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Synthetic Studies on the Ceveratrum Alkaloid Skeleton

Keith Jones [a]*, Roger F. Newton [b] and Christopher J. Yarnold [a]

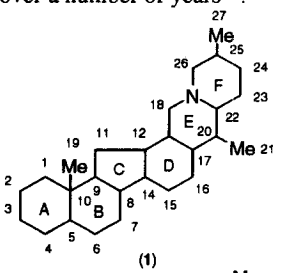
[a] Department of Chemistry, King's College London, Strand, London WC2R 2LS U.K.

[b] Glaxo Wellcome, Gunnels Wood Road, Stevenage, Herts SG1 2NY UK.

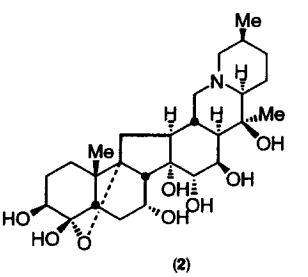
Abstract: 1-(2-Cyclohexenyl-1-carbonyl)-piperidine-2-carboxaldehyde oxime (**23**) was prepared in 5 steps from pyridine-2-carboxaldehyde. Oxidation with NaOCl afforded the corresponding nitrile oxide which cyclized to give a 1:1 ratio of diastereomers 2aα,3,4,5,5aα,9,10,11aβ,11cα-decahydro-6H,8H-[1,2] benzisoxazolo [3,4-ab] quinolizin-6-one (**24A**) and 2aα,3,4,5,5aα,9,10,11aα,11cα-decahydro-6H,8H-[1,2] benzisoxazolo [3,4-ab] quinolizin-6-one (**24B**) in a best yield of 30%.

The *ceveratrum* alkaloids are one of the two groups of alkaloids isolated from species of *veratrum*[1,2]. They possess the C-nor-D-homosteroid based cevanine skeleton (**1**)[3,4] typically adorned with up to 9 oxygen atoms, which in the natural products are acylated by a variety of carboxylic acids[3,4,5]. Germine (**2**) is one of the parent alkamines of this class of natural products[3,4] and was first isolated in 1937[6]. The structure and stereochemistry of germine was determined in a classic piece of work by Kupchan[7].

Little synthetic work on either the *ceveratrum* or *jeveratrum* alkaloids has been published. The only total synthesis in this area was reported by Kutney who completed the synthesis of verticine (**3**) from the naturally occurring hecogenin (**4**)[8,9]. Other early work in the area has been reviewed[1]. Recent work has included a Diels-Alder approach to the ABC rings of this class[10]. The Stork group has been involved in an approach to germine over a number of years[11].



(1)



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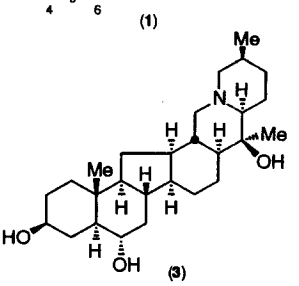

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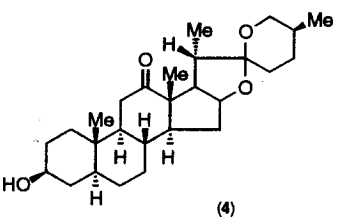

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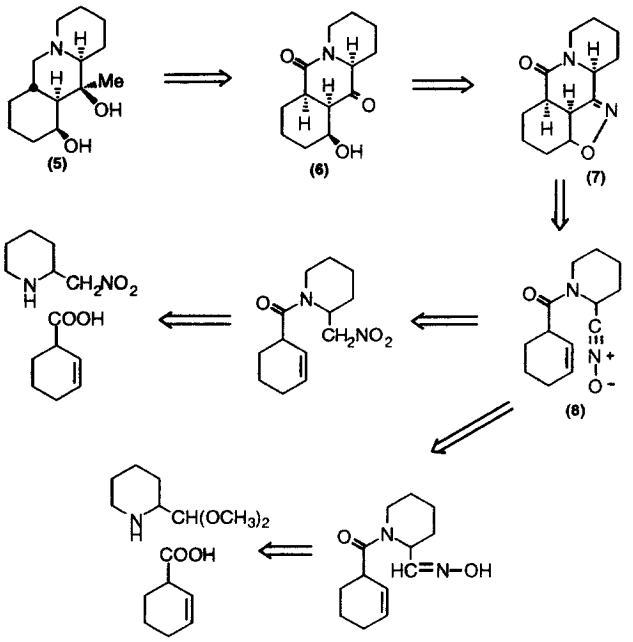
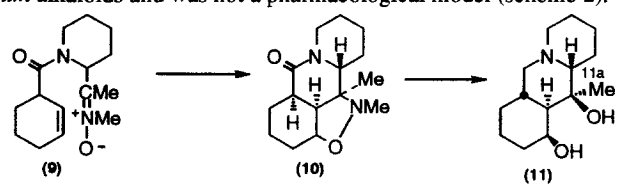
We now wish to report our work on an approach to the DEF ring system of germine (**3**) using an intramolecular nitrile oxide cycloaddition (INOC) as a key step in the route[12]. Our retrosynthetic analysis is shown in scheme 1. The target diol (**5**) can be seen as arising from the ketoamide (**6**) by addition of an

