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A versatile radical based approach to *O*-alkylated hydroxylamines and oximes

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ABSTRACT

O-Alkylhydroxylamines, often used for the preparation of bioconjugates, can be readily obtained by radical addition to suitable *O*-alkenylhydroxylamine derivatives. In the case of *N*-Boc-*O*-allylhydroxylamine, the addition is unexpectedly followed by elimination resulting in an overall allylation of the radical species.

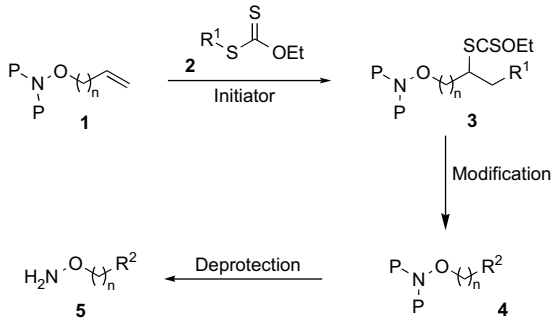
1. Introduction

Reactions between aldehydes or ketones and *O*-alkylated hydroxylamines to form oximes are both high-yielding and require only mild conditions. These reactions have been used for the chemical ligation of steroids,[1] oligonucleotides,[2] modified peptides,[3] antibodies,[4] viruses[5] and natural products such as erythromycin.[6] The resulting bioconjugates have been shown to exhibit different biological activities and solubilities. Despite their utility, there are few established methods to prepare complex *O*-alkylated hydroxylamines.

We have developed a radical chain process based on the degenerative exchange of a xanthate group.[7] This chemistry has provided a simple, efficient and reasonably general method for the intermolecular formation of carbon–carbon bonds on non-activated alkenes. We herein describe a general approach, applying the xanthate transfer radical reaction, to the synthesis of *O*-alkylated hydroxylamines and oximes. It was anticipated that *N*-protected *O*-allylated or *O*-butenylated hydroxylamines **1** would undergo xanthate transfer addition reactions with xanthates **2** to form addition products **3**. Subsequent modification, in most cases xanthate reduction, would furnish protected hydroxylamines **4** and deprotection would provide the required *O*-alkylated hydroxylamines **5** (Scheme 1).

Alkenes **1a**–**d** were formed by treatment of the oxime or *N*-Boc-hydroxylamine with NaH, $^{n}Bu_4NI$ and allyl bromide or 4-bromo-1-butene as appropriate. Unfortunately, when allylic hydroxylamine **1a** was treated with xanthate **2a** and substoichiometric lauroyl peroxide (DLP) in 1,2-dichloroethane (DCE) at reflux none of the expected addition product was observed; alkene **6a**, resulting from β-elimination of the first-formed radical, was obtained in 69%. Using BEt_3/O_2 radical initiation conditions,[8] both at 0 °C and −78 °C, for the addition reaction of xanthate **2b** also led solely to the elimination product **6b**, according to ^{1}H NMR analysis of the reaction mixtures (Scheme 2). This unexpected elimination process is surprisingly facile, occurring even at very low temperatures.

In stark contrast, xanthate transfer additions to oximes **1b** and **1c** proceeded cleanly and in good yields. This observation is again surprising, since β-elimination of the more stabilised iminoxyl would have been expected to occur more readily. It appears that polar effects are more important than thermodynamic factors in determining the rate of fragmentation in the present case. The electron-withdrawing Boc group thus exerts ultimately a greater influence by lowering the energy level of the antibonding σ* of the C–O bond and bringing it closer to the level of the SOMO of the radical. The resulting stronger interaction between the σ* and the SOMO increases the rate of fragmentation of the C–O bond, even though the ensuing oxygen centred departing radical, BocNHO•, is less stable than the iminoxyl radical, RR′C═N–O•, that would be generated from the *O*-allyloxime adducts. The use of a butenyl group, rather than an allyl group, in hydroxylamine **1d** removed the possibility of β-elimination, thus providing access to Boc-protected substrates. A variety of functionalities are tolerated



Scheme 1.

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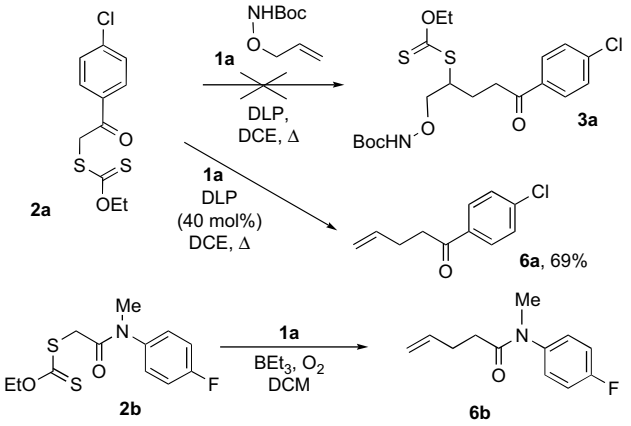


Scheme 2.

in the xanthate: ketones (**2a**,**c**,**d**,**f**,**j**); amides (**2b**,**e**,**g**); lactones (**2i**). In the case of the bis-xanthate **2k**, a mixture of the mono- (**3m**) and bis-addition products (**3n**) were obtained. The bis-addition product (**3n**) is not trivial to prepare otherwise and would be interesting in cross-linking processes. When using acetophenone derived xanthates **2a** and **2d**, small quantities of the products (**4a** and **4b**) arising from cyclisation onto the aromatic ring were obtained (Fig. 1, Table 1).

By using stoichiometric amounts of DLP it is possible to induce complete radical cyclisation onto aromatic rings. This allowed the conversion of adduct **3e** into the respective tetralone **4a** in 56% yield. A more difficult cyclisation to form a seven-membered tetracycle **4d** also proved possible, although competitive elimination and xanthate reduction lowered the effective yield to 40% (Scheme 3).

Before the hydroxylamine functionality could be liberated it was necessary to remove the xanthate groups. The standard conditions for the reductive elimination of xanthate groups use 2-propanol as both the solvent and hydrogen source, with DLP as the radical initiator.[9] Under these conditions, however, substrates **3i** and **3j** gave a mixture of products, indicating that the hydrogen abstraction from 2-propanol was slow compared to other possible pathways, such as the β-elimination already discussed. Instead, reduction of a range of substrates was achieved in good yields using the triethyl ammonium salt of hypophosphorous acid as a faster hydrogen source and AIBN as the initiator (Table 2).[10]

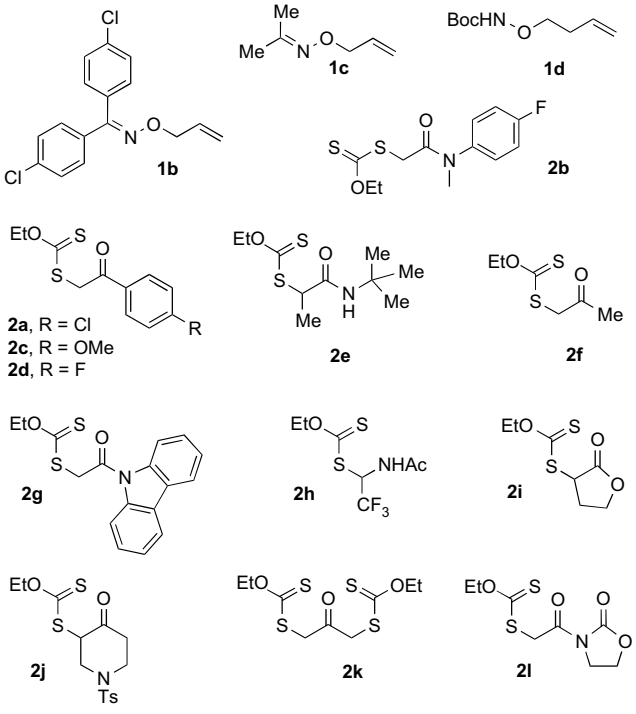


Figure 1.

Liberation of the Boc protecting groups was effected using trifluoroacetic acid; hydroxylammonium salts **6a** and **6b** were formed in near quantitative yields from their respective Boc-protected compounds **4i** and **4j**. Upon treatment with K_2CO_3 in MeOH/H_2O, **6a** furnished the expected hydroxylamine **5a**. Under the same conditions, however, **6b** formed hydroxylamine **5b**, in which the oxazolidinone functionality has been replaced by methanol. When ketone **4h** was treated with trifluoroacetic acid, the liberated hydroxylamine condensed with the ketone functionality to form oxazocine **6c** as a mixture of oxime geometric isomers (Scheme 4). Only one example of such [1,2]-oxazocines has been reported in the literature according to the Beilstein database.[11] The present route should expand considerably the access to this very rare family of heterocycles.

While neither unanticipated nor unwelcome, the formation of heterocycle **6c** exemplifies the lack of compatibility between *O*-alkylated hydroxylamines and certain common functional groups. The creation, via the formation of an oxime, of a bioconjugate containing a ketone constituent would be difficult to achieve without the use of protecting groups. If, however, an oxime incorporating an alkene was synthesised, a subsequent xanthate transfer radical reaction could insert the required ketone functionality.

