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X=Y–ZH systems as potential 1,3-dipoles. Part 56: Cascade 1,3-azaprotio cyclotransfer–cycloaddition reactions between aldoximes and divinyl ketone: the effect of oxime *E*/*Z* isomerism on cycloaddition stereoselectivity☆

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Abstract—The cascade 1,3-azaprotiocyclotransfer (1,3-APT)-1,3-dipolar-cycloaddition (1,3-DC) reaction between aldoximes and divinyl ketone affords mixtures of *exo* and *endo*-isomers of substituted 1-aza-7-oxabicyclo[3.2.1]octan-4-ones, the ratio of which is dependent on the *E*/*Z* geometry of the starting oxime and its ability to isomerise under the thermal reaction conditions.

In the preceeding paper we discussed the general features of cascade 1,3-APT-1,3-DC processes involving ketoximes and divinyl ketone.[1] In this paper we report full details of related studies with aldoximes and divinyl ketone and the role of oxime *E*/*Z*-stereochemistry in these processes.

The reaction between an aldoxime **1** and divinyl ketone **2** represents a Class 2a process where both the azaprotiophile (nitrone generating functionality) and dipolarophile are located in the same molecule (Scheme 1).[2] In the case of ketoximes, such processes lead to the formation of 1-aza-7-oxabicyclo[3.2.1]octan-4-ones **3** and 1-aza-8-oxabicyclo-[3.2.1]octan-4-ones **4**. Control of the cascade outcome is achieved by a judicious choice of experimental conditions.[3] In non-symmetrical ketoxime cases diastereomeric products are also possible at C(8) in **3** and C(7) in **4**.

In contrast, under thermal conditions (81°C, MeCN) aldoximes (R or R′=H) afford mixtures of *exo*-**4** and *endo*-**4** and **3** is rarely detected.[4] The mechanism of the cascade is outlined in Scheme 1. Thermal *E*/*Z* interconversion of oximes is expected to be rapid. Due to steric blockade of the aldoxime lone pair by the R moiety in *E*-**1**, the rate of *E*-oxime 1,3-APT is sluggish ($k_2 \gg k_4$). We expect that k_3, $k_5 \gg k_6$, k_{-6} since the intramolecular cycloaddition is expected to be rapid and the barrier to nitrone isomerisation is high (E_a=25–36 kcal mol^{-1}). Thus we have assumed that k_6 and k_{-6} are essentially zero. Isomerisation of *endo*-**4a** to *exo*-**4a**, which would occur via a retro-cycloaddition–*E*/*Z*-nitrone isomerisation–cycloaddition sequence, was found to be slow[†] showing that the *exo*/*endo*-ratio, under our normal conditions (81°C, 48 h) is the outcome of an essentially kinetically controlled process (k_{-3}, k_{-5} very small). We propose that the outcome of the cascade is controlled by the relative rates of *E*/*Z* oxime isomerism (k_1 and k_{-1}) and 1,3-APT (k_2 and k_4) if 1,3-APT is essentially irreversible at 81°C[5] (k_{-2}, $k_{-4} \approx 0$).

It is proposed that path a and path b (Scheme 1) have different rate determining steps. In path a, oxime isomerisation may become the rate determining step when the aldoxime R substituent is large. In such cases the steric compression between R and the hydroxyl moiety in the *Z*-oxime retards the *E*/*Z*-isomerism. In contrast, 1,3-APT may be rate determining in path b because the R group impedes the reactivity of the lone pair. The ratio of *exo* and *endo*-products is determined by the relative rates of these steps which are, in turn, determined by the nature of R.

☆ For part 55, see Ref. 1.

Keywords: aliphatic oximes; isomerism; cycloaddition.

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† A 3:1 mixture of *endo*-**4a** and *exo*-**4a** was heated at 81°C in CD_3CN to afford, after 84 h, a 1:1 mixture and after 136 h a 1:2 mixture of *endo*-**4a**/*exo*-**4a**.

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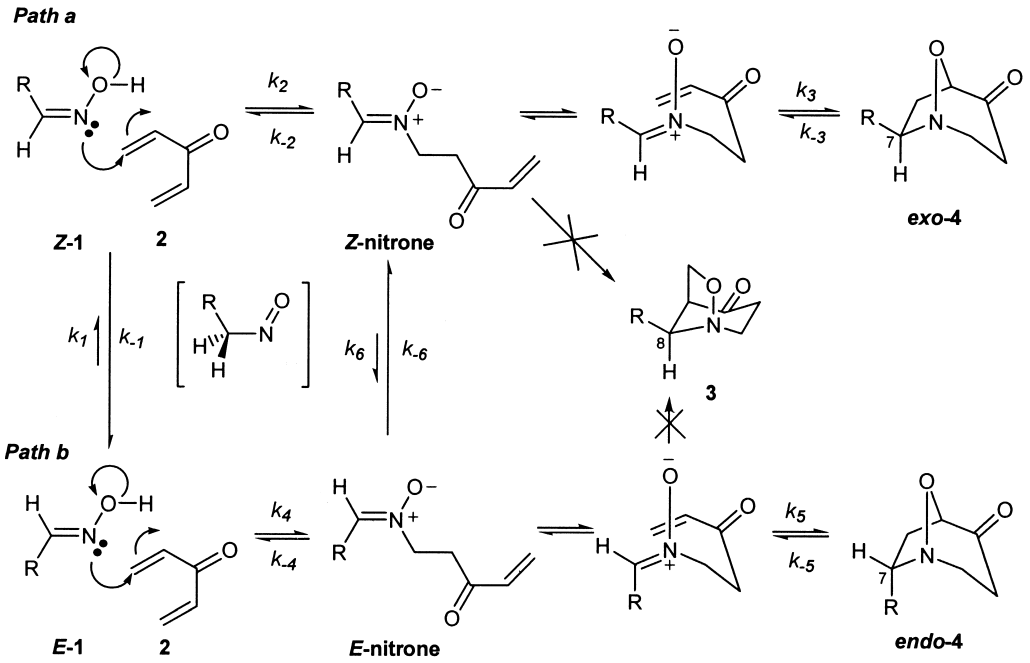
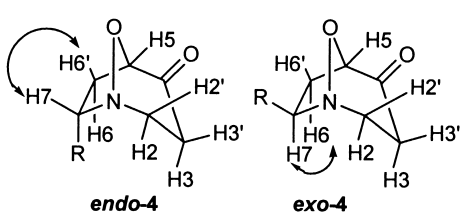


Scheme 1.

Table 1. Reactions between aldoximes and **2** carried out in a STEM block

Oxime	R	R′	Temperature (°C)[a]	Conversion (%)[b]	Ratio[b] *exo*-**4**/*endo*-**4**	Yield (%)[c]
1a	Me	H	80	>95	3.4:1	59
1b	Et	H	80	>95	2.0:1	41
1c	*i*-Pr	H	80	90	1.5:1	34
1d	*t*-Bu	H	80	25	>20:1	11
1e	Bn	H	80	>95	3.0:1	65
1a	Me	H	95	>95	5.6:1	59
1b	Et	H	95	>95	2.7:1	53
1c	*i*-Pr	H	95	90	2.0:1	54
1d	*t*-Bu	H	95	45	>20:1	37
1e	Bn	H	95	>95	4.3:1	57
1a	Me	H	120[d]	>95	8.0:1	65
1a	Me	H	150[d]	>95	5.0:1	70
1e	Bn	H	120[d]	>95	8.0:1	81

Reaction conditions: **1** (1 mol equiv.), **2** (1.2 mol equiv.), acetonitrile (15 mL mmol^{-1} oxime), 48 h.
[a] Temperature of STEM block.
[b] Measured from the ^{1}H NMR spectra of the crude products.
[c] Combined isolated yield.
[d] Reaction carried out in a Schlenk tube, estimated reaction temperature, temperature of oil bath is 130 or 160°C.



A survey of aldoximes **1a**–**e** showed that the diastereoselectivity of the reaction is dependent on the size of the aldoxime R group (Table 1). Predominant formation of *exo*-**4** (e.g. for aldoximes **1a**, **1e**, Table 1) indicates that oxime *E*/*Z*-isomerisation is faster than *E*-oxime 1,3-APT. These reactions were carried out in a STEM block utilising the SK233 Automated Workstation. Increasing the size of the R group (aldoximes **1a**–**d**) resulted in a decrease in *exo*-selectivity. Oxime **1d** affords *exo*-**4d** as the sole product in a slow process (25% conversion at 80°C, 45% conversion at 95°C). The stereochemistry of *exo*-**4d** was determined by X-ray crystallography of its oxime **5** (Fig. 1) whilst the

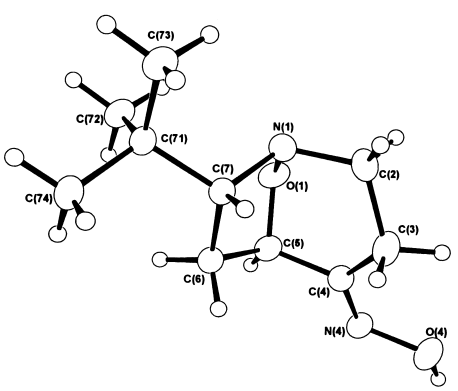


Figure 1. X-Ray crystal structure of **5** (the oxime of *exo*-**4d**).

