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Model studies toward the synthesis of kirkine

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In model studies towards the synthesis of kirkine, the carbon skeleton was constructed using a radical cascade reaction. Two different approaches towards the synthesis have been examined as well as the regioselectivity of the radical cyclisation.

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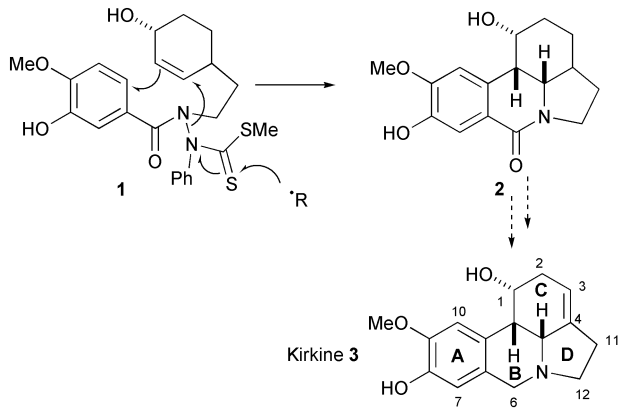
Introduction

Kirkine (**3**), a lycorine type alkaloid isolated from the bulbs of the East African grassland plant *Crinum kirkii*, exhibits interesting antiviral activity. It is characterised by its galanthane type tetracyclic skeleton, substituted on the aromatic ring by a methoxy group at the C-9 position and a hydroxyl group at the C-8 position. The C-1 position also bears a hydroxyl group in the axial position and the fusion of cycles B and C is in the *cis* mode.[1]

Two important issues needed to be addressed when planning the synthesis of kirkine: the construction of the carbon skeleton and the regioselectivity. Our approach hinged on a radical cyclisation sequence to put the ring system in place, starting with an amidyl radical produced from a thiosemicarbazide precursor **1** (Scheme 1).



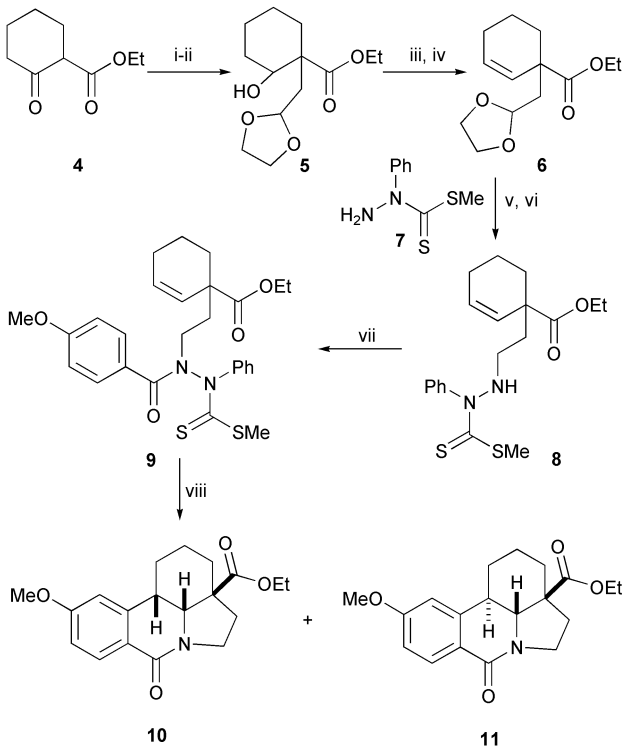
Scheme 1 Proposed route to kirkine.

This would result in the formation of rings B and D in one step, giving a structure in which the junction of rings B and C would be *cis*, as required for the synthesis of kirkine. The feasibility of such a radical cascade has already been demonstrated by our recent synthesis of γ-lycorane,[2,3] whereby the galanthane structure was obtained by treatment of a thiosemicarbazide precursor with tributylstannane under reflux conditions to give γ-lycorane as a 6 : 4 mixture of regioisomers in 60% yield. Although, the regiochemical issues for this synthesis still needed to be resolved, this was an encouraging route for application to the synthesis of kirkine.

It was envisaged that the hydroxyl group on ring C of the kirkine skeleton could be introduced early in the synthesis with the olefin being introduced later following cyclisation, then reduction of the lactam would produce kirkine (**3**).

