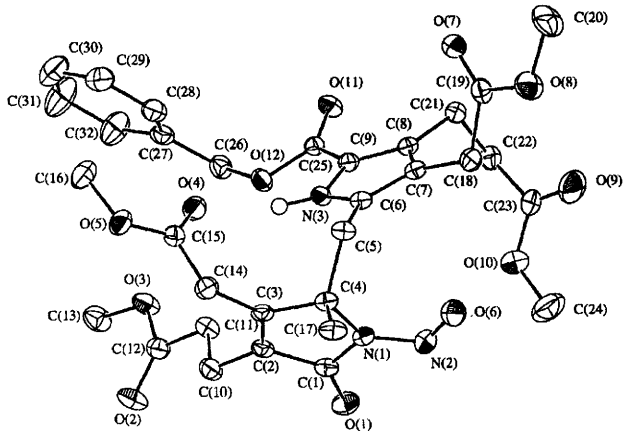


Fig. 1 X-Ray structure of **18** with atom numbering scheme. Ellipsoids are drawn at the 50% level. All H atoms have been omitted for clarity with the exception of that on N(3), which forms an intramolecular hydrogen bond to O(4), [O(4)···N(3) 2.858 Å]

also known which have been shown to be more efficient nitrosating agents.[28] We evaluated six procedures[28–32] for *N*-nitrosation of lactam **10**. Dinitrogen tetroxide–sodium acetate in CH_2Cl_2 at 0 °C was the best method, routinely giving the *N*-nitroso lactam§ **18** in over 80% yield from lactam **10**. Similarly the *N*-nitroso lactam§ **19** was prepared in 87% yield from lactam **17** (Scheme 5). Pyridine could also be used as base and gave very similar results.

N-Nitroso lactam **18** shows a carbonyl absorption at *ca.* 1730 cm^{-1} in the infra-red (overlaid by ester carbonyl absorptions, *cf.* 1695 cm^{-1} for lactam **10**), and a new absorption shoulder at *ca.* 250 nm in the UV, both characteristic of an *N*-nitroso amide. Finally, the structure of the *N*-nitroso lactam **18** was confirmed by X-ray crystallography (Fig. 1).

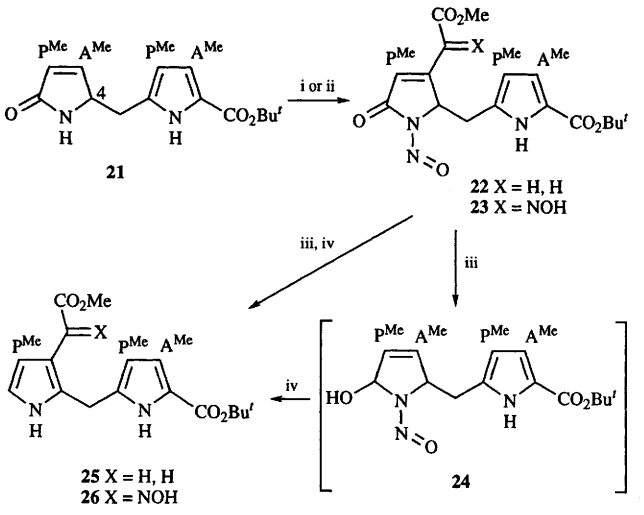
Using the *N*-nitroso lactam **18**, seven reducing agents based on boron and aluminium hydrides were screened for their ability to convert this lactam into the corresponding *N*-nitroso carbinolamine **20** under a variety of conditions of solvent and temperature. Of these, only zinc borohydride and $LiEt_3BH$ showed useful reactivity. The others either failed to react or preferentially reduced one or more of the methyl esters to the corresponding alcohols. The former reagent used in tetrahydrofuran (THF) at ambient temperature gave the *N*-nitroso carbinolamine **20**, but the reaction was slow and was accompanied by extensive cleavage of the nitroso group to give lactam **10**. In contrast, one molar equivalent of $LiEt_3BH$ reacted in under 5 min at −78 °C in THF to give the *N*-nitroso carbinolamine§ **20** (Scheme 5). As we did not wish to handle the rather unstable product, methods for reductive cleavage of the N–N bond *in situ* were sought. Freshly prepared samarium(II) iodide in THF added at −78 °C to the unisolated reduction product **20**, followed by warming to room temperature, achieved this cleavage very efficiently. The product of this 'one-pot' process was the pyrrolenine **12** in yields of 60–70% from *N*-nitroso lactam **10** (Scheme 5); the final dehydration probably occurs during the work-up.

Attention then turned to the possibility of using this approach for the reduction of dipyrromethanones, *e.g.* **21**. These compounds carry a hydrogen atom at the C-4 centre which is blocked by a methyl group in the lactams **10** and **17**. Thus, an analogous half-reduction of a pyrromethanone followed by dehydration and tautomerisation would generate the second pyrrole nucleus of a dipyrromethane. These compounds are used extensively for the synthesis of tetrapyrroles such as hydroxymethylbilane **2** and uroporphyrinogen III **4**.[33] A mild method for their preparation from dipyrromethanones would greatly help our work on the synthesis of dipyrromethanes made chiral by isotopic labelling at the interpyrrolic methylene group, which are needed for biosynthetic studies.[34,35]

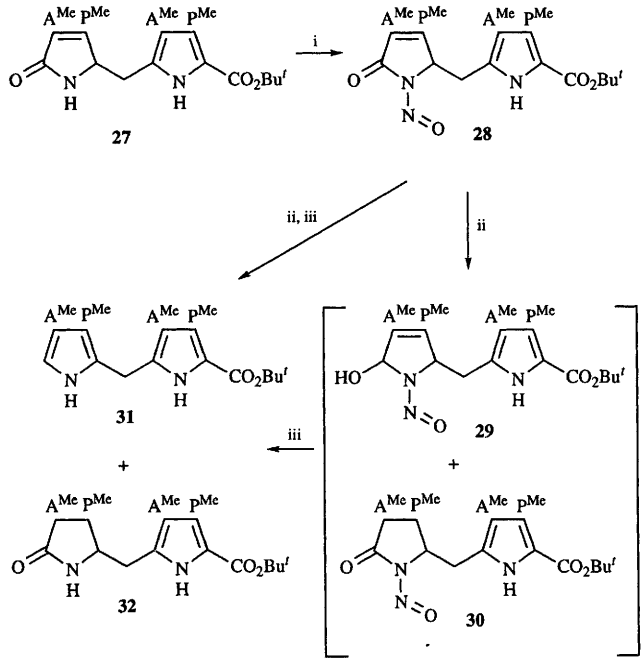
Accordingly, dipyrromethanone **21** was *N*-nitrosated as above to give the *N*-nitroso lactam **22** in 81% yield. This reaction was best carried out at −20 °C and, in contrast to the *N*-nitrosation of pyrrolomethyl lactams **10** and **17**, pyridine could not be employed as base as its use resulted in additional *C*-nitrosation at the methylene of one of the acetate methyl esters, giving the oxime **23** (Scheme 6). When the *N*-nitroso lactam **22** was subjected to the 'one-pot' half-reduction sequence, the α-free dipyrromethane **25** was formed in 73% yield. Interestingly, the oxime **23** could be converted into the α-free dipyrromethane oxime **26** under these conditions, though in poor yield.