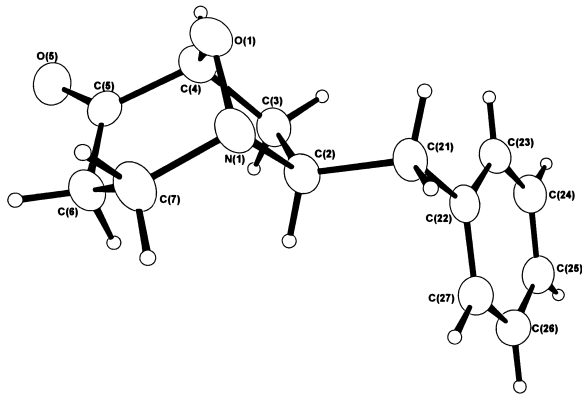


Figure 2. X-Ray crystal structure of *exo*-**4e**.

stereochemistry of the remaining isomers was established by nOe studies. In *exo*-**4** irradiation of H7 results in enhancement at H6′, whereas in *endo*-**4** irradiation of H7 results in enhancement at H6. The signals corresponding to H6 and H6′ are easily identified by their coupling constants to H5; $J_{H6'-H5}$ ca. 8 Hz and J_{H6-H5}=0 Hz (dihedral angle H6–H5=90°). The structure of *exo*-**4e** was confirmed by X-ray crystallography (Fig. 2). Overlapping signals in the ^{1}H NMR spectra of *exo*-**4h** and *exo*-**4i** hampered nOe studies; the stereochemistry was assigned by comparison of the values of $J_{H6'-H7}$ (9.0 Hz in *exo*-**4h** and 9.1 Hz in *exo*-**4i**) with that obtained for *exo*-**4k** ($J_{H6'-H7}$=8.9 Hz). The latter structure was established by X-ray crystallography (Fig. 3)

An increase in the size of the aldoxime R group is expected to decrease both the rate of *E*-oxime isomerisation (Scheme 1, k_1) and *E*-oxime 1,3-APT (k_4) but we propose that the steric effect is more pronounced on the oxime isomerisation step due to the developing steric compression between the R group and the hydroxyl moiety in *Z*-**1**. The *E*-oxime 1,3-APT step can occur provided the oxime R substituent contains an α-hydrogen (as in **1a–c** and **1e**). This allows conformations where a C–H bond, as opposed to a C–R bond, impedes the reactivity of the lone pair. As the size of R increases, the increasing suppression of the *E*-oxime 1,3-APT step is reflected in lower yields and conversions (Table 1). When the oxime R substituent contains no α-hydrogens (**1d**) severe impediment of the N-lone pair reactivity is unavoidable and 1,3-APT proceeds via the *Z*-oxime (path a), affording *exo*-**4d** only (Scheme 1). The slow rate of oxime isomerisation for **1d** is reflected in the low conversion (25% after 48 h in STEM block at 80°C) and yield (11%). We were able to obtain complete

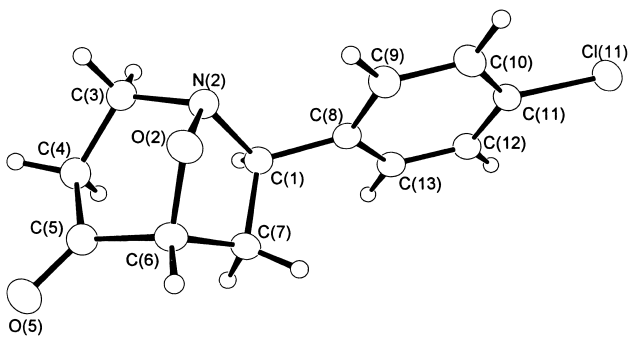


Figure 3. X-Ray crystal structure of *exo*-**4k**.

Table 2. Reactions between aldoximes **1a–e** and **2**

Oxime	R	R′	Conversion (%)[a]	Ratio[b] *exo*-**4**/*endo*-**4**	Yield (%)[a]
1a	Me	H	>95	3.4:1	59
1b	Et	H	>95	2.0:1	50
1c	*i*-Pr	H	90	1.5:1	38
1d	*t*-Bu	H	25	>20:1	11
1d	*t*-Bu	H	>95[c]	>20:1	59
1e	Bn	H	>95	3.0:1	60

Reaction conditions: **1** (1 mol equiv.), **2** (1.2 mol equiv.), acetonitrile (15 mL mmol^{-1} oxime), 48 h.
[a] Combined isolated yield.
[b] Measured from the ^{1}H NMR spectra of the crude products.
[c] 2.8 mol equiv. of **2** used, reaction time 96 h—see Section 3.

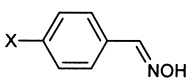
conversion of **1d** by portionwise addition of **2** (2.8 mol equiv.) over 96 h, affording *exo*-**4d** in 59% yield (Table 2).

Increasing the temperature of the STEM block from 80 to 95°C resulted in an increase in the propensity of aliphatic aldoximes to form *exo*-**4** (Table 1). The results obtained using conventional laboratory reactions are reported in Table 2. The STEM block in conjunction with the ReactArray condenser system mimics a closed system to some extent since the degree of *exo*-selectivity is significantly higher at 95°C. We were able to utilise this effect in the case of phenyl acetaldehyde oxime (**1e**), attaining an *exo*-selectivity of 8:1 (81%) when the reaction temperature was 120°C (closed system) (Table 1). Similarly, **1a** afforded an 8:1 ratio of *exo*-**4b** to *endo*-**4b** (65%). However increasing the temperature of the system further (150°C) resulted in reduced levels of *exo*-selectivity (5:1). A 3:1 mixture of *exo*-**4a** and *endo*-**4a** was recovered (89%) unchanged, after heating in a closed system at 120°C for 1 h indicating that a cycloreversion–cycloaddition pathway does not account for the increased *exo*-selectivity. Increased temperatures will facilitate higher rates of *E*/*Z*-oxime equilibration, *E*-1,3-APT (k_4, Scheme 1) and *Z*-1,3-APT (k_2, Scheme 1) but not all to the same degree. It is proposed that the effect is most pronounced on the *E*/*Z* oxime isomerisation step (k_1/k_{-1}, Scheme 1), such that *Z*-1,3-APT (k_2, Scheme 1) becomes the rate determining step under 'high temperature' conditions.

Unlike aliphatic oximes, *E*-benzaldoxime **1f** does not isomerise at 81°C. However, both *E* and *Z*-isomers can be prepared and stored separately.[6] The observation that *E*-**1f** forms *endo*-**4f** exclusively while *Z*-**1f** affords *exo*-**4f** exclusively (Table 3) supports the mechanism outlined in Scheme 1. The application of microwave activation to the reaction of *Z*-**1f** has been briefly studied. As expected microwave heating to 150°C decreases the reaction from 48 h to 15 min. whilst retaining the excellent diastereoselectivity observed at the lower temperature (Table 4). However, the regioselectivity suffers somewhat in that a significant amount (14%) of *exo*-**3f** is also produced showing that the *Z*-nitrone conversion to **3** becomes activated at these higher temperatures.