As an example, glucose pentaacetate was treated with the trifluoroacetic acid salt of *O*-allylhydroxylamine to furnish a complex mixture of products arising from acetate migration onto the first-formed alcohol. Acetylation of this mixture using acetic anhydride gave alkene **1e** as a 5:1 mixture of geometrical isomers. Addition of xanthate **2g**, followed by reduction furnished oxime **4k** in 49% overall yield over four steps. In a further example, treatment of alkene **1f**, derived from epiandrosterone and *O*-butenylhydroxylamine, furnished oxime **4l** in 54% overall yield. The radical addition and subsequent cyclisation reaction were conducted in a single pot, with the reaction being diluted once TLC analysis showed that the addition reaction was complete (Scheme 5).

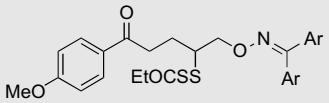
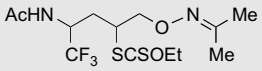
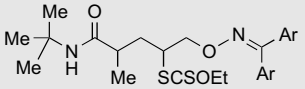
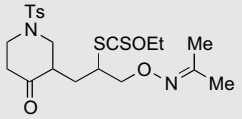
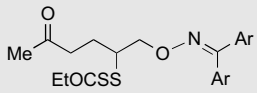
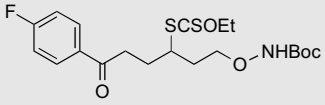
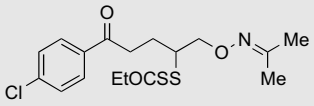
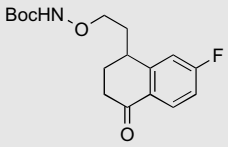
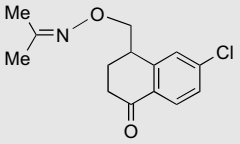
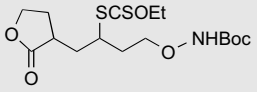
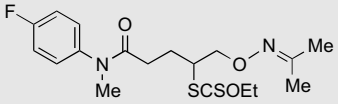
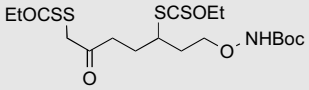
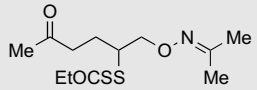
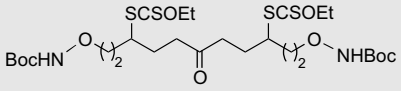
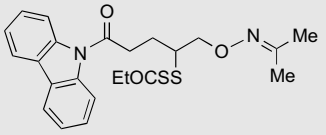
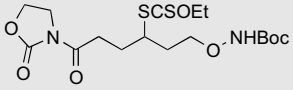
To conclude, the xanthate transfer radical reaction can provide access to complex hydroxylamines and oximes, which would otherwise prove difficult to synthesise. It allows the preparation of compounds containing functional groups that would be incompatible with usual methods of forming oxime-linked bioconjugates.

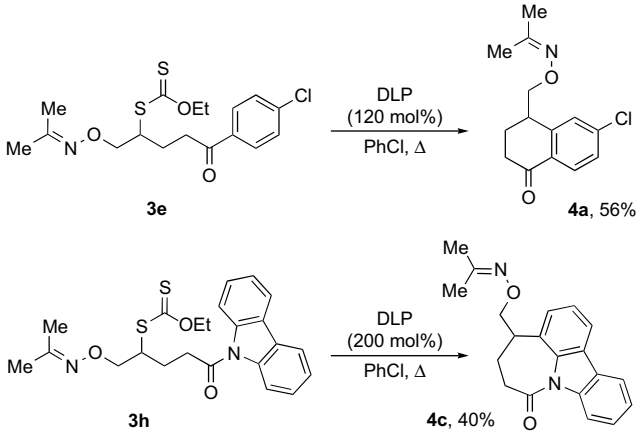
2. Experimental

2.1. General conditions

All reactions were carried out under an inert atmosphere. Commercial reagents were used as-received without further purification. All products were purified by using silica gel (SDS, Silice 60 A. C. C. 40–63 mm) or by crystallisation. Analytical TLC was carried out on Merck silica gel plates using short wave (254 nm) UV light, 1% aq $KMnO_4$ solution to visualise components. NMR spectra were recorded in $CDCl_3$ using a Bruker AMX400 operating at 400 MHz for ^1H and 100 MHz for ^{13}C. The chemical shifts are expressed in parts per million (ppm) referenced to residual chloroform. ^1H NMR data are reported as follows: d, chemical shift; multiplicity (recorded as: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quadruplet; qt, quintuplet; ht, heptuplet; dd, double doublet; ddd, double double

Table 1
Addition of xanthates to *O*-allyl and *O*-homoallyl hydroxylamine derivatives (Ar=*p*-ClC_6H_4–)

Alkene **1**	Xanthate **2**	Adduct **3**		Alkene **1**	Xanthate **2**	Adduct **3**	
1b	**2c**		**3b**, 91%	**1c**	**2h**		**3i**, 69%
1b	**2e**		**3c**, 68%	**1c**	**2j**		**3j**, 93%
1b	**2f**		**3d**, 85%				**3k**, 79%
			**3e**, 64%	**1d**	**2d**		**4b**, 13%
1c	**2a**		**4a**, 7%	**1d**	**2i**		**3l**, 79%
1c	**2b**		**3f**, 58%				**3m**, 24%
1c	**2f**		**3g**, 87%	**1d**	**2k**		**3n**, 56%
1c	**2g**		**3h**, 84%	**1d**	**2l**		**3o**, 81%



Scheme 3.

doublet; dddd, double double double doublet; dt, double triplet; ddt, double double triplet; dq, double quadruplet; tt, triple triplet; td; triple doublet; tdd, triple double doublet; m, multiplet), coupling constants (*J* are given in hertz, Hz) and integration. Infrared Absorption spectra were recorded as thin films or as solutions in CCl_4 with a Perkin–Elmer 1600 Fourier Transform Spectrophotometer. Mass spectra were recorded with an HP 5989B mass spectrometer via direct introduction for chemical positive ionisation (CI) using ammonia as the reagent gas. Melting points were determined by Reichert microscope apparatus and were uncorrected. HRMS was performed on JEOL JMS-GcMate II, GC/MS system spectrometer. Xa represents the xanthate group, –SC(=S)OEt.

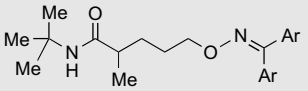
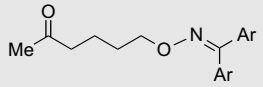
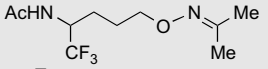
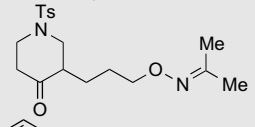
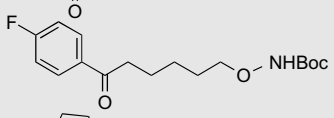
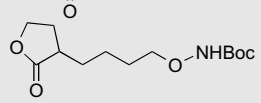
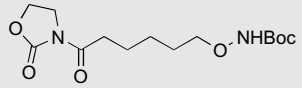
2.2. General procedure A. Xanthate transfer radical addition

Alkene and xanthate were dissolved in dichloroethane (1 M concentration) and the mixture was heated at reflux for 15 min under nitrogen. 5 mol % DLP was added every hour until TLC analysis showed the reaction had gone to completion. The mixture was concentrated in vacuo. Column chromatography furnished the product.

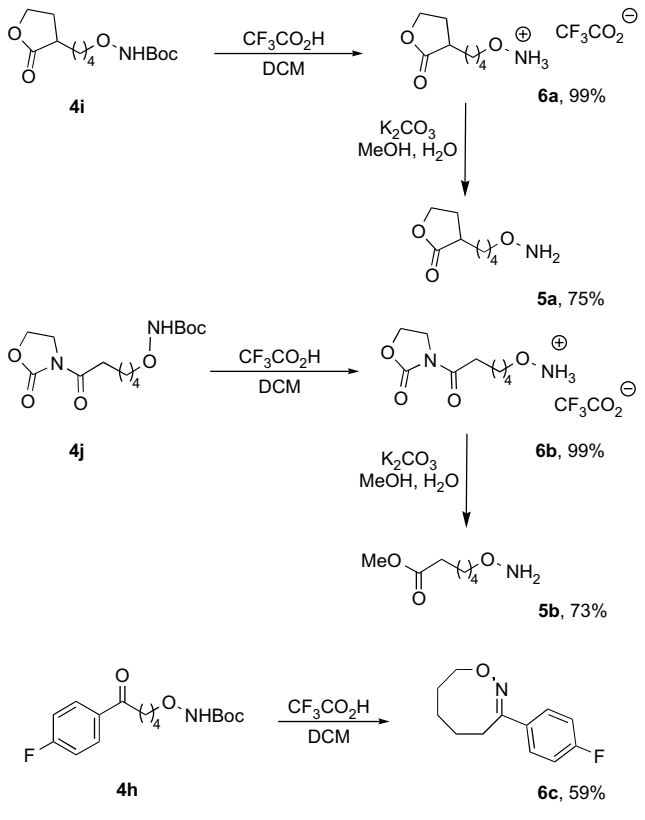
*2.2.1. S-1-(Bis(4-chlorophenyl)methyleneaminooxy)-5-(4-methoxyphenyl)-5-oxopentan-2-yl O-ethyl carbonodithioate (**3b**)*