The next experiments explored the effect of reversing the acetate and propionate side chains on the lactam portion of the dipyrromethanone. Nitrosation of dipyrromethanone **27** as before gave the *N*-nitroso lactam **28** in 81% yield (Scheme 7) which was reduced by the now standard sequence to yield the dipyrromethane **31** but in only 24% yield. The major product was the saturated lactam **32** (63%). It appeared that reversing the positions of the substituents on the unsaturated lactam had

§ **CAUTION**: *N*-Nitrosoamines are known to be powerful carcinogens. Although *N*-nitrosoamides have often been prepared and are well known, a very recent report (M. Ramajaki, A. Vigroux, L. Chahoua, A. J. Kresge and J. C. Fishbein, ACS National Meeting, Anaheim, CA, April 2–6, 1995, abstract ORGN 162) indicates that it would be wise to regard them and *N*-nitroso carbinolamines as potential carcinogens. Both should therefore be manipulated with all the appropriate rigorous precautions.



Scheme 6 *Reagents and conditions:* i, N_2O_4, NaOAc, CH_2Cl_2; ii, N_2O_4, pyridine, CH_2Cl_2; iii, $LiEt_3BH$, THF, −78 °C; iv, SmI_2, THF, then aq. NH_4Cl



Scheme 7 *Reagents and conditions:* i, N_2O_4, NaOAc, CH_2Cl_2; ii, $LiEt_3BH$, THF, −78 °C; iii, SmI_2, THF, then aq. NH_4Cl

the effect of diverting the reduction to favour what is formally a 1,4-hydride reduction over the required 1,2-hydride reduction.

To gain more insight into this process, the $LiEt_3BH$ reduction was carried out on the *N*-nitroso lactam **28** and the samarium(II) iodide step was omitted. It was apparent from the ^1H NMR spectrum of the crude product that there were essentially two compounds present which had resonances consistent with the expected products of 1,4-hydride reduction, *N*-nitroso lactam **30**, and 1,2-hydride reduction, *N*-nitroso carbinolamine **29** (Scheme 7). Their relative ratio (*ca.* 3:1, by ^1H NMR) mirrored the isolated yields of saturated lactam **32** and α-free dipyrromethane **31** in the complete 'one-pot' reaction described above. The analogous reaction using *N*-nitroso lactam **21** (having the reversed acetate–propionate substitution pattern) gave almost exclusively the *N*-nitroso carbinolamine intermediate **24** by 1,2-hydride reduction, again in agreement with the outcome of the earlier complete half-reduction process (Scheme 6). The exact origin of this difference in reactivity between the isomeric unsaturated lactams present in dipyrromethanones **21** and **27** remains to be elucidated.

In summary, a mild new method has been developed for the half-reduction of αβ-unsaturated pyrrolidinones to pyrrolenines and α-free pyrroles. The method exploits (i) the susceptibility of *N*-nitroso lactams to chemoselective 1,2-hydride reduction by $LiEt_3BH$ and (ii) efficient *in situ* reductive cleavage of the *N*-nitroso bond by samarium(II) iodide without isolation of intermediates.

Experimental

General directions

All reactions were carried out under argon with magnetic stirring. Anhydrous solvents were dried by distillation from drying agents as follows: THF (Na–benzophenone), CH_2Cl_2 (CaH_2). Mps: Kofler hot stage; uncorrected. UV: Cecil 5501, using 1 cm quartz cuvettes. IR: Perkin-Elmer 1600, using 0.5 mm NaCl cells. ^1H NMR: on a Bruker AM400 FT spectrometer, with solvent deuterium as internal reference. ^{13}C NMR: at 100 MHz on a Bruker AM400 FT spectrometer. MS: Kratos MS890 (+FAB and high resolution MS), Kratos MS50TC (FD), VG Bio-Q (electrospray). Preparative TLC was performed on 20 × 20 cm plates coated to a thickness of 0.25 or 1.0 mm with Merck Kieselgel 60 F_{254}. 'Drying' refers to the use of AnalaR grade Na_2SO_4 and 'evaporation' refers to removal of solvents at water aspirator reduced pressure on a Buchi RE III rotary evaporator. Dinitrogen tetroxide was purchased from Argo International, and solutions of samarium(II) iodide in THF were freshly prepared according to the method of Crombie.[36]

Benzyl 2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-4-methyl-10-nitroso-1,4,5,10-tetrahydro-1-oxodipyrrin-9-carboxylate 18

To a solution of lactam **10**[1] (55 mg, 0.09 mmol) in anhydrous CH_2Cl_2 (2 cm^3) was added fused sodium acetate (15 mg, 0.18 mmol) and the resulting suspension cooled to 0 °C under argon. A solution of dinitrogen tetroxide in CH_2Cl_2 (330 mm^3, 0.09 mmol; 0.28 M) was added dropwise. After 2 h the solution was evaporated and the residue purified by preparative TLC eluting with 7:3 ethyl acetate–hexane followed by recrystallisation from ethyl acetate–hexane to give the N-*nitroso lactam* **18** as small pale yellow rods (47 mg, 82%), mp 124–126 °C (Found: MH^+, 656.2459. $C_{32}H_{37}N_3O_{12}$ requires M + H, 656.2455); $\lambda_{max}(CD_3CN)$/nm 270, 250; $\nu_{max}(CHCl_3)/cm^{-1}$ 3320, 2954, 1733, 1452, 1438, 1292, 1266, 1173, 1136, 1064; $\delta_H(CDCl_3$, 400 MHz) 1.47 (3 H, s, CCH_3), 2.39–2.63 (6 H, propionate CH_2), 2.75–2.83 (1 H, propionate CH_2), 2.78 (1 H, d, J 15.5, bridge C*H*H), 2.88–2.93 (1 H, propionate CH_2), 3.22 (1 H, d, J 17, acetate C*H*H), 3.30 (1 H, d, J 17, acetate CH*H*), 3.35 (1 H, d, J 18, acetate C*H*H), 3.47 (1 H, d, J 15.5, bridge CH*H*), 3.57, 3.63, 3.63 and 3.77 (each 3 H, each s, 4 × OCH_3), 3.82 (1 H, d, J 18, acetate CH*H*), 5.19 (1 H, d, J 12, C*H*HPh), 5.30 (1 H, d, J 12, CH*H*Ph), 7.25–7.40 (5 H, aromatic CH), 9.95 (1 H, br s, NH); $\delta_C(CDCl_3$, 200 MHz) 19.8 and 20.4 (2 × $CH_2CH_2CO_2$), 20.6 (CCH_3), 29.0, 29.9, 30.3, 30.5 and 34.5 (4 × CH_2CO_2 + bridge CH_2), 51.4, 51.8, 51.9 and 53.5 (4 × OCH_3), 65.7 (CH_2Ph), 67.7 (CCH_3), 116.4, 118.7, 126.7, 130.2, 134.6, 136.1 and 154.0 (6 × C=C + ipso C), 127.9, 128.3 and 128.4 (aromatic CH) 160.1 (CO_2Bn), 166.5, 170.7, 172.3, 173.2 and 173.6 (4 × CO_2CH_3 + CON); m/z (+FAB) 656, (MH^+, 5%), 626 ($MH - NO^+$, 25), 372, ($C_{20}H_{22}NO_6^+$, 100).