Results and discussion

The synthesis of a simplified thiosemicarbazide precursor **9** was first implemented to test our cyclisation strategy (Scheme 2). Alkylation of commercially available ethyl 2-oxocyclohexanecarboxylate (**4**) with a masked aldehyde in the form of a dioxolane, followed by reduction of the ketone using sodium borohydride gave alcohol **5**.[4] This was subsequently transformed into the corresponding mesylate,[5] which underwent elimination upon heating in the presence of DBU to produce olefin **6**.[6] The formation of hydrazide **8** was achieved by deprotection under acidic conditions, followed by condensation of the resulting aldehyde with thiosemicarbazide **7**.[7] Reduction of the hydrazone with sodium cyanoborohydride gave the corresponding hydrazide **8**, which was subsequently acylated with 4-methoxybenzoyl chloride to produce the requisite thiosemicarbazide **9**.



Scheme 2 *Reagents and conditions*: i, 2-bromomethyl-1,3-dioxolane, K_2CO_3–KI, DMSO, 100 °C, 61%; ii, $NaBH_4$, MeOH–H_2O, rt, 75%; iii, $MeSO_2Cl$, pyridine, rt, 76%; iv, DBU, NaI, 80 °C, 88%; v, **7**, HCl (10%), EtOH, rt, 93%; vi, $NaBH_3CN$, MeOH–AcOH, 89%; vii, 4-methoxybenzoyl chloride, pyridine, 80 °C, 93%; viii, DLP, chlorobenzene, reflux, 81% (79% **10**; 2% **11**).

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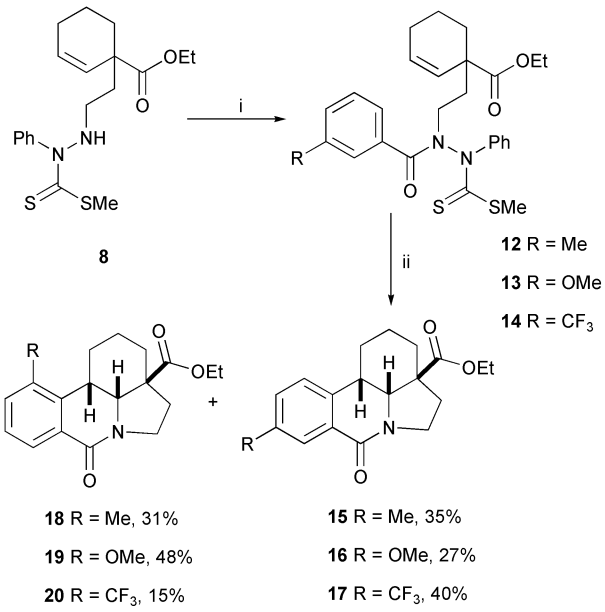
To avoid the use of tin as in the synthesis of γ-lycorane, lauroyl peroxide (DLP) was employed as initiator for the cyclisation as well as an oxidant for the cyclohexadienyl radical arising from the cyclisation to the aromatic ring (hence the need for stoichiometric amounts). Gratifyingly, addition of lauroyl peroxide to a refluxing solution of **9** in chlorobenzene yielded 81% of the cyclised product **10** and its isomer **11** in a ratio of 40 : 1 in favour of the *cis* configuration.

We next examined the regioselectivity issue. To implement these studies, the C-9 position of the aromatic ring was substituted with various groups exhibiting different electronic properties in the *meta* position (Scheme 3).

