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Synthesis of racemic brevioxime and related analogues

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Abstract—Racemic brevioxime and the related model compounds have been synthesised starting from *N*-propionyl-2-pyrroline by intramolecular cyclisation of a β-ketoamide using nitrosyl chloride. © 2001 Published by Elsevier Science Ltd.

We report full details of our total synthesis of racemic brevioxime **1** and related analogues. Brevioxime **1** (Fig. 1) is a novel juvenile hormone biosynthesis inhibitor which was isolated from *Penicillium brevicompactum* by Primo-Yufera and co-workers in 1997.[1] The related compounds **2** and **5** have also been derived from the same fungus. The important nature of **1** has encouraged research groups to synthesise and investigate the biological activity of brevioxime and related analogues. Two syntheses of racemic brevioxime have been published[2,3] which are significantly longer than ours.[4] Clark has reported[5] the first synthesis of (−) brevioxime via epoxidation of acyl enamine **2**.

Our synthetic strategy, which is based on intramolecular cyclisation of β-ketoamide **2** utilising nitrosyl chloride, is shown in Scheme 1. We reasoned that pyrrolidine could be readily transformed into *N*-propionyl-2-pyrroline **6** which could then be acylated with 6-octenoyl imidazolide **7** to obtain the key β-ketoamide **2**. Finally, reaction of **2** with nitrosyl chloride should afford the bicyclic brevioxime **1**.

The synthesis of *N*-propionyl-2-pyrroline **6** was achieved as shown in Scheme 2 using the method of Kraus and Neuenschwander.[6] Pyrrolidine **8** was oxidised to pyrroline **9** using sodium persulfate and sodium hydroxide in the presence of silver nitrate. Pyrroline **9** underwent rapid trimerisation at room temperature to the triazine **10** which was subsequently cracked in boiling THF to give the monomer which was co-distilled with THF and trapped at

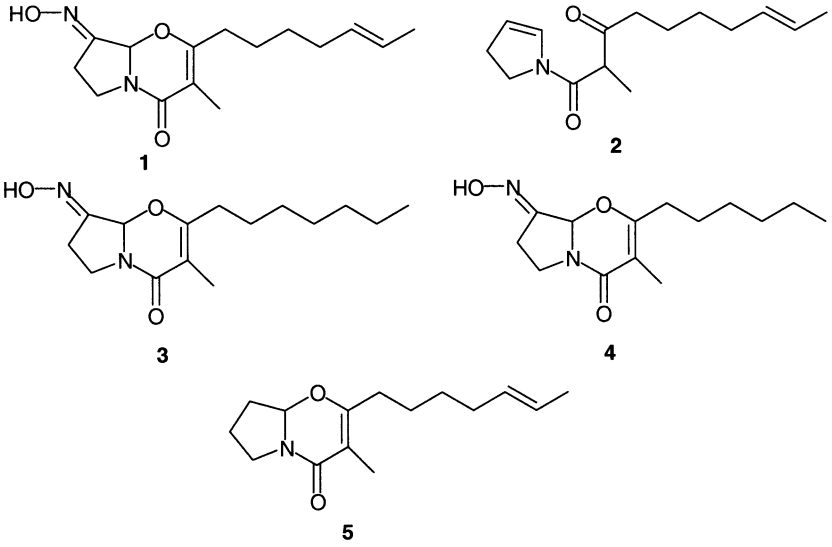

Figure 1.