General procedure A. Alkene **1b** (305 mg; 1 mmol); xanthate **2c** (405 mg; 1.5 mmol); solvent: DCE (1 mL); DLP: 4×20 mg (0.2 mmol); column: petrol/EtOAc (10:1). Yield of **3b**: 523 mg (91%); ν_{max} (thin film)/cm^{-1} 2928m, 1680s, 1599m; δ_H ($CDCl_3$, 400 MHz) 1.39 (3H, t, *J* 7.2, Xa-C**H$_3$**), 1.95–2.02 (1H, m, C**H**H′), 2.26–2.30 (1H, m, CH**H**′), 3.09 (2H, app t, *J* 7.4, C**H$_2$**), 3.87 (3H, s, O**Me**), 4.20–4.24 (1H, m, C**H**Xa), 4.34 (1H, dd, *J* 11.6, 6.4,

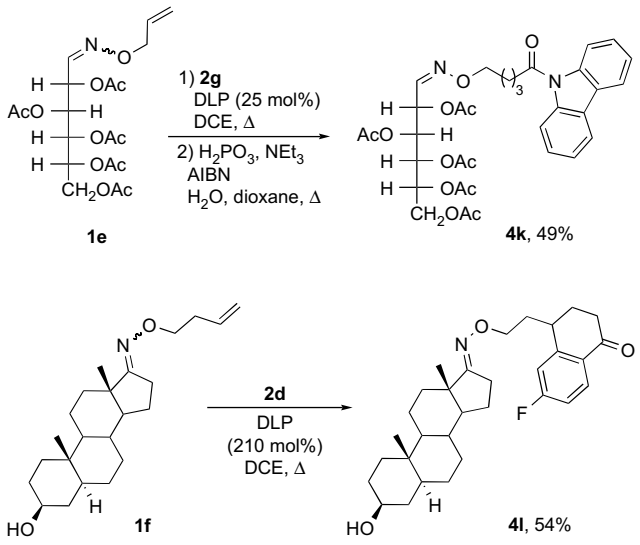
Table 2
Reduction of xanthates adducts **3** (Ar=*p*-ClC$_6$H$_4$–)

Xanthate **3**	Reduced product **4**	
3c		**4d**, 73%
3d		**4e**, 75%
3i		**4f**, 85%
3j		**4g**, 88%
3k		**4h**, 74%
3l		**4i**, 88%
3o		**4j**, 87%

C**H**H′ON), 4.46 (1H, dd, *J* 11.6, 5.2, CH**H**′ON), 4.67 (2H, m, Xa-C**H$_2$**), 6.91 (2H, d, *J* 8.8, 2×Ar-**H**), 7.29 (2H, d, *J* 8.4, 2×Ar-**H**), 7.31 (2H, d, *J* 8.4, 2×Ar-**H**), 7.40 (2H, d, *J* 8.4, 2×Ar-**H**), 7.42 (2H, d, *J* 8.4, 2×Ar-**H**), 7.89 (2H, d, *J* 8.8, 2×Ar-**H**). δ_C (CDCl$_3$, 100 MHz) 13.8, 25.7, 35.4, 49.8, 55.5, 70.2, 76.2, 128.6, 128.6, 128.6, 129.2, 129.8, 130.3, 130.7, 130.7, 130.8, 130.9, 134.4, 135.1, 135.7, 155.4, 163.5, 197.6; *m*/*z* (CI$^+$) 457 (MH$^+$, 55%), 459 (30), 516 (12), 575 (M$^+$, 100), 576 (35), 577 (75), 578 (20).



Scheme 4.



Scheme 5.

2.2.2. *S-1-(Bis(4-chlorophenyl)methyleneaminooxy)-5-(tert-butylamino)-4-methyl-5-oxopentan-2-yl O-ethyl carbonodithioate (**3c**)*

General procedure A. Alkene **1b** (307 mg, 1 mmol); xanthate **2e** (355 mg, 1.5 mmol); solvent: DCE (1 mL); DLP: 8×20 mg (0.40 mmol); column: petrol/DCM (1:1). Yield of **3c**: 378 mg (68%). The product was obtained as a mixture of diastereoisomers, which was characterised as the monoisomeric xanthate reduction product **4d**.

2.2.3. *S-1-(Bis(4-Chlorophenyl)methyleneaminooxy)-5-oxohexan-2-yl O-ethyl carbonodithioate (**3d**)*

General procedure A. Alkene **1b** 307 mg (1 mmol); xanthate **2f** (267 mg, 1.5 mmol); Solvent: DCE (1 mL); DLP: 5×20 mg (0.25 mmol); column: petrol/ether (20:1). Yield of **3d**: 412 mg (85%); ν_{max} (thin film)/cm^{-1} 2928m, 1714s, 1598w; δ_H (CDCl$_3$, 400 MHz) 1.45 (3H, t, *J* 7.2, Xa-C**H$_3$**), 1.76–1.87 (1H, m, C**H**H′), 2.10–2.22 (2H, m, CH**H**′), 2.14 (3H, s, **Me**), 2.63 (2H, app t, *J* 7.4, C**H$_2$**), 4.11–4.18 (1H, m, C**H**Xa), 4.34 (1H, dd, *J* 11.6, 6.4, C**H**H′ON), 4.46 (1H, dd, *J* 11.6, 5.6, CH**H**′ON), 4.67 (2H, q, *J* 7.2, Xa-CH$_2$), 7.33 (2H, d, *J* 8.4, 2×Ar-**H**), 7.35 (2H, d, *J* 8.4, 2×Ar-**H**), 7.45 (2H, d, *J* 8.4, 2×Ar-**H**), 7.45 (2H, d, *J* 8.4, 2×Ar-**H**). δ_C (CDCl$_3$, 100 MHz) 13.9, 24.9, 30.1, 40.6, 49.6, 70.3, 76.1, 128.6, 128.6, 129.2, 130.7, 130.9, 134.3, 135.1, 135.8, 155.4, 207.5, 213.4; *m*/*z* (CI$^+$) 484 (MH$^+$, 100%), 485 (32), 486 (83), 487 (21), 488 (18); HRMS found 363.0796; $C_{22}H_{23}O_3NCl_2S_2$ (M$^+$) requires 363.0793.

2.2.4. *S-5-(4-Chlorophenyl)-5-oxo-1-(propan-2-ylidene-aminooxy)pentan-2-yl O-ethyl carbonodithioate (**3e**)*

General procedure A. Alkene **1c** (113 mg,1 mmol); xanthate **2a** (275 mg, 1 mmol); Solvent: DCE (1 mL); DLP: 10×20 mg (0.50 mmol); column: petrol/ether (10:1). Yield of **3e**: 249 mg (64%); ν_{max} (thin film)/cm^{-1} 2922m, 1687s, 1588w; δ_H (CDCl$_3$, 400 MHz) 1.41 (3H, m, Xa-C**H$_3$**), 1.60–1.66 (1H, m, C**H**H′), 1.85 (3H, s, **Me**), 1.87 (3H, s, **Me**) 2.01–2.12 (1H, m, CH**H**′), 2.32–2.37 (2H, m, C**H$_2$**), 4.10–4.16 (1H, m, C**H**Xa), 4.21 (1H, dd, *J*

10.8, 6.4, CHH′ON), 4.25 (1H, dd, *J* 10.8, 4.8, CHH′ON), 4.58–4.66 (2H, m, Xa-C**H**$_2$), 7.43 (2H, d, *J* 8.6, 2×Ar-**H**), 7.91 (2H, d, *J* 8.6, 2×Ar-**H**). δ_C ($CDCl_3$, 100 MHz), 13.8, 15.7, 21.9, 25.6, 35.9, 49.8, 70.2, 74.5, 129.0, 129.5, 135.1, 139.6, 155.8, 197.9, 213.7; *m*/*z* (CI^+) 315 (15%), 388 (MH^+, 100), 389 (22), 390 (42); HRMS (EI^+) found 314.0192; $C_{14}H_{15}O_2ClS_2$ ($M^+-HON{=}CMe_2$) requires 314.0202.

2.2.5. 6-Chloro-4-((propan-2-ylideneaminooxy)methyl)-3,4-dihydronaphthalen-1(2H)-one (*4a*)

Further elution yielded **4a** as a viscous oil (19 mg, 7%). ν_{max} (thin film)/cm^{-1} 2925m, 1687s, 1590m; δ_H ($CDCl_3$, 400 MHz) 1.91 (3H, s, **Me**), 1.94 (3H, s, **Me**), 2.16–2.35 (2H, m, CHH′), 2.66 (1H, dt, *J* 17.7, 5.3, CHH′), 2.84 (1H, ddd, *J* 17.7, 11.6, 5.2, CHH′), 3.36–3.42 (1H, m, CHAr), 4.25–4.35 (2H, m, CHH′ON), 7.36, (1H, dd, *J* 8.5, 1.8, Ar-**H**), 7.44 (1H, d, *J* 1.8, Ar-**H**), 8.02 (1H, d, *J* 8.5); δ_C ($CDCl_3$, 100 MHz) 15.8, 21.9, 24.8, 35.2, 37.7, 75.3, 127.6, 128.8, 129.0, 131.0, 139.8, 146.3, 155.7, 197.0; *m*/*z* (CI^+) 266 (MH^+, 100%), 268 (36); HRMS could not be obtained.