We also carried out the process with both *E*- and *Z*-*para*-substituted benzaldoximes (Table 3). Table 3 shows that *Z*-benzaldoxime and *Z*-benzaldoximes with a *para*-electron withdrawing group (CF_3, CN, NO_2) (Table 3, entries 3, 5, 7

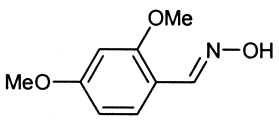
Table 3. Reactions between aromatic aldoximes and **2**

Entry		Isomer	p*K*a of OH[9]	Conversion (%)[a]	Ratio *exo*-**4**/*endo*-**4**[a]	Yield (%)[b]
1	H[c]	*E*-**1f**[c]	11.37	10	1:>20	–
2	H	*E*-**1f**	11.37	55	1:>20	18
3	H	*Z*-**1f**	11.37	>95	>20:1	79
4	CF_3	*E*-**1g**	10.81	<5	–	–
5	CF_3	*Z*-**1g**	10.81	>95	>20:1	76
6	CN	*E*-**1h**	10.68	<5	–	–
7	CN	*Z*-**1h**	10.68	90	>20:1	44
8	NO_2	*E*-**1i**	10.57	<5	–	–
9	NO_2	*Z*-**1i**	10.57	55	>20:1	19
10	MeO	*E*-**1j**	11.49	80	4:1[d]	55
11	MeO	*Z*-**1j**	11.49	>95	7:1	78
12	Cl	*E*-**1k**	11.05	>95	10:1[e]	61
13	Cl	*Z*-**1k**	11.05	>95	8:1	76
14	F	*E*-**1l**	11.18	>95	8:1	72
15	F	*Z*-**1l**	11.18	>95	12:1	70
16	2, 4-diMeO	*E*-**1m**	11.72	80	1:2	50

Reaction conditions: **1** (1 mol equiv.), **2** (1.2 mol equiv.), acetonitrile (15 mL $mmol^{-1}$ oxime), reflux, 48 h.
[a] Measured from the ^1H NMR spectra of the crude products.
[b] Combined isolated yield.
[c] Reaction carried out in a STEM block at 80°C.
[d] 30% of *exo*-**3j** was obtained.
[e] 10% of *exo*-**3k** was obtained.

and 9) give *endo*-**4** products stereoselectively with little, if any, detectable *exo*-**4** isomer. Thus in these cases *E*/*Z*-oxime isomerisation is considerably slower than the 1,3-APT-1,3-DC sequence. *E*/*Z*-Isomerisation becomes more competitive with the 1,3-APT-1,3-DC sequence in *Z*-benzaldoximes with a *para*-donor group (MeO) or -I, π-donor groups (Cl, F) (Table 3, entries 11, 13 and 15). The strongest π-donor (MeO) furnishes a 7:1 mixture of *exo*-**4** and *endo*-**4** (entry 11) whilst the most electronegative halogen (F) exhibits less *E*/*Z*-isomerisation (entry 15) (12:1 mixture of *exo*-**4** and *endo*-**4**) than *para*-chloro benzaldoxime (entry 13, 8:1 mixture of *exo*-**4** and *endo*-**4**). As expected Z-benzaldoximes with the strongest electron withdrawing groups (CN, NO_2) give lower conversions (entries 7 and 9) mirroring the trend in p*K*a[7] and emphasizing the nucleophilic component in the 1,3-APT process.

In the reaction of *E*-oximes we observe that those bearing electron withdrawing groups are essentially configurationally stable under our reaction conditions with <5% conversion observed (Table 3, entries 4, 6 and 8). The low conversion illustrates the combined effect of low nitrogen nucleophilicity and the steric blockade of the nitrogen lone pair by the *syn*-aryl group in the 1,3-APT step i.e. this key initial step (Scheme 1, path b) is switched off. However, the *E*-benzaldoximes bearing electron donor groups afford mixtures of *exo* and *endo*-**4** with the former predominating (Table 3, entries 10, 12 and 14) except for the *E*-2,4-dimethoxybenzaldoxime in which *endo*-**4** is the predominant isomer (Table 3, entry 16). In these cases the electron donor substituents promote both 1,3-APT in the sterically hindered *E*-oximes and *E*/*Z*-isomerisation in proportion to their donor capability. It should be remembered that aryl groups are stereochemically anisotropic and can project an edge or face of the aryl ring towards the nitrogen lone pair in the *E*-benzaldoximes. Note that we have previously reported MNDO calculations which indicate that C–N bond formation is in advance of C–H bond formation in the 1,3-APT transition state.[8]



***E*-1m**

Table 4. Microwave induced reactions between (*Z*)-benzaldoxime and **2**

Time (min)	Conversion %[a,b]	*exo*-**4f**/*endo*-**4f**	*exo*-**4f**/*exo*-**3f**[a]	Yield (%)
5	88	16:1	6:1	–
10	93	>20:1	6:1	–
15	>95	>20:1	5.5:1	66[c]
30	>95	>20:1	5.5:1	–
60	>95	>20:1	6:1	–

Reaction conditions: **1f** (2 mmol), **2** (2.4 mmol), acetonitrile (2.5 mL $mmol^{-1}$ oxime), reactions carried out in a sealed tube.
[a] Measured from the ^1H NMR spectra of the crude products.
[b] In all cases trace amount (<5%) of benzaldehyde are formed.
[c] Combined yield.

In summary, we have shown that the ratio of *exo*/*endo* isomers in tandem 1,3-azaprotio cyclotransfer–cycloaddition reactions between divinyl ketone and aldoximes is dependent on the relative rates of *Z*/*E* oxime isomerisation and 1,3-APT.

1. Experimental

Melting points were determined on a Koffler hot-stage apparatus and are uncorrected. Mass spectral data were obtained on an Autospec instrument at 70 eV. Nuclear magnetic resonance spectra were recorded on Brucker AM

250, Brucker DPX 300 and Brucker DRX 500 machines. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane (TMS) as internal standard. All spectra were recorded in deuteriochloroform. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=double doublet, bs=broad singlet, C_q=quaternary carbon. Microanalyses were obtained using a Carbo Erba MOD11016 instrument. Infra-red data were recorded on films, prepared by evaporation of a dichloromethane solution on a Spectra-Tech Inc. Trough Plate Ark on a Nicolet Magna-IR 560 spectrometer. HPLC analysis was performed on Gilson instruments. X-Ray analysis was performed on a Stoe STADI 4-circle machine or a Nonius Kappa CCD area-detector diffractometer. The term 'petroleum ether' refers to the fraction of petroleum ether with boiling point between 40 and 60°C. Column chromatography was performed using flash silica gel (Merck 9385).

Assignment of the geometry of aldoxime isomers is based on the chemical shift of the imine proton which is deshielded when it is *cis* to the hydroxy moiety. In the absence of any literature data, or comparison with the opposite isomer, oximes were assumed to be the (*E*)-isomers.

Oximes **1a**, *E*-**1f**, *E*-**1i**, *E*-**1l** and *E*-**1m** were obtained from commercial sources. Oximes **1b–e**, *E*-**1f–h**, *E*-**1j**, *E*-**1k**, *Z*-**1f**, *Z*-**1h** and *Z*-**1j** were prepared according to the general procedure and gave identical spectroscopic data to that reported in the literature.[10] Divinyl ketone was prepared according to the literature procedure.[11]

1.1. General procedure for the preparation of aldoximes

The appropriate ketone was added to a solution of hydroxylamine hydrochloride and sodium acetate in 2:1 v/v acetonitrile–water and the resulting mixture stirred at ambient temperature for 18 h. The mixture was then extracted with chloroform and the combined organic extracts were washed with water, dried ($MgSO_4$), filtered and the filtrate concentrated in vacuo. The residue was crystallised or distilled as appropriate.

1.2. General procedure for *Z*-aryl aldoximes

The appropriate (*E*)-oxime was added to an excess of concentrated hydrochloric acid with cooling. The mixture was then cooled further to 5°C and the resulting precipitate filtered and slowly added to a stirred solution of saturated aqueous sodium bicarbonate and the resulting slurry warmed for a few minutes. The precipitate was collected by filtration and crystallised.

1.2.1. (*Z*)-4-Trifluoromethylbenzaldoxime (*Z*-1g). (*E*)-4-Trifluoromethylbenzaldoxime (3.00 g, 16 mmol) was treated with concentrated hydrochloric acid (7 mL) according to the general procedure. Subsequent work up afforded the product (2.17 g, 72%) which crystallised from diethyl ether as colourless needles, mp 115–117°C. Found C, 51.1; H, 3.3; N, 7.4; $C_8H_6F_3NO$ requires C, 50.8; H, 3.2; N, 7.4%; δ_H (250 MHz, d_6-DMSO) 12.05 (s, 1H, NOH), 8.18 (d, 2H, *J*=8.2 Hz), 7.82 (d, 2H, *J*=8.3 Hz, 2×ArH) and 7.60 (s, 1H, NCH); *m/z* (FAB) 190 (M+1, 100); ν (cm^{-1}) 3179 (OH) and 1653 (C=N).

1.2.2. (*Z*)-4-Nitrobenzaldoxime (*Z*-1i). (*E*)-4-Nitrobenzaldoxime (5.00 g, 30 mmol) was treated with concentrated hydrochloric acid (15 mL) according to the general procedure. Subsequent work up afforded the product (4.25 g, 85%) which crystallised from acetone–pentane as yellow needles, mp 175–177°C. Found: C, 50.6; H, 3.95; N, 17.1; $C_7H_6N_2O_3$ requires C, 50.6; H, 3.65; N, 16.85%; δ_H (250 MHz; d_6-DMSO) 12.22 (s, 1H, NOH), 8.18 (m, 4H, 4×ArH) and 7.59 (s, 1H, NCH); *m/z* (EI; %) 166 (M^+, 48), 76 (67), 75 (73), 74 (44), 65 (95), 63 (48), 51 (52), 50 (100) and 39 (79); ν (cm^{-1}) 3168 (OH), 1643 (C=N), 1519 (NO) and 1342 (NO).