organometallic derivative to the ketone group. The amide carbonyl is present to allow stereocontrol at the ring junction via equilibration. Ketoamide (**6**) can be derived from isoxazoline (**7**) which is the product of an INOC reaction of (**8**).



Scheme 1

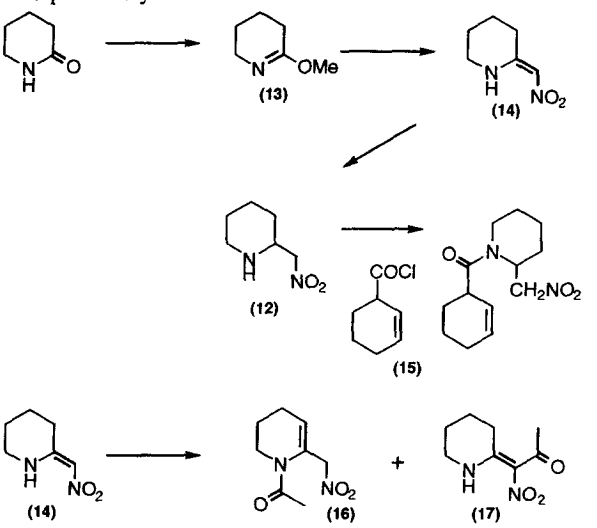
An important contribution to this area has been made by the Schering group who utilised an intramolecular nitrone cycloaddition of (**9**) to give (**10**) which was transformed to (**11**) via a series of reactions[13,14]. Unfortunately the stereochemistry at C-11a of diol (**11**) was epimeric to the corresponding carbon of the *ceveratrum* alkaloids and was not a pharmacological model (scheme 2).



Scheme 2

We chose to begin by investigating the preparation of the nitrile oxide cycloaddition substrate *via* the nitromethyl piperidine (**12**). Thus δ-valerolactam was treated with dimethyl sulphate in benzene to give imidate (**13**) in 39% yield (scheme 3). Imidate (**13**) was immediately reacted with neat nitromethane at reflux to generate the nitro-olefin (**14**) in 49% yield[15]. X-Ray studies have shown the nitro group to be *cis* to the ring nitrogen[16]. Reduction of (**14**) using sodium borohydride in methanol gave a white solid as a crude product (**12**) which was water soluble. Further purification of this very polar material was impossible. The acid chloride (**15**) required for the acylation of (**12**) was prepared from 2-cyclohexene-1-carboxylic acid[17] by refluxing the acid with oxalyl chloride in toluene. Attempted acylation of (**12**) with acid chloride (**15**) failed under a variety of reaction conditions. Consequently, attention was turned to acylation at the nitroenamine stage i.e. (**14**). In such systems there are two sites at which acylation can occur[15], the nitrogen or carbon α to the nitro group. Reaction of (**14**) with acetyl chloride was used as a model for the reaction with (**15**).

Addition of acetyl chloride to (**12**) in the presence of base resulted in a low yielding reaction with two acylated products isolated. N-Acetylation occurred with migration of the double bond to give (**16**) in 4% yield. The C-acylated product (**17**) was obtained in 10% yield. This preference for C-acylation in a nitroenamine has been noted previously[18].