X-Ray structure determination on *N*-nitroso lactam 18

Crystal data for 18. $C_{32}H_{37}N_3O_{12}$, M_r = 655.65, monoclinic, a = 14.047(2), b = 14.463(2), c = 16.802(2) Å, β = 111.279(7)°, V = 3180.6(6) $Å^3$ (from 2θ values of 25 reflections measured at ±ω, 87.5 < 2θ < 97.5°), Z = 4, D_c = 1.369 g cm^{-3}, $F(000)$ = 1384, μ(Cu-Kα) = 0.889 mm^{-1}, λ = 1.541 78 Å, space group $P2_1/c$, T = 123(1) K.

Data collection and processing. Rigaku AFC7R diffracto-

meter, crystal size 0.35 × 0.30 × 0.20 mm, $\omega/2\theta$ scan mode, $2\theta_{max}$ 140°, T = 123(1) K, index ranges h 0 to 17, k 0 to 17, l −20 to 19, scan width (1.42 + 0.14 tan θ)°, scan rate 32° min^{-1}, (in ω), weak reflections, [$I < 25\sigma(I)$] were rescanned, (maximum of 5 scans) and the counts accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak to background counting time was 2:1. The intensities of three standard reflections (measured every 150 reflections) decreased by 5.53% over the course of the data collection. A polynomial correction factor was applied to the data to account for this phenomenon. No absorption correction was applied.; 6310 reflections measured, 5793 unique, R_{int} = 0.0118, 4831 with $F_o > 4\sigma(F_o)$.

Structure solution and refinement. The structure was solved by direct methods[37] and expanded using Fourier techniques. Refinement was based on F^2 for all 5793 reflections.[38] Non-hydrogen atoms were refined anisotropically. Hydrogen atoms located from a difference synthesis were included in the model and their positional and thermal parameters refined. Weighting scheme used $w = 1/[\sigma^2(F_o^2) + (0.0480P)^2 + 1.67P]$, where $P = [\max (F_o^2) + 2(F_c^2)]/3$. At convergence, $wR^2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{\frac{1}{2}} = 0.1023$ for all data, conventional R [on F values for 4831 reflections with $F_o > 4\sigma(F_o)$] = 0.0370, S = 1.006 for 572 parameters, maximum shift/esd 0.007, final difference electron density, max 0.428, min −0.223 e Å^{-3}. Sources of scattering factors are given in reference 38. Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/39.

Benzyl 2,7-bis(2-methoxycarbonylethyl)-3,8-bis(methoxycarbonylmethyl)-4-methyl-10-nitroso-1,4,5,10-tetrahydro-1-oxodipyrrin-9-carboxylate 19

To a solution of lactam **17**[2] (35 mg, 0.05 mmol) in anhydrous CH_2Cl_2 (2 cm^3) was added fused sodium acetate (9 mg, 0.10 mmol) and the resulting suspension cooled to 0 °C under argon. A solution of dinitrogen tetroxide in CH_2Cl_2 (112 mm^3, 0.05 mmol; 0.50 M) was added dropwise. After 2 h the solution was evaporated and the residue purified by preparative TLC eluting with 7:3 ethyl acetate–hexane to give the N-*nitroso lactam* **19** as a yellow oil (32 mg, 87%) (Found: MH$^+$, 656.2426. $C_{32}H_{37}N_3O_{12}$ requires M + H, 656.2455); $\lambda_{max}(CD_3CN)$/nm 275, 251; $\nu_{max}(CHCl_3)$/cm^{-1} 3320, 2954, 1734, 1699, 1456, 1438, 1265, 1174, 1136; $\delta_H(CDCl_3$, 400 MHz) 1.49 (3 H, s, CCH_3), 2.27–2.61 (7 H, propionate CH_2), 2.73–2.80 (1 H, propionate CH_2), 2.75 (1 H, d, J 16, bridge C*H*H), 3.38 (1 H, d, J 18, acetate C*H*H), 3.46 (1 H, d, J 17, acetate C*H*H), 3.52 (3 H, s, OCH_3), 3.58 (1 H, d, J 16, bridge CH*H*), 3.63, 3.63 and 3.78 (each 3 H, each s, 3 × OCH_3), 3.80 (1 H, d, J 18, acetate CH*H*), 3.63, 3.63 and 3.78 (each 3 H, each s, 3 × OCH_3), 3.80 (1 H, d, J 18, acetate CH*H*), 3.83 (1 H, d, J 17, acetate CH*H*), 5.19 (1 H, d, J 12, C*H*HPh), 5.24 (1 H, d, J 12, CH*H*Ph), 7.26–7.38 (5 H, aromatic CH), 9.91 (1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 19.6 and 20.7 (2 × $CH_2CH_2CO_2$), 19.9 (CCH_3), 30.0, 30.3, 30.7 and 34.9 (4 × CH_2CO_2 + bridge CH_2), 51.6, 51.8, 51.8 and 53.5 (4 × OCH_3), 65.7 (CH_2Ph), 67.8 (CCH_3), 119.6, 122.7, 122.9, 125.9, 134.6, 136.1 and 154.1 (6 × C=C + ipso C), 128.0, 128.3 and 128.3 (aromatic CH) 160.2 (CO_2Bn), 166.7, 170.6, 172.0, 173.3 and 173.4 (4 × CO_2CH_3 + CON); m/z (+FAB) 656, (MH$^+$, 3%), 626 (MH − NO$^+$, 55), 372 ($C_{20}H_{22}NO_6^+$, 65), 307 (100).

Benzyl 2,8-bis(2-methoxycarbonylethyl)-3,7-bis(methoxycarbonylmethyl)-1-hydroxy-4-methyl-10-nitroso-1,4,5,10-tetrahydrodipyrrin-9-carboxylate 20

To a solution of the *N*-nitroso lactam **18** (23 mg, 0.035 mmol) in anhydrous THF (1 cm^3) at −78 °C under argon was added dropwise a solution of $LiEt_3BH$ in THF (35 mm^3, 0.035 mmol; 1.0 M). The solution was stirred at −78 °C for 2 h and then degassed saturated aqueous ammonium chloride (1 cm^3) was added and the reaction mixture was warmed to room temperature over 15 min. Ethyl acetate (10 cm^3) and degassed water (5 cm^3) were added, the phases were separated and the aqueous extracts re-extracted with dichloromethane (2 × 10 cm^3). The combined organic extracts were dried and evaporated to give the crude N-*nitrosocarbinolamine* **20** as a yellow oil (21 mg, ~90%) (Found: MH$^+$, 658.2603. $C_{32}H_{39}N_3O_{12}$ requires M + H, 658.2612); $\lambda_{max}(CH_2Cl_2)$/nm 277; $\nu_{max}(CHCl_3)$/cm^{-1} 3320, 2954, 1732, 1437, 1266, 1175, 1072; $\delta_H(CDCl_3$, 400 MHz) 1.76 (3 H, s, CCH_3), 2.37–2.52 (4 H, propionate CH_2), 2.84–3.43 (6 H, propionate CH_2 + acetate C*H*H + bridge C*H*H), 3.30 (2 H, s, acetate CH_2), 3.61, 3.63, 3.64 and 3.71 (each 3 H, each s, 4 × OCH_3 obscuring 2 H, acetate CH*H* + bridge CH*H*), 5.21 (1 H, d, J 12.5, C*H*HPh), 5.29 (1 H, d, J 12.5, CH*H*Ph), 5.91 (1 H, d, J 5, *CHOH*), 7.23–7.41 (5 H, aromatic CH), 10.41 (1 H, br s, NH); m/z (+FAB) 658, (MH$^+$, 1%), 610 (8), 307 (43), 154 (100).