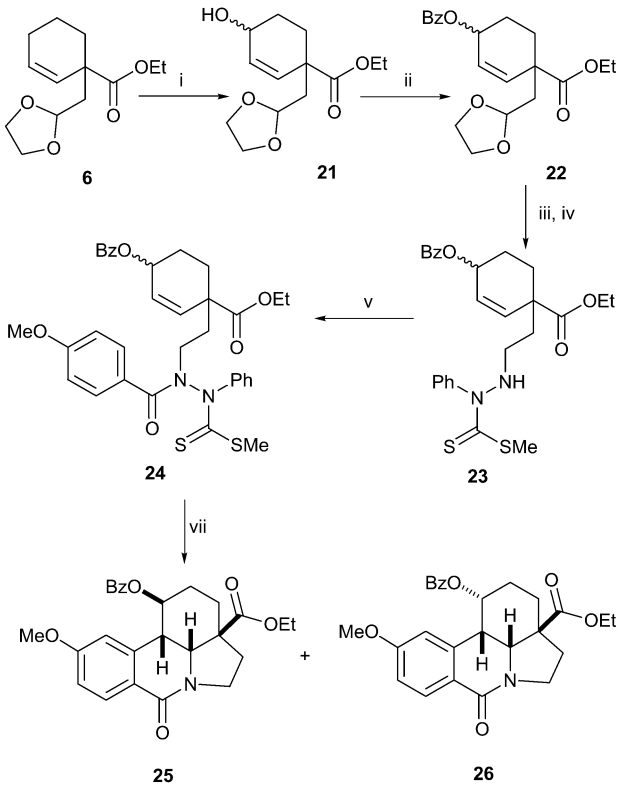


Scheme 3 *Reagents and conditions*: i, *m*-RC_6H_4COCl, pyridine, rt; ii, DLP, chlorobenzene, reflux.

As expected, the methyl group on the C-9 position of hydrazide **12** did not have much effect on the regioselectivity of the cyclisation, resulting in almost equal formation of the *para* and *ortho* (with respect to the newly formed bond) isomers **15** and **18** respectively (1.1 : 1). The electron donating methoxy group on **13** did, however, slightly favour the formation of the *ortho* isomer **19** over the *para* isomer **16** (1.7 : 1). In addition, the electron withdrawing trifluoro group on **14** favoured the formation of the *para* isomer **17** over the *ortho* isomer **20** (2.7 : 1). The influence of the R group on the C-9 position of the aromatic ring was thus observed to have an interesting, but rather small effect on the resulting regioselectivity of the radical cyclisation and was therefore considered to be a minor concern, which we hoped to later resolve for the overall synthesis of kirkine.

For our synthesis, the alcohol on the C-1 position of ring C was to be introduced prior to cyclisation, followed by the olefin later in the synthesis. Allylic oxidation of olefin **6** was therefore accomplished with selenium dioxide in the presence of formic acid to furnish the corresponding allylic alcohol **21** in 63% yield (improved to 77% overall yield after regeneration of alcohol **21** from the corresponding ketone and formate ester side products) as a mixture of isomers (2 : 1) (Scheme 4).[8]

The alcohol was subsequently protected as a benzoate, using benzoyl chloride in pyridine.[9] The synthesis of the thiosemicarbazide **23** was achieved by condensation of hydrazide **7** with the aldehyde formed from hydrolysis of acetal **22**, followed by subsequent reduction. Acylation with 4-methoxybenzoyl chloride gave precursor **24** in good yield. Hydrazide derivative **24** was then subjected to radical conditions, resulting in the formation of two isomers **25** and **26** in 71% yield, in a ratio of 1.7 : 1. It can be noticed that the presence of the benzoate group has little influence on the cyclisation as the yield is close



Scheme 4 *Reagents and conditions*: i, SeO_2–HCO_2H, dioxane, reflux, 63%; ii, PhCOCl, pyridine, rt, 74%; iii, **7**, HCl (10%), MeOH, rt, 80%; iv, $NaBH_3CN$, MeOH–AcOH, rt, 91%; v, 4-methoxybenzoyl chloride, pyridine, 80 °C, 64%; vi, DLP, chlorobenzene, reflux, 71% (45% **25**; 26% **26**).

to that of analogue **9** (Scheme 2). The mixture of allylic alcohol isomers **21** could be oxidised to the corresponding ketone and then selectively reduced to give the precursor with the desired relative stereochemistry.