Keywords: brevioxime; β-ketoamide; *n*-propionyl-2-pyrroline; nitrosyl chloride.
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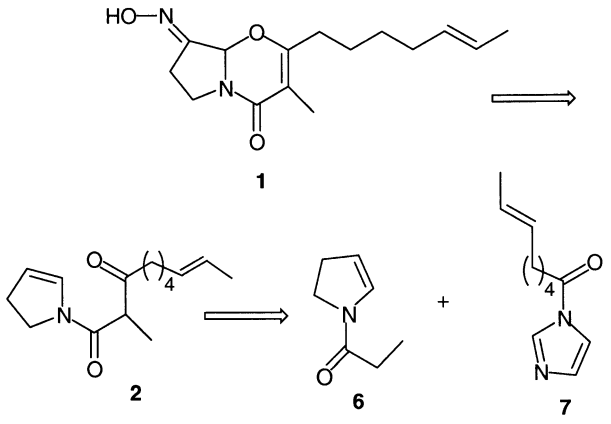
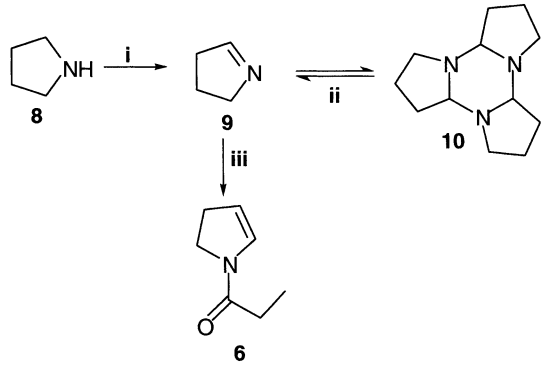


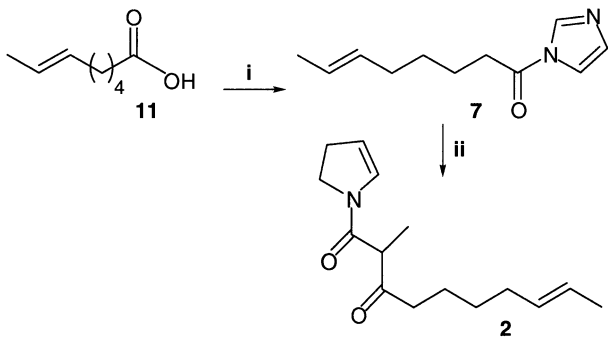
Scheme 1.

−78°C. This was immediately trapped with triethylamine and propionyl chloride to obtain the crude, protected enamine which was purified by column chromatography to give **6** in 15% overall yield.

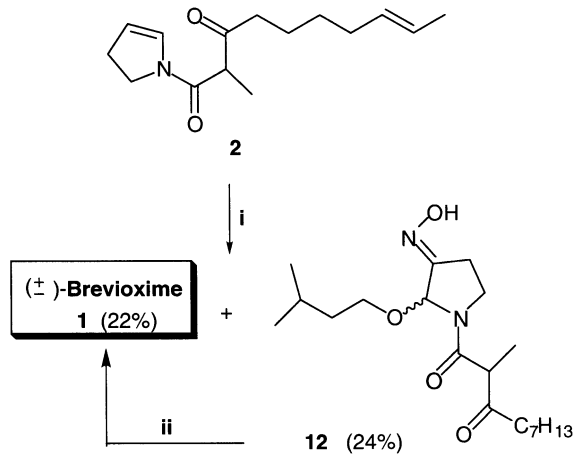
The next step involved the acylation of **6** with the activated amide **7** which is easily prepared from 6-octenoic acid **11** (Scheme 3). The acid **11** was prepared in turn by Hara's method[7] starting from commercially available 1,4-hexadiene. Treatment of 6-octenoic acid **11** with *N*,*N*′-carbonyldiimidazole (CDI) gave the desired acylimidazole **7** in situ. Subsequent reaction with the enolate of **6** (prepared by treatment with LDA at −78°C) gave the desired β-ketoamide **2** in 30% yield with 35% recovered starting material (Scheme 3).



Scheme 2. i. $Na_2S_2O_8$, NaOH, cat. $AgNO_3$, H_2O; ii. THF, reflux, trap monomer at −78°C; iii. NEt_3, CH_3CH_2COCl, −78°C, (15% overall).