2-[5-Benzyloxycarbonyl-4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethylpyrrol-2-ylmethyl]-4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethyl-2-methyl-2*H*-pyrrole 12

To a solution of the *N*-nitroso lactam **18** (49 mg, 0.075 mmol) in anhydrous THF (2 cm^3) at −78 °C under argon was added dropwise a solution of $LiEt_3BH$ in THF (90 mm^3, 0.090 mmol; 1.0 M). The solution was stirred at −78 °C for 30 min and then a solution of samarium(II) iodide in THF (1.57 cm^3, 0.157 mmol; 0.1 M) was added dropwise. After stirring for a further 30 min at −78 °C, degassed saturated aqueous ammonium chloride (1 cm^3) was added and the reaction mixture was allowed to warm to room temperature over 15 min. The mixture was shaken with ethyl acetate (10 cm^3) and degassed water (5 cm^3), the phases were separated, the aqueous extracts re-extracted with CH_2Cl_2 (2 × 10 cm^3) and the combined organic extracts dried and evaporated. The residue by preparative TLC using 7:3 ethyl acetate–hexane gave the *pyrrolenine* **12** as a pale brown oil (32 mg, 71%) (Found: M$^+$, 610.2535. $C_{32}H_{38}N_2O_{10}$ requires M, 610.2527); $\lambda_{max}(CH_2Cl_2)$/nm 278; $\nu_{max}(CHCl_3)$/cm^{-1} 3436, 3336, 2954, 1733, 1700, 1438, 1243, 1174, 1066, 909; $\delta_H(CDCl_3$, 400 MHz) 1.11 (3 H, s, CCH_3), 2.23 (1 H, d, J 15, bridge C*H*H), 2.45–2.62 (6 H, propionate CH_2), 2.91–3.02 (2 H, propionate CH_2), 3.10 (1 H, d, J 15, bridge CH*H*), 3.37 (1 H, d, J 17, acetate C*H*H), 3.38 (1 H, d, J 16, acetate C*H*H), 3.47 (1 H, d, J 17, acetate CH*H*), 3.48 (1 H, d, J 16, acetate CH*H*), 3.59, 3.63, 3.64 and 3.69 (each 3 H, each s, 4 × OCH_3), 5.23 (1 H, d, J 12, C*H*HPh), 5.32 (1 H, d, J 12, CH*H*Ph), 7.27–7.41 (5 H, aromatic CH), 7.94 (1 H, s, CH=N), 10.21 (1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 19.7 (CCH_3), 20.5 and 20.6 (2 × $CH_2CH_2CO_2$), 29.7, 31.2, 32.2, 32.7 and 34.8 (4 × CH_2CO_2 + bridge CH_2), 51.3, 51.7, 51.9 and 52.4 (4 × OCH_3), 65.5 (CH_2Ph), 83.3 (CCH_3), 115.3, 117.3, 129.7, 131.0, 136.4, 137.5 and 158.1 (6 × C=C + ipso C), 127.9, 128.1 and 128.5 (aromatic CH) 160.5 (CO_2Bn), 164.9 (CH=N), 170.1, 172.2, 172.8 and 173.7 (4 × CO_2CH_3); m/z (FD) 610 (M$^+$, 100%).

***tert*-Butyl 2,7-bis(2-methoxycarbonylethyl)-3,8-bis(methoxycarbonylmethyl)-10-nitroso-1,4,5,10-tetrahydro-1-oxodipyrrin-9-carboxylate 22**

To a solution of lactam **21**[34] (36mg, 0.06 mmol) in anhydrous CH_2Cl_2 (1 cm^3) was added fused sodium acetate (10.2 mg, 0.12 mmol) and the resulting suspension cooled to −20 °C under argon. A solution of dinitrogen tetroxide in CH_2Cl_2 (85 mm^3, 0.065 mmol; 0.77 M) was added dropwise. After 1 h at −78 °C, the solution was evaporated and the residue purified by preparative TLC eluting with 7:3 ethyl acetate–hexane to give the N-*nitroso lactam* **22** as a yellow oil (32.9 mg, 86%) (Found:

MH$^+$, 608.2477. $C_{28}H_{37}N_3O_{12}$ requires M + H, 608.2455); λ_{max}(CH_3CN)/nm 270, sh 250; ν_{max}(CH_2Cl_2)/cm^{-1} 3322, 2954, 1737, 1689, 1438, 1370, 1174; δ_H($CDCl_3$, 400 MHz), 1.49 [9 H, s, C(CH_3)$_3$], 2.30–2.37 (2 H, propionate CH_2), 2.46–2.49 (2 H, propionate CH_2), 2.59–2.70 (4 H, propionate CH_2), 2.98 (1 H, dd, J 15.5, 2.5, bridge, C*H*H), 3.26 (1 H, dd, J 15.5, 7.5, bridge CH*H*), 3.52 (2 H, s, acetate CH_2), 3.58 (1 H, d, J 17, acetate C*H*H), 3.61, 3.63, 3.64 and 3.75 (each 3 H, each s, 4 × OCH_3), 3.77 (1 H, d, J 17, acetate CH*H*), 4.95 (1 H, dd, J 7.5, 2.5, CHN), 9.37 (1 H, br s, NH); δ_C($CDCl_3$, 100 MHz) 18.8 and 19.4 (2 × $CH_2CH_2CO_2$), 25.2, 30.7, 30.7, 32.4 and 34.7 (4 × CH_2CO_2 + bridge CH_2), 28.3 [C(CH_3)$_3$], 51.6, 51.8, 51.8 and 53.1 (4 × OCH_3), 58.4 (CHN), 81.1 [C(CH_3)$_3$], 121.2, 121.4, 122.5, 124.6, 134.6 and 150.9 (6 × C=C), 160.2 (CO_2Bu^t), 166.7, 169.7, 171.9, 173.1 and 173.2 (4 × CO_2CH_3 + CON); m/z (+FAB) 608 (MH$^+$, 1%), 578 (7), *522 (20), 307 (100).*

