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X=Y–ZH Systems as potential 1,3-dipoles. Part 51:☆ Halogen-induced inter- and intra-molecular formation of nitrones from oximes and alkenes

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Abstract—Oximes possessing γ- and δ-alkenyl substituents are cyclised by *N*-bromo- or *N*-iodosuccinimide, iodine or ICl to the corresponding cyclic nitrones or their dimeric H-bonded hydroiodide salts in good yield; facially specific cycloaddition of these nitrones, and others derived by cyclisation of δ,δ-bis(alkenyl) ketoximes or by iodine induced addition of acetaldoxime to cyclohexene, furnish isoxazolidines.

The electrophile induced cyclisation of hetereoatom nucleophiles onto an appropriately located alkene is both a versatile and a powerful method for the construction of hetereocycles.[2] We have been developing an interface between these processes[3] and our oxime→nitrone→cycloaddition cascades.[4] In the preceding paper[1] we reported our results employing phenylselenyl bromide as the electrophile trigger for nitrone formation. In this paper we report full details of our studies with *N*-bromosuccinimide (NBS), *N*-iodo succinimide (NIS), I_2 and ICl[5] as the electrophile trigger.

Oximes are ambident nucleophiles with either the oxygen or nitrogen atom acting as the active site depending on the co-reagents, solvent and pH of the reaction mixture. In situations involving intramolecular nucleophilic attack the *E*/*Z*-stereochemistry of the oxime and the relative rates of *E*/*Z*-isomerisation versus *N*- or *O*-nucleophilic attack on, in this case, the halonium ion also play a role.[1] In cases of intermolecular nucleophilic attack of aldoximes the *Z*-oxime is sterically favoured over the *E*-oxime for *N*-attack due to eclipsing of the *N*-lone pair and *R* group in the latter case (Scheme 1). Analogous situations occur in ketoximes with sterically disparate substituents.

Oximes react readily with alkenes when treated with either NBS or iodine in methylene chloride at room temperature via attack of the *N*-atom on the intermediate halonium ion. Interesting differences arise because the reaction liberates a proton from the oxime hydroxy group, which is scavenged as succinimide in the former case but, unless a base is added, results in salt formation in the latter case. Thus, **1a**,**b** (*E*/*Z* 2:1) react with iodine (CH_2Cl_2, 25°C, 2 h) to produce the cyclic nitrone salts **2a**,**b** in essentially quantitative yield. Thus *E*/*Z*-isomerism is faster than the 5-*exo*-tet ring closure step. Work-up of **2a**,**b** without addition of base followed by crystallisation from methylene chloride–hexane affords the linear H-bonded dimeric salts **3a**,**b** (Scheme 2). A crystal structure of **3a** established the structure unequivocally (Fig. 1).[5,6]

Cyclic (*E*)-ketoxime **4**, prepared from ketoester **4a**, undergoes cyclisation (I_2, CH_2Cl_2, 25°C, 6 h) to a 5:1 mixture of *cis*- and *trans*- **5** in essentially quantitative yield. After washing with aqueous sodium thiosulphate and reduction (2 equiv. $LiAlH_4$, Et_2O, 35°C, 16 h) the major *cis*-isomer **6** (Me/CH_2OH) was obtained in 50% overall yield from **4**. The stereochemistry of **6** was unequivocally established by a single crystal X-ray structure determination (Fig. 2; Scheme 3). An analogous sequence on **1a** afforded a 4:1 mixture of *cis*-**8a** and *trans*-**7a** in 53% yield whilst **1b** affords a 3:1 mixture of *cis*-**8b** and *trans*-**7b** in 57% yield (Scheme 4).

Scheme 1.

☆ Part 50.[1]

Keywords: oximes; hetereoatom nucleophiles; dimeric nitrone salts cycloaddition.

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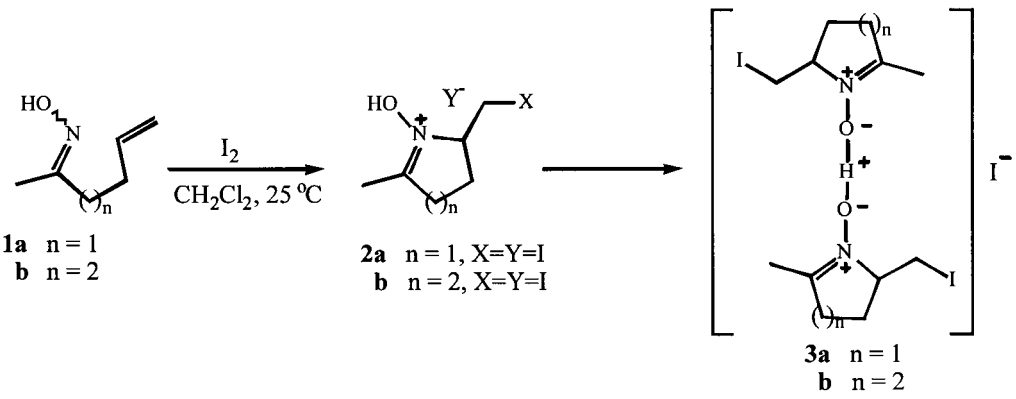


Scheme 2.

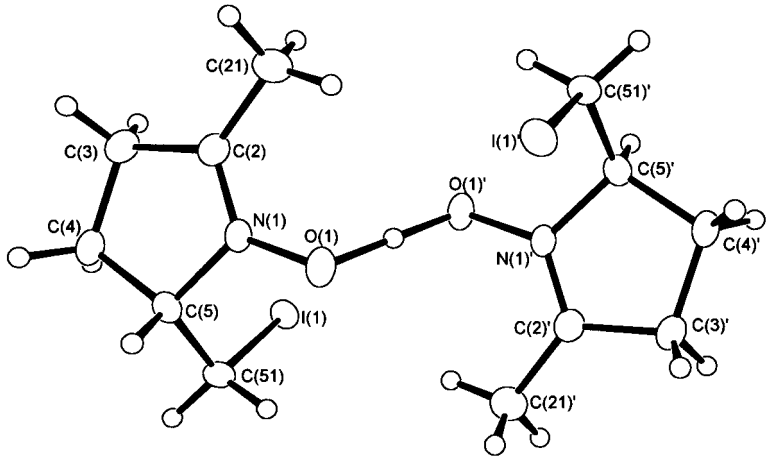


Figure 1. X-Ray crystal structure of **3a**.

A range of conditions was explored for cyclisation of **1a** to **9a** using iodine as the electrophile. The reaction occurred in CH_3CN, CH_3NO_2 or CH_2Cl_2 in the presence of K_2CO_3, Ag_2CO_3 or $Na_2S_2O_3$ in essentially quantitative yield in all cases. The subsequent cycloaddition of **9a** with NMM was optimised in benzene at 40°C (10 h) affording **11a** and **12a** as a 2:1 mixture (50%) of the *endo*- and *exo*-stereoisomers. The stereochemistry of cycloadducts **11a/12a** is based on n.O.e data (see Experimental). Oxime **1a** reacts (K_2CO_3, CH_2Cl_2, rt, N_2, 2 h) quantitatively with ICI giving corresponding nitrone **9a**, which was trapped in a subsequent cycloaddition reaction (NMM, CH_3CN, 80°C, 5 h) yielding a 2:1 mixture (58%) of *endo*-**11a** and *exo*-**12a**, respectively. Slow addition of NIS to **1a** (CH_2Cl_2, rt, N_2, 2 h) over a period of 1 h afforded not only corresponding nitrone **9a**, but trace amounts (ca 5%) of the oxazine **10a** also.

