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Tricyclic-isoxazolidine analogues via intramolecular 1,3-dipolar cycloaddition reactions of nitrones

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ABSTRACT

The tricyclic-isoxazolidine analogues tetrahydrothiochromenoisoxazoles, hexahydroisoxazolequinolines and tetrahydroisoxazolepyranopyridines were prepared by an intramolecular 1,3-dipolar cycloaddition reaction of a nitrone with an alkene. For *N*-alkylated hexahydroisoxazolequinolines, reduction of the reaction time from two days to 40 min was achieved using microwave heating. The cyclization to form tetrahydroisoxazolepyranopyridines only proceeded when the alkene was substituted with an electron withdrawing group.

1. Introduction

Novel ring systems in natural products, such as Martinelline **1** often inspire synthetic chemists to extend the series or prepare new ring systems.[1] The fused pyrrolo-quinoline in alkaloid **1** shares structural similarity with the chromenoisoxazoles that have found use in a number of fields. For example, the dihydrochromenoisoxazoles have shown a range of biological activity, such as selective serotonin reuptake inhibitors and α_2-adrenoceptor antagonists,[2] whereas the tetrahydrochromenoisoxazoles **2** have been used successfully by Masamune as chiral auxiliaries in asymmetric natural product synthesis.[3]

We were therefore surprised to find no reports of the preparation of derivatiseable analogues, such as the tetrahydrothiochromenoisoxazoles **3**, nor of analogues with heteroaromatic rings (structure **4**). The hexahydroisoxazolequinoline **5** analogue had been prepared only as its *N*-methyl derivative by Oppolzer and Keller in 1970,[4] and recently bearing an *N*-chiral auxilary by Broggini et al.[5] We herein report our flexible approach to these ring systems using an intramolecular 1,3-dipolar cycloaddition reaction of a nitrone with an alkene group (Fig. 1).

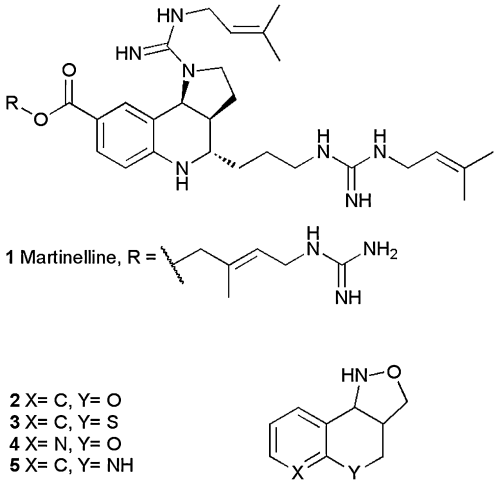

Figure 1. Structures of Martinelline **1** and isoxazolidine analogues **2**–**5**.

2. Results and discussion

2.1. Synthesis of tetrahydrothiochromenoisoxazoles

N-Substituted tetrahydrochromenoisoxazoles **2** have been prepared using 1,3-dipolar cycloaddition reactions of the nitrone formed from condensing a suitable aldehyde with *N*-substituted

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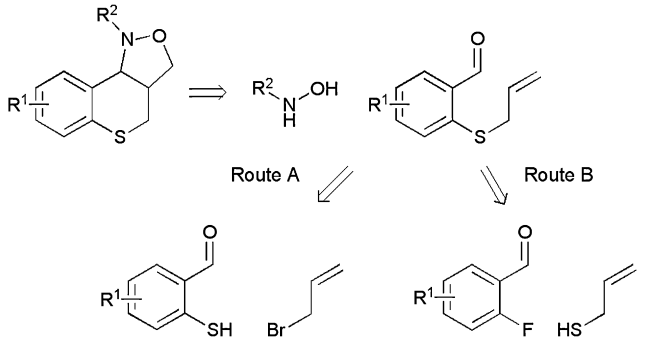
hydroxylamines.[4] We anticipated that the sulfur series **3** would also be available by this approach (Scheme 1).

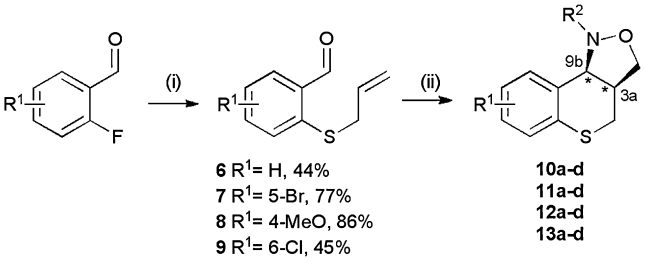


Scheme 1. Retrosynthesis of tetrahydrothiochromenoisoxazoles.

The utility of this approach would then depend on accessing a range of 2-alkenylthiobenzaldehydes. These thioethers could be prepared readily using two approaches. The first approach that we considered (Route A, Scheme 1) was the alkylation of thiosalicylaldehydes with allylbromide. Production of tetrahydrothiochromenoisoxazoles would then be limited to the availability of substituted thiosalicylaldehydes.

Recent work by Wemple described robust conditions for the Newman–Kwart rearrangement of phenols to thiophenols.[6] This approach had in earlier work allowed us to prepare a number of novel thiosalicylic acids from substituted salicylic acids,[7] and these acids could in principle be used to prepare the desired thiosalicylaldehydes. However, during the earlier work we observed variable yields with several *ortho*-substituted thiophenols, and hence looked elsewhere for our current thioether synthesis.

The second approach investigated (route B, Scheme 1) was the nucleophilic aromatic substitution of variously substituted 2-fluorobenzaldehydes with allyl mercaptan.[8] This approach gave consistently high yields across a variety of substrates. In this way we were able to prepare the *S*-allyl-2-thiobenzaldehydes **6**–**9** shown in Scheme 2.



Scheme 2. Reagents: (i) allyl mercaptan, K_2CO_3, DMF; (ii) R^2NHOH, Et_3N, $PhCH_3$, reflux, 2.5 days.

Each of the 2-(allylthio)benzaldehydes **6**–**9** were reacted with methylhydroxylamine, isopropylhydroxylamine, cyclohexylhydroxylamine and benzylhydroxylamine as their hydrochloride salts in the presence of triethylamine in refluxing toluene for two days. A small amount of methanol could be added as a final component to improve solubility of the hydroxylamine hydrochlorides used in these reactions.[9] All 16 reactions could be conveniently conducted in parallel using Radleys Carousels.[10] The reaction mixtures were absorbed onto a small cartridge of silica, washed with hexanes to remove highly non-polar material, then with ethyl acetate to elute the tetrahydrothiochromenoisoxazoles **10**–**13** in high yield (Table 1).