The next step required the introduction of a hydroxyl group at the C-8 position of the aromatic ring. Compound **23** had thus to be acylated with a benzoyl chloride containing a methoxy group in the 4-position and a protected hydroxyl group in the 3-position. The protecting group could also serve to control the regiochemistry of the ring closure on the aromatic nucleus. Therefore, it was thought that a bulky group such as a pivaloyl would be sufficient to direct the cyclisation in the correct position. Compound **23** was thus acylated with 4-methoxy-3-pivaloylbenzoyl chloride in the presence of triethylamine to furnish cyclisation precursor **27** (Scheme 5).[10] The thiosemicarbazide **27** was then subjected to the action of lauroyl peroxide to give two pairs of regioisomers in an overall yield of 66%. The sequential cyclisation gave a 1 : 1.2 ratio of the mixture of regioisomers, in favour of the desired *para* regiochemistry (36%), of which, 15% had the same stereochemistry of kirkine, with respect to the benzoyl group at C-1. Unfortunately, the bulky pivalate group had not directed the cyclisation efficiently.

Surprisingly, however, when the radical cascade was performed on precursor **28**, containing a 3,4-dimethoxy group on the aromatic ring, the two pairs of regioisomers were formed in an overall improved yield of 86%. The pair of epimers with the desired regiochemistry were produced in a total of 78% yield, a great improvement on the previous case. The reason for this increased and welcome regioselectivity is not clear at the moment but may be due to a repulsion from the 4-methoxy group pushing the neighbouring 3-methoxy into the path of the radical and hindering its approach.

With an efficient method permitting access to the kirkine skeleton in hand, the necessary functionalisation steps were investigated. The remaining reactions required saponification of the benzoate **35**, followed by decarboxylation providing the

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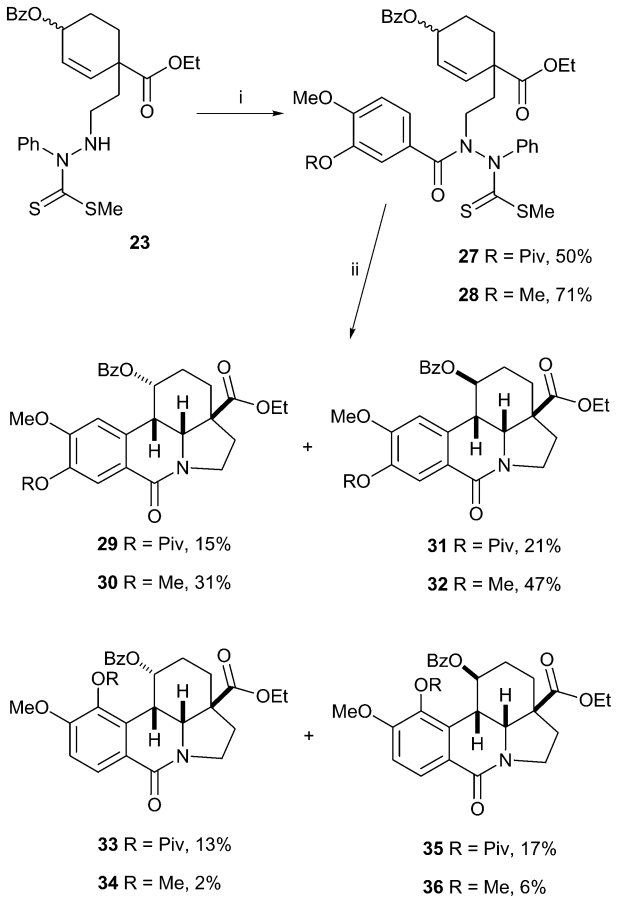
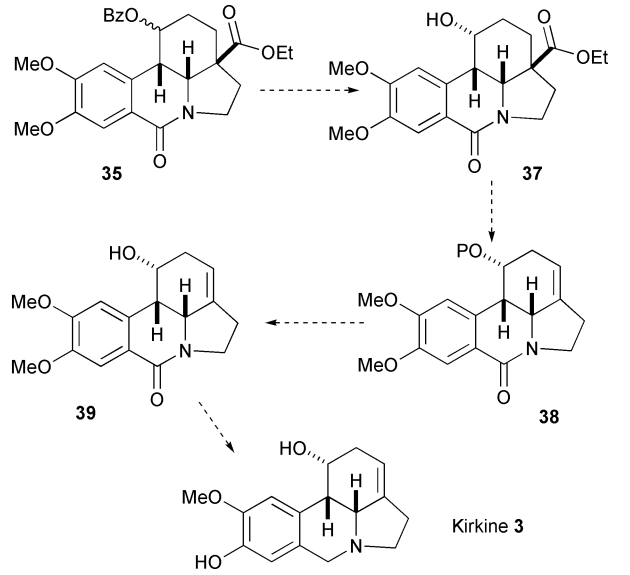