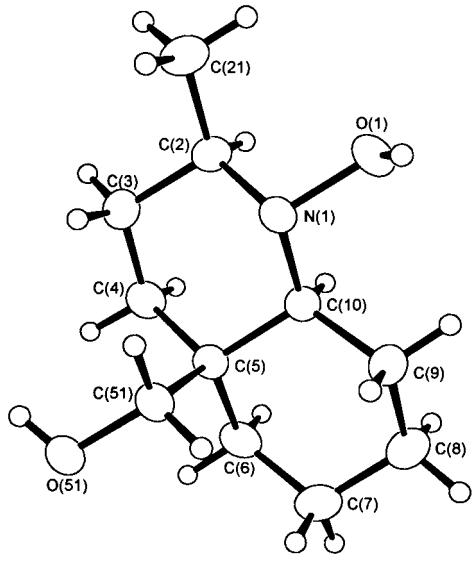
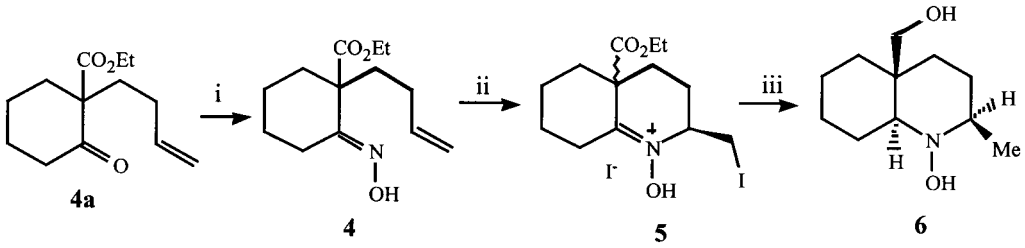
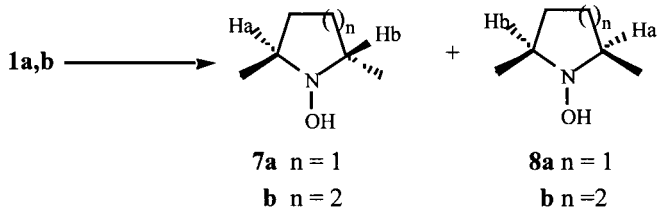


Figure 2. X-Ray crystal structure of **6**.

The reaction of **1b** with I_2 (CH_2Cl_2, rt, 2 h) gives a mixture of the nitrone salt **2b** and unreacted *Z*-**1b** in a 2:1 ratio, respectively. This ratio is a reflection of the *E*/*Z* ratio of **1b** and is a further example in which the rate of the nitrone forming cyclisation exceeds the rate of *E*/*Z*-isomerisation. In contrast to the analogous reaction of **1a** O-alkylation to give 7-membered ring oxazine **10b** was not observed. Using anhydrous K_2CO_3 to liberate **1b** was unfavourable as it destroyed the nitrone. With Tl_2CO_3 (NMM, THF, 40°C, 7 h) cycloaddition took place affording a 2:1 mixture of *endo*-**11b** and *exo*-**12b** in a very low yield (11% overall, 16% relative to *E*-**1b**). Repeating the iodine induced cyclisation of **1b** to **2b** (CH_2Cl_2, rt) over 10 h gave a consistent ratio of **2b**:*Z*-**1b** of 3.6:1. After washing with aqueous sodium thiosulphate and cycloaddition (C_6H_6, 40°C, 7 h) a



Scheme 3. (i) $NH_2OH{\cdot}HCl$, CH_3COONa, CH_3CN, H_2O, 20°C; (ii) I_2, CH_2Cl_2, 25°C, 6 h; (iii) $Na_2S_2O_3$ (aq), $LiAlH_4$, Et_2O, 35°C, 16 h.

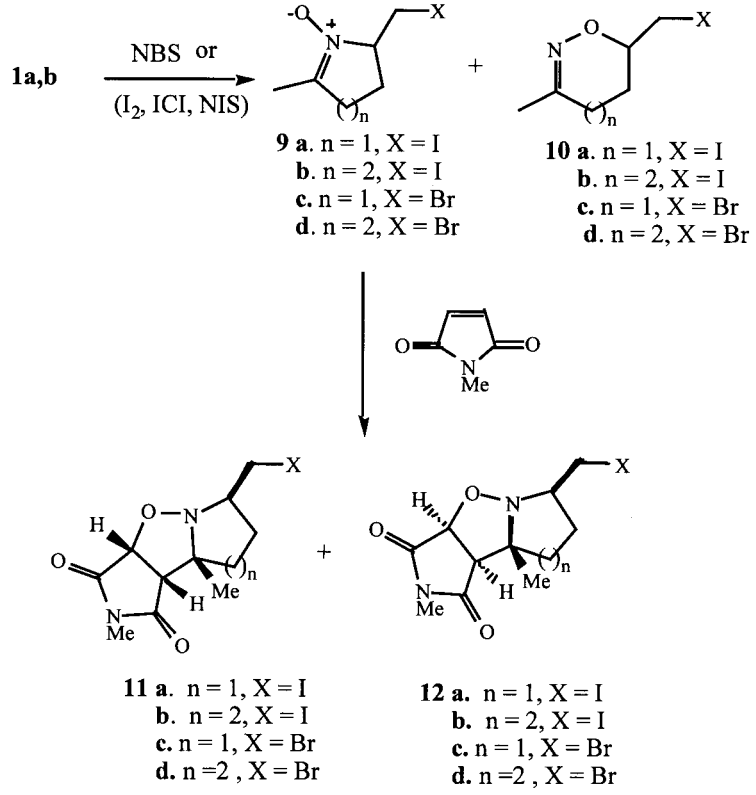


Scheme 4.

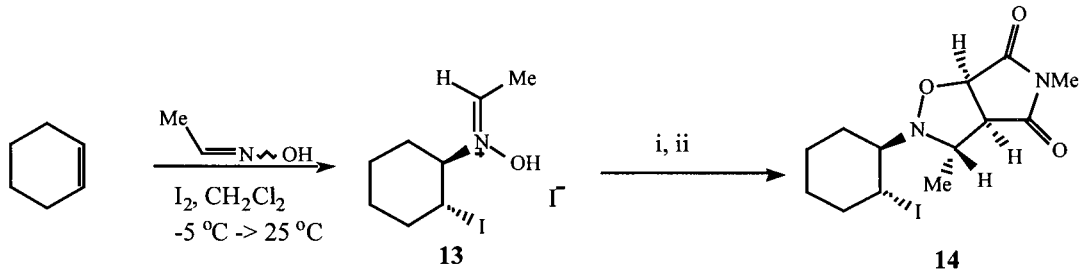
2:1 mixture (50% overall) of **11b** and **12b** was obtained. Stereochemical assignments of cycloadducts are based on n.O.e data (see Experimental).