***tert*-Butyl 2,7-bis(2-methoxycarbonylethyl)-3,8-bis(methoxycarbonylmethyl)-5,10-dihydrodipyrrin-9-carboxylate 25**

To a solution of the *N*-nitroso lactam **22** (10.5 mg, 0.017 mmol) in anhydrous THF (2 cm^3) at −78 °C under argon was added dropwise a solution of $LiEt_3BH$ in THF (20.7 mm^3, 0.021 mmol; 1.0 M). The solution was stirred at −78 °C for 10 min and then a solution of samarium(II) iodide in THF (346 mm^3, 0.035 mmol, 0.1 M) was added dropwise. After stirring for a further 1 h at −78 °C, degassed saturated aqueous ammonium chloride (1 cm^3) was added and the reaction mixture allowed to warm to room temperature over 15 min. The mixture was shaken with ethyl acetate (10 cm^3) and degassed water (5 cm^3), the phases were separated, the aqueous extracts re-extracted with CH_2Cl_2 (2 × 10 cm^3) and the combined organic extracts dried and evaporated. The residue was purified by preparative TLC eluting with 6:4 ethyl acetate–hexane to give the dipyrromethane[39] **25** (7.1 mg, 73%), mp 63–64.5 °C (diethyl ether–hexane), identified by NMR spectroscopy with the material prepared earlier[39] (Found: M$^+$, 562.2503. $C_{28}H_{38}N_2O_{10}$ requires M, 562.2526); λ_{max}(CH_3OH)/nm 281; ν_{max}(CH_2Cl_2)/cm^{-1} 3370, 1735, 1690; δ_H($CDCl_3$, 400 MHz) 1.49 [9 H, s, C(CH_3)$_3$], 2.53, 2.57, 2.73 and 2.78 (each 2 H, each t, J 8, 2 × $CH_2CH_2CO_2$), 3.50 (2 H, s, acetate CH_2), 3.63, 3.66, 3.67 and 3.75 (each 3 H, each s, 4 × OCH_3), 3.78 (2 H, s, acetate CH_2), 3.85 (2 H, s, bridge CH_2), 6.43 (1 H, d, J 2.5, α-H), 8.80 and 9.84 (each 1 H, each br s, 2 × NH); m/z (FD) 562 (M$^+$, 100%).

***tert*-Butyl 3-(1-hydroxyimino-1-methoxycarbonylmethyl)-2,7-bis(2-methoxycarbonylethyl)-8-methoxycarbonylmethyl-10-nitroso-1,4,5,10-tetrahydro-1-oxodipyrrin-9-carboxylate 23**

To a solution of lactam **21**[34] (75 mg, 0.13 mmol) in anhydrous CH_2Cl_2 (4 cm^3) was added pyridine (21 mm^3, 0.26 mmol) and the resulting solution cooled to −20 °C under argon. A solution of dinitrogen tetroxide in CH_2Cl_2 (202 mm^3, 0.15 mmol; 0.77 M) was added dropwise. After 2 h at −20 °C, the solution was evaporated and the residue purified by preparative TLC eluting with 7:3 ethyl acetate–hexane to give the following compounds.

Oxime 23a. A single, but undetermined, stereoisomer (higher R_f) in admixture with *N*-nitroso lactam **22** as a yellow oil [10 mg, ratio ~1:2, (**23a**:**22**) by ^{1}H NMR]; δ_H($CDCl_3$, 400 MHz) (diagnostic resonances for **23a**) 1.49 [9 H, s, C(CH_3)$_3$], 3.52, 3.67, 3.72 and 3.94 (each 3 H, each s, 4 × OCH_3), 5.15 (1 H, dd, J 8, 3, CHN), 8.89 (1 H, br s, NH); m/z (electrospray) 659 (MNa$^+$, 100%).

Oxime 23b. A single, but undetermined stereoisomer (lower R_f) (28.2 mg, 36%) as a yellow oil (Found: MH$^+$, 637.2333. $C_{28}H_{36}N_4O_{13}$ requires M + H, 637.2357); λ_{max}(CH_3CN)/nm 272, sh 250; ν_{max}(CH_2Cl_2)/cm^{-1} 3325, 1736, 1688, 1438, 1339, 1280, 1174, 1029, 909; δ_H($CDCl_3$, 400 MHz) 1.47 [9 H, s, C(CH_3)$_3$], 2.32–2.69 (8 H, propionate CH_2), 3.02 (1 H, d, J 15, bridge C*H*H), 3.14 (1 H, dd, J 15, 8, bridge CH*H*), 3.55 (1 H, d, J 17, acetate C*H*H), 3.61, 3.63, 3.67 and 3.85 (each 3 H, each s, 4 × OCH_3), 3.81 (1 H, d, J 17, acetate CH*H*), 5.41 (1 H, d, J 8, CHN), 9.63 (1 H, br s, NH); δ_C($CDCl_3$, 100 MHz) 18.9 and 21.6 (2 × $CH_2CH_2CO_2$), 26.0, 30.1, 30.6 and 34.8 (3 × CH_2CO_2 + bridge CH_2), 28.3 [C(CH_3)$_3$], 51.7, 51.8, 52.0 and 53.4 (4 × OCH_3), 57.4 (CHN), 81.5 [C(CH_3)$_3$], 120.9, 121.3, 123.0, 125.1, 137.6, 142.4 and 144.7 (6 × C=C + C=NOH), 160.9 (CO_2Bu^t), 162.3, 166.3, 172.6, 172.6 and 173.3 (4 × CO_2CH_3 + CON); m/z (+FAB) 637 (MH$^+$, 37%), 613 (100).

Lactam 21.[34] (37.4 mg, 50%).

***tert*-Butyl 3-(1-hydroxyimino-1-methoxycarbonylmethyl)-2,7-bis(2-methoxycarbonylethyl)-8-methoxycarbonylmethyl-5,10-dihydrodipyrrin-9-carboxylate 26**

To a solution of the oxime **23a** (10 mg, 0.016 mmol) in anhydrous THF (1 cm^3) at −78 °C under argon was added dropwise a solution of $LiEt_3BH$ in THF (20 mm^3, 0.020 mmol; 1.0 M) dropwise. The solution was stirred at −78 °C for 30 min and then a solution of samarium(II) iodide in THF (330 mm^3, 0.033 mmol; 0.1 M) was added dropwise. After stirring for a further 1 h at −78 °C, degassed saturated aqueous ammonium chloride (1 cm^3) was added and the reaction mixture allowed to warm to room temperature over 15 min. The mixture was shaken with ethyl acetate (10 cm^3) and degassed water (5 cm^3), the phases were separated, the aqueous solution was re-extracted with CH_2Cl_2 (2 × 10 cm^3) and the combined organic extracts were dried and evaporated. Purification of the residue by preparative TLC using 7:3 ethyl acetate–hexane gave the *dipyrromethane* **26** (a single, but undetermined stereoisomer) as a pale yellow oil (2.7 mg, 29%) (Found: MH$^+$, 592.2485. $C_{28}H_{37}N_3O_{11}$ requires M + H, 592.2506); λ_{max}(CH_3CN)/nm 278 nm; ν_{max}(CH_2Cl_2)/cm^{-1} 3685, 3367, 2954, 1732, 1687, 1437, 1368, 1173; δ_H($CDCl_3$, 400 MHz) 1.48 [9 H, s, C(CH_3)$_3$], 2.51, 2.57, 2.65 and 2.74 (each 2 H, each t, J 8, 2 × $CH_2CH_2CO_2$), 3.63, 3.64, 3.64 and 3.66 (each 3 H, each s, 4 × OCH_3), 3.75 (2 H, s, acetate CH_2), 3.91 (2 H, s, bridge CH_2), 6.56 (1 H, d, J 2.5, α-H), 9.14 and 9.53 (each 1 H, each br s, 2 × NH); m/z (+FAB) 592 (MH$^+$, 45%), 574 (40), 536 (70), 518 (90), 267 (100).