The tetrahydrothiochromenoisoxazoles produced in this manner were racemic and with *cis*-ring fusion, as indicated by a coupling constant *J* 8 Hz between H3a and H9b in the ^1H NMR spectra, similar in value to the corresponding 7 Hz coupling reported for Martinelline **1** itself.[1]

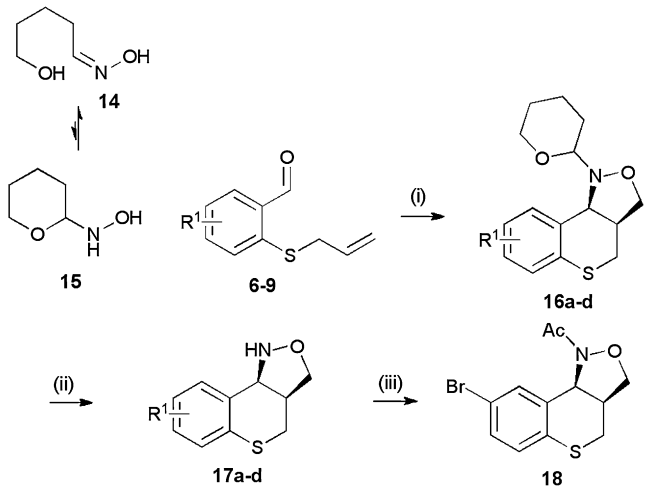
Table 1
Tetrahydrothiochromenoisoxazole yields and characterization[a]

Compound	R^1	R^2	Yield (%)	HRMS (*m*/*z*)	
				$[M^+]_{Calc}$	$[M^+]_{Obs}$
10a	H	Me	93	207.0712	207.0710
10b	H	^{i}Pr	76	235.1025	235.1025
10c	H	cyclohexyl	90	275.1338	275.1335
10d	H	Bn	92	283.1025	283.1026
11a	8-Br	Me	95	284.9804	284.9801
11b	8-Br	^{i}Pr	84	313.0117	313.0123
11c	8-Br	cyclohexyl	78	353.0430	353.0436
11d	8-Br	Bn	92	361.0128	361.0123
12a	7-MeO	Me	85	237.0818	237.0822
12b	7-MeO	^{i}Pr	39	265.1131	265.1129
12c	7-MeO	cyclohexyl	74	305.1417	305.1421
12d	7-MeO	Bn	90	313.1131	313.1132
13a	9-Cl	Me	87	241.0323	241.0325
13b	9-Cl	^{i}Pr	52	269.0636	269.0636
13c	9-Cl	cyclohexyl	59	309.0949	309.0942
13d	9-Cl	Bn	91	317.0627	317.0627

[a] Purity of samples determined to be >95% by ^1H NMR spectroscopy.

Preparation of tetrahydrothiochromenoisoxazoles in this manner is limited by the poor range of commercially available hydroxylamines. Oppolzer had tried using hydroxylamine to produce the parent tetrahydrochromenoisoxazole **2** but with poor yield.[4] Abiko used 5-hydroxypentanal oxime **14** for the in situ formation of *N*-(2-tetrahydropyranyl)hydroxylamine **15**. This forms a nitrone in the presence of catalytic dibutyltin oxide that undergoes the desired 1,3-dipolar cyclization to provide the isoxazolidine ring system **2** as its *N*-tetrahydropyranyl derivative.[11]

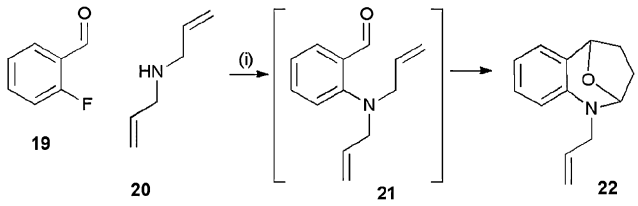
When we applied this method to the tetrahydrothiochromenoisoxazole series (Scheme 3), we found that the tetrahydropyranyl derivative **16c** could be obtained on prolonged heating of **8** and 5-hydroxypentanal oxime **14**. Mild acidic hydrolysis provided the *N*-unsubstituted tetrahydrothiochromenoisoxazole **17c** in excellent yields. Similarly, when benzaldehydes **6**, **7** and **9** were subjected to the same process, tetrahydrothiochromenoisoxazoles **17a**,**b** and **d** were obtained. Derivatization of the unprotected nitrogen could then provide access to analogues not available from *N*-substituted hydroxylamines. For example, **17b** was acetylated to form **18**.



Scheme 3. (a) R^1=H, (b) R^1=8-Br, (c) R^1=7-MeO, (d) R^1=9-Cl. Reagents: (i) Bu_2SnO, $PhCH_3$; (ii) aq HCl, MeOH, 61–82% (two steps); (iii) Ac_2O, pyridine, CH_2Cl_2, 96%.

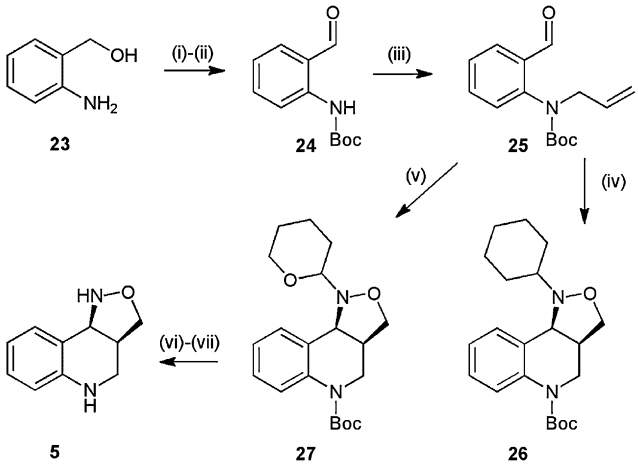
2.2. Synthesis of hexahydroisoxazolequinolines

To form hexahydroisoxazolequinoline **5**, we initially investigated the approach in Scheme 4, similar to that for the thiochromenoisoxazoles beginning with 2-fluorobenzaldehyde **19**. The use of diallylamine **20** would provide both an allyl group as a dipolarophile and a second allyl group as a nitrogen protecting group. Microwave heating in a sealed vial of the benzaldehyde and diallylamine in DMF in the presence of potassium carbonate formed no discernable products for temperatures below 220 °C. At 220 °C some decomposition occurred, but a major component could be isolated after considerable purification. The ^{1}H NMR spectrum of this product contained no aldehyde signal and signals for only one allyl group. Further investigation of the NMR and mass spectra revealed the product to be the oxo-benzazepine **22** formed via a cascade keto-ene/cyclization reaction of **21**. Jones and Brinson[12] have reported similar transformations for benzophenones and acetophenones, but with a much lower temperature for the formation of the aniline. Under our conditions, we were unable to observe the formation of aniline **21** without concurrent cyclization to give **22**.