In contrast to the iodine induced cyclisation, the reaction of **1a** with NBS (CH_2Cl_2, 25°C, 2 h) afforded a 2:1 mixture of nitrone **9c** and oxazine **10c**, which reflected the 2:1 ratio of *anti*- and *syn*-oximes in the starting material. Reaction of this product mixture (C_6H_6, 80°C, 13 h) with NMM afforded a 2:1 mixture (78%) of *endo*-**11c** and *exo*-**12c** cycloadducts together with **10c** (61%). The isolated yields are based on the *anti*/*syn* ratio of the oxime **1a**. Oxime **1b** treated in an analogous manner afforded **11d** and **12d** (33%) as a 2.3:1 mixture of *endo*- and *exo*-stereoisomers, but no oxazine **10d** was isolated in this case. The stereochemical assignments of cycloadducts are based on n.O.e data (see Experimental). The conversion of **1a**,**b** into **11/12a–d** constitute examples of Class 3 processes (intramolecular nitrone formation–intermolecular cycloaddition) (Scheme 5).[1]

An intermolecular example is provided by the addition of acetaldehyde oxime to cyclohexene (I_2, CH_2Cl_2, 25°C, 5 h), which affords **13** as a single stereoisomer but in low yield (Scheme 6). In this case, the oxime is a 40:60 mixture of *syn*-



Scheme 5.



Scheme 6. (i) $Na_2S_2O_3$ (aq); (ii) NMM, C_6H_6, 80°C, 1 h.

and *anti*-isomers and only the *anti*-isomer undergoes addition. This situation conforms to that illustrated in Scheme 1.

The free base derived from the salt **13** undergoes cycloaddition with NMM (C_6H_6, 80°C, 1 h) to give **14** as a single stereoisomer in 36% overall yield from acetaldoxime (Scheme 6). This is an example of Class 1 process (intermolecular nitrone formation–intermolecular cycloaddition).[1] The stereochemistry of **14** was established by an X-ray crystal structure determination (Fig. 3).[5,6]

A Class 4 process (intramolecular nitrone formation–intramolecular cycloaddition) is provided by the conversion (I_2, CH_2Cl_2, 25°C) of **16** to the nitrone salt in essentially quantitative yield followed by a sodium thiosulphate wash to give **17**, which on heating (C_6H_6, 80°C, 5 h) afforded **18** (53%) (Scheme 7).

In summary the inter- and intra-molecular halogen induced reactions of oximes with alkenes occur via attack of the oxime *N*-atom on the intermediate halonium ions. Reactions involving the oxime *O*-atom are either not observed or

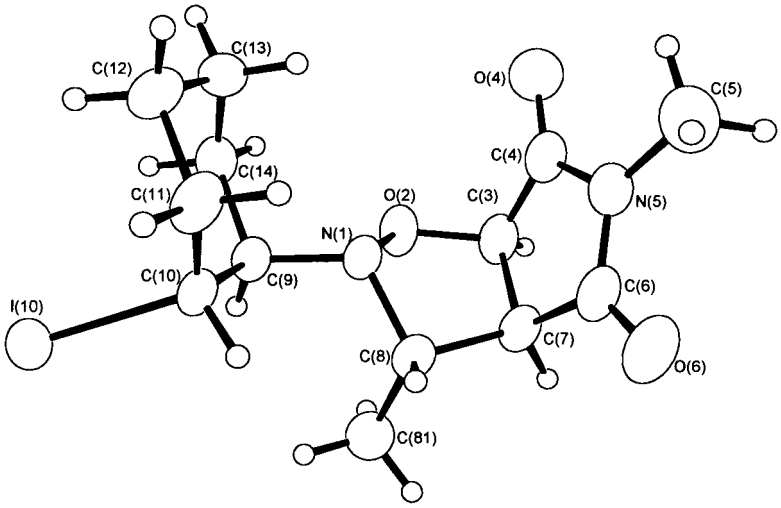
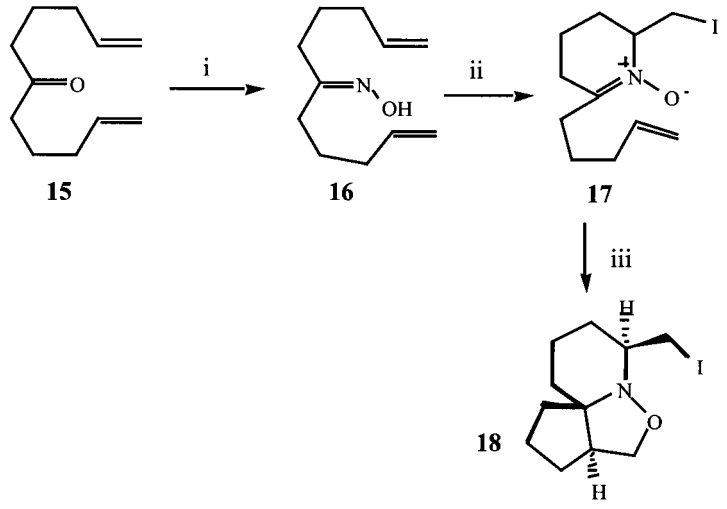


Figure 3. X-Ray crystal structure of **14**.



Scheme 7. (i) $NH_2OH{\cdot}HCl$, CH_3COONa, MeCN, H_2O, 20°C. (ii) I_2, CH_2Cl_2, 25°C, 16 h. (iii) C_6H_6, 80°C 5 h.

constitute a minor pathway. Thus in general *E*/*Z*-oxime isomerisation is faster than nucleophilic attack of oximes on the halonium ions. Examples of Class 1, 3 and 4 processes are provided.

1. Experimental

Nuclear magnetic resonance spectra and decoupling experiments were determined at 300 MHz on a Q.E 300 instrument and at 400 MHz on a Bruker AM400 spectrometer as specified. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane as internal standard. Spectra were determined in deuteriochloroform except where otherwise stated. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad and brs=broad singlet. Infrared spectra were recorded on a PU9706 IR Spectrophometer. Flash column chromatography was performed using silica gel 60 (230–400 mesh). Kieselgel columns were packed with silica gel GF_{254} (Merck 7730). Petroleum ether refers the fraction with bp 40–60°C unless otherwise specified. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Microanalyses were obtained using a Carlo–Erba Model 1106 instrument. Mass spectra were recorded at 70 eV on a VG Autospec mass spectrometer. Oximes **1a**,**b** and **4** were prepared by literature methods.[7,8]

1.1. General procedure for the oximation of aldehydes and ketones

$NH_2OH{\cdot}HCl$ (1.2 mmol) and NaOAC (1.5 mmol) were added to a stirred solution of the aldehyde (or ketone) (1.0 mmol) in 3:1 v/v CH_3CN–H_2O (30 mL) at room temperature and stirring continued for a further 3 h. Most of CH_3CN was removed under reduced pressure and the remaining aqueous solution was extracted with CH_2Cl_2 (2×30 mL). The combined organic extracts were washed with water (30 mL), dried ($MgSO_4$), filtered, the solvent removed under reduced pressure and the residue subjected to column chromatography on silica, eluting with petroleum ether–diethyl ether.

1.1.1. 1,10-Undecadien-6-one oxime 16. Obtained (76%) as a colourless oil. Found: C, 73.0; H, 10.8; N, 7.8. $C_{11}H_{19}NO$ requires C, 72.9; H, 10.55; N, 7.75%; *m*/*z* (%) 181 (M^+, 1), 164 (10), 140 (13), 127 (77), 112 941), 73 (97), 55, (47) and 41 (100). δ: 8.8 (brs, 1H, OH), 5.84 (m, 2H, 2×CH=), 5.0 (m, 4H, 2×CH_2), 2.35 (m, 2H), 2.20 (m, 2H), 2.09 (m, 4H) and 1.61 (m, 4H).