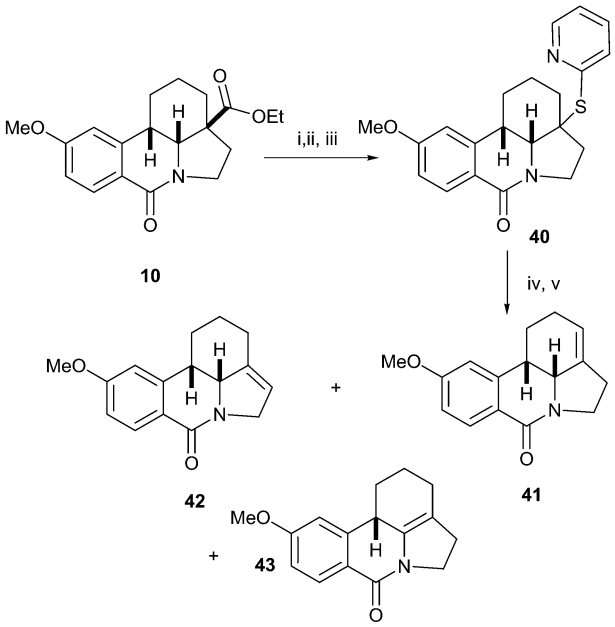
Scheme 5 *Reagents and conditions*: i, 4-methoxy 3-pivaloylbenzoyl chloride or 3,4-dimethoxybenzoyl chloride, Et_3N, Et_2O–heptane; ii, DLP, chlorobenzene, reflux.

double bond on cycle C to give **38**, reduction of the amide on cycle B and finally selective deprotection of the methoxy group on ring A (Scheme 6). It was also important to us to recycle benzoate **32** to give the desired stereochemistry on C-1 to increase the yield. Therefore an oxidation of the alcohols derived from **32** was also considered followed by selective reduction to give the correct isomer **37**.



Scheme 6 Final steps required for the synthesis of kirkine.

The proposed decarboxylation was firstly tested on the simpler cyclised analogue **10** to allow us to develop our method. The ethyl ester of **10**, was saponified using sodium hydroxide in ethanol, followed by formation of the corresponding acid chloride (Scheme 7). This was subsequently dissolved in a cyclohexane–toluene mixture and added slowly to *N*-hydroxy-2-thiopyridone and DMAP to give the Barton ester,[11] which furnished, upon heating, compound **40** in an overall yield of 55%. This was then oxidised to the sulfoxide, using *m*-CPBA in dichloroethane and subsequent elimination by heating in toluene rather disappointingly gave a mixture of three unsaturated compounds. These were not isolated, but NMR analysis indicated the structures to be compounds **41**, **42** and **43**. At this point in our studies, it became evident that this route for the synthesis of Kirkine was proving to be laborious, due to the formation of various mixtures of different regioisomers and stereoisomers at different stages along the synthesis.



Scheme 7 *Reagents and conditions*: i, NaOH, EtOH, rt, 100%, ii, $(COCl)_2$, CH_2Cl_2; iii, *N*-hydroxy-2-thiopyridone, DMAP, toluene–cyclohexane, reflux; iv, *m*-CPBA, CH_2Cl_2; v, reflux.

Subsequent problems were also encountered in the oxidation of the alcohol derived from benzoate **32**, in an attempt to correct the stereochemistry.[12] Under various standard oxidation conditions decomposition was observed. It was apparent that this route whereby the hydroxyl group was introduced early in the synthesis was providing further stereochemical problems. Alternative synthetic routes to try to avoid such problems were therefore sought.

We envisaged that reductive alkylation of benzoic acid to **44**, followed by iodolactonisation,[13] would provide a derivative **46** that would allow many possibilities for the functionalisation of ring C later in the synthesis (Scheme 8). The lactone would protect the free acid and also provide a more direct route to the kirkine skeleton than our previous synthesis.