2.2.6. O-Ethyl S-5-((4-fluorophenyl)(methyl)amino)-5-oxo-1-(propan-2-ylideneaminooxy)pentan-2-yl carbonodithioate (*3f*)

This compound was obtained in the same manner from alkene **1c** and xanthate **2b** in 58% yield; ν_{max} (thin film)/cm^{-1} 2925 m, 1653s, 1508 m; δ_H ($CDCl_3$, 400 MHz) 1.37 (3H, t, *J* 7.2, Xa-C**H**$_3$), 1.77 (3H, s, **Me**), 1.0–1.81–1.90 (1H, m, CHH′), 1.82 (3H, s, **Me**), 2.10–2.25 (1H, m, CHH′), 3.21 (3H, s, N**Me**), 3.89–3.92 (1H, m, CHXa), 4.05 (1H, dd, *J* 11.0, 6.2, CHH′ON), 4.16 (1H, dd, *J* 11.0, 5.0, CHH′ON), 4.54–4.61 (2H, m, Xa-C**H**$_2$), 7.05–7.20 (4H, m, 4×Ar-**H**); δ_C ($CDCl_3$, 100 MHz) (major rotamer) 13.7, 15.6, 21.7, 26.9, 31.5, 37.4, 49.7, 69.9, 74.4, 116.7 (d, *J* 22), 129.1 (d, *J* 9), 139.9 (d, *J* 3), 155.5, 161.7 (d, *J* 246), 172.1, 213.7; *m*/*z* (CI^+) 328 (12%), 401 (MH^+, 100), 402 (21); HRMS could not be obtained.

2.2.7. O-Ethyl S-5-oxo-1-(propan-2-ylideneaminooxy)hexan-2-yl carbonodithioate (*3g*)

General procedure A. Alkene **1c** (113 mg,1 mmol); xanthate **2f** (178 mg,1 mmol); solvent: DCE (1 mL); DLP: 7×20 mg (0.35 mmol); column: petrol/ether (10:1). Yield of **3g**: 254 mg (87%); ν_{max} (thin film)/cm^{-1} 2923 m, 1715s, 1643w; δ_H ($CDCl_3$, 400 MHz) 1.41 (3H, t, *J* 7.0, Xa-C**H**$_3$), 1.83–1.91 (1H, m, CHH′), 1.84 (3H, s, **Me**), 1.86 (3H, s, **Me**), 2.12–2.21 (1H, m, CHH′), 2.15 (3H, s, **Me**), 2.56–2.71 (2H, m, C**H**$_2$), 3.98–4.05 (1H, m, CHXa), 4.13 (1H, dd, *J* 11.2, 6.4, CHH′ON), 4.25 (1H, dd, *J* 11.2, 4.8, CHH′ON), 4.67 (2H, q, *J* 6.9, Xa-C**H**$_2$). δ_C ($CDCl_3$, 100 MHz) 13.8, 15.7, 12.8, 24.9, 30.0, 40.7, 49.7, 70.1, 74.4, 155.6, 207.6, 213.7; *m*/*z* (CI^+), 292 (MH^+, 100%), 293 (17); HRMS (EI^+) found 218.0436; $C_9H_{14}O_2S_2$ ($M^+-HON{=}CMe_2$) requires 218.0435.

2.2.8. S-5-(9H-Carbazol-9-yl)-5-oxo-1-(propan-2-ylideneaminooxy)pentan-2-yl O-ethyl carbonodithioate (*3h*)

General procedure A. Alkene **1c** (113 mg,1 mmol); xanthate, **2g** (329 mg, 1 mmol); solvent: DCE (1 mL); DLP: 8×20 mg (0.40 mmol); column: petrol/ether (20:1). Yield of **3h**: 371 mg (84%); mp 249 °C decomp.; ν_{max} (thin film)/cm^{-1} 2923 m, 1694s, 1597w; δ_H ($CDCl_3$, 400 MHz) 1.45 (3H, t, *J* 7.0, Xa-C**H**$_3$), 1.88 (3H, s, Me), 1.90 (3H, s, Me), 2.27–2.37 (1H, m, CHH′), 2.53–2.63 (1H, m, CHH′), 3.31–3.45 (2H, m, C**H**$_2$), 4.29–4.37 (2H, m, CHXa and CHH′ON), 4.45 (1H, dd, *J* 9.6, 3.6, CHH′ON), 4.67 (2H, q, *J* 7.2, Xa-C**H**$_2$, with doubling due to xanthate rotamers), 7.42 (2H, t, *J* 7.4, 2×Ar-**H**), 7.50 (2H, td, *J* 7.4, 1.2, 2×Ar-**H**), 8.02 (2H, d, 7.4, 2×Ar-**H**), 8.25 (2H, d, 7.4, 2×Ar-**H**). δ_C ($CDCl_3$, 100 MHz) 13.8, 15.7, 21.9, 26.8, 36.7, 49.8, 70.3, 74.9, 116.6, 119.8, 123.7, 126.5, 127.4, 138.5, 155.9, 172.4, 213.8; *m*/*z* (CI+) 365 (22%), 443 (MH+, 100), 444 (28); HRMS found 370.0946; $C_{20}H_{20}O_2NS_2$ ($MH^+-HON{=}CMe_2$) requires 370.0936.

2.2.9. O-Ethyl S-2-methyl-11-oxo-8-(trifluoromethyl)-4,10-dioxa-3,9-diazadodec-2-en-6-yl carbonodithioate (*3i*)

General procedure A. Alkene **1c** (113 mg, 1 mmol); xanthate **2h** (277 mg, 1 mmol); solvent: DCE (1 mL); DLP: 12×20 mg (0.60 mmol); column: petrol/ether (4:1). Yield of **3i**: 271 mg (69%). This product was obtained as a mixture of diastereoisomers and was characterised as the monoisomeric reduction product **4f** below.

2.2.10. O-Ethyl S-1-(4-oxo-1-tosylpiperidin-3-yl)-3-(propan-2-ylideneaminooxy)propan-2-yl carbonodithioate (*3j*)

General procedure A. Alkene **1c** 113 mg (1 mmol); xanthate **2j** (370 mg, 1 mmol); solvent: DCE (1 mL); DLP: 7×20 mg (0.35 mmol); column: petrol/ethyl acetate (10:1). Yield of **3j**: 447 mg (93%). This product was obtained as a 1:1 mixture of diastereoisomers, which was characterised as the monoisomeric reduction product **4g** below.

2.2.11. tert-Butyl 3-(ethoxycarbonothioylthio)-6-(4-fluorophenyl)-6-oxohexyloxycarbamate (*3k*)

General procedure A. Alkene **1d** (186 mg, 1 mmol); xanthate: **2d** (258 mg, 1 mmol); solvent: DCE (1 mL); DLP: 8×20 mg (0.40 mmol); column: petrol/ether (5:1). Yield of **3k**: 349 mg (79%); ν_{max} (thin film)/cm^{-1} 3299br m, 1732s, 1684s, 1597 m; δ_H ($CDCl_3$, 400 MHz) 1.41 (3H, m, Xa-C**H**$_3$), 1.50 (9H, m, (C**H**$_3$)$_3$), 2.00–2.32 (4H, m, 2×CHH′), 3.07–3.23 (2H, m, CHH′), 3.95–4.07 (3H, m, CHXa and CHH′ON), 4.58–4.66 (2H, m, Xa-C**H**$_2$), 7.14 (2H, t, *J* 8.8, 2×Ar-**H**), 7.43 (1H, s, N**H**), 8.00 (2H, dd, *J* 8.8, 5.2, 2×Ar-**H**), δ_C ($CDCl_3$, 100 MHz) (major rotamer) 13.8, 28.2, 28.7, 33.1, 35.8, 47.9, 70.1, 73.9, 81.7, 115.7 (d, *J* 21.7), 130.7 (d, *J* 9.3), 133.2 (d, *J* 3.0), 157.0, 165.8 (d, *J* 253.0), 197.6, 213.9; HRMS found 445.1381; $C_{20}H_{28}O_5NS_2F$ (M^+) requires 445.1393.

2.2.12. tert-Butyl 2-(7-fluoro-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl)ethoxycarbamate (*4b*)

Further elution yielded **4b** (41 mg, 13%). ν_{max} (thin film)/cm^{-1} 3378br m, 1740 m, 1681s, 1606w; δ_H ($CDCl_3$, 400 MHz) 1.55 (9H, m, (C**H**$_3$)$_3$), 1.97–2.20 (3H, m, CHH′ and CHH′), 2.31–2.41 (1H, m, CHH′), 2.65 (1H, dt, *J* 18.2, 5.2CHH′C=O), 2.80 (1H, ddd, *J* 18.2, 11. 6, 4.8 CHH′C=O), 3.25–3.31 (1H, m, CHAr), 3.99–4.06 (2H, m, CHH′ON), 7.05 (1H, td, *J* 8.4, 2.4, Ar-**H**), 7.12 (1H, dd, *J* 9.4, 2.6 Ar-**H**), 7.22 (1H, s, N**H**), 8.11 (1H, dd, *J* 8.4, 6.0, Ar-**H**); HRMS found 267.0906; $C_{13}H_{14}O_4NF$ ($M^+-H_2{=}Me_2$) requires 267.0907.

2.2.13. tert-Butyl 3-(ethoxycarbonothioylthio)-4-(2-oxotetrahydrofuran-3-yl)butoxycarbamate (*3l*)

General procedure A. Alkene **1d** (345 mg, 1.68 mmol); xanthate **2i** (316 mg, 1.68 mmol); solvent: DCE (1.7 mL); DLP: 7×34 mg (0.60 mmol); column: petrol/ethyl acetate (3:2). Yield of **3l**: 522 mg (93%). This product was obtained as a 1:1 mixture of diastereoisomers, which was characterised as the monoisomeric reduction product **4i** below.