1.2. Oxime→nitrone→cycloaddition cascades

1.2.1. Compound 3a. Iodine (0.23 g, 0.92 mmol) was added to a stirred solution of 5-hexen-2-one oxime **1a** (0.1 g, 0.92 mmol) in nitromethane (10 mL) and the mixture heated at 80°C for 2 h. After cooling, nitromethane was removed under reduced pressure. The residue was taken up in a minimum volume of acetonitrile and hexane was added until the solution became cloudy. It was then cooled in liquid nitrogen and the *product* (0.08 g, 26%) was induced to crystallise, as a pale brown prisms by scratching, mp 126–127°C. Found: C, 23.7; H, 3.5; N, 4.5, I, 62.9. $C_{12}H_{21}N_2O_2I_3$ requires C, 23.8; H, 3.7; N, 4.6; I, 62.7%). *m*/*z* (%) 240 (protonated nitrone, 100) and 113 (5). ν_{max} (nujol): 3450(br), 1710, 1640, 1440, 1400, 1360, 1210, 990, 860 cm^{-1}. δ (400 MHz) (C_6D_6): 4.70 (brs, 2H, NCH), 3.88 (dd, 2H, *J*=11.1, 4.0 Hz, CHI), 3.51 (d, 2H, *J*=11.5 Hz, CHI), 3.28 (brs, 1H, OH), 2.93 (m, 4H), 2.65 and 2.68 (2×m, 2H), 2.33 (s, 6H, Me) and 1.90 (m, 2H).

1.2.2. Compound 3b. Iodine (0.2 g, 0.78 mmol) was added to a stirred solution of 6-hepten-2-one oxime **1b** (0.1 g, 0.78 mmol) in acetonitrile and the reaction mixture stirred at room temperature for 24 h. Hexane was added to the mixture until the solution became cloudy. It was then cooled in liquid nitrogen and the *product* (0.15 g, 30%) was induced to crystallise, by scratching, as pale brown blocks, mp 144.5–145.5°C. Found: C, 26.4; H, 4.0; N, 4.3, I, 60.0. $C_{14}H_{25}N_2O_2I_3$ requires C, 26.4; H, 4.05; N, 4.4; I, 60.0%. *m*/*z* (%) 507 (M^+−I, 28), 254 (protonated nitrone, 100) and 127 (5.0). δ: 8.6 (brs, 1H, OH), 4.24 (brs, 2H, NCH) 3.85 (dd, 2H, *J*=11.5, 4.0 Hz, CHI), 3.61 (dd, 2H, *J*=11.5 Hz, CHI), 2.91 (m, 2H), 2.64 (m, 2H), 2.4 (s, 6H, Me), 2.39 (m, 2H), 2.15 (m, 4H) and 1.86 (m, 2H).

1.2.3. 4a-Hydroxymethyl-2-methyl-octahydro-quinolin-1-ol (6). Iodine (0.21 g, 0.83 mmol) was added to a stirred solution of oxime **4** (0.2 g, 0.83 mmol) in dry dichloromethane (10 mL) and the mixture was stirred at rt for 6 h. Dichloromethane (25 mL) was added and the mixture washed with aqueous $Na_2S_2O_3$ solution, dried ($MgSO_4$), and the solvent removed under reduced pressure. The residue was taken up in dry ether, $LiAlH_4$ (0.064 g, 1.67 mmol) added and the mixture boiled under reflux for 16 h. After cooling, 10% NaOH solution was added dropwise to the mixture until a clear ether layer was obtained. The ether layer was decanted and the precipitate washed further with (20 mL) ether. The combined ether layers were dried ($MgSO_4$) and the solvent removed under reduced pressure to give the *product* (0.08 g, 50%), which crystallised as colourless prisms from ether, mp 153–154°C. Found: C, 66.15; H, 10.8; N, 6.95. $C_{11}H_{21}NO_2$ requires C, 66.3; H, 10.6; N, 7.05%. *m*/*z* (%) 199 (M^+, 38), 184 (100), 182 (81) 168 (31) 166 (20) and 152 (28). δ (MHz): 4.18 (dd, 1H, *J*=11.0, 1.9 Hz, C*H*HOH), 3.4 (d, 1H, *J*=11.0 Hz, CH*H*OH), 2.58 (m, 1H, NC*H*Me), 2.4 (dd, 1H, *J*=11.5, 3.0 Hz, NCH), 2.23 (m, 1H), 1.96 (m, 1H), 1.85 (m, 1H), 1.65 (m, 2H), 1.47–1.21 (m, 6H), 1.19 (d, 3H, *J*=6.0 Hz, Me) and 1.07 (m, 1H).

1.2.4. *trans*-2,5-Dimethylpyrrolidin-1-ol (7a) and *cis*-2,5-dimethyl pyrrolidin-1-ol (8a). Iodine (0.68 g, 2.7 mmol) was added to a stirred solution of 6-hexen-2-one oxime **2a** (0.3 g, 2.7 mmol) in nitromethane (10 mL) and the reaction mixture heated at 80°C for 3 h. After cooling, nitromethane was removed under reduced pressure, the residue taken up in dichloromethane (20 mL) and washed with aqueous $Na_2S_2O_3$ solution (20 mL). The dichloromethane solution was dried ($MgSO_4$), the solvent removed under reduced pressure, the residue taken up in dry ether (10 mL), $LiAlH_4$ (0.21 g, 5.39 mmol) added and the mixture stirred at room temperature for 5 h. The mixture was then quenched by the addition of 2N NaOH dropwise until a clear ether layer was obtained. The ether was decanted, dried ($MgSO_4$), and the solvent removed under reduced pressure at room temperature to leave a colourless oil that comprised a 4:1 mixture (^1H NMR) of **7a** and **8a**. Purification by flash

chromatography eluting with diethyl ether afforded **7a** (0.03 g, 15%) and **8a** (0.08 g, 23%).

trans-**7a.** Obtained as a colourless liquid, found: C, 62.4; H, 11.5; N, 12.1. $C_6H_{13}NO$ requires C, 62.7; H, 11.4; N, 12.2%. *m/z* (%) (FAB): 115 (M^+, 11), 114 (100), 98 (15), 85 (12), 83 (29) and 56 (5). ν_{max} (nujol): 3250 (brs), 2950, 2860, 1590, 1370, 1120 and 860 cm^{-1}, δ: 3.31 (m, 2H, 2× NCH), 1.96 (m, 2H), 1.23 (m, 2H) and 1.15 (d, 6H, J= 6.0 Hz, 2×CH_3).

cis-**8a.** Obtained as a colourless liquid, found: C, 62.6; H, 11.3; N, 12.0. $C_6H_{13}NO$ requires C, 62.7; H, 11.4; N, 12.2%. *m/z* (%) (FAB): 116 (M^++1, 1), 114 (100), and 98 (16), ν_{max} (nujol): 3300 (brs), 2960, 2860, 1450, 1370, 1320, 1200, 1140, 1020, 970 and 820 cm^{-1}, δ: 6.30 (brs, 1H, OH), 2.78 (m, 2H, 2×NCH), 1.29, 1.43 (2×m, 2×2H) and 1.22 (d, 6H, J=6.0 Hz, 2×CH_3).