The synthesis of reduced product **44** under Birch conditions was achieved in 76% yield. The acid **44** was then transformed into the corresponding amide **45**,[14] followed by iodolactonisation to furnish lactone **46** in good yield. The thiosemicarbazide radical precursor **52** was subsequently prepared using the same methods as in the previous synthesis. Unfortunately, when compound **52** was subjected to radical conditions, the desired cyclised product was not formed and decomposition was observed. This is likely to be due to the presence of the iodine resulting in subsequent side reactions under the cyclisation conditions. The iodine was thus removed from the lactone **46** using tributylstannane to yield reduction product **47**.[15] The corresponding radical precursor **53** was synthesised using the same conditions as for analogue **52**. Gratifyingly, when subjected to radical conditions, cyclised product **54** was produced in 60% yield.

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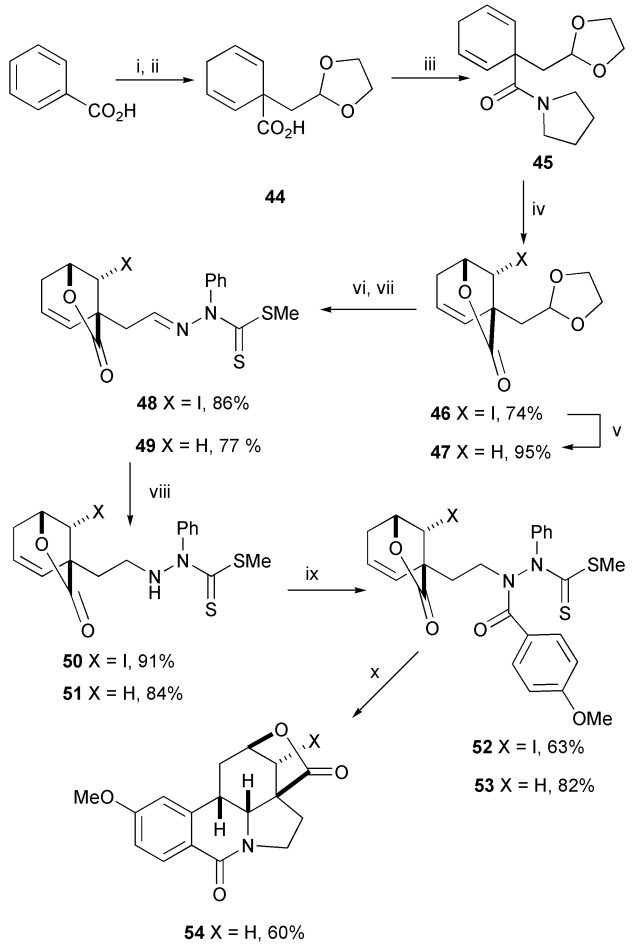
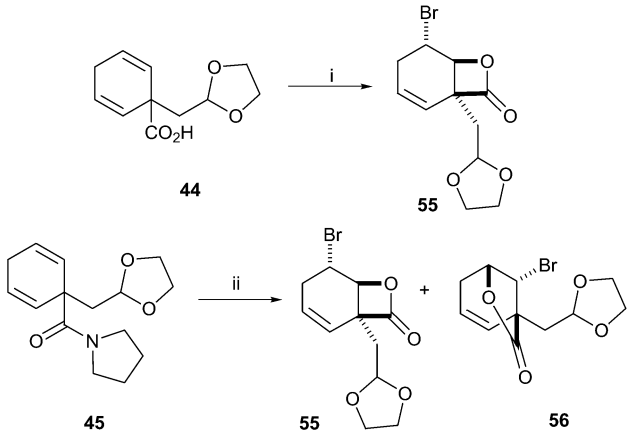