2.2.14. tert-Butyl 3,7-bis(ethoxycarbonothioylthio)-6-oxoheptyloxycarbamate (*3m*)

General procedure A. Alkene **1d** (155 mg, 0.83 mmol); xanthate **2k** (124 mg, 0.42 mmol); solvent: DCE (1 mL); DLP: 13×18 mg (0.54 mmol); column: petrol/ether (4:1). Yield of **3m**: 396 mg (24%); ν_{max} (thin film)/cm^{-1} 3300br m, 1721s; δ_H ($CDCl_3$, 400 MHz) 1.43–1.48 (3H, m, Xa-C**H**$_3$), 1.50 (9H, m, (C**H**$_3$)$_3$), 1.91–2.25 (4H, m, 2×CHH′), 2.76–2.90 (2H, m, CHH′), 3.86–3.94 (1H, m, CHXa), 3.96–4.06 (2H, m, CHH′ON), 4.02 (2H, C**H**$_2$Xa), 4.63–4.71 (4H, m, 2×Xa-C**H**$_2$), 7.30 (1H, s, N**H**). δ_H ($CDCl_3$, 400 MHz) 13.8, 13.8, 28.2, 28.3, 33.1, 39.1, 45.4, 47.7, 70.2, 70.9, 73.8, 81.8, 156.9, 202.5, 213.3, 213.9; *m*/*z* (CI^+) 380 (24%), 430 ($MH^+-H_2{=}CMe_2$, 100), 431 (19%).

*2.2.15. tert-Butyl (3,9-bis(ethoxycarbonothioylthio)-6-oxoundecane-1,11-diyl)bis(oxy)dicarbamate (**3n**)*

Further elution yields compound **3n** as a viscous oil (300 mg, 56%); ν_{max} (thin film)/cm^{-1} 3292br m, 1714s; δ_H ($CDCl_3$, 400 MHz) 1.45 (6H, t, *J* 7.2, 2×Xa-C**H$_3$**), 1.50 (18H, m, 2×(C**H$_3$**)$_3$), 1.86–2.18 (8H, m, 2×C**H**H′), 2.55–2.67 (4H, m, 2×C**H**H′), 3.82–3.90 (2H, m, 2×C**H**×a), 3.96–4.06 (4H, m, 2×C**H**H′ON), 4.66 (4H, q, *J* 7.2, 2×Xa-C**H$_2$**), 7.36 (2H, s, 2×N**H**). δ_H ($CDCl_3$, 400 MHz) 13.8, 28.1, 28.3, 33.0, 39.9, 47.9, 70.2, 73.8, 81.7, 156.9, 208.8, 214.0. HRMS could not be obtained.

*2.2.16. tert-Butyl 3-(ethoxycarbonothioylthio)-6-oxo-6-(2-oxooxazolidin-3-yl)hexyloxycarbamate (**3o**)*

General procedure A. Alkene **1d** (144 mg, 0.7 mmol); xanthate **2l** (193 mg, 0.7 mmol); solvent: DCE (0.7 mL); DLP: 4×15 mg (0.14 mmol); column: petrol/ethyl acetate (2:1).

Yield of **3o**: 273 mg (81%); ν_{max} (thin film)/cm^{-1} 3287br m, 1784s, 1711s δ_H ($CDCl_3$, 400 MHz) 1.47 (3H, t, *J* 7.2, Xa-C**H$_3$**), 1.52 (9H, m, (C**H$_3$**)$_3$), 2.00–2.32 (4H, m, 2×C**H**H′), 3.02–3.10 (1H, m, C**H**H′), 3.15–3.25 (1H, m, CH**H**′), 3.95–4.09 (5H, m, C**H**Xa and C**H**H′ON and oxazolidine C**H$_2$**), 4.46 (2H, t, *J* 8.4, oxazolidine C**H$_2$**), 4.58–4.66 (2H, m, Xa-C**H$_2$**), 7.43 (1H, s, N**H**). δ_C ($CDCl_3$, 100 MHz) (major rotamer) 13.8, 28.3, 29.0, 32.6, 32.6, 42.6, 47.4, 62.2, 70.2, 73.7, 81.7, 153.5, 156.9, 172.6, 214.0; HRMS found 380.0704; $C_{13}H_{19}O_7S_2N_2$ (M^+-H_2=Me_2) requires 380.0707.

2.3. General procedure B. Xanthate reduction

A solution of xanthate (1 equiv), hyposphosphorous acid (50% solution in water, 5 equiv), and triethylamine (5.5 equiv) in dioxane (1 mmol xanthate in 12 mL) was heated at reflux for 15 min. AIBN (10 mol %) was added and the reaction mixture was refluxed for 30–60 min. The reaction mixture was cooled and poured onto water. Extraction with ether and column chromatography provided the reduced product.

*2.3.1. 5-(Bis(4-Chlorophenyl)methyleneaminooxy)-N-tert-butyl-2-methylpentanamide (**4d**)*

General procedure B. Xanthate **3c** (0.2 mmol); column: petrol/DCM. Yield of **4d** 73%; ν_{max} (thin film)/cm^{-1} 2967 m, 1667s, 1599w; δ_H ($CDCl_3$, 400 MHz) 1.14 (3H, d, *J* 6.6, CH**Me**), 1.37 (9H, s, C(C**H$_3$**)$_3$), 1.39–1.41 (1H, m, C**H**H′), 1.65–1.76 (3H, m, CH**H**′C**H**H′), 2.07 (1H, app q, *J* 6.6, C**H**Me), 4.17–4.24 (2H, m, C**H**H′ON), 5.21 (1H, s, N**H**), 7.32 (2H, d, *J* 8.4, 2×Ar-**H**), 7.34 (2H, d, *J* 8.4, 2×Ar-**H**), 7.43 (2H, d, *J* 8.4, 2×Ar-**H**), 7.45 (2H, d, *J* 8.4, 2×Ar-**H**). δ_C ($CDCl_3$, 100 MHz) 18.1, 27.0, 28.9, 30.9, 42.0, 51.1, 74.8, 128.5, 128.6, 129.0, 130.8, 131.3, 134.7, 135.0, 135.5, 154.4, 175.6. HRMS found 435.1603; $C_{23}H_{29}O_2N_2Cl_2$ (MH^+) requires 435.1606.

*2.3.2. 6-(Bis(4-Chlorophenyl)methyleneaminooxy)hexan-2-one (**4e**)*

General procedure B. Xanthate **3d**; column: petrol/DCM (3:1). Yield of **4e**: 75%. ν_{max} (thin film)/cm^{-1} 1718s, 1601 m; δ_H ($CDCl_3$, 400 MHz), 1.63–1.78 (2H, m, C**H$_2$**C**H$_2$**), 2.15 (3H, s, **Me**), 2.48 (2H, t, *J* 6.6, C**H$_2$**), 4.22 (2H, t, *J* 6.2, C**H$_2$**ON), 7.32 (2H, d, *J* 8.4, 2×Ar-**H**), 7.34 (2H, d, *J* 8.4, 2×Ar-**H**), 7.44 (2H, d, *J* 8.4, 2×Ar-**H**), 7.45 (2H, d, *J* 8.4, 2×Ar-**H**). δ_C ($CDCl_3$, 100 MHz) 20.3, 28.6, 29.9, 43.3, 74.6, 128.5, 128.6, 129.1, 130.8, 131.3, 134.7, 135.0, 135.5, 154.4, 208.8; *m*/*z* (CI^+) 248 (22), 364 (MH^+, 100%), 365 (24), 366 (65); HRMS found 363.0791; $C_{19}H_{19}O_2NCl_2$ (M^+) requires 363.0789.

*2.3.3. Propan-2-one O-4-(acetoxyamino)-5,5,5-trifluoropentyl oxime (**4f**)*

General procedure B. Xanthate **3i** (140 mg; 0.36 mmol); column: petrol/ether (1:1). Yield of **4f**: 77 mg (85%); mp 61–63 °C; ν_{max} (thin film)/cm^{-1} 3277br s, 1667s, 1551 m; δ_H ($CDCl_3$, 400 MHz) 1.52–1.96 (4H, m, C**H**H′C**H**H′), 1.86 (3H, s, **Me**), 1.88 (3H, s, **Me**), 2.06 (3H, s, **Me**), 4.03 (1H, t, *J* 6.0C**H**H′ON), 4.55–4.70 (1H, C**H**CF_3), 6.36 (1H, br s, NHOAc). δ_H ($CDCl_3$, 400 MHz) 15.5, 21.8, 22.9, 24.7, 25.0, 50.3 (q, *J* 30), 71.9, 125.2 (q, *J*, 280), 155.1, 170.6; *m*/*z* (CI^+) 255 (MH^+, 100%); HRMS found 255.1312; $C_{10}H_{18}O_2N_2F_3$ (MH^+) requires 255.1320.