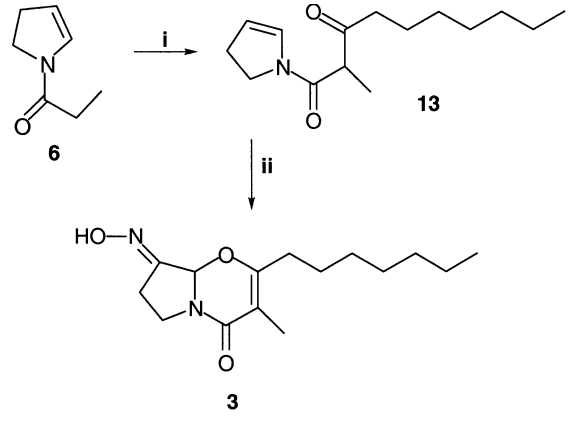
Scheme 3. i. CDI, THF, 4 h, rt.; ii. LDA, **6**, THF, −78°C, 1 h, 30%.



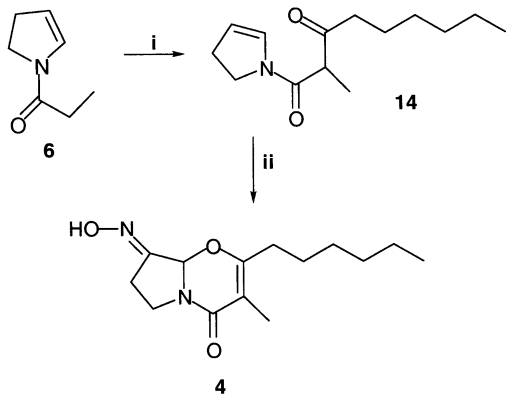
Scheme 4. i. *iso*-Amylnitrite, TMSCl, DCM, 22%; ii. PPTS, toluene, reflux, 1 h, 48%.

Following the preparation of β-ketoamide **2**, the next step was the introduction of the oxime at C-3 to provide brevioxime. To this end, we treated **2** with nitrosyl chloride (prepared according to the method of Weib and Wagner[8]) and obtained brevioxime **1** in 22% yield (Scheme 4). A diastereoisomeric mixture of uncyclised oxime **12** was also obtained in 24% yield. The uncyclised oxime **12** could be independently converted to racemic brevioxime in 48% yield by refluxing a solution of **12** in toluene with PPTS. The spectral data of the reaction product was identical to that reported for racemic brevioxime.[2,5]

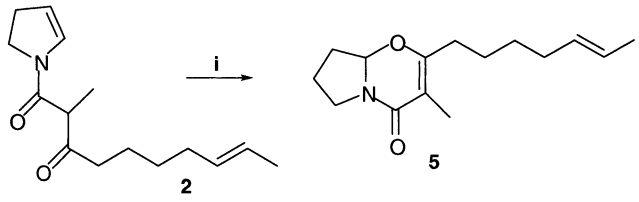
Having prepared **1**, we next sought to prepare related analogues such as **3** and **4**. Compound **3** was prepared as shown in Scheme 5. Formation of β-ketoamide **13** was achieved by treatment of commercially available methyl octanoate with the enolate of **6** prepared by treatment with LDA at −78°C in 45% yield. Having prepared β-ketoamide **13**, the next step was to perform an intramolecular cyclisation with nitrosyl chloride.[8] We applied the same reaction conditions which were used in the preparation of **1**. This reaction led to formation of our desired analogue **3** in 19% yield and also a diastereoisomeric mixture of uncyclised oximes as occurred during the synthesis of **1**.



Scheme 5. i. LDA, methyl octanoate, THF, −78°C, 45%; ii. *iso*-Amylnitrite, TMSCl, DCM, 19%.



Scheme 6. i. LDA, methyl heptanoate, THF, −78°C, 45%; ii. *iso*-Amylnitrite, TMSCl, DCM, 18%.