1.2.3. (*Z*)-4-Methoxybenzaldoxime *Z*-1j. (*E*)-4-Methoxybenzaldoxime (2.11 g, 14 mmol) was treated with concentrated hydrochloric acid (7 mL) according to the general procedure. The crude product was obtained as a colourless solid (1.61 g, 75%) which crystallised from dichloromethane–petroleum ether as colourless needles (0.72 g, 34%), mp 128–130°C. Found C, 63.6; H, 6.05; N, 9.25; $C_8H_9NO_2$ requires, C, 63.6; H, 6.0; N, 9.5%; δ_H (250 MHz) 9.80 (bs,1H, NOH), 7.95 (m, 2H, 2×ArH), 7.33 (s, 1H, NCH), 6.95 (m, 2H, 2×ArH) and 3.85 (s, 3H, Me); *m/z* (FAB; %) 152 (M+1, 100) and 151 (M^+, 53); ν cm^{-1}) (film) 3175 (OH), and 1601 (C=N).

1.2.4. (*Z*)-4-Chlorobenzaldoxime (*Z*-1k). (*E*)-4-Chlorobenzaldoxime (5.00 g, 32 mmol) was treated with concentrated hydrochloric acid (15 mL) according to the general procedure. Subsequent work up afforded the product (4.00 g, 80%) which crystallised from dichloromethane–pentane as colourless needles, mp 132–133°C. Found: C, 53.75; H, 4.15; N, 8.7; Cl, 22.5; C_7H_6NOCl requires C, 54.05; H, 3.9; N, 9.0; Cl, 22.8%; δ_H (250 MHz; d_6-DMSO) 11.85 (s, 1H, NOH), 8.01 (d, 2H, *J*=8.6 Hz, 2×ArH), 7.51 (d, 2H, *J*=8.6 Hz, 2×ArH) and 7.46 (s, 1H, NCH); *m/z* (FAB; %): 158 ^{37}(M+1, 35), 156 ^{35}(M+1, 100) and 149 (59); ν (cm^{-1}) 3159 (OH) and 1653 (C=N).

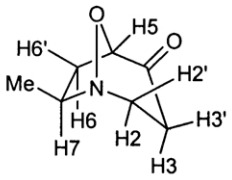
1.2.5. (*Z*)-4-Fluorobenzaldoxime (*Z*-1l). (*E*)-4-Fluorobenzaldoxime (5.00 g, 36 mmol) was treated with concentrated hydrochloric acid (17 mL) according to the general procedure. The product (4.45 g, 89%) crystallised from dichloromethane–pentane as colourless needles, mp 130–132°C. Found: C, 60.45; H, 4.35; N, 10.05; C_7H_6NOF requires C, 60.65; H, 4.35; N, 10.05; δ_H (250 MHz, d_6-DMSO) 11.71 (s, 1H, NOH), 8.07 (m, 2H, 2×ArH), 7.44 (s, 1H, NCH) and 7.28 (m, 2H, 2×ArH); *m/z* (EI; %) 139 (M^+, 61), 121 (33), 96 (78), 95 (79), 94 (35), 83 (32), 75 (100), 57 (36) and 50 (36); ν (cm^{-1}) 3190 (OH) and 1653 (C=N).

1.3. General procedure for the 1,3-APT-1,3-DC cascades

A solution of divinyl ketone (108 μL, 1.2 mmol) and oxime (1 mmol) in acetonitrile (15 mL) was heated at reflux with stirring for 48 h. After cooling the mixture was concentrated in vacuo and the residue purified by column chromatography.

1.3.1. 7-*exo*-Methyl-8-oxa-1-azabicyclo[3.2.1]octan-4-one (*exo*-4a) and 7-*endo*-methyl-8-oxa-1-azabicyclo[3.2.1]octan-4-one (*endo*-4a). Acetaldoxime (0.059 g, 1 mmol) and divinyl ketone (108 μL, 1.2 mmol) were reacted according to the general procedure for 48 h. Subsequent work up afforded the crude product as a brown gum, comprising of a 3.4:1 mixture of *exo*-**4a** and *endo*-**4a**. Flash chromatography, eluting with 1:4 v/v ethyl acetate–diethyl ether afforded the same isomeric mixture in a pure form (0.083 g, 59%). Partial separation was achieved by preparative HPLC: Chiralpak AD 250×20 mm^2; wavelength: 254 nm; mobile phase: 4:1 hexane–ethanol; flow rate: 1 mL min^{-1}; *exo*-**4a** t_R 14.48 and 15.56 min (enantiomers); *endo*-**4a** t_R 19.55 and 21.89 min (enantiomers).

exo-**4a**. Data were obtained from an enriched 10:1 mixture of *exo*-**4a** and *endo*-**4a**, obtained as a pale yellow oil. Found: C, 59.55; H, 7.9; N, 9.7; $C_7H_{11}NO_2$ requires: C, 59.55; H, 7.85; N, 9.9%; δ_H (500 MHz) 4.42 (d, 1H, *J*=8.1 Hz, H5), 3.71 (ddd, 1H, *J*=14.3, 10.7, 6.2 Hz, H2′), 3.52 (m, 1H, H7), 3.28 (ddt, 1H, *J*=14.3, 8.4, 1.1 Hz, H2), 2.52 (dddd, 1H, *J*=16.7, 10.7, 8.4, 0.5 Hz, H3), 2.44 (ddd, 1H, *J*=13.2, 6.4, 1.2 Hz, H6), 2.31 (ddt, 1H, *J*=16.7, 6.2, 1.2 Hz, H3′), 2.12 (dddd, 1H, *J*=13.2, 8.1, 4.3, 1.0 Hz, H6′) and 1.32 (d, 3H, *J*=6.6 Hz, CH_3); *m/z* (EI; %) 141 (M^+, 70), 98 (23), 70 (29), 56 (100), 55 (56), 43 (41), 42 (71) and 41 (37); ν (cm^{-1}) 1725 (C=O).

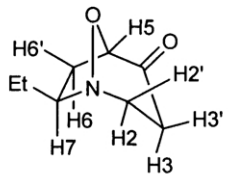


	Enhancement (%)				
Signal Irradiated	H5	H7	H6	H6'	CH_3
H6		**2.6**		8.2	
H6'	**2.5**		11.3		**2.9**
CH_3		1.4		**1.1**	

endo-**4a**. Data were obtained as an enriched 3.3:1 mixture of *endo*-**4a** and *exo*-**4a**, obtained as a pale yellow oil. Found: C, 59.55; H, 7.9; N, 9.7; $C_7H_{11}NO_2$ requires: 59.55; H, 7.85; N, 9.9%; δ_H (500 MHz) 4.37 (dd, 1H, *J*=8.7, 1.6 Hz, H5), 3.77 (dtd, 1H, *J*=9.6, 7.0, 6.9 Hz, H7), 3.70 (ddd, 1H, *J*=14.7, 10.7, 6.4 Hz, H2′), 3.49 (ddt, 1H, *J*=14.7, 8.5, 1.0 Hz, H2), 2.75 (dtd, 1H, *J*=12.9, 9.6, 1.1 Hz, H6′), 2.46 (m, 1H, H3), 2.28 (dd, 1H, *J*=16.9, 6.4 Hz, H3′), 1.69 (ddd, 1H, *J*=12.9, 6.9, 1.6 Hz, H6) and 1.40 (d, 3H, *J*=7.0 Hz, CH_3); *m/z* (EI; %) 141 (M^+, 66), 83 (32), 70 (37), 56 (100), 55 (78), 43 (54), 42 (93) and 41 (44); ν (cm^{-1}) 1718 (C=O).

1.3.2. 7-*exo*-Ethyl-8-oxa-1-azabicyclo[3.2.1]octan-4-one (*exo*-4b) and 7-*endo*-ethyl-8-oxa-1-azabicyclo[3.2.1]-octan-4-one (*endo*-4b). Propionaldoxime (0.073 g, 1 mmol) and divinyl ketone (108 μL, 1 mmol) were reacted according to the general procedure for 48 h. Subsequent work up afforded the crude product as a brown gum comprising of a 2:1 mixture of *exo*-**4b** and *endo*-**4b**. Flash chromatography, eluting with diethyl ether afforded *exo*-**4b** (0.050 g, 32%) and a 5:1 mixture of *endo*-**4b** and *exo*-**4b** (0.027 g, 17%).

exo-**4b**. The product was obtained as a pale yellow oil. Found C, 62.2; H, 8.65; N, 8.75; $C_8H_{13}NO_2$ requires C, 61.9; H, 8.4; N, 9.0%. δ_H (500 MHz) 4.39 (d, 1H, *J*=8.0 Hz, H5), 3.73 (ddd, 1H, *J*=14.1, 10.7, 5.9 Hz, H2′), 3.24 (dd, 1H, *J*=14.1, 8.4 Hz, H2), 3.19 (m, 1H, H7), 2.53 (ddd, 1H, *J*=16.8, 10.7, 8.4 Hz, H3), 2.39 (dd, 1H, *J*=13.1, 8.2 Hz, H6), 2.31 (dd, 1H, *J*=16.8, 5.9 Hz, H3′), 2.14 (ddd, 1H, *J*=13.1, 8.0, 4.7 Hz, H6′), 1.71–1.45 (dm, 2H, CH_2CH_3) and 1.00 (t, 3H, *J*=7.3 Hz, CH_2CH_3); *m/z* (EI; %) 155 (M^+, 92), 84 (76), 70 (100), 56 (82), 42 (78), 41 (74) and 39 (32); ν (cm^{-1}) 1730 (C=O).