*2.3.4. 3-(3-(Propan-2-ylideneaminooxy)propyl)-1-tosylpiperidin-4-one (**4g**)*

This compound was obtained from xanthate **3j** in 88% yield. ν_{max} (thin film)/cm^{-1} 2925s, 1719s, 1598w; δ_H ($CDCl_3$, 400 MHz) 1.30–1.42 (3H, m, C**H**H′ and C**H**H′), 1.64–1.74 (2H, m, C**H**H′), 1.85–1.90 (1H, m, C**H**C=O), 1.89 (3H, s, ON=C**Me**Me′), 1.91 (3H, s, ON=CMe**Me**′), 2.48 (3H, s, Ar**Me**), 2.60–2.72 (3H, m, C**H**H′C=O and TsNC**H**H′), 3.00 (1H, td, *J* 11.0, 4.4, TsNC**H**H′), 3.75–3.87 (2H, m, CH**H**′NTsCH**H**′), 4.03 (2H, t, *J* 6.4, C**H$_2$**ON), 7.48 (2H, d, *J* 8.0, 2×Ar-**H**), 7.71 (2H, d, *J* 8.0, 2×Ar-**H**); δ_C ($CDCl_3$, 100 MHz) 14.6, 20.5, 20.9, 22.8, 25.4, 39.1, 45.6, 48.2, 49.9, 71.7, 126.5, 128.9, 132.3, 143.1, 153.7, 206.6; HRMS could not be obtained.

*2.3.5. tert-Butyl 6-(4-fluorophenyl)-6-oxohexyloxycarbamate (**4h**)*

General procedure B. Xanthate **3k** (258 mg, 0.58 mmol); column: petrol/ether (5:1). Yield of **4h**: 139 mg (74%); ν_{max} (thin film)/cm^{-1} 3299br m, 1726s, 1686s; δ_H ($CDCl_3$, 400 MHz) 1.47–1.55 (2H, m, C**H$_2$**), 1.51 (9H, m, (C**H$_3$**)$_3$), 1.66–1.84 (4H, m, C**H$_2$**C**H$_2$**), 2.99 (2H, t, *J* 7.4, C**H$_2$**), 3.90 (2H, t, *J* 6.6, C**H$_2$**ON), 7.15 (2H, t, *J* 8.6, 2×Ar-**H**), 7.25 (1H, s, N**H**), 8.01 (2H, dd, *J* 8.6, 5.4, 2×Ar-**H**). δ_C ($CDCl_3$, 100 MHz) 24.0, 25.7, 27.9, 28.3, 38.4, 76.6, 81.6, 115.6 (d, *J* 22), 130.7 (d, *J* 9), 133.4 (d, *J* 3), 156.9, 165.9 (d, *J* 253), 198.7; HRMS found 257.1058; $C_{12}H_{16}O_4NF$ (M^+-H_2C=CMe_2) requires 257.1059.

*2.3.6. tert-Butyl 4-(2-oxotetrahydrofuran-3-yl)butoxycarbamate (**4i**)*

General procedure B. Xanthate **3l** (456 mg, 1.2 mmol); column: petrol/ether (3:2). Yield of **4i**: 288 mg (88%); ν_{max} (thin film)/cm^{-1} 3296br m, 1760s, 1720s; δ_H ($CDCl_3$, 400 MHz) 1.46 (9H, m, (C**H$_3$**)$_3$), 1.46–1.53 (3H, m, C**H**H′ and C**H**H′), 1.60–1.69 (2H, m, C**H**H′), 1.84–1.99 (2H, m, C**H**H′ and CH**H**′), 2.35–2.55 (2H, m, CH**H**′ and C**H**), 3.84 (2H, t, *J* 6.4, C**H$_2$**ON), 4.17 (1H, dt, *J* 9.0, 6.8, C**H**H′O), 4.32 (1H, td, *J* 9.0, 2.8, C**H**H′O), 7.43 (1H, s, N**H**). δ_C ($CDCl_3$, 100 MHz) 23.8, 27.8, 28.2, 28.6, 30.1, 39.2, 66.6, 76.2, 81.5, 156.9, 179.5; HRMS found 141.0920; $C_8H_{13}O_2$ (M^+−ONHBoc) requires 141.0916.

*2.3.7. tert-Butyl 6-oxo-6-(2-oxooxazolidin-3-yl)hexyloxycarbamate (**4j**)*

General procedure B. Xanthate **3o** 81 mg (0.19 mmol); column: petrol/ethyl acetate (1:1). Yield of **4j**: 52 mg (87%); ν_{max} (thin film)/cm^{-1} 3301br m, 1779s, 1701s; δ_H ($CDCl_3$, 400 MHz) 1.42–1.51 (2H, m, C**H$_2$**), 1.51 (9H, m, (C**H$_3$**)$_3$), 1.65–1.76 (4H, m, C**H$_2$**C**H$_2$**), 2.96 (2H, t, *J* 7.4, C**H$_2$**), 3.87 (2H, t, *J* 6.6, C**H$_2$**ON), 4.05 (2H, t, *J* 8.2, oxazolidine C**H$_2$**), 4.44 (2H, t, *J* 8.2, oxazolidine C**H$_2$**), 7.25 (1H, s, N**H**). δ_C ($CDCl_3$, 100 MHz) 24.0, 25.4, 27.8, 28.3, 35.0, 42.6, 62.1, 76.5, 81.6, 153.6, 157.0, 173.4; *m*/*z* (CI^+), 202 (15%), 217 (MH^+−Boc, 100), 261 (62), 278 (36); HRMS found 216.1114; $C_9H_{16}N_2O_4$ (M^+−Boc) requires 216.1110.

*2.3.8. 6-Chloro-4-((propan-2-ylideneaminooxy)methyl)-3,4-dihydronaphthalen-1(2H)-one (**4a**)*

Xanthate **3e** (80 mg, 0.21 mmol) was dissolved in chlorobenzene (1.5 mL) and the mixture was heated at reflux for 15 min. DLP (17 mg, 0.042 mmol, 20 mol %) was added every 20 min for 2 h (total—102 mg, 0.252 mmol, 120 mol %). The mixture was concentrated in vacuo. Column chromatography (20:1 petrol/ethyl acetate) furnished the product **4a** (28 mg, 56%). Spectroscopic data as above.

*2.3.9. 4-((Propan-2-ylideneaminooxy)methyl)-5,6-dihydroazepino[3,2,1-jk]carbazol-7(4H)-one (**4c**)*

Xanthate **3h** (230 mg, 0.52 mmol) was dissolved in chlorobenzene (1.5 mL) and the mixture was heated at reflux for 15 min. DLP (40 mg, 0.104 mmol, 20 mol %) was added every 20 min for 3 h (total—400 mg, 1.04 mmol, 200 mol %). The mixture was concentrated in vacuo. Column chromatography (20:1 petrol/ethyl acetate) furnished the product **4c** (67 mg, 40%) as a viscous oil; ν_{max} (thin film)/cm^{-1} 2925m, 1690s; δ_H ($CDCl_3$, 400 MHz) 1.88 (3H, s, **Me**), 1.93 (3H, s, **Me**) 2.31–2.43 (2H, m, C**H**H′), 3.14 (1H, ddd, *J* 16.6, 7.2, 2.9, C**H**H′), 3.25 (1H, ddd, *J* 16.6, 10.8, 3.6, CH**H**′), 3.70–3.77 (1H, m, C**H**Ar), 4.24 (1H, dd, *J* 11.0, 9.0,C**H**H′ON), 4.24 (1H, dd, *J* 11.0, 5.6, CH**H**′ON), 7.36–7.48 (3H, m, 3×Ar-**H**), 7.53 (1H, ddd, *J* 8.4, 7.2, 1.2, Ar-**H**), 7.95 (1H, dd, *J* 7.2, 1.2, Ar-**H**), 8.01 (1H, d, 7.6, Ar-**H**), 8.71 (1H, d, *J* 8.4, Ar-**H**). δ_C ($CDCl_3$, 100 MHz) 15.7, 21.9, 23.2, 35.6, 41.8, 76.2, 118.4, 118.4, 119.1, 123.6, 124.1, 126.2, 127.8, 127.9, 128.0, 129.4, 136.4, 139.6, 155.5, 173.8; HRMS found 247.0999; $C_{17}H_{13}NO$ (M^+−HON=Me_2) requires 247.0997.

*2.3.10. O-(4-(2-Oxotetrahydrofuran-3-yl)butyl)hydroxylammonium trifluoroacetate (**6a**)*

To a solution of Boc-protected amine **4i** (55 mg, 0.20 mmol) in DCM (1 mL) trifluoroacetic acid (1 mL) was added dropwise over 5 min. The mixture was stirred for a further 30 min before being concentrated in vacuo to yield the product **6a** as a colourless oil (57 mg, 99%); ν_{max} (thin film)/cm^{-1} 1756s, 1685s; δ_H (d_4-MeOD, 400 MHz) 1.17–1.30 (3H, m, C**H**H′ and **CH**H′), 1.42–1.60 (3H, m, CH**H**′ and C**H**H′), 1.70–1.82 (2H, m, C**H**H′), 2.15–2.26 (1H, m, CH**H**′), 2.45–2.54 (1H, m, C**H**), 3.85 (2H, t, *J* 6.4, C**H$_2$**ON), 4.06 (1H, dt, *J* 9.0, 6.8, C**H**H′O), 4.19 (1H, td, *J* 9.0, 2.8, C**H**H′O). δ_C ($CDCl_3$, 100 MHz) 24.4, 28.5, 29.6, 30.9, 40.4, 68.3, 76.1, 182.2; *m*/*z* (CI$^+$) 174 (MH^+, 100%); HRMS found 141.0918; $C_8H_{13}O_2$ (M^+−ONH_2) requires 141.0916.