***tert*-Butyl 3,8-bis(2-methoxycarbonylethyl)2,7-bis(methoxycarbonylmethyl)-10-nitroso-1,4,5,10-tetrahydro-1-oxodipyrrin-9-carboxylate 28**

To a solution of lactam **27**[34] (8 mg, 0.14 mmol) in anhydrous CH_2Cl_2 (3 cm^3) was added fused sodium acetate (23 mg, 0.28 mmol) and the resulting suspension cooled to −20 °C under argon. A solution of dinitrogen tetroxide in CH_2Cl_2 (189 mm^3, 0.14 mmol; 0.77 M) was added dropwise. After 1 h at this temperature the solution was evaporated and the residue purified by preparative TLC eluting with 7:3 ethyl acetate–hexane to give the N-*nitroso lactam* **28** as a yellow oil (68.1 mg, 81%) (Found: M$^+$, 607.2407. $C_{28}H_{37}N_3O_{12}$ requires M, 607.2377); λ_{max}(CH_3CN)/nm 269sh, 250; ν_{max}(CH_2Cl_2)/cm^{-1} 3427, 2954, 1737, 1697, 1437, 1369, 1170; δ_H($CDCl_3$, 400 MHz) 1.54 [9 H, s, C(CH_3)$_3$], 2.40–2.51 (4 H, 2 × $CH_2CH_2CO_2$), 2.84–2.93 (4 H, 2 × $CH_2CH_2CO_2$), 3.01 (1 H, dd, J 15.5, 7, bridge C*H*H), 3.12 (1 H, dd, J 15.5, 3, bridge CH*H*), 3.37 (1 H, d, J 16.5, acetate C*H*H), 3.42 (1 H, d, J 16.5, acetate CH*H*), 3.47 (2 H, s, acetate CH_2), 3.63, 3.65, 3.66 and 3.73 (each 3 H, each s, 4 × OCH_3), 4.96 (1 H, dd, J 7, 3, CHN), 8.83 (1 H, br s, NH); δ_C($CDCl_3$, 100 MHz) 20.6 and 22.5 (2 × $CH_2CH_2CO_2$), 26.8, 28.4, 29.5, 30.9 and 34.8 (4 × CH_2CO_2 + bridge CH_2), 28.3 [C(CH_3)$_3$], 51.4, 51.9, 52.1 and 52.6 (4 × OCH_3), 57.8 (CHN), 81.2 [C(CH_3)$_3$], 116.1, 120.4, 126.3, 126.6, 128.9 and 160.2 (6 × C=C), 161.0 (CO_2Bu^t), 166.8, 169.4, 172.2, 172.2 and 173.5 (4 × CO_2CH_3 + CON); m/z (+FAB) 607 (M$^+$, 3%), 578 (10), 522 (10), 282 (100).

***tert*-Butyl 3,8-bis(2-methoxycarbonylethyl)-2,7-bis(methoxycarbonylmethyl)-5,10-dihydrodipyrrin-9-carboxylate 31 and *tert*-butyl 3,8-bis(2-methoxycarbonylethyl)-2,7-bis(methoxycarbonylmethyl)-1,2,3,4,5,10-hexahydro-1-oxodipyrrin-9-carboxylate 32**

To a solution of the *N*-nitroso lactam **28** (20.4 mg, 0.034 mmol) in anhydrous THF (2 cm^3) at −78 °C under argon was added dropwise a solution of $LiEt_3BH$ in THF (42.0 mm^3, 0.04 mmol; 1.0 M). The solution was stirred at −78 °C for 1 h and then a solution of samarium(II) iodide in THF (672 mm^3, 0.067 mmol; 0.1 M) was added dropwise. After stirring for a further 10 min at −78 °C, degassed saturated aqueous ammonium chloride (1 cm^3) was added and the reaction mixture allowed to warm to room temperature over 15 min. The mixture was shaken with ethyl acetate (10 cm^3) and degassed water (5 cm^3), the phases were separated, the aqueous extracts re-extracted with CH_2Cl_2 (2 × 10 cm^3) and the combined organic extracts dried and evaporated. The residue was purified by preparative TLC eluting with 7:3 ethyl acetate–hexane to give the following compounds.

Dipyrromethane 31. Prepared earlier[40] as an intermediate, pale yellow oil (4.5 mg, 24%) (Found: MH^+, 563.2554. $C_{28}H_{38}N_2O_{10}$ requires *M* + H, 563.2604); $\lambda_{max}(CH_3CN)$/nm 277; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3342, 2954, 1732, 1685, 1437, 1368, 1353, 1171; $\delta_H(CDCl_3$, 400 MHz) 1.51 [9 H, s, $C(CH_3)_3$], 2.48, 2.60, 2.80 and 2.94 (each 2 H, each t, *J* 8, 2 × $CH_2CH_2CO_2$), 3.42 (2 H, s, acetate CH_2), 3.54 (2 H, s, acetate CH_2), 3.65, 3.67, 3.71 and 3.74 (each 3 H, each s, 4 × OCH_3), 3.86 (2 H, s, bridge CH_2), 6.57 (1 H, d, *J* 2, α-H), 9.27 and 9.55 (each 1 H, each br s, 2 × NH); $\delta_C(CDCl_3$, 100 MHz) 19.0 and 20.8 (2 × CH_2-CH_2CO_2), 22.2, 29.4, 31.5, 34.7 and 35.2 (4 × CH_2CO_2 + bridge CH_2), 28.4 [$C(CH_3)_3$], 51.5, 51.9, 52.0 and 52.5 (4 × OCH_3), 80.6 [$C(CH_3)_3$], 113.5, 113.7, 115.8, 119.8, 126.0, 127.9 and 132.4 (7 × *C*=*C*), 116.4 (α-CH), 160.6 (CO_2Bu^t), 172.9, 173.7, 174.6 and 174.7 (4 × CO_2CH_3); *m*/*z* (FD) 562 (M^+, 100%).

Lactam 32. A single isomer, of undetermined relative stereochemistry, as a colourless oil (12.3 mg, 63%) (Found: MH^+, 581.2750. $C_{28}H_{40}N_2O_{11}$ requires *M* + H, 581.2710); $\lambda_{max}(CH_3CN)$/nm 276; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3680, 3289, 2953, 1735, 1698, 1437, 1370, 1171; $\delta_H(CDCl_3$, 400 MHz) 1.38 [9 H, s, $C(CH_3)_3$], 1.90 (1 H, m, $CHCHCH_2$), 2.30–2.55 (8 H), 2.72–2.82 (4 H), 2.94 (1 H, m, $COCH$), 3.32 (1 H, d, *J* 15, acetate CHH), 3.44 (1 H, d, *J* 15, acetate CHH), 3.63, 3.64, 3.69 and 3.69 (each 3 H, each s, 4 × OCH_3), 3.71 (1 H, m, CHN), 7.54 (1 H, br s, CONH), 10.93 (1 H, br s, pyrrole NH); $\delta_C(CDCl_3$, 100 MHz) 20.9 and 23.2 (2 × $CH_2CH_2CO_2$), 26.4, 30.1, 32.1, 33.0 and 35.3 (4 × CH_2CO_2 + bridge CH_2), 28.3 [$C(CH_3)_3$], 41.2 ($COCHCH_2$), 44.4 ($NCHCHCH_2$), 51.4, 51.7, 51.8 and 52.0 (4 × OCH_3), 53.8 (CHN), 80.7 [$C(CH_3)_3$], 113.6, 119.4, 128.4 and 131.2 (4 × *C*=*C*), 161.3 (CO_2Bu^t), 172.5, 172.6, 173.3, 173.7 and 178.2 (4 × CO_2CH_3 + CON); *m*/*z* (electrospray) 603 (MNa^+, 40%), 581 (MH^+, 100).