1.2.5. *trans*-2,6-Dimethylpiperidin-1-ol (7b) and *cis*-2,6-dimethylpiperidin-1-ol (8b). Iodine (0.6 g, 2.3 mmol) was added to a stirred solution of 6-hepten-2-one oxime **2b** (0.3 g, 2.3 mmol) in nitromethane (10 mL) and the reaction mixture heated at 80°C for 1 h. After cooling, nitromethane was removed under reduced pressure, the residue taken up in dichloromethane (20 mL) and washed with aqueous $Na_2S_2O_3$ solution (20 mL). The dichloromethane solution was dried ($MgSO_4$), the solvent removed under reduced pressure, the residue taken up in dry ether (10 mL), $LiAlH_4$ (0.18 g, 4.7 mmol) added and the mixture stirred at room temperature for 16 h. The mixture was then quenched by the addition of 2N NaOH dropwise until a clear ether layer was obtained. The ether was decanted, dried ($MgSO_4$), and the solvent removed under reduced pressure at room temperature to leave a colourless oil that comprised a 3:1 mixture (^{1}H NMR) of **7b** and **8b**. Purification by flash chromatography eluting with diethyl ether afforded **7b** (34%) and **8b** (23%) as colourless solids.

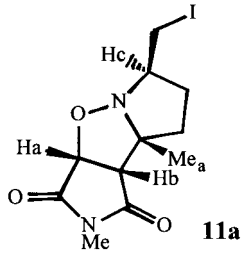
cis-**7b.** Crystallised as colourless needles from ether–petroleum ether, mp 125–126°C. Found: C, 64.9; H, 11.45; N, 10.65. $C_7H_{15}NO$ requires C, 65.05; H, 11.7; N, 10.85%. *m/z* (%) 130 (M^++1, 100), 129 (M^+, 5) and 128 (11). δ: 5.0 (brs, 1H, NOH), 2.52 (m, 2H, 2×NCH), 1.75 (m, 2H), 1.6 (m, 1H), 1.24 (m, 3H) and 1.2 (d, 6H, J=6.0 Hz, 2×CH_3).

trans-**8b.** Crystallised as colourless needles from ether–petroleum ether, mp 109–110°C. Found: C, 64.9; H, 11.8; N, 10.7. $C_7H_{15}NO$ requires C, 65.05; H, 11.7; N, 10.85%. *m/z* (%) 130 (M+1, 33) and 127 (90). δ: 3.42 (m, 1H, NCH), 3.0 (m, 1H, NCH), 1.35–1.92 (m, 6H) and 1.15 (d, 6H, J=6.4 Hz, 2×CH_3).

1.3. *endo*-6-Iodomethyl-2,8a-dimethylhexahydrodipyrrolo[1,2-*b*;3′,4′-*d*]isoxazole-1,3-dione (11a) and *exo*-6-iodomethyl-2,8a-dimethylhexahydrodipyrrolo-[1,2-*b*;3′,4′-*d*]isoxazole-1,3-dione (12a)

1.3.1. I_2 as the electrophile. A solution of 5-hexen-2-one oxime **1a** (0.10 g, 0.89 mmol), and iodine (0.23 g, 0.89 mmol) in dry dichloromethane (10 mL) were stirred at room temperature for 5 min followed by addition of anhydrous K_2CO_3 (0.14 g, 0.98 mmol) and stirring at room temperature for a further 1 h. The mixture was filtered and the filtrate evaporated under reduced pressure. The residual oil was dissolved in benzene (10 mL), NMM (0.1 g, 0.89 mmol) added and the resulting solution heated at 40°C for 6.5 h. After cooling, the solvent was removed under reduced pressure and the ^{1}H NMR spectrum of the product mixture revealed to comprise a 2:1 mixture of **11a** and **12a.** Purification by Kieselgel chromatography eluting with 1:1 v/v ethyl acetate–diethyl-ether afforded the *products* in 59% combined yield.

11a. Obtained as colourless needles from ethyl acetate–hexane, mp 139–141°C. Found: C, 37.6; H, 4.2; I, 36.0; N, 7.9. $C_{11}H_{15}IN_2O_3$ requires C, 37.7; H, 4.3; I, 36.2; N, 8.0%. *m/z* (%) 350 (M^+, 29), 335 (11) 239 (26), 209 (100), 112 (43), 55 (46) and 41 (30). ν_{max} (nujol): 2950, 1720, 1440, 1400, 1300, 1100, 990, 840 cm^{-1}. δ (400 MHz): 1.44 (s, 3H, Me_a), 1.72 (m, 1H), 1.89 (m, 2H), 2.55 (m, 1H), 3.01 (s, 3H, NMe), 3.12 (m,1H, Hc), 3.27 (dd, 1H, J=7.5, 10.0 Hz, CHI), 3.33 (d, 1H, J= 8.0 Hz, Hb), 3.51 (dd, 1H, J=4.4, 10.0 Hz, CHI) and 4.98 (d, 1H, J=8.0 Hz, Ha).

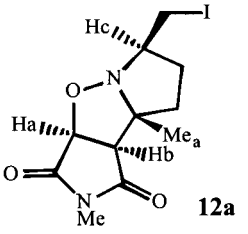


11a

Enhancement (%)

Irradiated hydrogen	Ha	Hb	Hc	Me_a
Ha		6.4		
Hb	9.3			5.0
Me_a		4.2		

12a. Obtained as colourless rhombs from ethyl acetate–hexane, mp 103–104°C. Found: C, 37.6; H, 4.4; I, 36.1; N, 7.9. $C_{11}H_{15}IN_2O_3$ requires C, 37.7; H, 4.3; I, 36.2; N, 8.0% *m/z* (%) 350 (M^+, 27), 335 (12) 239 (22), 209 (100), 112 (52), 98 (58), 86 (17), 55 (51) and 41 (59). ν_{max} (nujol): 2950, 1720, 1440, 1400, 1290 and 840 cm^{-1}. δ (400 MHz): 1.24 (s, 3H, Me_a), 1.79, 1.95, 2.16 and 2.34 (4×m, 4H), 3.03 (s, 3H, NMe), 3.19 (d, 1H, CHI), 3.82 (d, 1H, J=8.0 Hz, Hb), 3.36 (m, 2H, Hc and CHI) and 4.97 (d, 1H, J=8.0 Hz, Ha).



12a

Enhancement (%)

Irradiated hydrogen	Ha	Hb	Hc	Me_a
Ha		7.0		
Hb	9.0			
Me_a				

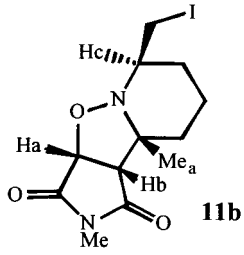
1.3.2. ICI as the electrophile. A solution of 5-hexen-2-one oxime **1a** (0.10 g, 0.89 mmol), ICI (0.14 g, 0.89 mmol) and anhydrous K_2CO_3 (0.12 g, 0.97 mmol) in dry dichloromethane (10 mL) was stirred at room temperature for 1.5 h, under a nitrogen atmosphere. The dichloromethane was removed under reduced pressure and acetonitrile (10 mL) and NMM (0.10 g, 0.89 mmol) were added and the mixture heated at 80°C for 4 h. After cooling, the solvent was removed under reduced pressure. The residual oil was purified by Kieselgel chromatography eluting with 1:1 v/v ethyl acetate–hexane, to give a 2:1 mixture of **11a** and **12a** (0.18 g, 58%). The cycloaddition was also carried out in benzene, which afforded a 2:1 mixture of **11a** and **12a** in 60% yield.