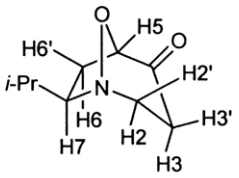
	Enhancement (%)					
Signal Irradiated	H5	H7	H6	H6'	CH_2CH_3	CH_3
H6		**4.0**		12.0		
H6'	**3.8**		12.1		**1.6**	**1.4**

endo-**4b**. Data were obtained from an enriched 5:1 mixture of *endo*-**4b** and *exo*-**4b**, obtained as a pale yellow oil. HRMS found 155.0936; $C_8H_{13}NO_2$ requires 155.0946; δ_H (500 MHz) 4.37 (m, 1H, H5), 3.69 (ddd, 1H, *J*=14.6, 10.6, 6.4 Hz, H2′), 3.53 (m, 1H, H7), 3.44 (ddt, 1H, *J*=14.6, 8.6, 1.0 Hz, H2), 2.69 (dtd, 1H, *J*=12.9, 9.6, 1.1 Hz, H6′), 2.41 (m, 1H, H3), 2.28 (distorted dd, 1H, *J*=16.9, 6.4 Hz, H3′), 1.82 (m, 1H, $CHHCH_3$), 1.67 (ddd, 1H, *J*=12.9, 7.1, 2.9 Hz, H6), 1.60 (m, 1H, $CHHCH_3$) and 1.10 (t, 3H, *J*=7.4 Hz, CH_3); *m/z* (EI; %): 155 (M^+, 81), 84 (61), 73 (93), 70 (98), 56 (100), 55 (90), 43 (42), 42 (95) and 41 (78).

1.3.3. 7-*exo*-Isopropyl-8-oxa-1-azabicyclo[3.2.1]octan-4-one (*exo*-4c) and 7-*endo*-isopropyl-8-oxa-1-azabicyclo-[3.2.1]octan-4-one (*endo*-4c). Isobutyraldoxime (0.087 g, 1 mmol) and divinyl ketone (108 μL, 1.2 mmol) were reacted according to the general procedure for 48 h. Subsequent work-up afforded the crude product as a brown gum, comprising of a 1.5:1 mixture of *exo*-**4c** and *endo*-**4c** and unreacted oxime (10%). Flash chromatography, eluting with diethyl ether, afforded *exo*-**4c** (0.034 g, 20%) and *endo*-**4c** (0.030 g, 18%).

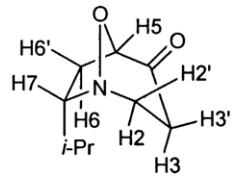
exo-**4c**. Obtained as a pale yellow oil. HRMS: Found 169.1106; $C_9H_{15}NO_2$ requires 169.1103; δ_H (500 MHz) 4.38 (m, 1H, H5), 3.71 (ddd, 1H, *J*=14.0, 10.7, 5.8 Hz, H2′), 3.20 (ddt, 1H, *J*=14.0, 8.4, 1.1 Hz, H2), 2.99 (m, 1H, H7), 2.53 (ddd, 1H, *J*=16.9, 10.7, 8.4 Hz, H3), 2.32 (ddt, 1H, *J*=16.9, 5.8, 1.1 Hz, H3′), 2.30–2.27 (m, 2H, H6′ and H6), 1.72 (m, 1H, $CH(CH_3)_2$), 1.02 (d, 3H, *J*=6.6 Hz, CH_3) and 0.93 (d, 3H, *J*=6.7 Hz, CH_3); *m/z* (EI; %) 169 (M^+, 54), 84

(100), 70 (55), 56 (77), 55 (93), 43 (62), 42 (99) and 40 (56); ν (cm^{-1}) 1730.



	Enhancement (%)		
Signal Irradiated	H2'	H2	H7
H7		**1.1**	
H2	15.3		**2.1**
H2'		13.5	

endo-**4c**. Obtained as a pale yellow oil. HRMS: Found 169.1106; $C_9H_{15}NO_2$ requires 169.1103; δ_H (500 MHz): 4.37 (d, 1H, J=8.8 Hz, H5), 3.70 (ddd, 1H, J=14.6, 10.6, 6.4 Hz, H2′), 3.49 (dd, 1H, J=14.6, 8.5 Hz, H2), 3.26 (ddd, 1H, J=11.2, 9.3, 7.7 Hz, H7), 2.65 (m, 1H, H6′), 2.46 (m, 1H, H3), 2.28 (dd, 1H, J=16.8, 6.4 Hz, H3′), 1.74–1.70 (m, 2H, H6 and C*H*(CH_3)$_2$), 1.14 (d, 3H, J=6.3 Hz, CH_3) and 1.07 (d, 3H, J=6.6 Hz, CH_3); *m/z* (EI; %) 169 (M^+, 34), 878 (50), 83 (41), 56 (37), 55 (100), 43 (42), 42 (45) and 41 (42); ν (cm^{-1}) 1730 (C=O).



	Enhancement (%)			
Signal Irradiated	H5	H7	H6'	H6 + C*H*(CH_3)$_2$[a]
H6'	**3.9**	**4.0**		15.2
H7	0.3		**2.8**	

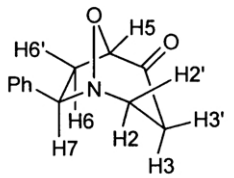
a. Overlapping signals.

1.3.4. 7-*exo*-*tert*-Butyl-8-oxa-1-azabicyclo[3.2.1]octan-4-one (*exo*-4d). Divinyl ketone (125 μL, 1.4 mmol) was added to a stirred solution of **1d** (0.101 g, 1 mmol) in dry acetonitrile (15 mL) and the resulting mixture was heated and stirred at reflux. After 24 and 48 h further additions of divinyl ketone (63 μL, 0.7 mmol) were made. After a total reaction time of 96 h the reaction mixture was allowed to cool. Subsequent work up afforded the crude product as a brown solid. Flash chromatography, eluting with diethyl ether, afforded the product as a colourless amorphous solid (0.108 g, 59%) that crystallised from pentane as colourless needles, mp 55–60°C. Found C, 65.55; H, 9.35; N, 7.35; $C_{10}H_{17}NO_2$ requires C, 65.45; H, 9.20; N, 7.60%; δ_H (500 MHz) 4.38 (d, 1H, J=7.9 Hz, H5), 3.73 (ddd, 1H, J=14.0, 10.5, 5.9 Hz, H2′), 3.18 (dd, 1H, J=14.0, 8.3 Hz, H2), 2.99 (dd, 1H, J=8.6, 6.1 Hz, H7), 2.54 (ddd, 1H, J=16.8, 10.5, 5.9 Hz, H3), 2.35 (m, 2H, H6′ and H3′), 2.17 (dd, 1H, J=13.5, 8.6 Hz, H6) and 0.94 (s, 9H, 3×Me); *m/z* (EI; %) 183 (M^+, 45), 126 (43), 84 (100), 70 (83), 57 (67), 56 (51), 42 (77), 43 (53) and 41 (90); ν (cm^{-1}) 1728 (C=O).

1.3.5. (4-*E*)-7-*tert*-Butyl-8-oxa-1-azabicyclo[3.2.1]octane-4-one oxime (5). 7-*exo*-*tert*-Butyl-8-oxa-1-azabicyclo-[3.2.1]octan-4-one (0.095 g, 0.52 mmol) (**4d**) and hydroxylamine hydrochloride (0.040 g, 0.57 mmol) were reacted according to the general procedure for 18 h. Subsequent work up afforded the crude product as an amorphous yellow solid (0.082 g, 80%) that crystallised from petroleum ether as pale yellow plates, mp 131–133°C. Found: C, 60.85; H, 9.15; N, 14.25; $C_{10}H_{18}N_2O_2$ requires: C, 60.6; H, 9.15; N, 14.15%; δ_H (500 MHz) 8.39 (s, 1H, NOH), 4.66 (d, 1H, J=7.3 Hz, H5), 3.52 (m, 1H, H2′), 2.95 (m, 3H, H7, H2 and H3), 2.28 (m, 2H, H3′ and H6′), 2.13 (dd, 1H, J=12.9, 8.6 Hz, H6) and 0.91 (s, 9H, 3×CH_3); *m/z* (EI; %) 198 (M^+, 100), 141 (73), 125 (31), 114 (36), 110 (31), 98 (75), 96 (35), 70 (54), 69 (52), 57 (67), 55 (43), 54 (47), 43 (32), 42 (96) and 39 (34); ν (cm^{-1}) 3238 (OH) and 1653 (C=N).