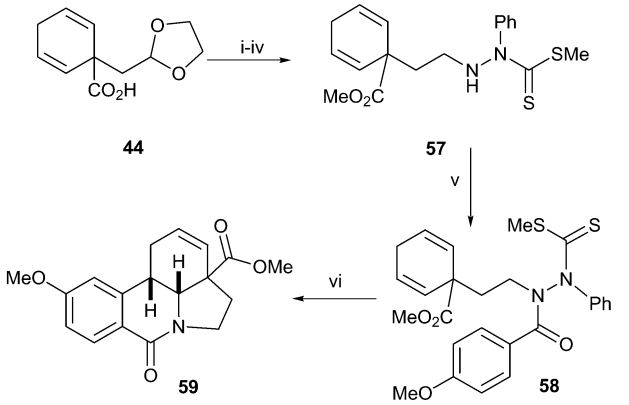
Scheme 8 *Reagents and conditions*: i, Li, NH_3; ii, 2-bromomethyl-1,3-dioxolane, THF, −78 °C, 76%; iii, $(PhO)_2P(O)N_3$, pyrrolidine, Et_3N, DMF, 0 °C, 88%; iv, I_2, THF, rt, 78%; v, Bu_3SnH, AIBN, benzene, reflux; vi, HCO_2H–H_2O, 0 °C; vii, **7**, AcOH–MeOH, rt; viii, $NaBH_3CN$, MeOH, rt; ix, 4-methoxybenzoyl chloride, DMAP, pyridine, 80 °C; x, DLP, chlorobenzene, reflux.

Although we were pleased to find that the cyclisation had been successful after the removal of the iodine, the C ring would now be more difficult to functionalise. We therefore envisaged replacing the iodine with the less reactive bromine. Bromolactonisation of reduction product **44** was thus carried out using NBS in DMF, but this unfortunately gave the β-lactone **55** in 91% yield (Scheme 9).[16] Bromolactonisation of the corresponding amide **45** was also attempted, however, this gave an inseparable mixture of the β- and γ-lactones **55** and **56** respectively (1 : 1.5).



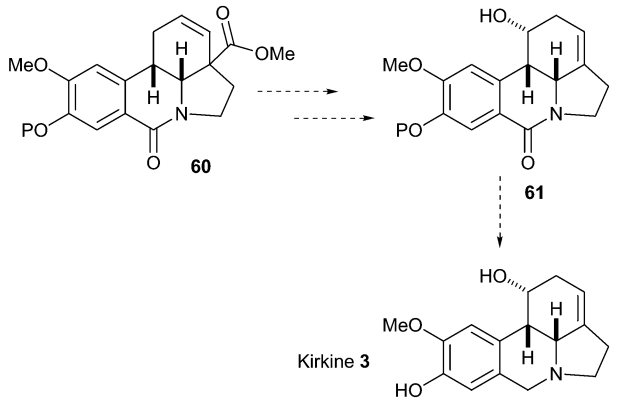
Scheme 9 *Reagents and conditions*: i, NBS, DMF, rt, 91%; ii, NBS, THF–H_2O, rt

Due to the problems posed by having a halogen on the C ring, we decided that it would be simpler and more direct to keep both double bonds of the reduction product **44** in place and simply protect the acid as an ester. This would allow further functionalisation of the resulting olefin following cyclisation. Protection of the acid using methyl iodide and DBU gave the corresponding methyl ester, which was subsequently transformed to the thiosemicarbazide radical precursor **58** using standard conditions (Scheme 10). We were concerned that the easily abstractable allylic hydrogens (corresponding to C-1) would cause difficulties with the more reactive radicals derived from DLP. Tributylstannane was therefore initially used to give the desired cyclised product **59** in 55% yield.[17] However, our worries were unfounded, since with DLP the same compound was obtained in 59% yield.



Scheme 10 *Reagents and conditions*: i, DBU, MeI, THF; ii, HCO_2H–H_2O; iii, **7**, AcOH–MeOH; iv, $NaBH_3CN$, MeOH (80% over 4 steps); v, 4-methoxybenzoyl chloride, DMAP, pyridine, 80 °C, 82%; vi, DLP, chlorobenzene, reflux, 59%.

These preliminary model studies have allowed us to establish the feasibility of obtaining the tetracyclic structure of kirkine with various substituents in place and without the need to use tributylstannane. A number of difficulties were brought to light and many were overcome. We hope to be able to use the olefin in ring C in a compound such as **60** to both introduce the hydroxy group at C-1 and direct the decarboxylative elimination in the correct direction (Scheme 11).