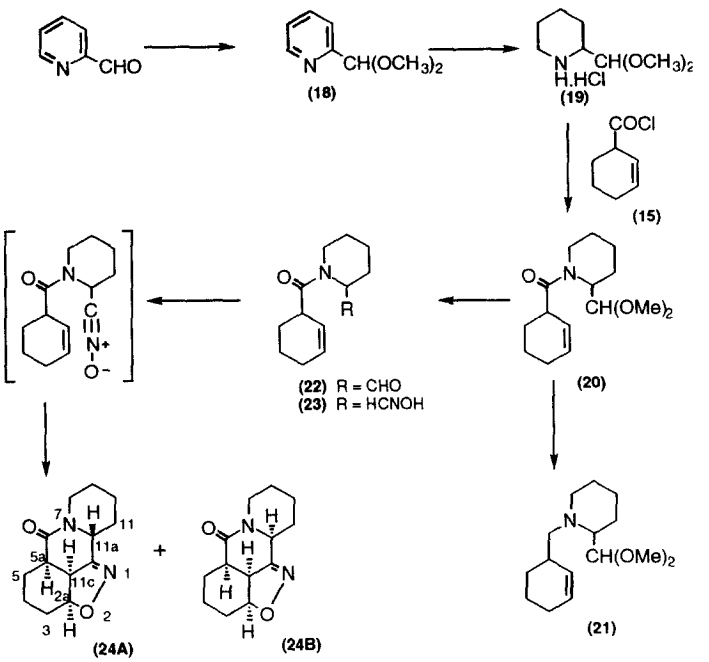


Scheme 3

Owing to our inability to prepare the required N-acylated nitropiperidine, we turned our attention to preparing the INOC cyclisation substrate via the aldoxime route[12,28]. Reaction of pyridine-2-carboxaldehyde with trimethyl orthoformate and methanol gave (**18**) in 37% yield after purification by distillation (scheme 4). The aldehyde was protected to avoid possible reduction to alcohol or formation of other undesired byproducts. Hydrogenation of (**18**) using Adam's catalyst and hydrogen (Parr apparatus, 60 p.s.i.) gave the hydrochloride salt (**19**) in 81% yield. Condensation of pyridine acetal (**19**) and 2-cyclohexene-1-carbonyl chloride (**15**) proceeded smoothly in the presence of two equivalents of Hünig's base (diisopropylethylamine) in dichloromethane to give 1-(2-cyclohexene-1-carbonyl)-2-(1,1-dimethoxymethyl)-piperidine (**20**) in 94% yield. The ^{13}C NMR spectrum revealed that, as expected, (**20**) was a mixture of diastereoisomers. The ^{1}H NMR spectrum also displayed evidence of restricted rotation in the form of peak-broadening. The diastereomers could be separated by column chromatography and were obtained in a 1:1 ratio by weight. All further reactions of amide (**20**) were performed on the diastereomeric mixture. In order to confirm the structure of amide (**20**) reduction to the amine (**21**) was carried out in 93% yield using $LiAlH_4$ in ether[19]. The ^{1}H NMR spectrum of this material was readily assignable.

Deprotection of the acetal in (**20**) proved somewhat troublesome as expected for an acetal with an adjacent electron-withdrawing group. Finally a modification of a Conia procedure[20] using HCl and silica gel gave aldehyde (**22**) in 82% yield. This rather unstable aldehyde was not purified but reacted with hydroxylamine hydrochloride[21] in pyridine to give aldoxime (**23**) in 55% yield (from amide acetal (**20**)) after chromatography. The ^{1}H NMR spectrum of (**23**) is complicated by restricted rotation (the amide), the presence of diastereomers (chiral centres) and the presence of *syn* and *anti* isomers (the aldoxime).

Aldoxime (**23**) was dissolved in dichloromethane and the vigorously stirred solution treated with aqueous sodium hypochlorite. Two new products were isolated from this reaction assigned as isoxazolines (**24A**) and (**24B**). The products were isolated in a 1:1 ratio in a best yield of 15% for each diastereomer. Unreacted starting material was also recovered. Efforts to increase the yield of the INOC reaction (NBS in DMF, Et_3N catalyst[22], CH_2Cl_2-t-butyl hypochlorite[23]) gave a lower return of product.



Scheme 4

Evidence supporting the assignment of isoxazolines (**24A**) and (**24B**) was provided by ^{1}H NMR, ^{13}C NMR, 2D-COSY and NOE experiments. The ^{1}H NMR spectra of isoxazoline (**24A**) and (**24B**) gave sharp signals indicating the loss of restricted rotation found in the starting aldoxime (**23**). Each isoxazoline gave six assignable signals downfield from an envelope of protons. Assignment of the relative stereochemistry of the four asymmetric carbon centres for the two isoxazolines required further NMR experiments. It was expected that the relationship between protons attached to stereocentres at C-5a, C-11c and C-2a would be *cis*. All previous work involving the synthesis of 6,6 fused carbocycles via the INOC route gave *cis* fused ring junctions where the ring junction substituents were hydrogen[24,25]. Molecular mechanics calculations on compactin related octahydronaphthisoxazoles have revealed the *cis* product as at least 3 kcal/mol more stable than the *trans* isomer[26]. Irradiation of the proton at C-2a collapsed the signal for the C-11c proton to a doublet with a coupling constant of 6.7 Hz found for both isoxazolines (**24A**) and (**24B**). From molecular models we were able to deduce that the angle between the DE-ring junction protons was ~45°. Fitting this value into the Karplus equation[27] gave an estimated coupling constant of 5 Hz. Models for a *trans* ring junction gave an angle of ~180° and theoretical coupling constant of 9.5 Hz. Hence the DE ring junction protons were assigned as *cis*.