Scheme 4. Reagents and conditions: (i) K_2CO_3, DMF, 220 °C, MW, 20%.

The hexahydroisoxazolequinoline analogues were prepared instead from 2-aminobenzylalcohol **23** by selectively protecting the amine as its *tert*-butylcarbamate (Scheme 5).[13] Oxidation of the alcohol to afford the aminobenzaldehyde **24** has been reported several times and we found Shapiro's protocol using MnO_2 most consistent.[14] An allyl group was introduced by using allylbromide and sodium hydride as base to give **25**.



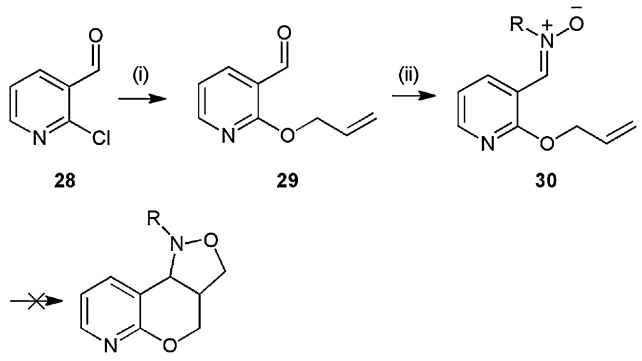
Scheme 5. Reagents: (i) $(Boc)_2O$, DCE; (ii) MnO_2, CH_2Cl_2, 66% (two steps); (iii) allylbromide, NaH, DMF, 91%; (iv) *N*-cyclohexylhydroxylamine hydrochloride, Et_3N, $PhCH_3$, 84%; (v) 5-hydroxypentanal oxime, Bu_2SnO, $PhCH_3$; (vi) aq HCl, MeOH; (vii) Amberlite IR-45, MeOH, 74% (three steps).

The *N*,*N*-disubstituted aminobenzaldehyde **25** and cyclohexylhydroxylamine hydrochloride were heated to 170 °C in toluene using microwave heating for 40 min. These higher temperatures for toluene could be achieved by the addition of silicon carbide chips into the reaction as a passive absorber of microwave radiation. Kappe has developed specialized silicon carbide plugs for this purpose,[15] but we found that chips were sufficient for our requirements.[16] The Boc protected hexahydroisoxazolequinoline **26** was obtained in 84% yield after workup and purification.

While microwave heating was suitable for the *N*-alkylated analogues, preparation of the *N*-tetrahydropyranyl analogue **27** by similar means resulted in extensive decomposition. Returning to conventional heating in toluene at 110 °C in the presence of catalytic dibutyltin oxide, followed by hydrolysis of the two protecting groups, afforded the hexahydroisoxazolequinoline parent ring system **5** in 74% yield over the two steps.

2.3. Synthesis of tetrahydroisoxazolepyranopyridines

Based on some recently reported quinoline work,[17] we envisaged that the tetrahydroisoxazolepyranopyridine analogues **4** would be available via the route shown in Scheme 6. Beginning with 2-chloropyridine-3-carbaldehyde **28**, the allyl ether **29** was formed by substitution of the chloride with the sodium allyl alkoxide. While the allyl ether **29** could be seen to undergo nitrone formation of **30** from the distinctive loss of the aldehyde signal in the ^{1}H NMR spectrum at δ 10.5 and appearance of a nitrone signal at δ 8.5,[4] we could not effect the cyclization by either conventional or microwave heating.



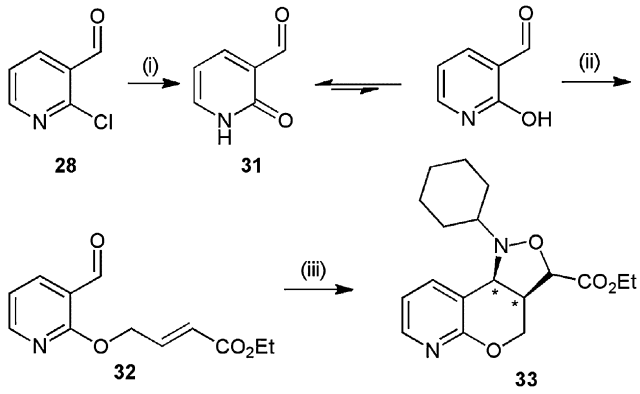
Scheme 6. Reagents: (i) allyl alcohol, NaH, (ii) alkylhydroxylamine.

We reasoned that a pyridine group is electron deficient relative to a phenyl group and that this may cause lowering of the $HOMO_{nitrone}$, that in turn would cause a greater energy difference between the $LUMO_{alkene}$ and the $HOMO_{nitrone}$ relative to the phenyl series, presuming this is a normal electron-demand reaction.[18] Attachment of an electron withdrawing group to the alkene would result in a lowering of the $LUMO_{alkene}$ energy and a reduction of the HOMO/LUMO energy gap. A convenient approach to a model substrate was a cross-metathesis (CM) reaction between methyl acrylate and pyridine allyl ether **29**, but we were unable to effect CM reactions on this substrate.[19]

An alternative route was sought beginning by hydrolyzing the 2-chloropyridine-3-carbaldehyde **28** (Scheme 7) to give pyridinone **31**. We found that microwave heating provided gram quantities of the desired pyridinone **31** in 10 min and near quantitative yield. Selective O-alkylation to form the ether **32** using ethyl 4-bromocrotonate was achieved by using silver carbonate in toluene.[20] Other bases and solvents surveyed afforded only the N-alkylated material or a mixture of both N- and O-alkylated pyridinone.

Treatment of pyridine crotonate ether **32** with *N*-cyclohexylhydroxylamine hydrochloride in toluene at 130 °C with microwave heating afforded the tetrahydroisoxazolepyranopyridine **33** in 65% yield after chromatography.

The X-ray crystal structure of **33** (Fig. 2) shows an almost L-shaped ring system formed by *cis*-ring fusion between the pyranopyridine rings and the isoxazolidine ring.[21]



Scheme 7. Reagents: (i) cat. HCl, cat. H_2O_2, H_2O, MW, 98.5%; (ii) Ag_2CO_3, ethyl 4-bromocrotonate, $PhCH_3$, 82%; (iii) *N*-cyclohexylhydroxylamine hydrochloride, Et_3N, $PhCH_3$, 65%.