Scheme 7. i. Nitrosonium tetrafluoroborate, THF, rt, 36%.

The other analogue **4** was prepared starting from commercially available methyl heptanoate which was treated with the enolate of **6** at −78°C to obtain the desired β-ketoamide **14** in 45% yield. The desired analogue **4** was obtained in 18% yield according to the procedure described for preparation of **1** and **3** (Scheme 6).

The use of using other nitrosating agents,[5] apart from nitrosyl chloride, was then investigated. Nitrosonium tetrafluoroborate was tried in the brevioxime series, but this led to formation of the cyclised product **5** in 36% yield, rather than brevioxime **1** (Scheme 7). Presumably this product is due to an alternative pathway mediated by HBF_4 present in the reaction mixture.

In conclusion, we have developed a very short synthesis of racemic brevioxime from *N*-propionyl-2-pyrroline **4**. The method is convergent and is applicable to the synthesis of other analogues such as **3** and **4**.

1. Experimental

1.1. General techniques

Reactions were conducted in flame-dried glassware, under a dry nitrogen atmosphere except when noted otherwise. Solvents and reagents were freshly distilled as follows: tetrahydrofuran (THF) was distilled from sodium/benzophenone; dichloromethane was distilled from CaH_2. Melting points (electrothermal apparatus, open capillary) are uncorrected. Reactions were monitored by thin layer chromatography (TLC) using pre-coated silica plates (Macherey Nagel Sil G UV_{254}). Compounds were visualised using ultra-violet fluorescence, alkaline potassium permanganate solution or acidic cerium(IV) sulfate solution. Column chromatography was carried out on Macheray Nagel Kieselgel 60 (230–240 mesh).

NMR spectra were recorded at 300MHz (Bruker Avance DPX 300). Chemical shifts are quoted as δ values downfield of tetramethylsilane (TMS) or relative to the residual solvent resonance. Resonance multiplets are abbreviated as follows: d=doublet, t=triplet, s=singlet, br=broad, quat=quaternary, m=multiplet. Infra-red spectra were recorded using a FT instrument (Perkin–Elmer 1720). Samples were analysed as nujol mulls or as thin films on NaCl plates. High-resolution mass spectra (HRMS) and electron ionisation mass spectra (EI) were obtained on a Fisons Instrument VG Autospec.

1.1.1. *N*-Propionyl-2-pyrroline 6. A solution of sodium persulfate (71.5 g, 0.3 mol) in water (250 ml) was added dropwise to a stirred solution of sodium hydroxide (24 g, 0.6 mol), silver nitrate (500 mg, 3 mmol) and pyrrolidine (25 ml, 0.3 mol) in water (250 ml). The reaction mixture was stirred overnight and then extracted with DCM (3×400 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo at 10°C to give an orange oil. A solution of the residue in THF was distilled into a flask (pre-cooled to −78°C) whilst maintaining a positive pressure of nitrogen. Triethylamine (42 ml, 0.3 mol) was added with stirring followed by propionyl chloride (26 ml, 0.3 mol) dropwise over 30 min. The white precipitate of triethylamine hydrochloride which formed after warming to room temperature, was filtered off and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (silica 50% petrol/ether) to give the desired product (**6**) as a pale yellow oil (R_f=0.26) (5.4 g, 0.044 mol, 15%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80–6.30 (m+m, 1H), 5.10–5.05 (m, 1H), 3.75 (t, *J*=9.0 Hz, 1H), 3.65 (t, *J*=8.9 Hz, 1H), 2.60–2.40 (m+m, 2H), 2.20–210 (q+q, *J*=7.5 Hz, 2H), 1.00 (t, *J*=7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 129.7, 129.2, 111.8, 110.4, 45.83, 45.24, 28.62, 28.32, 27.25, 27.79, 10.9, 10.7. ν_{max}/cm^{-1} (liquid film) 3110, 2977, 2938, 1650, 1614, 1428; LRMS: *m/z* 125 (M^+, 30%), 68 (97); HRMS (EI) Calcd for $C_7H_{11}NO$ (M^+): 125.0841; Found: 125.0846.