***tert*-Butyl 3,8-bis(2-methoxycarbonylethyl)-2,7- bis(methoxycarbonylmethyl)-1-hydroxy-10-nitroso-1,4,5,10-tetrahydrodipyrrin-9-carboxylate 29 and *tert*-butyl 3,8-bis(2-methoxycarbonylethyl)-2,7-bis(methoxycarbonylmethyl)-10-nitroso-1,2,3,4,5,10-hexahydro-1-oxodipyrrin-9-carboxylate 30**

To a solution of the *N*-nitroso lactam **28** (11.5 mg, 0.018 mmol) in anhydrous THF (2 cm^3) at −78 °C under argon was added dropwise a solution of $LiEt_3BH$ in THF (22.7 mm^3, 0.023 mmol; 1.0 M) and stirring was continued at −78 °C for 15 min. Degassed saturated aqueous ammonium chloride (1 cm^3) was added, the mixture was allowed to warm to room temperature over 15 min and then shaken with ethyl acetate (10 cm^3) and degassed water (5 cm^3). The phases were separated, the aqueous extracts re-extracted with CH_2Cl_2 (2 × 10 cm^3) and the combined organic extracts dried and evaporated to give the mixture of N-*nitroso carbinolamine* **29** and N-*nitroso lactam* **30** as a yellow oil (10.6 mg, ~90%). ^1H NMR of this crude mixture indicated a ratio of ~1:3 (**29**:**30**) by integration of the H-4 resonances. This mixture was purified by preparative TLC eluting with 7:3 ethyl acetate–hexane to give the following compounds.

***N*-Nitroso carbinolamine 29.** A single isomer, of undetermined relative stereochemistry, as a yellow oil (1.4 mg, 12%) [Found: $C_{28}H_{37}N_2O_{10}^+$, 561.2472. $C_{28}H_{39}N_3O_{12}$ requires $M - (NH_2O_2)^+$, 561.2448]; $\delta_H(CDCl_3$, 400 MHz) diagnostic resonances: 1.52 [9 H, s, $C(CH_3)_3$], 4.99 (1 H, d, *J* 4, CHN), 6.47 (1 H, d, *J* 9.5, $NCHOH$), 8.77 (1 H, br s, NH); *m*/*z* (+FAB) 562 [$MH - (NH_2O_2)^+$, 38%], 507 (58), 369 (81), 282 (100).

***N*-Nitroso lactam 30.** A single isomer, of undetermined relative stereochemistry, as a yellow oil (6.1 mg, 53%) (Found: M^+, 609.2493. $C_{28}H_{39}N_3O_{12}$ requires *M*, 609.2533); $\lambda_{max}(CH_3$-$CN)$/nm 275, sh 250; $\nu_{max}(CHCl_3)/cm^{-1}$ 3436, 2954, 1733, 1682, 1438, 1369, 1273, 1168; $\delta_H(CDCl_3$, 400 MHz) 1.53 [9 H, s, $C(CH_3)_3$], 2.11 (2 H, m), 2.30 (2 H, m), 2.47–2.59 (4 H), 2.80–3.04 (6 H), 3.44 (1 H, d, *J* 16, acetate CHH), 3.55 (1 H, d, *J* 16, acetate CHH), 3.60, 3.62, 3.65 and 3.70 (each 3 H, each s, 4 × OCH_3), 3.77 (1 H, dd, *J* 7, 6.5, CHN), 8.99 (1 H, br s, NH); $\delta_C(CDCl_3$, 100 MHz) 20.6 and 22.4 (2 × $CH_2CH_2CO_2$), 24.6, 29.8, 30.8, 31.4 and 34.9 (4 × CH_2CO_2 + bridge CH_2), 28.4 [$C(CH_3)_3$], 40.7 ($COCHCH_2$), 42.3 ($NCHCHCH_2$), 51.5, 51.6, 52.2 and 52.3 (4 × OCH_3), 53.8 (CHN), 81.2 [$C(CH_3)_3$], 115.3, 120.0, 128.0 and 129.2 (4 × *C*=*C*), 160.4 (CO_2 Bu^t 171.3, 172.3, 172.8, 172.9 and 173.6 (4 × CO_2CH_3 + CON); *m*/*z* (+FAB) 609, (M^+, 11%), 339 (50), 282 (90), 242 (100).

***tert*-Butyl 2,7-bis(2-methoxycarbonylethyl)-3,8-bis(methoxycarbonylmethyl)-1-hydroxy-10-nitroso-1,4,5,10-tetrahydrodipyrrin-9-carboxylate 24**

To a solution of the *N*-nitroso lactam **22** (10.5 mg, 0.017 mmol) in anhydrous THF (2 cm^3) at −78 °C under argon was added dropwise a solution of $LiEt_3BH$ in THF (20.7 mm^3, 0.027 mmol; 1.0 M). The rest of the experiment was as for the reduction of **28** to give the crude N-*nitroso carbinolamine* **24** (a single isomer of undetermined relative stereochemistry) as a yellow oil (10.1 mg, ~90%) [Found: $C_{28}H_{37}N_2O_{10}^+$, 561.2400. $C_{28}H_{39}N_3O_{12}$ requires $M - (NH_2O_2)^+$, 561.2448]; $\delta_H(CDCl_3$, 400 MHz) diagnostic resonances: 1.51 [9 H, s, $C(CH_3)_3$], 3.61, 2.64, 3.66 and 3.80 (each 3 H, each s, 4 × OCH_3), 4.98 (1 H, d, *J* 5, CHN), 6.29 (1 H, d, *J* 11.5, $NCHOH$), 10.18 (1 H, br s, NH); *m*/*z* (electrospray) 632 (MNa^+, 40%), 562 [$MH + (NH_2O_2)^+$, 100].