Mass spectra positive ion EI mass spectra were recorded on a ThermoQuest MAT95XL mass spectrometer using an ionization energy of 70 eV. Accurate mass measurements were obtained with a resolution of 5000–10,000 using PFK as the reference compound. Positive and negative ion APCI mass spectra were acquired with a VG Platform mass spectrometer using a cone voltage of 50 V and the source was maintained at 100 °C. Nitrogen was used as the nebulizer and sheath gas and the probe temperature was 400 °C. The solvent system used was methanol with a flow rate of 0.3 ml min^{-1}.

Infrared spectra were recorded on a Perkin–Elmer 842 spectrophotometer as neat films between two sodium chloride plates, or as discs with potassium bromide as the matrix.

Melting points were determined using an Electrothermal 9300 melting point apparatus and are uncorrected.

Microanalyses were determined by the Campbell Microanalytical Laboratory, Department of Chemistry University of Otago, New Zealand.

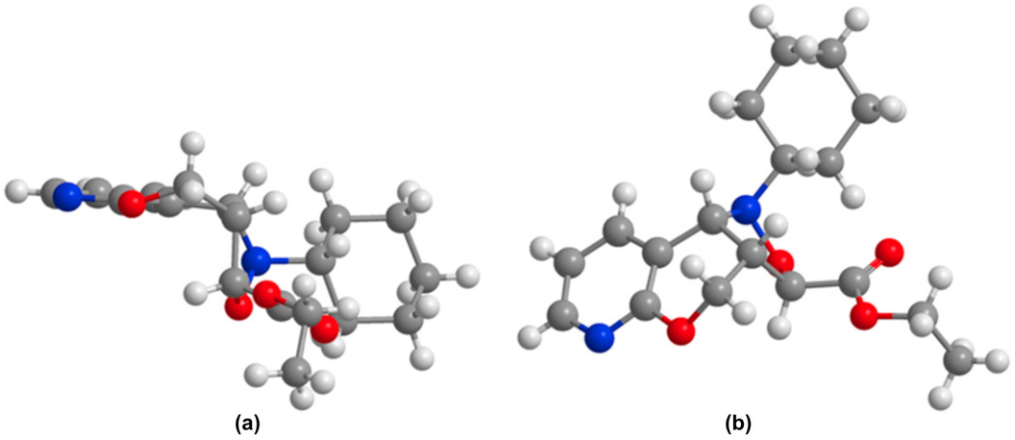


Figure 2. Chem3D produced image of the X-ray structure of 33:[21] (a) side view; (b) oblique view.

3. Conclusions

We have here demonstrated the utility of the intramolecular 1,3-dipolar cycloaddition reaction in constructing novel isoxazolidines as analogues of **1**, including the first report of the tetrahydroisoxazolepyranopyridine ring system. The use of oxime **14** allows for ready access to the parent isoxazolidine and allows for easy analoguing around the core ring system.

4. Experimental

4.1. General experimental

Microwave reactions were conducted in a Biotage Initiator-60 (300 W or 400 W) microwave oven in sealed glass vials. Reaction duration was timed from the point the reaction reached the recorded temperature.

^1H NMR and ^{13}C NMR spectra were recorded on Bruker DRX-500 (500 or 125 MHz), AV-400 (400 or 100 MHz), or AV-200 (200 or 50 MHz) instruments using an internal deuterium lock in chloroform-d_1 at room temperature, unless otherwise recorded. The chemical shift data for each signal is given in units δ relative to tetramethylsilane and referenced to the residual solvent. Coupling constants (J) are quoted in hertz. A doublet of multiplets is designated by 'dm'. Many of the signals in the ^{13}C NMR spectra for compounds **17a**,**b**,**d** and **5** were absent when the spectra were recorded at room temperature. Recording spectra for **17a**,**b** and **d** at 55 °C, and at 5 °C for **5** caused sufficient line narrowing to occur so that all signals could be observed.

Chromatography was carried out on silica gel [Merck 9385 Kieselgel 60 (230–400 ASTM)] or reverse phase C-18 silica gel [Fuji Silysia Chemicals Chromatorex ODS 100–200 mesh]. Solvent systems for flash chromatography were chosen to provide R_f=0.35 as preferred by Still et al.,[22] unless otherwise recorded.

Solvents were dried using a Solvent Dispensing System (Seca Solvent Systems). Reagents were used as obtained from the supplier. Brine refers to a saturated solution of sodium chloride in water. DMF refers to *N*,*N*-dimethylformamide. DMSO refers to dimethyl sulfoxide.

4.2. General procedure for allylthio ether formation

*4.2.1. 2-(Allylthio)benzaldehyde (**6**)*[23]. 2-Fluorobenzaldehyde (3 g, 24.2 mmol) and allyl mercaptan (3.58 g, 60%, 48.4 mmol) in DMF (15 ml) were treated with potassium carbonate. The reaction mixture was heated to 55 °C overnight. On cooling to room temperature, the reaction was poured into water and extracted with ethyl acetate. The organic extract was washed once with water, then brine, dried ($MgSO_4$) and concentrated. Flash chromatography using ethyl acetate–petroleum spirits (4:96) as eluant provided 2-(allylthio)benzaldehyde (1.91 g, 44%) as an oil. δ_H (400 MHz) 10.38 (s, 1H), 7.81 (dd, J 7.6, 1.5, 1H), 7.48 (t, J 7.6, 1H), 7.41 (d, J 7.9, 1H) 7.29 (dd, J 7.4, 1H), 5.86 (m, 1H), 5.15 (dm, J 17.0, 1H), 5.10 (dm, J 10.0, 1H), 3.56 (d, J 6.8, 2H); m/z (EI) $C_{10}H_{10}OS^+$ requires 178.0447, found 178.0445.

*4.2.2. 2-(Allylthio)-5-bromobenzaldehyde (**7**).* Oil. Yield 3.86 g (77%). δ_H (400 MHz) 10.34 (s, 1H), 7.94 (d, J 2.3, 1H), 7.60 (dd, J 8.4,

2.3, 1H), 7.31 (d, *J* 8.5, 1H), 5.84 (m, 1H), 5.09–5.16 (m, 2H), 3.55 (d, *J* 6.9, 2H); *m*/*z* (EI) $C_{10}H_9BrOS^+$ requires 255.9552, found 255.9551.