1.3.3. NIS as the electrophile. NIS (1.0 g, 4.45 mmol) was added slowly with stirring over 1 h to a solution of 5-hexen-2-one oxime **1a** (0.50 g, 4.45 mmol) in dry dichloromethane (20 mL) and stirring was continued at rt for 2 h. The dichloromethane was removed under reduced pressure and benzene (10 mL) and NMM (0.10 g, 0.89 mmol) were added to the residue and the mixture was heated at 40°C for 10 h. After cooling, the solvent was removed under reduced pressure. The residue was purified by Kieselgel chromatography eluting with 1:1 v/v ethyl acetate–hexane, to give a 2:1 mixture of **11a** and **12a** (0.65 g, 42%) together with the oxazine **10a** (0.03 g, 3%).

1.3.4. 6-Iodomethyl-3-methyl-5,6-dihydro-4*H*-[1,2]oxazine (10a). Obtained as colourless rhombs from ethyl acetate, mp 39–40°C. Found: C, 30.0; H, 4.2; N, 6.0. $C_6H_{10}INO$ requires C, 30.2; H, 4.2; N, 5.9%, *m/z* (%) 239 (M^+, 48), 170 (6), 141 (10), 127 (19), 112 (61), 98 (39), 81 (21), 68 (24), 56 (46) and 41 (39). ν_{max} (nujol): 2990, 2840, 1620, 1440, 1360 1320, 1300, 1250, 1210, 1090, 1040, 1000, 920, 890, 830, 690 cm^{-1}. δ (400 MHz): 3.68 (m, 1H, OCH), 3.36 (dd, 1H, *J*=4.0, 10.0 Hz, CHI), 3.19 (dd, 1H, *J*=7.5, 10.0 Hz, CHI), 2.22 (m, 2H) 2.16 (m, 1H) 1.93 (s, 3H, Me) and 1.72 (m, 1H).

1.3.5. *endo*-7-Iodomethyl-2,3b-dimethyl-8-oxa-2,7a-diazacyclopenta[*a*]indene-1,3-dione (11b) and *exo*-7-iodomethyl-2,3b-dimethyl-8-oxa-2,7a-diazacyclopenta[*a*]-indene-1,3-dione (12b). Iodine (0.68 g, 2.70 mmol) was added to a stirred solution of 6-hepten-2-one oxime **1b** (0.20 g, 1.50 mmol) in dry dichloromethane (10 mL) and stirring was continued at room temperature for 10 h. The mixture was then washed with saturated aqueous $Na_2S_2O_3$ (20 mL), extracted with dichloromethane (2×20 mL), the combined organic extracts dried ($MgSO_4$), filtered, and the solvent evaporated under reduced pressure. The residual oil was taken up in benzene (20 mL), NMM (0.18 g, 1.50 mmol) added and the mixture heated at 80°C for 5 h. After cooling the solvent was removed under reduced pressure and the ^1H NMR spectrum of the residue showed it to comprise a 2:1 mixture of **11b** and **12b**. Kieselgel column chromatography eluting with 1:1 v/v ethyl acetate–hexane afforded **11b** and **12b** (0.29 g, 50%). Only **12b** could be isolated pure by fractional crystallisation. Found (mixed isomers): C, 39.6; H, 4.8; I, 38.8; N, 7.6. $C_{12}H_{17}IN_2O_3$ requires C, 39.6; H, 4.7; I, 34.9; N, 7.7%). *m/z* (%) (mixed isomers) 364 (M^+, 19), 349 (11), 223 (100), 110 (6), 55 (10) and 41 (21). ν_{max} (nujol) (mixed isomers):1770, 1690, 1440, 1340, 1280, 1140 and 960 cm^{-1}.

11b. Contaminated with **12b**. δ (400 MHz): 1.26 (s, 3H, Me_a), 1.52 and 1.62 (2×m, 2H), 1.72 (m, 2H), 2.14 and 2.33 (2×m, 2H), 2.65 (m, 1H, Hc), 2.97 (s, 3H, NMe), 3.16 (t, 1H, *J*=7.5 Hz, CHI), 3.28 (d, 1H, *J*=8.0 Hz, Hb), 3.52 (dd, 1H, *J*=2.0, 9.5 Hz, CHI) and 4.88 (d, 1H, *J*=8.0 Hz, Ha).

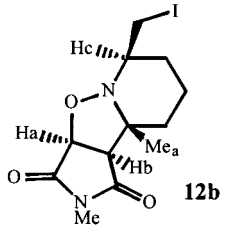


11b

Enhancement (%)

Irradiated hydrogen	Ha	Hb	Hc	Me_a
Ha		4.5		
Hb	10.6			8.8
Me_a		5.2		

12b. Obtained as colourless fine needles from ethyl acetate–hexane, mp 133–134°C. δ (400 MHz): 1.21 (s, 3H, Me_a), 1.52 and 1.62 (2×m, 2H), 1.72 (m, 2H), 2.14 and 2.33 (2×m, 2H), 2.57 (m, 1H, Hc), 3.01 (s, 3H, NMe), 3.06 (dd, 1H, *J*=8.5, 11.0 Hz, CHI), 3.61 (dd, 1H, *J*=2.5, 10.0 Hz, CHI) 3.65 (d, 1H, *J*=8.5 Hz, Hb), and 5.12 (d, 1H, *J*=8.5 Hz, Ha).



12b

Enhancement (%)

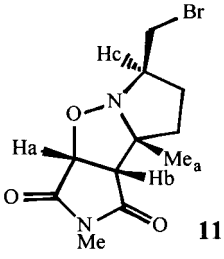
Irradiated hydrogen	Ha	Hb	Hc	Me_a
Ha		6.3	7.6	
Hb	7.9		6.2	
Hc	11.5	12.0		

1.3.6. *endo*-6-Bromomethyl-2,8a-dimethyl-hexahydro-dipyrrolo[1,2-*b*;3′, 4′-*d*]isoxazole-1,3-dione (11c) and *exo*-6-Bromomethyl-2,8a-dimethyl-hexahydro-dipyrrolo-[1,2-*b*;3′,4′-*d*]isoxazole-1,3-dione (12c). A solution of 5-hexen-2-one oxime **1a** (0.50 g, 4.45 mmol) and NBS (0.79 g, 4.45 mmol) in dry dichloromethane (20 mL) was stirred at room temperature for 2 h. The dichloromethane was removed under reduced pressure, the residue taken up in benzene (20 mL), NMM (0.5 g, 4.45 mmol) added and the resulting solution heated at 60°C for 13 h. After cooling, the solvent was removed under reduced pressure to leave a yellow brown oil, which was purified by flash chromatography eluting with 1:1 v/v ethyl acetate–hexane to give a 2:1 mixture of **11c** and **12c** (0.70 g, 78% relative to *E*-**1a**) and the oxazine **10c** (0.17 g, 61% relative to *Z*-**1a**).

10c. Obtained as colourless rhombs from diethylether–hexane, mp 25–26°C. Found: C, 37.4; H, 5.2; Br, 41.8; N,

7.4. $C_6H_{10}BrNO$ requires C, 37.5; H, 5.2; Br, 41.6; N, 7.3%. *m/z* (%) 193 (M^+, 16), 191 (M^+, 16), 98 (100), 94 (7), 81 (9), 68 (20) and 56 (18). δ: 3.87 (m, 1H, OCH), 3.54 (dd, 1H, J=5.0, 10.5 Hz, CHBr), 3.39 (dd, 1H, J=6.5, 10.5 Hz, CHBr), 2.25 (m, 2H), 2.17 (m, 1H), 1,93 (s, 3H, Me) and 1.79 (m, 1H).