1.1.2. *N*-(2-Methyl-3-oxodec-8-enoyl)-2-pyrroline 2. To a stirred solution of diisopropylamine (0.63 ml, 4.44 mmol) in THF (5 ml) at 0°C was added *n*-BuLi (2.2 M in hexanes, 1.97 ml, 4.44 mmol). The mixture was then stirred for 20 min at 0°C before being cooled to −78°C. A solution of *N*-propionyl-2-pyrroline **6** (529 mg, 4.23 mmol) in THF (2 ml) was added slowly and the reaction mixture was stirred for 1 h at −78°C. The acyl imidazole **7**, prepared by treatment of *N*,*N*′-carbonyldiimidazole (756 mg, 4.65 mmol) with 6-octenoic acid **11** (600 mg, 4.23 mmol) in THF (20 ml) at room temperature for 4 h, was then added and the resulting mixture was stirred at −78°C for 4 h and a further 12 h at room temperature. After this period, the mixture was quenched by addition of a saturated solution of ammonium chloride (50 ml), and extracted with ether (3×100 ml). The combined organic extracts were washed with brine (100 ml), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (silica, 10% petrol/ether) to give the desired product **2** as a

pale yellow oil (R_f=0.41) (305 mg, 1.22 mmol, 30%). ^{1}H NMR (300 MHz, CD_2Cl_2) δ 6.80–6.40 (m+m, 1H), 5.40–5.30 (m, 2H), 5.20–5.15 (m, 1H), 3.80–3.70 (m, 2H), 3.60–3.39 (q+q, J=7 Hz, 1H), 2.75–2.50 (m+m, 2H), 2.40–2.25 (m, 2H), 2.01–1.80 (m, 2H), 1.57–1.50 (m, 3H), 1.50–1.40 (m, 2H), 1.23 (m, 5H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 207.0, 166.4, 166.1, 131.4, 129.4, 128.7, 126.2, 125.3, 112.3, 111.8, 52.95, 52.84, 46.23, 45.74, 40.16, 39.99, 32.63, 29.27, 28.50, 23.37, 18.00,13.3, 13.1. ν_{max}/cm^{-1} (liquid film) 2957, 1723, 1624, 1455, 1311, 840. LRMS: *m/z* 249 (M^+, 37%), 180 (25); HRMS (EI) Calcd for $C_{15}H_{23}NO_2$ (M^+): 249.1730; Found: 249.1728.

1.1.3. *N*-(2-Methyl-3-oxo-decanoyl)-2-pyrroline 13. To a stirred solution of diisopropylamine (1.2 ml, 8.4 mmol) in THF (5 ml) at 0°C was added *n*-BuLi (2.5 M in hexanes, 3.5 ml, 8.4 mmol). The mixture was then stirred for 20 min at 0°C before being cooled to −78°C. A solution of *N*-propionyl-2-pyrroline **6** (1 g, 8 mmol) in THF (2 ml) was added slowly. The reaction mixture was stirred for 1 h at −78°C. Methyl octanoate, (0.72 ml, 4.0 mmol) in THF (1 ml) was added and the resulting mixture was stirred at −78°C for 4 h and a further 12 h at room temperature. After this period, the mixture was quenched by addition of a saturated solution of ammonium chloride (100 ml), and extracted with ether (3×100 ml). The combined organic extracts were washed with brine (100 ml), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (silica, 10% petrol/ether) to give the desired product **13** as a pale yellow oil (R_f=0.45) (420 mg, 1.67 mmol, 45%). ^{1}H NMR (300 MHz, *d*-MeOH) δ 6.90–6.80 (m+m, 1H), 5.40 (m, 1H), 3.80 and 3.60 (m+m, 3H), 2.90–2.70 (m+m, 2H), 2.50 (m, 2H), 1.80 (m, 2H), 1.40–1.20 (m, 11H), 0.80–0.90 (t, J=6.5 Hz 3H); ^{13}C NMR (75 MHz, *d*-MeOH) δ 208.6, 169.4, 169.1, 130.1, 129.8, 115.3, 114.9, 53.60, 53.10, 47.50, 46.90, 41.70, 33.30, 31.30, 30.60, 30.50, 29.50, 25.10, 24.10, 14.80, 13.61; ν_{max}/cm^{-1} (liquid film) 2950, 2830 1720, 1620. LRMS: *m/z* 251 (M^+, 30%); HRMS (EI) Calcd for $C_{15}H_{25}NO_2$ (M^+): 251.1885; Found: 251.1864.