The stereospecific INOC reaction affords the *cis* isoxazoline product when a *cis* dipolarophile is employed hence protons at C-2a and C-11c (J = 8.5 Hz) are *cis* [28]. Isoxazolines (**24A**) and (**24B**) were distinguished from each other by NOE expriments. Irradiation of the proton bonded to C-11a for isoxazoline (**24A**) gave no enhancement of the proton signal attached to C-11c. An *anti* (*trans*) relationship was deduced and isoxazoline (**24A**) termed the *cis, anti* isomer. The NOE experiment was repeated for isoxazoline (**24B**) and an enhancement for the proton at C-11c was observed when the proton attached to C-11a was irradiated. The result indicates a *syn* (*cis*) stereochemistry for isoxazoline (**24B**) and this isomer termed the *cis, syn* isomer.

In summary we have prepared two separable diastereomeric isoxazolines (**24A**) and (**24B**) via an intramolecular nitrile oxide cycloaddition from an oxime precursor. A 1:1 ratio of isoxazolines was obtained

in a best yield of 15% for each diastereomer. Isoxazoline (**24B**) possessed the *cis, syn* relative stereochemistry required for further elaboration to the model target. This work will be detailed in a further report.

Acknowledgements
We should like to thank Glaxo Group Research for a Glaxo Studentship to CJY.

Experimental

Infrared spectra were recorded as solutions in carbon tetrachloride except where indicated on a Perkin-Elmer 938 G instrument with polystyrene (1601 cm^{-1}) as standard. Infrared values are quoted as wave numbers (cm^{-1}). Proton and carbon NMR spectra were recorded on either a Bruker 360 MHz, or Bruker 250 MHz instrument. Chemical shifts are reported as values in ppm from an internal tetramethylsilane reference. High resolution mass spectra were performed at the Chemistry Department, King's College, London University or SERC Mass Spectrometry Centre, Chemistry Department, University College Swansea. Melting points were measured on a Gallenkamp heating block and are uncorrected. Column chromatography was carried out using the flash technique using Merck 60 (230-400 mesh) silica gel. Thin layer chromatography (TLC) was carried out on Merck glass backed TLC plates coated with silica gel 60 F-254. TLC plates were visualised using either ultraviolet light, iodine or 10% dodeca-molybdenum polyphosphoric acid-ethanol. All chiral compounds prepared are racemic, however only one enantiomer is depicted.

2-Methoxy-3,4,5,6-tetrahydropyridine (13)

Dimethyl sulfate (126 g, 1 mol) was added dropwise over 2.5 hours to a refluxing solution of δ-valerolactam (100 g, 1 mol) in benzene (300 ml). The solution was refluxed for 16 hours. The two-phase system was cooled and slowly treated with 50% aq. K_2CO_3 solution. The organic phase was separated, the aqueous phase was extracted twice with benzene and the combined organic fractions dried ($MgSO_4$). Evaporation of the solvent under reduced pressure at room temperature followed by distillation gave (**13**), (44.5 g, 39%) colourless oil, b.p. 68-71°C/45 mm Hg [Lit.[29] 70°C/60 mm Hg] ν_{max}/cm^{-1} 2945 (C-H), 1645 (C=N); δ_H (360 MHz; $CDCl_3$), 3.46 (3H, s, OCH_3), 3.36 (2H, m, H-6,6'), 2.10 (2H, m, H-3,3'), 1.56 (4H, m, H-4,4',5,5').