*2.3.11. 3-(4-(Aminooxy)butyl)dihydrofuran-2(3H)-one (**5a**)*

To a solution of triflate salt **6a** (55 mg 0.19 mmol) in MeOH/H_2O (1 mL, 1:1 v/v) was added K_2CO_3 (83 mg, 0.6 mmol) and the mixture was stirred for 1 h before being poured onto H_2O (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Column chromatography (EtOAc) yielded the product **5a** as an oil (24 mg, 74%); ν_{max} (thin film)/cm^{-1} 3418br m, 1762s; δ_H ($CDCl_3$, 400 MHz) 1.45–1.56 (3H, m, C**H**H′ and **CH**H′), 1.62–1.70 (3H, m, CH**H**′ and C**H**H′), 1.88–2.03 (2H, m, C**H**H′), 2.40–2.48 (1H, m, CH**H**′), 2.52–2.61 (1H, m, C**H**), 3.71 (2H, t, *J* 6.4, C**H$_2$**ON), 4.23 (1H, dt, *J* 9.0, 6.8, C**H**H′O), 4.37 (1H, td, *J* 9.0, 2.8, C**H**H′O). δ_C ($CDCl_3$, 100 MHz) 24.0, 28.2, 28.6, 30.2, 39.2, 39.3, 66.5, 75.6, 179.5; *m*/*z* (CI+) 174 (MH^+, 100%); HRMS found 141.0921; $C_8H_{13}O_2$ (M^+−ONH_2) requires 141.0916.

*2.3.12. O-(6-Oxo-6-(2-oxooxazolidin-3-yl)hexyl)hydroxylammonium (**6b**)*

To a solution of Boc-protected amine **4j** (85 mg, 0.27 mmol) in DCM (1 mL) trifluoroacetic acid (1 mL) was added dropwise over 5 min. The mixture was stirred for a further 30 min before being concentrated in vacuo to yield the product **6b** as a colourless oil (89 mg, 99%); ν_{max} (MeOH)/cm^{-1} 3409br m, 1781s, 1679s; δ_H (d_4-MeOD, 400 MHz) 1.44–1.52 (2H, m, C**H$_2$**), 1.65–1.77 (4H, m, C**H$_2$** and C**H$_2$**), 2.90 (2H, t, *J* 7.4, C**H$_2$**), 3.97 (2H, t, *J* 8.2, oxazolidine C**H$_2$**), 4.07 (2H, t, *J* 6.6, C**H$_2$**ON), 4.41 (2H, t, *J* 8.2, oxazolidine C**H$_2$**). δ_C (d_4-MeOD, 100 MHz) 24.9, 26.2, 28.5, 35.8, 43.8, 63.8, 76.2, 155.8, 174.9; *m*/*z* (CI$^+$) 217 (M^+, 100%); HRMS found 217.1184; $C_9H_{17}N_2O_4$ (M^+) requires 217.1188.

*2.3.13. Methyl 6-(aminooxy)hexanoate (**5b**)*

To a solution of triflate salt **6b** (75 mg 0.23 mmol) in MeOH/H_2O (1 mL, 1:1 v/v) was added K_2CO_3 (94 mg, 0.6 mmol) and the mixture was stirred for 1 h before being poured onto H_2O (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Column chromatography (EtOAc) yielded the product **5b** as a colourless oil (25 mg, 68%); ν_{max} (thin film)/cm^{-1} 3444br m, 1733s; δ_H ($CDCl_3$, 400 MHz) 1.35–1.45 (2H, m, C**H$_2$**), 1.58–1.73 (4H, m, C**H$_2$** and C**H$_2$**), 2.35 (2H, t, *J* 7.4, C**H$_2$**), 3.68 (2H, t, *J* 6.6, C**H$_2$**ON), 3.69 (3H, s, Me), 4.50 (2H, br s, N**H$_2$**); δ_C ($CDCl_3$, 100 MHz) 24.8, 25.6, 28.1, 34.0, 51.5, 75.8, 174.2; *m*/*z* (CI+) 162 (MH^+, 100%); HRMS (EI$^+$) found 162.1122; $C_7H_{16}NO_3$ (MH^+) requires 162.1130.

*2.3.14. 3-(4-Fluorophenyl)-5,6,7,8-tetrahydro-4H-[1,2]oxazocine (**6c**)*

To a solution of Boc-protected amine **4h** (85 mg, 0.27 mmol) in DCM (1 mL) trifluoroacetic acid (1 mL) was added dropwise over 5 min. The mixture was stirred for a further 30 min before being concentrated in vacuo to yield oxime **6c** (trans) as a white solid (10 mg, 62%); mp 105–106 °C; ν_{max} (thin film)/cm^{-1} 2930 m, 1608w; δ_H ($CDCl_3$, 400 MHz) 1.26–1.40 (4H, m, 2×C**H$_2$**), 1.72–1.79 (2H, m, C**H$_2$**), 2.85 (2H, t, *J* 7.4, C**H$_2$**C=NO), 4.21 (2H, t, *J* 5.6, C**H$_2$**ON), 7.10 (2H, t, *J* 8.8, 2×Ar-**H**), 7.69 (2H, dd, *J* 8.8, 5.2, 2×Ar-**H**); δ_C ($CDCl_3$, 100 MHz) 26.5, 26.6, 26.6, 28.7, 73.2, 115.4 (d, *J* 21), 128.0 (d, *J* 8), 132.0 (d, *J* 0.3), 157.2, 163.2 (d, *J* 124); *m*/*z* (CI$^+$) 208 (MH^+, 100%); HRMS found 207.1067; $C_{12}H_{14}ONF$ (M^+) requires 207.1059.

Further elution yielded oxime **6c** (cis) as a white solid (2 mg, 12%); mp 115–118 °C; ν_{max} (thin film)/cm^{-1} 2923 m, 1607w; δ_H ($CDCl_3$, 400 MHz) 1.51–1.69 (4H, m, 2×C**H$_2$**), 1.73–1.83 (2H, m, C**H$_2$**), 2.80 (2H, t, *J* 7.4, C**H$_2$**C=NO), 4.22 (2H, t, *J* 5.6, C**H$_2$**ON), 7.09 (2H, t, *J* 8.8, 2×Ar-**H**), 7.65 (2H, dd, *J* 8.8, 5.2, 2×Ar-**H**); δ_C ($CDCl_3$, 100 MHz) 26.1, 26.5, 26.5, 28.8, 34.2, 73.8, 115.4 (d, *J* 21), 128.0 (d, *J* 8), 132.1 (d, *J* 0.3), 157.3, 163.3 (d, *J* 123); *m*/*z* (CI$^+$) 208 (MH^+, 100%); HRMS found 208.1139; $C_{12}H_{15}ONF$ (MH^+) requires 208.1138.

*2.3.15. (2R,3R,4R,5S)-6-(Allyloxyimino)hexane-1,2,3,4,5-pentayl pentaacetate (**1e**)*

To a solution of protected hydroxylamine **1a** (258 mg, 1.5 mmol) in DCM (1 mL), trifluoroacetic acid (1 mL) was added dropwise over 5 min. The mixture was stirred for a further 30 min before being concentrated in vacuo. The resultant oil was dissolved in pyridine (5 mL), glucose pentaacetate **7a** (390 mg, 1 mmol) was added and the mixture was heated at 60 °C for 150 min before being allowed to cool to room temperature. The mixture was diluted with ethyl acetate (20 mL), poured onto 1 M aqueous HCl solution (20 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (2×20 mL) and the combined organics were dried over $MgSO_4$ and concentrated in vacuo to furnish a mixture of oxime diastereoisomers and acetate regioisomers. The mixture was dissolved in acetic anhydride (5 mL), pyridine (1 drop) and DMF (1 drop) were added and the mixture was stirred for 16 h before being concentrated in vacuo. Column chromatography (4:1 petrol/ethyl acetate) furnished alkene **1e** as a 5:1 mixture of diastereoisomers as a white solid (295 mg, 66%); mp 66–72 °C; ν (thin film)/cm^{-1} 2966m, 1751s, 1644w; δ_H ($CDCl_3$, 400 MHz) 2.07 (3H, s, **Me**, minor diastereoisomer), 2.08 (6H, app s, 2×**Me**, major diastereoisomer), 2.09 (3H, s, **Me**, minor), 2.09 (3H, s, **Me**, minor), 2.10 (3H, s, **Me**, major), 2.10 (3H, s, **Me**, major), 2.11 (3H, s, **Me**, minor), 2.15 (3H, s, **Me**, major), 2.16 (3H, s, **Me**, minor), 4.09 (1H, dd, *J* 12.4, 5.4, C**H**H′OAc, major), 4.15 (1H, dd, *J* 12.2, 6.4, C**H**H′OAc, minor), 4.27 (1H, dd, *J* 12.4, 3.4, C**H**H′OAc, major), 4.15 (1H, dd, *J* 12.2, 3.6, C**H**H′OAc, minor), 4.57, (1H, dt, *J* 4.8, 1.4, C**H$_2$**CH=, major), 4.63 (1H, dt, *J* 4.8, 1.2, C**H$_2$**CH=, minor), 5.10 (1H, m, C**H**OAc, minor), 5.12 (1H, ddd, *J* 8.0, 5.4, 3.4, CHOAc, major), 5.24 (1H, dq, *J* 10.4, 1.4,=C**H**H′, major), 5.25 (1H, dq, *J* 10.4, 1.2,=C**H**H′, minor), 5.31 (1H, dq, *J* 17.2, 1.4,=CH**H**′, major), 5.34 (1H, dq, *J* 17.2, 1.2,=CH**H**′, minor), 5.41 (1H, dd, *J* 8.0, 2.4, C**H**OAc, major), 5.44 (1H, dd, *J* 6.4, 4.8, C**H**OAc, minor), 5.50–5.54 (2H, m, C**H**OAcC**H**OAc, major), 5.51–5.56 (1H, m, C**H**OAc,

minor), 5.62 (1H, t, *J* 5.2, C**H**OAc, minor), 5.93–6.04 (1H, m, C**H$_2$**CH═, major), 5.97–6.07 (1H, m, C**H$_2$**CH═, minor), 6.59 (1H, d, *J* 5.6, C**H**═NO, minor), 7.33 (1H, d, *J* 5.6, C**H**═NO, major); δ_C ($CDCl_3$, 100 MHz) major diastreoisomer 20.6, 20.7, 20.7, 20.8, 20.8, 61.8, 68.2, 68.4, 69.3, 69.5, 75.5, 118.3, 133.5, 143.8, 169.5, 169.5, 169.8, 169.8, 170.5—minor diastereoisomer 20.5, 20.6, 20.7, 20.8, 20.8, 61.5, 66.1, 68.9, 68.9, 75.8, 118.0, 133.6, 145.6, 169.5, 169.5, 169.6, 169.8, 170.5; *m*/*z* (CI^+) 381 (75%), 382 (15), 446 (MH^+, 100%), 447 (22), 463 (18); HRMS found 445.1586; $C_{19}H_{27}NO_{11}$ (M^+) requires 445.1584.