11c. Obtained as colourless rhombs from ethyl acetate–hexane, mp 116–117°C. Found: C, 43.9; H, 5.1; Br, 26.6; N, 9.4. $C_{11}H_{15}BrN_2O_3$ requires C, 43.6; H, 5.0; Br, 26.4; N, 9.2%. *m/z* (%) 304 (M^+, 10), 302 (M^+, 10), 289 (13), 287 (13), 209 (100), 193 (19), 191 (19), 112 (75) and 98 (65). ν_{max} (nujol): 2940, 1790, 1720, 1450, 1390, 1290, 1140 and 990 cm^{-1}. δ: 4.99 (d, 1H, J=8.0 Hz, Ha), 3.51 (dd, 1H, J=5.5, 10.5 Hz, CHBr), 3.34 (d, 1H, J=8.0 Hz, Hb), 3.12 (m, 1H, Hc), 3.02 (s, 3H, NMe), 2.56 (m, 1H), 1.86 (m, 2H), 1.69 (m, 2H), and 1.44 (s, 3H, Me_a).

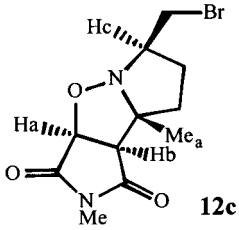


11c

Enhancement (%)

Irradiated hydrogen	Ha	Hb	Hc	Me_a
Ha		5.2		
Hb	9.7			3.8
Me_a		4.8		

12c. Obtained as colourless rhombs from ethyl acetate–hexane, mp 133–134°C. (Found: C, 43.9; H, 5.1; N, 9.4. $C_{11}H_{15}BrN_2O_3$ requires C, 43.6; H, 5.0; N, 9.2%). *m/z* (%) 304 (M^+, 12), 302 (M^+, 13), 287 (12), 285 (12), 209 (100), 193 (27), 191 (18), 112 (85), 55 (37) and 41 (47). ν_{max} (nujol): 2940, 1790, 1720, 1450, 1360, 1290, 1140 and 990 cm^{-1}. δ: 5.00 (d, 1H, J=8.0 Hz, Ha), 3.66 (m, 2H, Hc and CHBr), 3.47 (d, 1H, J=8.0 Hz, Hb), 3.19 (m, 1H, CHBr), 3.04 (s, 3H, NMe), 2.36, 2.18, 2.11 and 1.79 (4×m, 4×H) and 1.25 (s, 3H, Me_a).



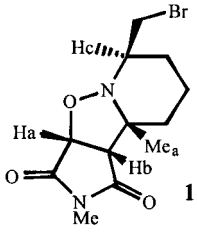
12c

Enhancement (%)

Irradiated hydrogen	Ha	Hb	Hc	Me_a
Ha		6.9	3.8	
Hb	9.1		4.2	
Hc	5.2	4.8		

1.3.7. *endo*-7-Bromomethyl-2,3b-dimethyl-hexahydro-8-oxa-2,7a-diazacyclopenta[*a*]indene-1,3-dione (11d) and *exo*-7-bromomethyl-2,3b-dimethyl-hexahydro-8-oxa-2,7a-diazacyclopenta[*a*]indene-1,3-dione (12d). A solution of 6-hepten-2-one oxime **1b** (0.20 g, 1.60 mmol), and NBS (0.28 g, 1.60 mmol) in dry dichloromethane (20 mL) were stirred at room temperature for 2 h. The dichloromethane was removed under reduced pressure. The residue was taken up in benzene (20 mL), NMM (0.18 g, 1.60 mmol) added and the resulting solution heated at 60°C for 13 h. After cooling the solvent was removed under reduced pressure and the residual oil purified by flash chromatography eluting with 1:1 v/v ethyl acetate–hexane to give a 1:2.3 mixture (0.16 g, 33%) of **11d** and **12d**. Found (mixed isomers): C, 45.2; H, 5.4; Br, 25.3; N, 8.8. $C_{12}H_{17}BrN_2O_3$ requires C, 45.4; H, 5.7; Br, 25.2; N, 8.8%). *m/z* (%) (mixed isomers) 318 (M^+, 2), 316 (M^+, 2), 303 (7), 301 (7), 223 (100), 112 (6), 55 (17), and 41 (21). ν_{max} (nujol) (mixed isomers): 1780, 1700, 1440, 1370, 1340, 1280, 1140 and 960 cm^{-1}.

11d. Obtained as colourless solid contaminated with **12d** δ: 4.88 (d, 1H, J=8.1 Hz, Ha), 3.70 (dd, 1H, J=2.5, 8.9 Hz, CHBr), 3.28 (d, 1H, J=8.6 Hz, Hb), 3.24 (CHBr signal overlapping with doublet of Hb and triplet of CHBr of **12d**) 2.98 (s, 3H, NMe), 2.63 (m, 1H, Hc), 2.40 (m, 1H), 1.82 (m, 2H), 1.36 (s, 3H, Me_a) and 1.23 (m, 2H).

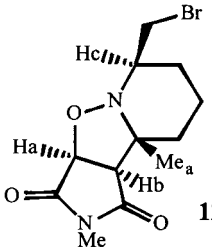


11d

Enhancement (%)

Irradiated hydrogen	Ha	Hb	Hc	Me_a
Ha		6.3		
Hb	1.9			1.7
Me_a	1.4	5.8		

12d. Obtained as colourless needles from ethyl acetate–hexane, mp 129–130°C. δ: 5.14 (d, 1H, J=8.4 Hz, Ha), 3.78 (dd, 1H, J=2.5, 10.0 Hz, CHBr), 3.66 (d, 1H, J=8.5 Hz, Hb), 3.24 (dd, 1H, J=9.0, 10.0 Hz, CHBr), 3.02 (s, 3H, NMe), 2.76 (m, 1H, Hc), 1.76 and 2.24 (2×m, 2×2H), 1.23 and 1.47 (2×m, 2×1H) and 1.21 (s, 3H, Me_a).



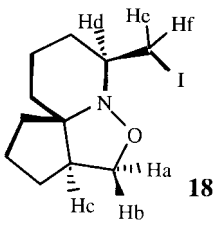
12d

Enhancement (%)

Irradiated hydrogen	Ha	Hb	Hc	Me_a
Ha		5.8	7.3	
Hb	7.5		5.8	
Hc	10.3	8.5		

1.3.8. 2-(2-Iodo-cyclohexyl)-3,5-dimethyltetrahydropyrrolo[3,4-*d*]isoxazole-4,6-dione (14). An ice cold solution of acetaldehyde oxime (0.14 g, 2.43 mmol) in dry dichloromethane (5 mL) was added to a solution of cyclohexene (0.20 g, 2.43 mmol) and iodine (0.63 g, 2.43 mmol) in dry dichloromethane (20 mL) cooled to 0°C. The reaction mixture was stirred and allowed to reach room temperature. The solution was then washed with saturated aqueous $Na_2S_2O_3$ (30 mL), extracted with dichloromethane (2×20 mL), the combined organic layers dried ($MgSO_4$), filtered and the filtrate evaporated under reduced pressure. The residual oil was immediately taken up in benzene (10 mL), NMM (0.27 g, 2.43 mmol) added and the solution heated under reflux for 1 h. After cooling the solvent was evaporated under reduced pressure. The residual deep brown oil was purified by Kieselgel column chromatography eluting with 2:3 v/v diethylether–ethyl acetate to afford the *product* (0.2 g, 25%), which crystallised from ethyl acetate–hexane as colourless cubes, mp 128–129°C. Found: C, 41.1; H, 5.1; I, 33.7; N, 7.5. $C_{13}H_{19}IN_2O_3$ requires C, 41.3; H, 5.1; I, 33.5; N, 7.4%. *m/z* (%) 378 (M^+, 12), 251 (11), 209 (37), 170 (6), 112 (10), 81 (100), 55 (12) and 41 (40). ν_{max} (nujol): 2900, 1710, 1450, 1370, 1290, 1280, 1190, 1050, 940 and 860 cm^{-1}. δ (400 MHz) (C_6D_6): 4.19 (m, 1H), 3.89 (d, 1H, J=7.5 Hz), 3.42 (q, 1H, J=6.5 Hz), 2.87 (m, 1H), 2.67 (s, 3H, NMe), 2.29 (d, 1H, J=7.5 Hz), 1.92 (m, 2H), 1.51 (m, 4H), 1.08 (m, 4H) and 0.63 (d, 1H, J=6.5 Hz, NCMe).