2-(Nitromethylene)-piperidine (14)

A solution of 2-methoxy-3,4,5,6-tetrahydropyridine (**13**) (33.9 g, 0.3 mol) and nitromethane (36.6 g, 0.6 mol) was refluxed for 3 days, cooled and quenched in cold diethyl ether (1 l). Filtration gave a solid crude product. The crude product was continuously extracted from a Soxhlet thimble with ether for 18 hours after which time only a small amount of dark oil remained. The solvent now containing crystallized product was cooled and the orange solid filtered. Recrystallization of the crude orange solid from methanol gave (**14**) (20.9 g, 49%), m.p. 74-75°C [Lit.[15] 80.5-81°C], (Found: M^+ 142.0735. $C_6H_{10}N_2O_2$ requires 142.0742) ν_{max}/cm^{-1} 2953 (C-H), 1611 (C=C); δ_H (360 MHz, $CDCl_3$) 10.61 (1H, br s, N-H), 6.51 (1H, s, $C\underline{H}NO_2$), 3.50 (2H, m, H-6,6'), 2.42 (2H, t, *J*6.4 Hz, H-3,3'), 1.90 (2H, m, H-5,5'), 1.80 (2H, m, H-4,4'); **m/z** 142 (61%, M^+), 125 (9%, M-OH), and 69 (100%, M-C_5H_9).

2-(Nitromethyl)-piperidine (12)

To a solution of 2-(nitromethylene)-piperidine (**14**) (100 mg, 0.7 mmol) in absolute ethanol (25 ml) was added sodium borohydride (32 mg, 0.84 mmol) and the solution stirred for 3 hours. Water (25 ml) was then added and the solution extracted with ether (3 x 25 ml). The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. No product was isolated from the organic layer. Evaporation of the aqueous layer gave a crude white product, m.p. > 211°C decomp, (Found: $M+H^+$, 145.0977. $C_6H_{12}N_2O_2+H$ requires 145.0976) $\nu_{max}/(KBr/cm^{-1})$ 3359 (N-H), 1641; δ_H (360 MHz, δ_6-DMSO) 3.42 (2H, m), 3.25 (1H, m), 2.50 (2H, br s), 1.05 (6H, m); **m/z** 145 (0.5%, $M+H^+$), 98 (19%, M-NO_2), 84 (100%, $C_5H_{10}N$).

1-Acetyl-2-(nitromethyl)-1,6,4,5-tetrahydropiperidine (16) and 1'-acetyl-2-(nitromethylene)-piperidine (17)

To a stirred solution of 2-(nitromethylene)-piperidine (**14**) (250 mg, 1.7 mmol) in dichloromethane (50 ml) was added diisopropylethylamine (0.29 ml, 1.7 mmol) at 0°C. Acetyl chloride (0.12 ml, 1.7 mmol) was added dropwise. The solution was then stirred at 25°C for 2 hours. The organic phase was washed with water (3 x 25ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. Flash chromatography (40-60°C petrol-ethyl acetate, 1:1 v/v) afforded two separable products, (**16**) R_F 0.48 (13 mg, 4%) oil (Found: M^+, 184.0847. $C_8H_{12}N_2O_3$ requires 184.0847) ν_{max}/cm^{-1} 2950 (C-H), 1670 (C=O), 1550; δ_H (360 MHz, $CDCl_3$) 5.46 (1H, t, *J*3.76 Hz, H-3), 5.38 (2H, s, $C\underline{H}_2NO_2$), 3.59 (2H, m, H-6,6'), 2.26 (2H, m, H-4,4'), 2.16 (3H, s, $COCH_3$), 1.93 (2H, m, H-5,5'); **m/z** 184 (15%, M^+), 142 (29%, M-CH_3CO+H), 138 (33%, M-NO_2), 96 (100%).

Data for (**17**) R_F 0.39 (31 mg, 10%) oil; (Found: M^+, 184.0847. $C_8H_{12}N_2O_3$ requires 184.0847) ν_{max} /cm^{-1} 2954 (C-H), 1680 (C=O), 1511 (C-NO_2); δ_H 12.50 (1H, br s, N-H), 3.50 (2H, m, H-6,6'), 2.82 (2H, m, H-3,3'), 2.39 (3H, s, $COCH_3$), 1.84 (4H, m, H-4,4',5,5'); **m/z** 184 (58%, M^+), 167 (53%, M-OH), 140 (15%), 125 (63%).