2.3.16. (11S,12R,13R,14R)-6-(3-(9H-Carbazol-9-yl)-3-oxopropyl)-4-thioxo-3,8-dioxa-5-thia-9-azapentadec-9-ene-11,12,13,14,15-pentayl pentaacetate

Alkene **1e** (90 mg, 0.2 mmol) and xanthate **2g** (100 mg, 0.3 mmol) were dissolved in dichloroethane (0.3 mL) and the mixture was heated at reflux for 15 min. DLP (4 mg, 5 mol %) was added every hour for 5 h (20 mg, 25 mol %). The mixture was concentrated in vacuo and column chromatography (4:1 petrol/ethyl acetate) furnished the product (120 mg, 76%) as a mixture of diastereoisomers, which was characterised as the monoisomeric reduction product **4k** below.

2.3.17. (2R,3R,4R,5S)-6-(5-(9H-Carbazol-9-yl)-5-oxopentyloxyimino)hexane-1,2,3,4,5-pentayl pentaacetate (**4k**)

The above xanthate (120 mg, 0.15 mmol) was subjected to reduction according to General procedure B and the product purified by column chromatography (petrol/ethyl acetate 1:1). Yield of **4k**: 63 mg (64%) as a mixture from which the major *trans* oxime isomer could be isolated (24 mg, 24%).

Major isomer: mp 212 °C decomp.; ν_{max} (thin film)/cm^{-1} 2938m, 1750s, 1693m; δ_H ($CDCl_3$, 400 MHz) 1.88–1.95 (2H, m, C**H$_2$**), 2.03–2.08 (2H, m, C**H$_2$**), 2.07 (3H, s, **Me**), 2.10 (3H, s, **Me**), 2.11 (3H, s, **Me**), 2.12 (3H, s, **Me**), 2.15 (3H, s, **Me**), 3.25 (2H, t, *J* 7.6, C**H$_2$**C═O), 4.09 (1H, dd, *J* 12.4, 5.6, C**H**H′OAc), 4.21 (2H, t, *J* 6.4, C**H$_2$**ON), 4.27 (1H, dd, *J* 12.4, 3.2, CH**H**′OAc), 5.12–5.17 (1H, ddd, *J* 8.0, 5.6, 3.2C**H**OAc), 5.43 (1H, dd, *J* 8.0, 2.8, C**H**OAc), 7.31 (1H, d, *J* 6.0, C**H**═NO), 7.44 (2H, t, *J* 7.4, 2×Ar-**H**), 7.53 (2H, td, *J* 7.4, 1.2, 2×Ar-**H**), 8.05 (2H, d, *J* 7.4, 2×Ar-**H**), 8.28 (2H, d, *J* 7.4, 2×Ar-**H**). δ_C ($CDCl_3$, 100 MHz) 19.4, 20.6, 20.7, 20.8, 21.3, 27.3, 28.2, 38.8, 61.8, 68.3, 68.4, 69.3, 69.6, 74.3, 116.5, 119.9, 123.6, 126.5, 127.4, 169.4, 169.5, 169.8, 170.5, 173.0; *m*/*z* (CI^+), 656 (MH^+, 100), 659 (25), 673 (18); HRMS found 655.2535; $C_{33}H_{39}N_2O_{12}$ (MH^+) requires 655.2503.

2.3.18. (5aS,7S,9aS,11aS)-3-Hydroxy-10,13-dimethyltetradecahydro-1H-cyclopenta[a]phenanthren-17(2H)-one O-but-3-enyl oxime (**1f**)

To a solution of protected hydroxylamine **1d** (279 mg, 1.5 mmol) in DCM (1 mL) trifluoroacetic acid (1 mL) was added dropwise over 5 min. The mixture was stirred for a further 30 min before being concentrated in vacuo. The resultant oil was dissolved in pyridine (5 mL), epiandrosterone (306 mg, 1 mmol) was added and the mixture was heated at 60 °C for 150 min before being allowed to cool to room temperature. The mixture was diluted with ethyl acetate (20 mL), poured onto 1 M aqueous HCl solution (20 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (2×20 mL) and the combined organics were dried over $MgSO_4$ and concentrated in vacuo. Column chromatography (3:2 petrol/ether) furnished the oxime **1f** as a 15:1 mixture of diastereoisomers (318 mg, 86%); mp 157–160 °C; ν (thin film)/cm^{-1} 3414br m, 2929m, 1671s; δ_H ($CDCl_3$, 400 MHz) 0.85 (3H, s, steroid-**Me**), 0.91 (3H, s, steroid-**Me**), 0.7–2.0 (20H, m, 20×steroid-**H**), 2.03 (1H, br s, O**H**), 2.36–2.52 (4H, m, C**H**H′C═NO and C**H$_2$**CH$_2$CH═CH$_2$), 3.57–3.65 (1H, m, C**H**OH), 4.99 (1H, t, *J* 6.8, C**H$_2$**CH═CH$_2$, minor diastereoisomer), 4.08 (1H, t, *J* 6.8, C**H$_2$**CH═CH$_2$, major diastereoisomer), 5.05 (1H, d, *J* 10.0,═C**H**H′), 5.10 (1H, dq, *J* 17.2, 1.6,═CH**H**′), 5.80–5.90 (1H, m, C**H**═CHH′). δ_C ($CDCl_3$, 100 MHz) 12.4, 17.3, 20.8, 23.2, 25.8, 28.6, 31.5, 31.6, 33.9, 34.3, 35.0, 35.7, 37.0, 38.1, 44.0, 44.9, 53.9, 54.6, 71.2, 72.4, 116.3, 135.3, 170.8.

2.3.19. 6-Fluoro-4-(2-((E)-((3S,5S,10S,13S)-3-hydroxy-10,13-dimethyldodecahydro-1H-cyclopenta[a]phenanthren-17(2H,10H,14H)-ylidene)aminooxy)ethyl)-3,4-dihydronaphthalen-1(2H)-one (**4l**)

Alkene **1f** (300 mg, 0.81 mmol) and xanthate **2d** (315 mg, 1.2 mmol) were dissolved in dichloroethane (1.2 mmol) and the mixture was heated at reflux for 15 min. DLP (16 mg, 5 mol %) was added every hour for 10 h (160 mg, 50 mol % in total). The mixture was diluted with dichloroethane (4 mL) and DLP (74 mg, 20 mol %) was added every 30 min for 4 h (592 mg, 160 mol % in total). The mixture was concentrated in vacuo and column chromatography (2:1 petrol/ether) furnished oxime **4l** (215 mg, 54%) as a 1:1 mixture of diastereoisomers; mp 208–210 °C; ν (thin film)/cm^{-1} 3408 br s, 2928s, 1682s, 1606m; δ_H ($CDCl_3$, 400 MHz) 83 (3H, s, steroid-**Me**), 0.92 (3H, s, steroid-**Me**), 0.70–2.52 (20H, m, 20×steroid-**H** and 2×C**HH**′), 2.62 (1H, dt, 17.6, 4.8, C**H**H′C═O), 2.80 (1H, ddd, *J* 17.6, 11.6, 4.8, CH**H**′C═O), 3.12–3.17 (1H, m, ArC**H**), 3.59–3.67 (1H, m, C**H**OH), 7.00–7.05 (2H, m, 2×Ar-**H**), 8.10 (1H, dd, *J* 9.6, 7.4, Ar-**H**); δ_C ($CDCl_3$, 100 MHz) peaks which exhibit doubling due to diastereoisomeric mixture are labelled *d* 12.4, 17.4*d*, 20.9, 23.3, 25.9, 27.0*d*, 28.6, 31.5, 31.6, 33.7*d*, 34.3*d*, 34.8, 35.0, 35.3, 35.7, 37.0, 38.2, 44.2, 44.9, 54.0*d*, 54.6, 70.8, 71.2, 114.4 (d, *J* 22), 114.9 (d, *J* 21), 128.7 (d, *J* 1), 130.6 (d, 10), 151.2*d*, 165.8 (d, *J* 253), 171.0, 196.8; *m*/*z* (CI^+) 496 (MH^+, 100%), 497 (37); HRMS found 495.3146; $C_{31}H_{41}O_3NF$ (M^+) requires 495.3149.

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References and notes

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