1.3.9. 7-Iodomethyl-octahydro-cyclopenta[3,4]isoxazolo-[2,3-*a*]pyridine (18). A solution of undeca-1,10-dien-6-one oxime **16** (0.20 g, 1.10 mmol), iodine (0.28 g, 1.10 mmol) and the base (K_2CO_3 or Tl_2CO_3) (1.22 mmol) in dry dichloromethane (10 mL) was stirred at room temperature for 16 h. The solution was then washed with saturated aqueous $Na_2S_2O_3$ (30 mL), extracted with dichloromethane (2× 20 mL), the combined organic layers dried ($MgSO_4$), filtered and the filtrate evaporated under reduced pressure. The residual oil was immediately taken up in dry benzene (10 mL) and the solution heated under reflux for 5 h. After cooling the solvent was removed under reduced pressure to leave a viscous deep brown oil, which was purified by Kieselgel column chromatography eluting with 1:1 v/v diethyl ether–ethyl acetate to afford the *product* (0.11 g, 33%) as a viscous colourless oil. Found: C, 43.3; H, 6.2; I, 41.2; N, 4.5. $C_{11}H_{18}INO$ requires C, 43.0; H, 6.4; I, 41.0; N, 4.6% *m/z* (%) 307 (M^+, 12), 180 (9), 166 (100), 112 (8), 55 (9) and 41 (25). ν_{max} (nujol): 2920, 2860, 1440, 1360, 1250, 1170, 1090, 1040, 940, 900 and 720 cm^{-1}. δ: 1.38 (m, 3H), 1.60 and 1.76 (m, 6H), 1.98 and 2.09 (m, 3H), 2.51 (m, 1H, Hc), 2.62 (m, 1H, Hd), 3.03 (t, 1H, J=9.5 Hz, Hf), 3.48 (dd, 1H, J=4.0, 8.5 Hz, Hb), 3.57 (dd, 1H, J=2.5, 9.5 Hz, He) and 4.23 (t, 1H, J=9.0 Hz, Ha).



18

Enhancement (%)

Irradiated hydrogen	Ha	Hb	Hc	Hd	Hf
Ha		23.5	5.4	7.7	
Hb	22.3				
Hc	5.2				
Hd	6.5				4.2
He				3.5	21.3

1.4. Single crystal X-ray diffraction analysis of 3a, 6 and 14

Crystallographic data for all three structures were measured on a Stoe STADI4 4-circle diffractometer using $\omega-\theta$ scans. The data sets of **3a** and **14** were corrected for absorption semi-empirically using azimuthal y-scans. All three structures were solved by direct methods using SHELXS-86[9] and were refined by full-matrix least-squares (based on F^2) using SHELXL-93.[10] The weighting scheme used in all refinements was $w = [\sigma(F_o^2) + (xP)2 + yP]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$. In all cases, all non-hydrogen atoms were refined with anisotropic displacement parameters whilst hydrogen atoms were constrained to predicted positions using a riding model a rotational parameter for methyl and hydroxyl groups. The residuals wR_2 and R_1, given below, are defined as $wR_2 = (\sum[w(F_o - F_c^2)^2]/\sum[wF_o^4])^{1/2}$ and $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$.

1.4.1. Crystal data for 3a. $[C_{12}H_{12}I_2N_2O_2][I]$, 0.46×0.30×0.27 mm, M=606.01, monoclinic, space group $I2/a$, a=14.9833(14), b=11.1692(7), c=10.9067(8) Å, β=92.700(7)°, U=1823.2(2) $Å^3$, Z=4, D_c=2.208 Mg m^{-3}, μ=5.038 mm^{-1}, $F(000)$=1132, T=160 K.

1.4.2. Data collection. Graphite monochromated MoK_α radiation, λ=0.71069 Å, scan speeds 1.5–8.0° min^{-1}, ω scan widths 1.05°+α-doublet splitting, $4.0<2\theta<50.0°$. Maximum and minimum transmission factors: 0.853, 0.576. 3323 data collected, 1603 of which were unique, R_{int}=0.0228. There were 1536 reflections with $F_o>4.0\sigma(F_o)$.

1.4.3. Structure refinement. Number of parameters=90, goodness of fit, s=1.161; weighting parameters x, y=0.0166, 2.6681; wR_2=0.0435, R_1=0.0185.

1.4.4. Crystal data for 6. $C_{11}H_{21}NO_2$, 0.53×0.30×0.27 mm, M=199.29, orthorhombic, space group $P2_12_12_1$, a=8.3897(3), b=11.2676(5), c=11.4629(5) Å, U=1083.61(8) $Å^3$, Z=4, D_c=1.222 Mg m^{-3}, μ=0.658 mm^{-1}, $F(000)$=440, T=290 K.

1.4.5. Data collection. Graphite monochromated CuK_α radiation, λ=1.54184 Å, scan speeds 1.5–8.0° min^{-1}, ω scan widths 1.05°+α-doublet splitting, $4.0<2\theta<130.0°$. 2120 Data collected, 1787 of which were unique, R_{int}=0.0186. There were 1676 reflections with $F_o>4.0\sigma(F_o)$.

1.4.6. Structure refinement. Number of parameters=130, goodness of fit, s=1.061; weighting parameters x, y=0.0568, 0.1128; wR_2=0.0903, R_1=0.0326.

1.4.7. Crystal data for 14. $C_{13}H_{19}IN_2O_2$, 0.72×0.38×0.2 mm, M=378.2, orthorhombic, space group *Pbca*, a=9.7403(14), b=13.950(2), c=21.889(2) Å, U=2974.2(7) Å^3, Z=8, D_c=1.689 Mg m^{-3}, μ=2.159 mm^{-1}, F(000)=1504, T=293 K.

1.4.8. Data collection. Graphite monochromated MoK$_\alpha$ radiation, λ=0.71069 Å, scan speeds 1.5–8.0° min^{-1}, ω scan widths 1.05°+α-doublet splitting, $4.0<2\theta<50.0°$. Maximum and minimum transmission factors: 0.853, 0.576. 5228 Data collected, 2614 of which were unique, R_{int}=0.0183. There were 2092 reflections with $F_o>4.0\sigma(F_o)$.

1.4.9. Structure refinement. Number of parameters=174, goodness of fit, s=1.078; weighting parameters x, y=0.0408, 2.6738; wR_2=0.0876, R_1=0.0329.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers, compound **3a** CCDC 152013; compound **6** CCDC 152014; compound **14** CCDC 152015.

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