2-(1,1-Dimethoxymethyl)-pyridine (18)

Pyridine-2-carboxaldehyde (12.8 g, 0.12 mol), trimethylorthoformate (19.04 g, 0.18 mol), ammonium chloride (2 g, 0.04 mol) and methanol (200 ml) were refluxed for 60 hours. The reaction mixture was cooled, mixed with sodium carbonate (3.8 g, 0.04 mol) and the solvent evaporated. The residue was extracted from water (500 ml) with dichloromethane (4 x 150 ml), dried ($MgSO_4$) and distilled yielding (**18**), (6.8 g, 37%), b.p. 62°C/2.5 mm Hg (Found: $[M+H]^+$ 154.0868. $C_8H_{11}NO_2$+H requires 154.0865) ν_{max}/cm^{-1} 3058 (C-H ar), 2931 (C-H aliph.), 2828, 1589, 1441; δ_H (360 MHz, $CDCl_3$) 8.60 (1H, ddd, *J*0.9, *J*1.6, *J*4.9 Hz, H-6), 7.70 (1H, overlapping ddd, *J*1.7, *J*7.7 Hz, H-4) 7.56 (1H, br d, *J*7.8 Hz, H-3), 7.23 (1H, ddd, *J*1.2, *J*4.8, *J*7.5 Hz, H-5), 5.39 (1H, s, $C\underline{H}(OMe)_2$), 3.39 (6H, s, 2 x OMe); **m/z** 154 (100%, $M+H^+$), 122 (20%, M-CH_3OH), 107 (68%).

2-(1,1-Dimethoxymethyl)-piperidine hydrochloride (19)

2-(1,1-Dimethoxymethyl) pyridine (**18**) (7 g, 45 mmol), PtO_2 (Adam's catalyst) (1.45 g, 6.4 mmol), trimethylorthoformate (4.85 g, 46 mmol), ammonium chloride (2.45 g, 46 mmol) and methanol (200 ml) were hydrogenated (Parr apparatus 60 p.s.i.) for 30 hours. The reaction mixture was filtered through celite and the solvent reduced *in vacuo* to 50 ml. Cold diethyl ether (200 ml) was added to the flask. The white precipitate formed was removed by filtration; the solvent then reduced *in vacuo* to 20 ml. Diethyl ether (200 ml) was added and the flask swirled vigorously. The white precipitate formed was recovered by filtration and was obtained (7.1 g, 81%) as the HCl salt, m.p. 139-141°C. (Found: M^+ 159.1254 (free base). $C_8H_{17}NO_2$ requires 159.1259) ν_{max}/(KBr/cm^{-1}) 3200 (N-H), 2929 (C-H), 2859 (OMe); δ_H (360 MHz, $CDCl_3$) 9.53 (1H, br s, N-$\underline{H}$), 9.00 (1H, br s, N-$\underline{H}$), 4.76 (1H, d, *J*6.7 Hz, $C\underline{H}(OMe)_2$), 3.64 (1H, br d, *J*11.2 Hz, $NCH\underline{H}CH_2$), 3.53 and 3.48 (6H, 2 x s, $(O\underline{Me})_2$), 3.05 (1H, m, $C\underline{H}CH(OMe)_2$), 2.81 (1H, m, $NC\underline{H}HCH_2$), 2.00-1.48 (6H, -$(CH_2)_3$-); **m/z** 159 (3%, M^+ free base), 128 (10%, M-OCH_3), 84 (100%, M-$CH(OMe)_2$).

1-(2-Cyclohexenyl-1-carbonyl)-2-(1,1-dimethoxymethyl)-piperidine (20)

To a stirred solution of 2-(1,1-dimethoxymethyl)-piperidine hydrochloride (**19**) (1.2 g, 6.1 mmol) and Pr^i_2NEt (2.7 ml, 15.5 mmol) in dichloromethane (25 ml) at 0°C under argon was added 2-cyclohexene-1-carbonyl chloride (**15**)[30] (1.1 g, 7.6 mmol) in CH_2Cl_2 (5 ml). The reaction mixture was stirred for 2.5 hours (0°C) and then allowed to rise to room temperature. Water (20 ml) was added and the organic phase separated. Extraction of the aqueous layer (CH_2Cl_2, 2 x 20 ml), combination of organic extracts, drying ($MgSO_4$) and evaporation *in vacuo* gave a crude oil. Flash chromatography (40-60°C petrol-ethyl acetate, 1:1 v/v) afforded (**20**) as a mixture of diastereomers, (1.54 g, 94%) oil, (Found: M^+ 267.1821. $C_{15}H_{25}NO_3$ requires 267.1834) ν_{max}/cm^{-1} 2933 (C-H), 2864 (O-Me), 2834 (O-Me), 1635 (C=O); δ_H (360 MHz, $CDCl_3$) 5.81-5.53 (2H, m, $C\underline{H}$=$C\underline{H}$), 4.81-4.89 (2H, m, $C\underline{H}(OMe)_2$ and $C\underline{H}N$), 3.96, 3.75, 3.50, 3.19, 2.53 (3H, multiplets, $CH\underline{H}$Nax, $C\underline{H}$Heq, $C\underline{H}$CO), 3.41-3.28 (6H, singlets, $CH(O\underline{Me})_2$), 2.04-1.39 (12H, br); δ_C (90