*4.2.3. 2-(Allylthio)-4-methoxybenzaldehyde (**8**).* Oil. Yield 4.81 g (86%). δ_H (400 MHz) 10.16 (s, 1H), 7.75 (d, *J* 8.6, 1H), 6.87 (d, *J* 2.4, 1H), 6.77 (dd, *J* 8.6, 2.4, 1H), 5.88 (m, 1H), 5.23 (dm, *J* 17.0, 1H), 5.14 (dm, *J* 10.1, 1H), 3.85 (s, 3H), 3.57 (d, *J* 6.7, 2H); *m*/*z* (EI) $C_{11}H_{12}O_2S^+$ requires 208.0553, found 208.0549.

*4.2.4. 2-(Allylthio)-6-chlorobenzaldehyde (**9**).* Oil. Yield 2.50 g (45%). δ_H (400 MHz) 10.60 (s, 1H), 7.36 (t, *J* 8.0, 1H), 7.26 (d, *J* 8.1, 1H), 7.20 (d, *J* 7.8, 1H), 5.89 (m, 1H), 5.33 (dm, *J* 17.0, 1H), 5.20 (dm, *J* 10.1, 1H), 3.59 (d, *J* 6.6, 2H); *m*/*z* (EI) $C_{10}H_9ClOS^+$ required 212.0057, found 212.0054.

4.3. General procedure for *N*-substituted tetrahydrothiochromenoisoxazoles: 1-cyclohexyl-7-methoxy-3,3a,4,9b-tetrahydro-1*H*-thiochromeno[4,3-*c*]isoxazole (12c)

The benzaldehyde **8** (220 mg, 1.06 mmol), cyclohexylhydroxylamine hydrochloride (288 mg, 1.90 mmol) and triethylamine (0.5 ml) in toluene (6 ml) were treated with methanol (0.5 ml) and heated to reflux for 2.5 days. The reaction was concentrated to a yellow paste, dissolved in ethyl acetate–petroleum spirits (1:4) and filtered through a small plug of silica using ethyl acetate–petroleum spirits (1:4) as eluant. The filtrate was concentrated to afford the title compound (238 mg, 74%) as a solid. Mp 122–124 °C; ν_{max}/cm^{-1} 3420, 2944, 2850, 1602; δ_H (400 MHz) 7.40 (d, *J* 8.6, 1H), 6.80 (d, *J* 2.6, 1H), 6.72 (dd, *J* 8.6, 2.7, 1H), 4.21 (d, *J* 8.5, 1H, H-9b), 4.13 (t, *J* 8.2, 1H), 3.87 (dd, *J* 8.1, 5.4, 1H), 3.77 (s, 3H), 3.38 (tq, *J* 8.2, 5.3, 1H), 3.09 (dd, *J* 13.2, 5.1, 1H), 2.63–2.74 (m, 2H), 2.09 (d, *J* 12.6, 1H), 1.90–1.15 (m, 9H); δ_C (100 MHz) 158.09 (s), 136.30 (s), 131.45 (d), 127.56 (s), 112.92 (d), 112.54 (d), 69.71 (t), 61.53 (d), 60.88 (d), 55.32 (q), 44.11 (d), 32.02 (t), 30.81 (t), 28.24 (t), 25.98 (t), 25.04 (t), 24.78 (t); *m*/*z* (EI) $C_{17}H_{23}NO_2S^+$ requires 305.1417, found 305.1421.

4.4. General procedure for *N*-unsubstituted tetrahydrothiochromenoisoxazoles: 7-methoxy-3,3a,4,9b-tetrahydro-1*H*-thiochromeno[4,3-*c*]isoxazole (17c)

The benzaldehyde **8** (0.80 g, 4.15 mmol), 5-hydroxypentanal oxime **14** (535 mg, 4.5 mmol) and dibutyltin oxide (10 mg) in toluene (20 ml) were heated in a Dean–Stark trap for five days. On cooling, the reaction was filtered through a small pad of silica and concentrated. The residue was dissolved in ethanol (9 ml) and treated with aq hydrochloric acid (1 M, 3 ml). The reaction was stirred at room temperature for two days, then concentrated to 3 ml. The residue was diluted with saturated aq sodium bicarbonate, and extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography using ethyl acetate–petroleum spirits (1:1) afforded the title compound (626 mg, 68%) as an oil. ^{1}H NMR indicated a purity >95%. ν_{max}/cm^{-1} 3422, 2940, 2840, 1602; δ_H (400 MHz) 7.35 (d, *J* 8.5, 1H), 6.84 (d, *J* 2.6, 1H), 6.72 (dd, *J* 8.5, 2.6, 1H), 5.01 (br s, 1H), 4.47 (t, *J* 8.1, 1H), 4.39 (d, *J* 8.1, 1H), 3.94 (dd, *J* 8.4, 6.1, 1H), 3.78 (s, 3H), 3.20 (m, 1H), 2.90 (dd, *J* 13.5, 4.5, 1H), 2.70 (dd, *J* 13.5, 6.3, 1H); δ_C (50 MHz) 159.26 (s), 135.89 (s), 133.43 (d), 121.73 (br s), 113.61 (d), 112.65 (d), 75.67 (t), 61.80 (d), 55.37 (q), 43.15 (d), 30.46 (t); *m*/*z* (EI) $C_{11}H_{13}NO_2S^+$ requires 223.0662, found 223.0659.

*4.4.1. 3,3a,4,9b-Tetrahydro-1H-thiochromeno[4,3-c]isoxazole (**17a**).* The benzaldehyde **6** (0.98 g, 5.5 mmol), 5-hydroxypentanal oxime **14** (0.77 g, 6.6 mmol) and dibutyltin oxide (60 mg) in toluene (300 ml) were heated in a Dean–Stark trap for two days. The reaction was processed as above for **17c**, providing the title compound (0.83 g, 78%) as an oil. ^{1}H NMR indicated a purity >95%. δ_H (500 MHz, 55 °C) 7.42 (d, *J* 7.35, 1H), 7.29 (dd, *J* 7.6, 1.4, 1H), 7.18 (dt, *J* 7.6, 1.7, 1H), 7.14 (dt, *J* 7.4, 1.5, 1H), 5.14 (br s, 1H), 4.42 (t, *J* 7.9, 1H), 4.35 (d, *J* 8.2, 1H), 3.88 (dd, *J* 8.4, 6.2, 1H), 3.19 (m, 1H), 2.90 (dd, *J* 13.4, 4.7, 1H), 2.64 (dd, *J* 13.4, 6.5, 1H); δ_C (125 MHz, 55 °C) 134.79, 132.17 (br), 130.60 (br), 128.80, 128.06, 125.96, 75.57, 62.28 (br), 43.67 (br), 30.54; *m*/*z* (EI) $C_{10}H_{11}NOS^+$ requires 193.0556, found 193.0560.