1.1.4. *N*-(2-Methyl-3-oxo-nonanoyl)-2-pyrroline 14. According to the procedure described for preparation of **13**, **14** (430 mg, 45%) was obtained from methyl heptanoate (0.4 ml, 4 mmol) as a pale yellow oil (R_f=0.48, 10% petrol/ether); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 6.70–6.30 (m+m, 1H), 5.20–5.10 (m, 1H), 3.80 and 3.60 (m, 2H), 3.40–3.30 (q+q, 1H), 2.60–2.30 (m+m, 2H), 2.20–2.10 (m, 2H), 1.40–1.20 (m, 2H), 1.10–0.80 (m, 9H), 0.70–0.60 (m, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 207.5, 166.5, 166.3, 129.8, 129.1, 113.3, 112.2, 53.20, 53.10, 46.50, 46.10, 40.70, 40.50, 32.30, 29.40, 28.90, 24.20, 23.20, 14.50, 13.70, 13.50; ν_{max}/cm^{-1} (liquid film) 2940, 2810, 1720, 1637; LRMS: *m/z* 237 (M^+, 25%); HRMS (EI) Calcd for $C_{14}H_{23}NO_2$ (M^+): 237.1729; Found: 237.1721.

1.1.5. Brevioxime 1. A mixture of TMSCl (0.05 ml, 0.4 mmol) and *iso*-amyl nitrite (0.053 ml, 0.4 mmol) was refluxed for 30 min and then cooled to room temperature. A solution of β-ketoamide **2** (50 mg, 0.2 mmol) in DCM (2 ml) was then added and the mixture was stirred at room temperature for 2 h. After evaporation of the solvent, the residue was purified by flash column chromatography (silica, 50% petrol/diethyl ether) to afford brevioxime as a white solid (R_f=0.31, 10% petrol/ether): mp 135–140°C (lit.[5] 133–140°C) (12 mg, 22%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 5.60 (s, 1H), 5.40–5.30 (m, 2H), 4.20–4.10 (m, 1H), 3.60–3.40 (m, 1H), 3.0–2.80 (m, 2H), 2.40–2.30 (m, 2H), 1.80 (m, 3H), 1.65–1.35 (m, 7H), 1.40–1.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 163.7, 158.3, 132.2, 125.6, 107.4, 84.5, 42.10, 32.60, 31.10, 29.50, 26.70, 24.10, 18.30, 10.50; ν_{max}/cm^{-1} (liquid film) 3256, 2951, 1641, 1447; LRMS: *m/z* 278 (M^+, 30%), 261 (15); HRMS EI) Calcd for $C_{15}H_{22}N_2O_3$ (M^+): 278.1630; Found: 278.1628.