1.3.6. 7-*exo*-Benzyl-8-oxa-1-azabicyclo[3.2.1]octan-4-one (*exo*-4e). (*Z*)-Phenylacetaldoxime (0.135 g, 1 mmol) and divinyl ketone (108 μL, 1.2 mmol) were reacted according to the general procedure for 48 h. Subsequent work-up afforded the crude product as a yellow solid, comprising of a 3:1 mixture of *exo*-**4e** and *endo*-**4e**. Flash chromatography, eluting with 4:1 v/v diethyl ether–pentane, afforded the same isomeric mixture in a pure form (0.130 g, 60%). Crystallisation from cyclohexane afforded the pure 7-*exo* isomer as colourless needles, mp 119–121°C. Found C, 72.05; H, 6.75; N, 6.4; $C_{13}H_{15}NO_2$ requires C, 71.85; H, 6.95; N, 6.45%; δ_H (300 MHz) 7.34–7.21 (m, 5H, 5×ArH), 4.43 (d, 1H, J=6.9 Hz, H5), 3.71 (ddd, 1H, J=14.1, 10.2, 5.7 Hz, H2′), 3.63–3.54 (m, 1H, H7), 3.19 (dd, 1H, J=14.1, 8.4 Hz, H2), 3.09 (dd, 1H, J=13.6, 7.6 Hz, PhC*H*H), 2.69 (dd, 1H, J=13.6, 6.9 Hz, PhCH*H*), 2.54–2.42 (m, 1H, H3) and 2.36–2.20 (m, 3H, H3′, H6′ and H6); *m/z* (%) 218 (M+1, 7), 217 (M^+, 46), 146 (9), 126 (53), 91 (100), 84 (73), 70 (54) and 56 (53); ν (cm^{-1}) (DCM solution) 1725.

1.3.7. 7-*exo*-Phenyl-8-oxa-1-azabicyclo[3.2.1]octan-4-one (*exo*-4f). (a) (*Z*)-Benzaldoxime (0.242 g, 2 mmol) and divinyl ketone (215 μL, 2.4 mmol) were reacted according to the general procedure for 48 h. Subsequent work-up afforded the crude product as a pale brown solid. Flash chromatography, eluting with 9:1 v/v diethyl ether–pentane afforded the product (0.320 g, 79%) which crystallised from toluene as colourless plates, mp 110–112°C. Found C, 70.7; H, 6.25; N, 7.15; $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.45; N, 6.9; δ (400 MHz) 7.40–7.24 (m, 5H, 5×PhH), 4.57 (d, 1H, J=8.0 Hz, H5), 4.46 (dd, 1H, J=8.9, 5.1 Hz, H7), 3.84 (ddd, 1H, J=14.2, 10.7, 6.0 Hz, H2′), 3.42 (dd, 1H, J=14.2,

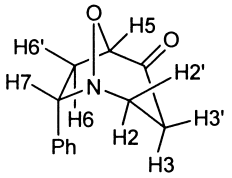


	Enhancement			
Signal Irradiated	H5	H6	H6'	H7
H6			21	**7**
H6'	**9**	20		
H7		**5**		

8.4 Hz, H2), 2.84 (dd, 1H, *J*=13.3, 8.9 Hz, H6), 2.71–2.62 (m, 1H, H3), 2.57 (ddd, 1H, *J*=13.3, 8.0, 5.1 Hz, H6′) and 2.42 (dd, 1H, *J*=16.9, 6.0 Hz, H3′); *m/z* (%) 204 (M+1, 9), 203 (M^+, 62), 186 (14), 175 (41), 132 (20), 118 (47), 105 (100), 91 (67), 77 (50) and 55 (40); ν (cm^{-1}) (DCM solution) 1730.

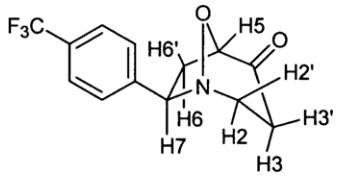
(b) Microwave procedure: divinyl ketone **2** (215 μL, 2 mmol) was added to a solution of (*Z*)-benzaldoxime (0.254 g, 2 mmol) in acetonitrile (5 mL). The reaction mixture was stirred and heated at 150°C in a CEM Discover instrument for the appropriate time before being allowed to cool to room temperature. The reaction mixture was then evaporated to dryness to afford a pale yellow oil consisting of a 6:1 mixture of *exo*-**4** and *exo*-**3**, which crystallised from n-heptane as colourless plates which comprised a 24:1 mixture of *exo*-**4**/*exo*-**3**.

1.3.8. 7-*endo*-Phenyl-8-oxa-1-azabicyclo[3.2.1]octan-4-one (*endo*-4f). (*E*)-Benzaldoxime (0.121 g, 1 mmol) and divinyl ketone (108 μL, 1.2 mmol) were reacted according to the general procedure for 48 h. Subsequent work-up afforded the crude product as a brown oil, comprising of *endo*-**157a** (55%) and unreacted (*E*)-oxime (45%). Flash chromatography, eluting with 9:1 v/v diethyl ether–pentane afforded the product as a colourless solid (0.037 g, 18%). Found C, 71.1; H, 6.75; N, 6.65; $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.45; N, 6.9; δ (400 MHz) 7.50–7.36 (m, 5H, 5×ArH), 5.01–4.97 (m, 1H, H7), 4.61 (d, 1H, *J*=8.5 Hz, H5), 3.56 (ddd, 1H, *J*=14.4, 9.6, 7.0 Hz, H2′), 3.01 (dd, 1H, *J*=14.4, 8.3 Hz, H2), 2.93–2.85 (m, 1H, H6′), 2.52 (ddd, 1H, *J*=13.1, 7.5, 1.7 Hz, H6), 2.35–2.26 (m, 1H, H3) and 2.20 (dd, 1H, *J*=16.9, 7.0 Hz, H3′); *m/z* (%) 204 (M+1, 9), 203 (M^+, 60), 186 (27), 175 (43), 132 (30), 104 (100), 91 (79), 77 (62) and 55 (69); ν (cm^{-1}) (DCM solution) 1730.



	Enhancement				
Signal Irradiated	H5	H6	H6'	H7	Ph
H6					**15**
H6'	**8**	**16**		**8**	**2**
H7			**3**		6

1.3.9. 7-*exo*-(4-Trifluoromethylphenyl)-8-oxa-1-azabicyclo-[3.2.1]octan-4-one(*exo*-4g). (*Z*)-4-Trifluoromethylbenzaldoxime (0.400 g, 2.1 mmol) and divinyl ketone (226 μL, 2.5 mmol) were reacted according to the general procedure for 48 h. Subsequent work up afforded the crude product as a viscous orange oil comprising of *exo*-**4g** only. Flash chromatography, eluting with 3:2 v/v ethyl acetate–pentane afforded the product (0.438 g, 76%) which crystallised from dichloromethane–petroleum ether as colourless rods, mp 116–118°C. Found C, 57.35; H, 4.55; N, 5.05; $C_{13}H_{12}F_3NO_2$ requires C, 57.55; H, 4.45; N, 5.15%. δ_H (500 MHz) 7.62 (m, 2H, 2×ArH), 7.52 (m, 2H, 2×ArH), 4.56 (d, 1H, *J*=8.0 Hz, H5), 4.52 (dd, 1H, *J*=9.0, 4.9 Hz, H7), 3.86 (ddd, 1H, *J*=14.4, 10.7, 6.1 Hz, H2′), 3.42 (dd, 1H, *J*=14.4, 8.5 Hz, H2), 2.87 (ddd, 1H, *J*=13.5, 9.0, 1.1 Hz, H6), 2.66 (m, 1H, H3), 2.52 (dddd, 1H, *J*=13.5, 8.0, 4.9, 1.0 Hz, H6′) and 2.44 (dd, 1H, *J*=17.0, 6.1 Hz, H3′); *m/z* (FAB; %) 272 (M+1, 100) and 136 (35); ν (cm^{-1}) 1733 (C═O).