*4.4.2. 8-Bromo-3,3a,4,9b-tetrahydro-1H-thiochromeno[4,3-c]isoxazole (**17b**).* The benzaldehyde **7** (1.66 g, 6.5 mmol), 5-hydroxypentanal oxime **14** (0.91 g, 7.8 mmol) and dibutyltin oxide (30 mg) in toluene (250 ml) were heated in a Dean–Stark trap overnight. The reaction was processed as above for **17c**, providing the title compound (1.44 g, 82%) as an oil. ^{1}H NMR indicated a purity >95%. δ_H (500 MHz, 55 °C) 7.62 (s, 1H), 7.31 (dd, *J* 8.3, 2.1, 1H), 7.17 (d, *J* 8.3, 1H), 5.15 (br s, 1H), 4.40 (m, 1H), 4.32 (d, *J* 8.3, 1H), 3.88 (dd, *J* 8.4, 6.1, 1H), 3.23 (m, 1H), 2.93 (dd, *J* 13.4, 4.7, 1H), 2.63 (dd, *J* 13.4, 6.9, 1H); δ_C (125 MHz, 55 °C) 134.70 (br), 134.11, 131.12 (br), 130.19, 127.13 (br), 119.45, 75.72, 61.89 (br), 43.80 (br), 30.60; *m*/*z* (EI) $C_{10}H_{10}BrNOS^+$ requires 270.9667, found 270.9822.

*4.4.3. 9-Chloro-3,3a,4,9b-tetrahydro-1H-thiochromeno[4,3-c]isoxazole (**17d**).* The benzaldehyde **9** (1.17 g, 5.5 mmol), 5-hydroxypentanal oxime **14** (0.78 g, 6.0 mmol) and dibutyltin oxide (30 mg) in toluene (300 ml) were heated in a Dean–Stark trap overnight. The reaction was processed as above for **17c**, providing the title compound (0.76 g, 61%) as an oil. ^{1}H NMR indicated a purity >95%. δ_H (500 MHz, 55 °C) 7.22 (d, *J*=8.1, 1H), 7.20 (d, *J* 8.2, 1H), 7.10 (t, *J* 7.9, 1H), 5.29 (br s, 1H), 4.88 (d, *J* 8.1, 1H), 4.41 (t, *J* 7.8, 1H), 3.99 (dd, *J* 8.3, 6.1, 1H), 3.22 (m, 1H), 2.93 (dd, *J* 13.5, 4.4, 1H), 2.75 (dd, *J* 13.3, 4.0, 1H); δ_C (125 MHz, 55 °C) 137.65, 137.35, 128.73 (br), 128.66, 127.56, 127.44, 74.75, 58.99 (br), 43.26, 30.64 (br); *m*/*z* (EI) $C_{10}H_{10}ClNOS^+$ requires 227.0166, found 227.0166.

*4.4.4. 8-Bromo-1-acetyl-3,3a,4,9b-tetrahydro-1H-thiochromeno[4,3-c]isoxazole (**18**).* A solution of 8-bromo-3,3a,4,9b-tetrahydro-1*H*-thiochromeno[4,3-*c*]isoxazole **17b** (27 mg, 0.10 mmol) in dichloromethane (5 ml) was treated with acetic anhydride (5 drops) and pyridine (five drops). The solution was stirred at room temperature for 1 h, then quenched with water (five drops). After a further 20 min, the reaction mixture was filtered through a plug of silica using ethyl acetate as eluant to afford the title compound as an oil (30 mg, 96%). δ_H (200 MHz) 7.66 (dd, *J* 2.1, 0.9, 1H), 7.28 (ddd, *J* 8.3, 2.2, 0.7, 1H), 7.13 (d, *J* 8.3, 1H), 5.39 (d, *J* 8.9, 1H), 4.03 (m, 2H), 3.36 (m, 1H), 2.68 (d, *J* 10.0, 1H), 2.61 (d, *J* 10.0, 1H), 2.23 (s, 3H); δ_C (50 MHz) 174.73 (s), 135.67 (s), 133.18 (d), 130.41 (d), 129.73 (d), 128.18 (d), 119.69 (s), 74.74 (t), 55.56 (d), 44.63 (d), 30.15 (t), 20.16 (q); *m*/*z* (EI) $C_{12}H_{12}BrNO_2S^+$ requires 312.9767, found 312.9764.

*4.4.5. 1-Allyl-2,3,4,5-tetrahydro-1H-2,5-epoxy-1-benzazepine (**22**).* A solution of 2-fluorobenzaldehyde (124 mg, 1.0 mmol) and *N*,*N*-diallylamine (194 mg, 2.0 mmol) in DMF (2 ml) was treated with potassium carbonate (140 mg, 1.0 mmol) and sealed in a microwave vial. The reaction mixture was heated to 220 °C for 50 min, cooled to room temperature and poured into water (20 ml). The aq mixture was extracted twice with ethyl acetate, and the combined organic extracts in turn washed with twice with water and once with brine. After drying and concentrating, the brown gum obtained was purified by flash chromatography using ethyl acetate–petroleum spirits (5:95) to afford the title compound as a yellow oil (40 mg, 20%). δ_H (200 MHz) 7.11 (dd, *J* 7.7, 1.7, 1H), 6.91 (dd, *J* 7.4, 1.7, 1H), 6.70 (dt, *J* 7.4, 1.1, 1H), 6.66 (d, *J* 8.2, 1H), 5.94 (dddd, *J* 17.1, 10.3, 5.5, 4.9, 1H), 5.38–5.12 (m, 3H), 5.03 (m, 1H), 3.91 (tdq, *J* 16.8, 4.8, 1.7, 2H), 2.28–1.98 (m, 4H); δ_C (50 MHz) 141.87 (s), 134.79 (d), 128.25 (s), 128.00 (d), 124.25 (d), 117.71 (d), 116.37 (t),

114.37 (d), 89.79 (d), 77.91 (d), 54.42 (t), 36.81 (t), 33.74 (t); *m*/*z* ($APCI^+$) 202 (5%), 200 (5, M^+), 184 (20), 161 (30), 143 (100), 132 (50).