1.1.6. 2-Heptyl-6,7-dihydro-3-methyl-4*H*-pyrrole[2,1-*b*]-[1.3]oxazine-4,8(8a*H*)-dione 8-oxime 3. According to the procedure described for preparation of **1**, **3** (43 mg, 19%) was obtained from **13** (200 mg, 0.79 mmol) as a white solid (10% petrol/ether, R_f=0.37): mp 115–120°C. ^{1}H NMR (300 MHz, $CDCl_3$,) δ 8.10 (br s, 1H), 5.40 (s, 1H) 4.20–4.09 (m, 1H), 3.50–3.40 (m, 1H), 3.10–2.90 (m, 2H), 2.30–2.20 (m, 2H), 1.80 (s, 3H), 1.60–1.50 (m, 2H), 1.40–1.20 (m, 8H), 0.80 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 164.3, 158.1, 107.4, 84.90, 42.40, 32.50, 31.50, 30.10, 29.80, 27.50, 24.4, 23.4, 14.6, 10.5; ν_{max}/cm^{-1} (liquid film) 3280, 2951, 1644; LRMS: *m/z* 280 (M^+, 34%), 263 (15); HRMS (EI) Calcd for $C_{15}H_{24}N_2O_3$ (M^+): 280.1787; Found: 280.1780.

1.1.7. 2-Hexyl-6,7-dihydro-3-methyl-4*H*-pyrrole[2,1-*b*]-[1.3]oxazine-4,8(8a*H*)-dione 8-oxime 4. According to the procedure described for preparation of **1** and **3**, **4** (20 mg, 18%) was obtained from **14** (100 mg, 0.42 mmol) as a white solid (10% petrol/ether, R_f=0.36): mp 105–110°C. ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.40 (br s, 1H), 5.40 (s, 1H), 3.80–3.70 (m, 1H), 3.30–3.20 (m, 1H), 2.70–2.50 (m, 2H), 2.10–1.90 (m, 2H), 1.60 (s, 3H), 1.40–1.30 (m, 2H), 1.20–1.05 (m, 6H), 0.70 (m, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 166.8, 165.6, 160.3, 109.4, 86.50, 43.30, 33.10, 32.30, 31.10, 29.10, 25.9, 24.8, 15.3, 12.1; ν_{max}/cm^{-1} (liquid film) 3240, 2925, 1644, 1435; LRMS: *m/z* 266 (M^+, 75%), 249(10); HRMS (EI) Calcd for $C_{14}H_{22}N_2O_3$ (M^+): 266.1630; Found: 266.1632.

1.1.8. 2-(Hept-5-enyl)-3-methyl-4-oxo-6,7,8,8a-tetrahydro-4*H*-pyrrolo [2,1-*b*]-1,3-oxazine 5. To a stirred solution of nitrosonium tetrafluoroborate (35 mg, 0.3 mmol) in DCM (2 ml) was added *N*-(2-methyl-3-oxodec-8-enoyl)-2-pyrroline **2** (50 mg, 0.2 mmol) at room temperature. The reaction mixture was stirred for 30 min, and then poured into distilled water (20 ml). The seperated aqueous layer was extracted with DCM (3×100 ml) and the combined organic extracts were washed with brine (50 ml), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (silica, 50% petrol/ether) to give the product **5** as a pale yellow oil (R_f=0.39) (17 mg, 0.07 mmol, 35%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.45–5.40 (m, 2H), 5.21 (dd, J=6 and 4.7 Hz, 1H), 3.80–3.50 (m+m, 2H), 2.40–2.30 (m, 2H), 2.20–2.10 (m, 2H), 2.05–1.95 (m, 3H), 1.90–1.85 (m, 1H), 1.80 (s, 3H), 1.67–1.65 (m, 3H), 1.55–1.50 (m, 2H), 1.40–1.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 163.9, 131.4, 125.6, 106.9, 87.92, 44.71, 32.68, 32.15, 30.87, 29.56,

26.71, 22.33, 18.35, 10.54; ν_{max}/cm^{-1} (liquid film) 2935, 2859, 1723, 1645, 1615, 1424, 1374, 967; LRMS: *m*/*z* 249 (M^+, 45%), 180 (5); HRMS (EI) Calcd for $C_{15}H_{23}NO_2$ (M^+): 249.1728; Found: 249.1720.

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