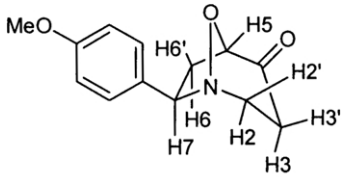


	Enhancement (%)				
Signal Irradiated	H7	H2	H6	H6'	H5
H7		**3.6**	**3.5**		
H6	**4.3**			21.1	
H6'			21.5		8.3

1.3.10. 4-(4-Oxo-8-oxa-1-azabicyclo[3.2.1]oct-7yl)benzonitrile (*exo*-4h). (*Z*)-4-Cyanobenzaldoxime (0.292 g, 2 mmol) and divinyl ketone (216 μL, 2.4 mmol) were reacted according to the general procedure for 48 h. Subsequent work up afforded the crude product as a viscous orange oil comprising of *exo*-**4h** and unreacted (*E*)-oxime (10%). Flash chromatography, eluting with 4:1 v/v ethyl acetate–diethyl ether, afforded the product (0.201 g, 44%) which crystallised from dichloromethane–pentane as colourless needles, mp 148°C. Found C, 68.2; H, 5.35; N, 12.3; $C_{13}H_{12}N_2O_2$ requires: C, 68.4; H, 5.3; N, 12.3%; δ_H (300 MHz) 7.65 (d, 2H, *J*=8.4 Hz, 2×ArH) 7.53 (d, 2H, *J*=8.4 Hz, 2×ArH), 4.57 (d, 1H, *J*=8.7 Hz, H5), 4.53 (dd, 1H, *J*=9.0, 4.9 Hz, H7), 3.87 (ddd, 1H, *J*=14.3, 10.7, 6.0 Hz, H2′), 3.43 (ddt, 1H, *J*=14.3, 8.3, 1.1 Hz, H2), 2.90 (ddd, 1H, *J*=13.5, 9.0, 1.1 Hz, H6), 2.67 (dddd, 1H, *J*=17.1, 10.7, 8.3, 2.1 Hz, H3) and 2.48 (m, 2H, H3′ and H6′); *m/z* (EI; %) 228 (M^+, 27), 143 (68), 130 (84), 129 (81), 1116 (46), 83 (30), 55 (100), 43 (75) and 41 (64); ν (cm^{-1}) 2227 (CN) and 1729 (C═O).

1.3.11. 7-*exo*-(4-Nitrophenyl)-8-oxa-1-azabicyclo[3.2.1]-octan-4-one (*exo*-4i). (*Z*)-4-Nitrobenzaldoxime (0.332 g, 2 mmol) and divinyl ketone (215 μL, 2.4 mmol) were reacted according to the general procedure for 48 h. Subsequent work up afforded the crude product as a yellow crystalline solid, comprising of *exo*-**4i** and unreacted (*E*)-oxime (45%). Flash column chromatography, eluting with diethyl ether, afforded the product (0.095 g, 19%) which crystallised from dichloromethane–pentane as pale yellow rods, mp 162–164°C. Found C, 57.9: H, 4.8; N, 11.35; $C_{12}H_{12}N_2O_4$ requires C, 58.1; H, 4.85; N, 11.3%; δ_H (300 MHz) 8.21 (d, 2H, *J*=8.8 Hz, 2×ArH), 7.59 (d, 2H, *J*=8.8 Hz, 2×ArH), 4.58 (m, 2H, H7 and H5), 3.89 (ddd, 1H, *J*=14.2, 11.0, 6.1 Hz, H2′), 3.44 (dd, 1H, *J*=14.2, 8.3 Hz, H2), 2.92 (dd, 1H, *J*=13.5, 9.1 Hz, H6), 2.68 (dddd, 1H, *J*=17.3, 11.0, 8.3, 2.3 Hz, H3), and 2.49 (m, 2H, H3′ and H6′); *m/z* (%) 248 (M^+, 19), 205 (39), 150 (59), 149 (74), 130 (33), 119 (33), 117 (59), 104 (100), 102 (49), 91 (38), 90 (47), 89 (40), 78 (31), 77 (97), 76 (34), 75 (34), 63 (39), 55 (78), 51 (57), 50 (49) and 42 (53); ν (cm^{-1}) 1730 (C═O), 1515 (NO) and 1345 (NO).

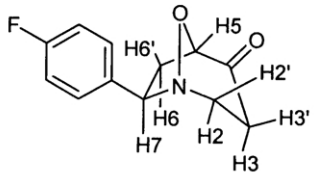
1.3.12. 7-*exo*-(4-Methoxyphenyl)-8-oxa-1-azabicyclo[3.2.1]-octan-4-one (*exo*-4j). (*Z*)-4-Methoxybenzaldehyde oxime (0.302 g, 2 mmol) and divinyl ketone (215 μL, 2.4 mmol) were reacted according to the general procedure for 48 h. Subsequent work up afforded the crude product as a dark brown solid, comprising of a 7:1 mixture of *exo*-**4j** and *endo*-**4j**. Flash chromatography, eluting with diethyl ether, afforded the same isomeric mixture (0.182 g, 78%) in a pure form. Fractional crystallisation from dichloromethane–pentane afforded a pure sample of *exo*-**4j** as colourless plates, mp 111°C. Found: C, 66.7; H, 6.4; N, 6.0; $C_{13}H_{15}NO_3$ requires: C, 66.9; H, 6.5; N, 6.0%; δ_H (500 MHz) 7.30 (d, 2H, *J*=8.7 Hz, 2×ArH), 6.78 (d, 2H, *J*=8.7 Hz, 2×ArH), 4.55 (d, 1H, *J*=8.0 Hz, H5), 4.41 (dd, 1H, *J*=8.8, 5.0 Hz, H7), 3.81 (ddd, 1H, *J*=14.2, 10.7, 6.0 Hz, H2′), 3.79 (s, 3H, MeO), 3.40 (dd, 1H, *J*=14.2, 8.4 Hz, H2), 2.79 (ddd, 1H, *J*=13.4, 8.8, 1.1 Hz, H6), 2.64 (ddd, 1H, *J*=16.9, 10.7, 8.4 Hz, H3), 2.54 (dddd, 1H, *J*=13.4, 8.0, 5.0, 0.9 Hz, H6′) and 2.40 (dd, 1H, *J*=16.9, 6.0 Hz, H3′); *m/z* (FAB; %): 234 (M+1, 100) and 233 (M^+, 58); ν (cm^{-1}) 1727 (C═O).



	Enhancement (%)				
Signal Irradiated	H5	H7	H2	H6	H6'
H7			4.1	**3.8**	
H6		**4.8**			25.7
H6'	**8.4**			22.0	

1.3.13. 7-*exo*-(4-Chlorophenyl)-8-oxa-1-azabicyclo[3.2.1]-octan-4-one (*exo*-4k). (*E*)-4-Chlorobenzaldoxime (0.311 g, 2 mmol) and divinyl ketone (215 μL, 2.4 mmol) were reacted according to the general procedure for 48 h. Subsequent work up afforded a viscous brown oil, comprising of a 10:1:1 mixture of *exo*-**4k**, *endo*-**4k** and *exo*-**3k**. Flash chromatography, eluting with diethyl ether, afforded *exo*-**4k** as a colourless solid (0.289 g, 61%) that crystallised from dichloromethane–pentane as colourless prisms, mp 129–130°C. Found C, 60.5; H, 5.1; N, 5.8; Cl, 14.85; $C_{12}H_{12}ClNO_2$ requires C, 60.6; H, 5.1; N, 5.9; Cl, 14.9%; δ_H (300 MHz) 7.31 (m, 4H, 4×ArH), 4.55 (d, 1H, *J*=8.0 Hz, H5), 4.44 (dd, 1H, *J*=8.9, 5.0 Hz, H7), 3.82 (ddd, 1H, *J*=14.2, 10.7, 6.0 Hz, H2′), 3.40 (dd, 1H, *J*=14.2, 8.3 Hz, H2), 2.83 (ddd, 1H, *J*=13.5, 8.9, 1.1 Hz, H6), 2.64 (ddd, 1H, *J*=16.9, 10.7, 8.3 Hz, H3), 2.50 (dddd, 1H, *J*=13.5, 8.0, 5.0, 0.8 Hz, H6′) and 2.42 (ddt, 1H, *J*=16.9, 6.0, 1.2 Hz, H3′); *m/z* (EI; %) 239 $^{37}(M^+$, 5), 237 $^{35}(M^+$, 31), 152 (51), 140 (41), 138 (100), 131 (32), 125 (51), 103 (62), 77 (35) and 55 (43); ν (cm^{-1}) 1731 (C═O).