*4.4.6. N-tert-Butylcarboxy-2-aminobenzaldehyde (**24**)*[14]. A solution of 2-aminobenzylalcohol **23** (1.0 g, 8.1 mmol) in 1,2-dichloroethane (50 ml) was treated with di-*tert*-butyl dicarbonate (1.9 g, 8.9 mmol, 1.1 equiv) and heated at reflux for 2 h. On cooling, the reaction was concentrated to a viscous oil, which was dissolved in dichloromethane (50 ml). This solution was treated with manganese(IV) oxide (6.4 g, 81 mmol, 10 equiv) and heated at reflux for 4 h. The reaction was cooled to room temperature and filtered through Celite and concentrated to a viscous oil. This material was suitable for use in the following step, but for characterization purposes was further purified by flash chromatography using ethyl acetate–petroleum spirits (1:4) as eluant to provide the title compound as an oil (1.3 g, 66%). δ_H (400 MHz) 10.39 (br s, 1H), 9.89 (s, 1H), 8.45 (d, *J* 8.5, 1H), 7.62 (d, *J* 7.7, 1H), 7.56 (t, *J* 7.9, 1H), 7.13 (t, *J* 7.5, 1H), 1.53 (s, 9H).

*4.4.7. N-Allyl-N-tert-butylcarboxy-2-aminobenzaldehyde (**25**).* A solution of *N*-*tert*-butylcarboxy-2-aminobenzaldehyde **24** (1.29 g, 5.83 mmol) and allylbromide (0.76 ml, 8.75 mmol 1.5 equiv) in DMF (10 ml) cooled to 0 °C was added to a pre-cooled suspension of sodium hydride (0.26 g, 60% dispersion in oil, 6.41 mmol, 1.2 equiv) in DMF (4 ml), maintaining an internal temperature below 5 °C. The deep yellow solution was stirred at 0 °C for 2 h, by which time the colour had almost dispersed. The reaction was quenched with saturated aq ammonium chloride (50 ml), and extracted with a mixture of ethyl acetate–petroleum spirits (1:4) (3×30 ml). The combined organic extracts were washed with water (3×20 ml), then brine (30 ml). The organic phase was dried ($MgSO_4$) and concentrated to a pale yellow oil. Flash chromatography on silica gel using ethyl acetate–petroleum spirits (1:9) as eluant afforded the title compound as a colourless oil that solidified on standing (1.39 g, 91%). ν_{max}/cm^{-1} 3356, 3079, 2979, 1706, 1598; δ_H (400 MHz) 10.02 (1H, s, CHO), 7.81 (1H, d, *J* 7.6 Hz), 7.52 (1H, dd, *J* 7.6, 7.5 Hz), 7.31 (1H, t, *J* 7.5, 7.3 Hz), 7.20 (1H, d, *J* 7.3 Hz), 6.01–5.62 (1H, m, CH═CH2), 5.18–4.83 (2H, m, CH═CH2), 4.20 (2H, br s, CH2), 1.27 (9H, br s); δ_C (50 MHz, $CDCl_3$) 189.76 (d, CHO), 154.01 (br s, NCO_2), 144.20 (s), 134.42 (d), 132.83 (br d, ═CH), 132.50 (s), 128.25 (br d), 127.85 (br d), 127.09 (d), 118.33 (br t, $=CH_2$), 80.99 (t), 53.04 (br s), 27.90 (q).

*4.4.8. tert-Butyl 1-cyclohexyl-1,3a,4,9b-tetrahydroisoxazolo[4,3-c]quinoline-5(3H)-carboxylate (**26**).* *N*-Allyl-*N*-*tert*-butylcarboxy-2-aminobenzaldehyde **25** (200 mg, 0.765 mmol) and cyclohexylhydroxylamine hydrochloride (128 mg, 0.84 mmol, 1.1 equiv) in toluene (3 ml) were treated with triethylamine (128 μl, 0.92 mmol, 1.2 equiv). Silicon carbide chips (50 mg) were added to the suspension, which was sealed in a microwave vial and heated to 170 °C for 40 min. On cooling to room temperature, the solution was filtered through a small plug of silica using ethyl acetate as eluant. Further chromatography using ethyl acetate–petroleum spirits (1:4) as eluant afforded the title compound as a colourless foam (230 mg, 84%). δ_H (200 MHz) 7.43 (d, *J* 7.8, 1H), 7.36 (dd, *J* 7.4, 1.7, 1H), 7.21–7.02 (m, 2H), 4.31 (d, *J* 8.7, 1H), 4.08 (t, *J* 8.4, 1H), 3.76 (m, 3H), 3.25 (m, 1H), 2.67 (m, 1H), 2.07 (m, 1H), 1.95–1.15 (m, 9H), 1.50 (s, 9H); δ_C (50 MHz) 153.65 (s), 139.57 (s), 130.22 (s), 129.74 (d), 126.62 (d), 124.43(d), 123.96(d), 80.89 (s), 68.44 (t), 61.18 (d), 60.90(d), 45.44 (t), 43.43 (d), 31.97 (t), 28.96 (t), 28.23 (q), 25.84 (t), 24.76 (t), 24.53 (t).

*4.4.9. 1,3,3a,4,5,9b-Hexahydroisoxazolo[4,3-c]quinoline (**5**).* A mixture of *N*-allyl-*N*-*tert*-butylcarboxy-2-aminobenzaldehyde **25** (100 mg, 0.38 mmol), 5-hydroxypentanal oxime **14** (99 mg, 0.84 mmol, 2.2 equiv) and dibutyltin oxide (19 mg, 0.076 mmol, 0.2 equiv) in toluene (20 ml) was heated to reflux in a Dean–Stark trap for 18 h. On cooling, the solution was concentrated to an oil, then dissolved in methanol (5 ml) and treated with concd aq hydrochloric acid (four drops). The solution was stirred at room temperature for 2 h, then concentrated to a pale yellow solid; being the hydrochloride salt of the title compound it was freely soluble in water. For ease of characterization, the free base was prepared by stirring a methanolic solution of the salt in the presence of Amberlite IR-45 weakly basic ion exchange resin. Concentration of the filtered solution afforded a yellow wax. Flash chromatography using neat ethyl acetate as eluant afforded the title compound (50 mg, 74%) as a colourless solid. Mp 119–121 °C; δ_H (500 MHz, CD_3OD, 5 °C) 7.21 (d, *J* 7.6, 1H), 7.05 (t, *J* 7.7, 1H), 6.69 (d, *J* 8.1, 1H), 6.67 (t, *J* 7.4, 1H), 4.26 (br s, 1H), 4.09 (m, 1H), 3.69 (m, 1H), 3.20 (dd, *J* 11.3, 5.0, 1H), 2.88 (t, *J* 10.9, 1H), 2.81 (m, 1H); δ_C (125 MHz, CD_3OD, 5 °C) 148.29, 132.39 (2C), 129.75, 118.80, 116.39, 74.91, 59.95, 42.97, 41.65 (br); *m*/*z* (EI) $C_{10}H_{12}N_2O^+$ requires 176.0944, found 176.0941.