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References

1 W. M. Stark, G. J. Hart and A. R. Battersby, *J. Chem. Soc., Chem. Commun.*, 1986, 465; W. M. Stark, C. J. Hawker, G. J. Hart, A. Philippides, P. M. Petersen, J. D. Lewis, F. J. Leeper and A. R. Battersby, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2875.
2 M. A. Cassidy, N. Crockett, F. J. Leeper and A. R. Battersby, *J. Chem. Soc., Chem. Commun.*, 1991, 384; M. A. Cassidy, N. Crockett, F. J. Leeper and A. R. Battersby, *J. Chem Soc., Perkin Trans. 1*, 1996, 2079; A. C. Spivey, A. Capretta, C. S. Frampton, F. J. Leeper and A. R. Battersby, *J. Chem. Soc., Chem. Commun.*, 1995, 1789; A. C. Spivey, A. Capretta, C. S. Frampton, F. J. Leeper and A. R. Battersby, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2091.
3 F. J. Leeper and A. R. Battersby, *Chem. Rev.*, 1990, **90**, 1261; F. J. Leeper, *Nat. Prod. Rep.*, 1989, **6**, 171.
4 R. C. Larock, *Comprehensive Organic Transformations*, VCH, New York, 1989, pp. 432–434.
5 S. Dayagi and Y. Degani, in *The Chemistry of the Carbon-Nitrogen Double Bond*, ed. S. Patai, Wiley Interscience, New York, 1970; R. W. Layer, *Chem. Rev.*, 1963, **63**, 489; S. Pawlenko, in *Houben-Weyl:*

Methoden der Organischen Chemie, vol. E14b, ed. D. Klamann and H. Hagemann, Georg Thieme Verlag, Stuttgart, 1990.
6 P. G. M. Wuts, J. E. Cabaj and J. L. Havens, *J. Org. Chem.*, 1994, **59**, 6470 and references cited therein.
7 K. A. Jorgensen, R. Shabann, S. Scheibye and S.-O. Lawesson, *Bull. Soc. Chim. Belg.*, 1980, **84**, 247.
8 A. Nishinaga, S. Yamazaki and T. Matsuura, *Tetrahedron Lett.*, 1988, **29**, 4115.
9 J. J. Cornejo, K. D. Larson and G. D. Mandenhall, *J. Org. Chem.*, 1985, **50**, 5382.
10 M. F. Grundon and B. E. Reynolds, *J. Chem. Soc.*, 1964, 2445.
11 D. Keirs and K. Overton, *J. Chem. Soc.*, 1987, 1660; Y. Jinbo, H. Kondo, M. Taguchi, F. Sakamoto and G. Tsukamoto, *J. Org. Chem.*, 1994, **59**, 6057.
12 A. Goti and M. Romani, *Tetrahedron Lett.*, 1994, **35**, 6567.
13 S.-I. Murahashi, *Pure Appl. Chem.*, 1992, **64**, 403; S.-I. Murahashi, T. Naota and H. Taki, *J. Chem. Soc., Chem. Commun.*, 1985, 613.
14 P. Muller and D. M. Gilabert, *Tetrahedron*, 1988, **44**, 7171.
15 J. P. Marino and R. D. Larsen, Jr., *J. Am. Chem. Soc.*, 1981, **103**, 4045.
16 A. R. Battersby, H. A. Broadbent and C. J. R. Fookes, *J. Chem. Soc., Chem. Commun.*, 1983, 1240; A. R. Battersby, M. G. Baker, H. A. Broadbent, C. J. R. Fookes and F. J. Leeper, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2027.
17 B. Hardegger, PhD thesis No. 5347, ETH, Zurich, *Untersuchungen in der Corrin-Reihe und Eine Neue Methode zur Reduktion der Lactam-Gruppe*, 1974; A. Pfaltz, B. Hardegger, P. M. Muller, S. Farooq, B. Krautler and A. Eschenmoser, *Helv. Chim. Acta*, 1975, **58**, 1444; A. Eschenmoser, *Chem. Soc. Rev.*, 1976, **5**, 377; V. Rasetti, A. Pfaltz, C. Kratky and A. Eschenmoser, *Proc. Natl. Acad. Sci., USA*, 1981, **78**, 16.
18 D. J. A. Schedler, A. G. Godfrey and B. Ganem, *Tetrahedron Lett.*, 1993, **34**, 5035.
19 See for example: C. J. Hawker, W. M. Stark and A. R. Battersby, *J. Chem. Soc., Chem. Commun.*, 1987, 1313.
20 W. M. Stark, C. J. Hawker, P. M. Petersen, A. C. Spivey, F. J. Leeper and A. R. Battersby, unpublished results.
21 T. J. Lobl, *J. Chem. Ed.*, 1972, **49**, 730; J. E. Saavadra, *J. Org. Chem.*, 1979, **44**, 860; S. Paik and E. H. White, *Tetrahedron Lett.*, 1994, **35**, 7731; J. Garcia and J. Vilarrasa, *Tetrahedron Lett.*, 1982, **23**, 1127; J. Garcia, J. Gonzalez, R. Segura and J. Vilarrasa, *Tetrahedron*, 1984, **40**, 3121.
22 W. Flitsch and S. R. Schindler, *Synthesis*, 1975, 685; M. Natsume, M. Takahashi and H. Sugaya, *Chem. Pharm. Bull.*, 1971, **19**, 2648; J. E. Baldwin, A. J. Edwards, C. N. Farthing and A. T. Russell, *Synlett*, 1993, 49.
23 Y. Ohfune and M. Tomiata, *J. Am. Chem. Soc.*, 1982, **104**, 3511; D. L. Flynn, R. E. Zelle and P. A. Greico, *J. Org. Chem.*, 1983, **48**, 2424; T. Nagasaka, H. Tamano and F. Hamaguchi, *Heterocycles*, 1986, **24**, 1231; M. D. Kaufman and P. A. Greico, *J. Org. Chem.*, 1994, **59**, 7197.
24 N. Langlois and A. Rojas, *Tetrahedron Lett.*, 1993, **34**, 2477.
25 C. Pedregal, J. Ezquerra, A. Escribano, M. C. Carreno and J. L. G. Ruano, *Tetrahedron Lett.*, 1994, **35**, 2053 and references cited therein.
26 A. S. Kende and J. S. Mendosza, *Tetrahedron Lett.*, 1991, **32**, 1699.
27 W. M. Stark, C. J. Hawker, G. J. Hart, A. Philippides, P. M. Petersen, J. D. Lewis, F. J. Leeper and A. R. Battersby, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2875.
28 D. L. H. Williams, *Nitrosation*, Cambridge University Press, 1988.
29 G. A. Olah and J. A. Olah, *J. Org. Chem.*, 1965, **30**, 2386.
30 J. M. Simpson, *Synthesis*, 1979, 100.
31 R. Weiss and K.-G. Wagner, *Chem. Ber.*, 1984, **117**, 1973.
32 E. H. White, *J. Am. Chem. Soc.*, 1955, **77**, 6008.
33 A. R. Battersby, C. J. R. Fookes, K. E. Gustafson-Potter, E. McDonald and G. W. J. Matcham, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2427.
34 D. H. Williams, PhD Thesis, *The Synthesis of Chirally Deuterated Dipyrromethanes*, Cambridge, 1992.
35 F. J. Leeper, in *The Biosynthesis of Tetrapyrrole Pigments*, Ciba Foundation Symposium 180, Wiley, Chichester, 1994, p. 111.
36 L. Crombie and L. J. Rainbow, *J. Chem. Soc., Perkin Trans. 1*, 1994, 673.
37 G. M. Sheldrick, *Acta Crystallogr., Sect. A*, 1990, **46**, 467.
38 G. M. Sheldrick, SHELXL-93, University of Göttingen, Germany, 1993.
39 A. R. Battersby, C. J. R. Fookes, K. E. Gustafson-Potter, E. McDonald and G. W. J. Matcham, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2413.
40 A. R. Battersby, S. Kishimoto, E. McDonald, F. Satoh and H. K. W. Wurziger, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1927.

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