MHz, $CDCl_3$) 175.8, 175.1, 173.7, 173.6 (C=O), 129.9, 129.4, 129.3, 128.1, 126.4, 125.5, 125.3, 125.2 (C=C), 102.8, 102.7, 102.38, 102.23 ($\underline{C}(OMe)_2$), 57.69, 57.6, 54.8, 54.6, 52.8, 52.6 (OCH_3), 55.24, 55.11, 48.16, 48.01, 39.06, 38.7, 38.5 (CCON and NCH), 42.57, 38.4, 38.31 (CH_2N), 26.58, 26.2, 25.8, 25.7, 25.25, 25.1, 24.77, 24.68, 24.57, 23.84, 21.58, 21.19, 21.03, 19.9 (CH_2); **m/z** 267 (2%, M^+), 236 (6%, M-OCH_3), 192 (36%, M-CH$(OMe)_2$), 84 (100%, $C_4H_{10}N$).

1-(2-Cyclohexenyl-1-methyl)-2-(1,1-dimethoxymethyl)-piperidine (21)

$LiAlH_4$ (0.374 ml, 1M soln. in ether, 0.374 mmol) was added to dry ether (10 ml) under argon. 1-(2-Cyclohexenyl-1-carbonyl)-2-(1,1-dimethoxymethyl)-piperidine (**20**) (147 mg, 0.55 mmol) was added dropwise in dry ether (5 ml) to this solution at room temperature. The solution was refluxed for 1 hour. The reaction was quenched with water (0.748 ml) followed by aq. NaOH (15%, w/w, 0.374 ml). An aqueous solution of saturated sodium potassium tartrate (50 ml) was added to the mixture followed by ether (50 ml) and the biphasic solution stirred for 15 minutes. The organic layer was separated and the aqueous phase extracted with ether (2 x 50 ml). The organic fractions were combined, dried and the solvent removed *in vacuo* (129 mg, 93%), (Found: $[M+H]^+$ 254.2120. $C_{15}H_{27}NO_2$+H requires 254.2110) ν_{max}/cm^{-1} 2933 (C-H), 2833 (O-Me), 1673 (C=C), 1445, 1075; δ_H (360 MHz, $CDCl_3$) 5.65 (2H, m, C$\underline{H}$=C$\underline{H}$), 4.44 (1H, t, *J*5.4 Hz, C$\underline{H}(OMe)_2$), 3.37 (6H, s, CH$(O\underline{Me})_2$), 2.91, 2.56 and 2.24 (6H, multiplets, CO$\underline{CH}$, $\underline{CH_2}N(\underline{CH}\text{-})\underline{CH_2}$), 1.95 (2H, br, $\underline{CH_2}$CH=CH), 1.66-1.44 (12H); **m/z** 254 (100%, $M+H^+$), 222 (28%, M-CH_3OH), 178 (22%, M-CH$(OMe)_2$).

1-(2-Cyclohexenyl-1-carbonyl)-piperidine-2-carboxaldehyde oxime (23)

Aqueous concentrated HCl (15 drops) was added with continuous stirring to a slurry of silica gel (3 g) in CH_2Cl_2 (6 ml). The slurry was stirred for 3 minutes. 1-(2-Cyclohexenyl-1-carbonyl)-2-(1,1-dimethoxymethyl)-piperidine (**20**) (280 mg, 1 mmol) was added dropwise to the slurry and the solution stirred for 12 hours. The acidic solution was neutralized with solid sodium hydrogen carbonate and filtered. Evaporation of dichloromethane *in vacuo* gave aldehyde (**22**) as an oil which was used without further purification (189 mg, 82%). The crude aldehyde (**22**) (189 mg, 0.85 mmol) was dissolved in pyridine (10 ml) and recrystallized hydroxylamine hydrochloride (119 mg, 1.7 mmol) was added. The mixture was stirred for 14 hours, poured into dichloromethane (50 ml), washed with water (4 x 25 ml), dried and concentrated *in vacuo*. Flash chromatography (40-60°C petrol-ethyl acetate 1:1 v/v) provided (**23**) oil, a mixture of *syn* and *anti* isomers (131 mg, 55%), (Found: M^+ 236.1526. $C_{13}H_{20}N_2O_2$ requires 236.1524); ν_{max}/cm^{-1} 3591, 3308 (O-H), 2937 (C-H), 1639 (C=O), 1419, 1643; δ_H (250 MHz, $CDCl_3$) 7.28 and 7.24 (1H, br, C$\underline{H}$=NOH), 5.78 and 5.50 (2H, m, C$\underline{H}$=C$\underline{H}$), 4.71 and 4.56 (1H, m, C$\underline{H}$CH=N), 3.78 (1H, t, *J*13.99 Hz, CH$\underline{H}$N), 3.31 (1H, t, *J*14.1 Hz, CH=CHC$\underline{H}$), 3.12 (1H, t, *J*13.38 Hz, C$\underline{H}$HN), 260 and 2.15 (1H, m), 2.20-1.18 (11H); **m/z** 236 (32%, M^+), 218 (28%, M-H_2O), 192 (20%, M-CHNOH), 155 (77%), 81 (100%).