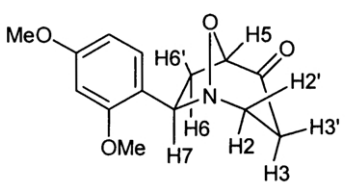
1.3.14. 7-*exo*-(4-Fluorophenyl)-8-oxa-1-azabicyclo[3.2.1]-octan-4-one (*exo*-4l). (*Z*)-4-Fluorobenzaldoxime (0.278 g, 2 mmol) and divinyl ketone (215 μL, 2.4 mmol) were reacted according to the general procedure for 48 h. Subsequent work up afforded an orange solid comprising of a 12:1 mixture of *exo*-**4l** and *endo*-**4l**. Flash chromatography, eluting with diethyl ether afforded the product *exo*-**4l** (0.155 g, 70%) which crystallised from dichloromethane–pentane as colourless plates, mp 91–93°C. Found C, 65.1; H, 5.55; N, 6.45; $C_{12}H_{12}NO_2F$ requires C, 65.15; H, 5.45; N, 6.35%; δ_H (500 MHz) 7.36 (m, 2H, 2×ArH), 7.02 (m, 2H, 2×ArH), 4.56 (d, 1H, *J*=8.0 Hz, H5), 4.44 (dd, 1H, *J*=8.9, 5.0 Hz, H7), 3.83 (ddd, 1H, *J*=14.2, 10.7, 6.0 Hz, H2′), 3.40 (dd, 1H, *J*=14.2, 8.4 Hz, H2), 2.82 (ddd, 1H, *J*=13.5, 8.9, 1.1 Hz, H6), 2.65 (m, 1H, H3), 2.52 (m, 1H, H6′) and 2.42 (ddt, 1H, *J*=17.0, 6.0, 1.2 Hz, H3′); *m/z* (EI; %); 221 (M^+, 10), 193 (17), 136 (36), 123 (62), 122 (95), 109 (82), 103 (42), 84 (41), 75 (40), 55 (68), 49 (100) and 42 (66); ν (cm^{-1}) 1730 (C═O).



	Enhancement (%)				
Signal Irradiated	H5	H7	H2	H6	H6'
H5					**2.7**
H7			**3.4**	**3.3**	
H6		**4.6**			19.5

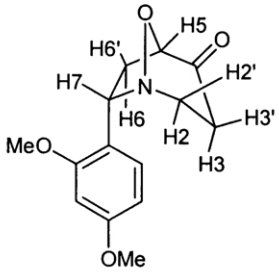
1.3.15. 7-*endo*-(2,4-Dimethoxyphenyl)-8-oxa-1-azabicyclo-[3.2.1]octan-4-one (*endo*-4m) and 7-*exo*-(2,4-dimethoxyphenyl)-8-oxa-1-azabicyclo[3.2.1]octan-4-one (*exo*-4m). (*E*)-2,4-Dimethoxybenzaldoxime (0.905 g, 5 mmol) and divinyl ketone (538 μL, 6 mmol) were reacted according to the general procedure for 48 h. Subsequent work up afforded a pale brown solid comprising of a 2:1 mixture of *endo*-**4m** and *exo*-**4m** and unreacted oxime (20%). Flash chromatography, eluting with 4:1 v/v diethyl ether–pentane, afforded *endo*-**4m** as a pale yellow oil (0.400 g, 30%) and *exo*-**4m** as a pale yellow oil (0.258 g, 20%).

exo-**4m**. Crystallisation from diethyl ether afforded the product as colourless needles, mp 92–94°C. Found: C, 63.55; H, 6.55; N, 5.35; $C_{14}H_{17}NO_4$ requires: C, 63.85; N, 6.5; N, 5.3%; δ_H (500 MHz) 7.51 (d, 1H, *J*=8.5 Hz, ArH), 6.50 (dd, 1H, *J*=8.5, 2.4 Hz, ArH), 6.44 (d, 1H, *J*=2.4 Hz, ArH), 4.72 (dd, 1H, *J*=8.7, 5.0 Hz, H7), 4.47 (d, 1H, *J*=8.0 Hz, H5), 3.81 (s, 3H, MeO), 3.80 (s, 3H, MeO), 3.78 (m, 1H, H2′), 3.37 (dd, 1H, *J*=14.1, 8.5 Hz, H2), 2.80 (dd, 1H, *J*=13.5, 8.7, H6), 2.70 (distorted dd, 1H, *J*=16.9, 8.5 Hz, H3) and 2.36 (m, 2H, H3′ and H6′); *m/z* (FAB; %): 264 (M+1, 100) and 263 (M^+, 66); ν (cm^{-1}) 1728 (C═O).



	Enhancement (%)			
Signal Irradiated	H7	H2	H6	H6'
H6	**6.3**			26.7
H7		4.3	**4.2**	

endo-**4m**. Crystallisation from diethyl ether afforded the product as pale yellow rods, mp 99–101°C. Found C, 63.85; H, 6.4; N, 5.45; $C_{14}H_{17}NO_4$ requires: C, 63.85; N, 6.5; N, 5.3%; δ_H (500 MHz; $CDCl_3$) 7.30 (d, 1H, J=8.4 Hz, ArH), 6.51 (m, 2H, 2×ArH), 5.03 (dd, 1H, J=9.9, 7.6 Hz, H7), 4.52 (d, 1H, J=7.9 Hz, H5), 3.87 (s, 3H, MeO), 3.84 (s, 3H, MeO), 3.52 (ddd, 1H, J=14.4, 9.1 and 7.3 Hz, H2′), 2.88 (dd, 1H, J=14.4, 8.5 Hz, H2), 2.76 (dtd, 1H, J=13.5, 9.9, 1.0 Hz, H6′), 2.50 (dd, 1H, J=13.5, 7.6, 1.9 Hz, H6), 2.40 (ddd, 1H, J=17.4, 9.1, 8.5 Hz, H3) and 2.23 (dd, 1H, J=17.4, 7.3 Hz, H3′); m/z (FAB; %) 264 (M+1, 100) and 263 (M^+, 29); ν (cm^{-1}) (film) 1729 (C=O).



	Enhancement (%)			
Signal Irradiated	H6	H6'	H7	H5
H7		**5.6**		
H5		**4.5**		
H6'	20.4		**13.0**	**11.2**

1.4. Single-crystal X-ray analyses

Crystallographic data for all three compounds were measured on a Nonius KappaCCD area-detector diffractometer using a mixture of area detector ω and ϕ-scans and Mo Kα radiation (λ=0.71073 Å). All three structures were solved by direct methods using SHELXS-86[12] and were refined by full-matrix least-squares (based on F^2) using SHELXL-97.[13] All non-hydrogen atoms were refined with anisotropic displacement parameters whilst hydrogen atoms were constrained to predicted positions using a riding model. The residuals wR_2 and R_1, given below, are defined as $wR_2 = (\sum[w(F_o^2 - F_c^2)^2]/\sum[wF_o^2]^2)^{1/2}$ and $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$.

Crystal data for ***4e***. $C_{10}H_{18}N_2O_2$, M=198.26, monoclinic, space group $C2/c$, a=34.309(3), b=5.8733(5), c=10.7105(5) Å, β=96.918(4)°, U=2142.5(3) Å^3, Z=8, D_c=1.23 g cm^{-3}, μ=0.086 mm^{-1}, F(000)=864, T=150 K.

Data collection. 3.52<θ<25.99°; 2001 unique data were collected (R_{int}=0.044); 1602 reflections with F_o>4.0σ(F_o).

Structure refinement. Number of parameters=132, goodness of fit, s=1.030; wR_2=0.1196, R_1=0.0431.

Crystal data for ***4k***. $C_{12}H_{12}ClNO_2$: M=237.68, orthorhombic, space group $P2_12_12_1$, a=9.1352(6), b=10.5378(8), c=11.1591(11) Å, U=1074.2(2) Å^3, Z=4, D_c=47 g cm^{-3}, μ=0.338 mm^{-1}, F(000)=496, T=150 K.

Data collection. 2.50<θ<30.0°; 2051 unique data were collected (R_{int}=0.053); 1973 reflections with F_o>4.0σ(F_o).

Structure refinement. Number of parameters=146, goodness of fit, s=1.059; wR_2=0.1038, R_1=0.0404.

Crystal data for ***5***. $C_9H_{14}N_2O_3$: M=198.22, monoclinic, space group $C2/c$, a=17.3718(3), b=11.7339(3), c=11.2632(2) Å, β=122.979(1)°, U=1925.94(7) Å^3, Z=8, D_c=1.37 g cm^{-3}, μ=0.103 mm^{-1}, F(000)=848, T=190 K.

Data collection. 3.50<θ< 30.0°; 2263 unique data were collected (R_{int}=0.039); 1967 reflections with F_o>4.0σ(F_o).

Structure refinement. Number of parameters=138, goodness of fit, s=1.081; wR_2=0.1163, R_1=0.0353.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC182398, 182399 and 182400. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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