*4.4.10. Pyridin-2-one-3-carbaldehyde (**31**)*[24]. 2-Chloropyridine-3-carbaldehyde **28** (1.50 g, 10.6 mmol) suspended in water (15 ml) was treated with concd hydrochloric acid (three drops) and aq H_2O_2 (3 drops, 30%). The mixture was sealed in a microwave vial, and heated to 170 °C for 15 min. A pressure of 15 bar was reached during the course of the reaction. On cooling, the dark yellow solution was concentrated to afford the title compound (1.285 g, 98.5%) after drying at 50 °C/0.1 bar overnight. δ_H (400 MHz, DMSO-d_6) 12.4 (1H, br s, NH), 10.07 (1H, s, CHO), 7.96 (1H, dd, *J* 7.2, 2.3 Hz), 7.80 (1H, dd, *J* 6.9, 2.2 Hz), 6.36 (1H, t, *J* 6.7 Hz).

*4.4.11. (E)-Ethyl 4-(3-formylpyridin-2-yloxy)but-2-enoate (**32**)*[20]. Finely ground, dried pyridin-2-one-3-carbaldehyde **31** (100 mg, 0.81 mmol) and dried silver carbonate (450 mg, 1.62 mmol) in toluene (4 ml) were treated with (*E*)-ethyl 4-bromocrotonate (160 μl, 75%, 0.87 mmol) and heated to 55 °C in the dark for 18 h. The reaction was cooled, filtered, and concentrated to a yellow oil. Flash chromatography on silica gel using petroleum spirits–ethyl acetate (1:1) afforded the title compound (135 mg, 70%) as a colourless oil, which solidified as an off-white wax on standing.

Subsequently, reactions conducted with 1.5 g of pyridin-2-one-3-carbaldehyde **31**, and purified using reverse phase C-18 silica with methanol–water (5:1) as eluant provided the product **32** in 82% yield. δ_H (400 MHz, CD_3CN) 10.34 (1H, s, CHO), 8.35 (1H, dd, *J* 4.8, 1.8, 4′-H), 8.09 (1H, dd, *J* 5.3, 2.2, 6′-H), 7.04–7.13 (2H, m, 3-H and 5′-H), 6.15 (1H, dt, *J* 15.9, 2.1, 2-H), 5.14 (2H, dd, *J* 4.2, 2.0, 4-H_2), 4.15 (2H, q, *J* 7.2, CH_2CH_3), 1.24 (3H, t, *J* 7.2, CH_2CH_3); δ_C (100 MHz, CD_3CN) 189.6 (d), 166.6 (s), 163.9 (s), 153.6 (d), 143.4 (d), 139.0 (d), 122.4 (d), 119.8 (s), 118.9 (d), 65.4 (t), 61.2 (t), 14.4 (q).

4.4.12. Ethyl 3(R),3a(S*),9b(R*)-1-cyclohexyl-1,3a,4,9b-tetrahydro-3H-isoxazolo[3′,4′:4,5]pyrano[2,3-b]pyridine-3-carboxylate (**33**).* A solution of (*E*)-ethyl 4-(3-formylpyridin-2-yloxy)but-2-enoate **32** (240 mg, 1.02 mmol) in toluene (4 ml) was treated with cyclohexylhydroxylamine hydrochloride (170 mg, 1.12 mmol) and triethylamine (170 μl, 1.2 mmol). The reaction vial was sealed and heated to 130 °C in the microwave for 20 min (pressure rises to 1 bar). On cooling, the reaction was concentrated to a yellow syrup. Filtration through a small pad of reverse phase C-18 silica using methanol–water (1:1) as eluant afforded a clear yellow oil that solidified on standing. Recrystallization from ethanol–water afforded colourless needles in a yellow supernatant liquid. The liquid was decanted, and the crystals were triturated with water until colourless. The crystals were then dried at the pump, providing the title compound (220 mg, 65%) as a colourless solid. (Found C, 65.1; H, 7.3; N, 8.5. $C_{18}H_{24}O_4N_2$ requires C, 65.0; H, 7.3; N, 8.4%). Mp 127–129 °C; δ_H (400 MHz, CD_3CN) 8.07 (1H, dd, *J* 4.7 and 1.8, H-7), 7.69 (1H, dm, *J* 7.5, H-9), 6.98 (1H, dd, *J* 7.5 and 4.8, H-8), 4.78 (1H, d, *J* 7.2, H-9b), 4.46 (1H, dd, *J* 12.2 and 2.3, H-4_A), 4.45 (1H, d, *J* 7.7, H-3), 4.38

(1H, dd, *J* 12.2 and 2.2, H-4$_B$), 4.20 (2H, m, OC*H*$_2$CH$_3$), 3.39 (1H, dddd, *J* 7.6, 7.2, 2.3 and 2.2, H-3a), 2.67 (1H, m), 2.34 (1H, m), 1.71–1.83 (3H, m), 1.62 (1H, m), 1.38–1.18 (5H, m), 1.27 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$); δ_C (100 MHz, CD$_3$CN) 172.9 (s, *C*O$_2$Et), 162.3 (s, C5a), 148.3 (d, C7), 140.8 (d, C9), 119.2 (d, C8), 119.1 (s, C9a), 78.2 (d, C3), 65.2 (t, C4), 63.0 (d), 62.1 (t, O*C*H$_2$CH$_3$), 59.4 (d, C9b), 44.7 (d, C3a), 32.3 (t), 31.1 (t), 26.7 (t), 25.1 (t), 24.9 (t), 14.4 (q, OCH$_2$*C*H$_3$); *m*/*z* (EI) 332 (100%, M), 289 (50), 218 (60); HRMS (EI) $C_{18}H_{24}O_4N_2^+$ requires 332.1731, found 332.1725.

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21. CCDC 653858 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033. Crystal data for 33. $C_{18}H_{24}N_2O_4$, M=332.39, T=130.0(2) K, λ=0.71069, Orthorhombic, space group Pbca, a=9.1074(9), b=18.264(2), c=20.736(2) Å, V 3449.2(6) Å^3, Z=8, D_c=1.280 mg M^{-3} μ(Mo Kα) 0.091 mm^{-1}, F(000)=1424, crystal size 0.5×0.06×0.03 mm. 17094 reflections measured, 3034 independent reflections (R_{int}=0.12) the final R was 0.0445 [$I>2\sigma(I)$] and $wR(F^2)$ was 0.0789 (all data).
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