2aα,3,4,5,5aα,9,10,11aβ,11cα-Decahydro-6H,8H-[1,2] benzisoxazolo [3,4-ab] quinolizin-6-one (24A) and 2aα,3,4,5,5aα,9,10,11aα,11cα-decahydro-6H,8H [1,2] benzisoxazolo [3,4-ab] quinolizin-6-one (24B)

To a vigorously stirred solution of 1-(2-cyclohexenyl-1-carbonyl)-piperidine-2-carboxaldehyde oxime (**23**) (200 mg, 0.84 mmol) in CH_2Cl_2 (20 ml) at 0°C was added 6% sodium hypochlorite solution (2 ml, 0.84 mmol) dropwise. After 2 hours the transient blue-green colour faded and the solution was allowed to warm to room temperature. The solution was stirred for 24 hours, diluted with water and the organic phase separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 ml). The combined organic fractions were combined; dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (1:4 petrol-ethyl acetate v/v) afforded (**24A**) R_F 0.24 as an oil which solidified on standing (30 mg, 15%), m.p. 182-186°C (Found: M^+ 234.1368. $C_{13}H_{18}N_2O_2$ requires 234.1364); ν_{max}/cm^{-1} 2941 (C-H), 1643 (C=O), 1552, 1442; δ_H (360 MHz, $CDCl_3$) 4.82 (1H, m, $\underline{H}$-2a), and 4.75 (1H, br d, *J*12.8 Hz, $\underline{H}$-8eq), 4.24 (1H, br d, *J*10.9 Hz, $\underline{H}$11a), 3.62 (1H, t, *J*8.55 Hz, $\underline{H}$11c), 2.81 (1H, m, $\underline{H}$5a), 2.54 (1H, m, $\underline{H}$8ax), 2.36-1.00 (12H, br envelope); δ_C(90 MHz, $CDCl_3$) 169.43 (C=O), 156.02 (C=N), 78.05 (C-O), 55.07 (C-N), 45.89 (C-11c), 43.35, 39.43 (C-5a), 31.76, 26.82, 26.60, 24.88, 23.88, 18.24; **m/z** 234 (75%, M^+), 217 (20%, M-OH), 204 (80%, M-NO), 162

(100%). The diastereomer (**24B**) R_F 0.18 was isolated (29.6 mg, 15 %), m.p. 183-186°C (Found: M^+ 234.1368. $C_{13}H_{18}N_2O_2$ requires 234.1364); ν_{max}/cm^{-1} 2941 (C-H), 1643 (C=O), 1552, 1442; δ_H (360 MHz, $CDCl_3$) 4.83 (1H, m, H-2a), 4.75 (1H, br d, *J*13.4 Hz, H-8eq), 4.29 (1H, br d, *J*10.5 Hz, H11a), 3.71 (1H, t, *J*8.57 Hz, H-11c), 2.81 (1H, m, H5a), 2.50 (1H, m, H8ax); δ_C (90 MHz, $CDCl_3$) 169.66 (C=O), 155.57 (C=N), 77.81 (C-O), 54.48 (C-N), 44.77 (C-11c), 43.17, 39.43 (C-5a), 33.46, 26.38, 25.68, 24.64, 23.97, 17.87; **m/z** 234 (100%, M^+), 217 (20%, M-OH), 204 (80%, M-NO).

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30. 2-Cyclohexene-1-carbonyl chloride (**15**) was prepared by heating 2-cyclohexene-1-carboxylic acid (1.9g, 15mmol) at reflux with oxalyl chloride (4.8 g, 38 mmol) in toluene for 24 hours. Removal of the solvent *in vacuo* gave crude acid chloride (2.17 g) (**15**) which was used in this preparation without further purification.

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