Scheme 11 Final steps envisaged for the synthesis of kirkine.

Experimental

General experimental

All reactions were carried out under an inert atmosphere. Commercial reagents were used as received without further purification. All products were purified using silica gel SDS 60 C. C. 40–63 or by crystallisation. NMR spectra were recorded in

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$CDCl_3$ with TMS as an internal standard at room temperature on a Bruker AMX400 or Bruker AMX300. Infrared absorption spectra were recorded using KBr disks with a Perkin-Elmer 1600 Fourier Transform Spectrophotometer. Mass spectra were determined at 70 eV with an AutoSpec Micromass or an HP 5989B mass spectrometer using ammonia as the reagent gas. Melting points were determined by Reichert microscope apparatus and are uncorrected.

1-[1,3]Dioxolan-2-ylmethyl-2-hydroxycyclohexanecarboxylic acid ethyl ester (5)

A solution containing ethyl 2-oxocyclohexanecarboxylate (**4**) (5.0 g, 29.4 mmol), 2-bromomethyl-1,3-dioxolane (9.8 g, 58.7 mmol), potassium carbonate (12.2 g, 88.1 mmol) and potassium iodide (4.8 g, 29.4 mmol) in DMSO (30 mL) was stirred at 100 °C for 20 h. When the starting material was completely consumed, cold H_2O was added and the mixture was extracted with $CHCl_3$, dried (Na_2SO_4) and the solvent removed *in vacuo*. Purification by flash column chromatography (heptane–EtOAc 19 : 1 to 9 : 1) afforded the desired alcohol (4.6 g, 61%) as a colourless oil. ν_{max}/cm^{-1} 2893 (O–CH–O), 1715 (C=O), 945 (O–CH_2–CH_2–O); δ_H (300 MHz, $CDCl_3$) 5.03 (1H, t, J = 4.5 Hz, OC*H*O), 4.19–4.26 (2H, dq, J = 7.5, 1.2, OCH_2CH_3), 3.78–3.95 (4H, m, OCH_2), 2.48–2.65 (2H, m, CH_2), 2.31 (1H, dd, J = 14.4, 4.2 Hz, CH_2CHO), 2.00–2.04 (1H, m, CH_2), 1.90 (1H, dd, J = 14.3, 7.5 Hz, CH_2CHO), 1.50–1.77 (5H, m, CH_2); 1.27 (3H, t, J = 7.2 Hz, 3H, CH_3); δ_C (75 MHz, $CDCl_3$) 207.4 (*C*=O), 171.5 (O*C*=O), 101.9 (O*C*HO), 64.8 (OCH_2), 64.6 (OCH_2), 61.5 (OCH_2CH_3), 58.7 (*Cq*), 40.9 (CH_2CH), 39.1 (CH_2), 36.7 (CH_2), 27.6 (CH_2), 22,4 (CH_2), 14.1 (CH_3); MS *m*/*z* 257 ($M + H^+$), 274 (NH_4^+). The above alcohol (3.7 g, 14.5 mmol) was dissolved in MeOH (94 mL) and sodium borohydride (1.9 g, 50.2 mmol) in H_2O (20 mL) was added. The reaction mixture was stirred at ambient temperature for 2 h. When the starting material was consumed, aq. AcOH (10%) was added and the solvent was removed *in vacuo*. The mixture was extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (heptane–EtOAc 4 : 1 to 7 : 3) gave alcohol **5** (2.8 g, 75%) as a colourless oil. ν_{max}/cm^{-1} 3497 (OH), 1719 (C=O), 1034 (CHOH), 943 (OCH_2CH_2O); δ_H (300 MHz, $CDCl_3$) 5.11 (1H, t, J = 5.0 Hz, OC*H*O), 4.23 (2H, dddd, J = 11.0, 9.0, 4.5 Hz, OCH_2CH_3), 3.79–3.97 (2H, m, OCH_2CH_2O), 3.53 (1H, s, *H*OCH), 2.22 (1H, dd, J = 15.0 Hz, 6.0 Hz, CH_2CHO), 1.97 (1H, dd, J = 14.4, 5.0 Hz, CH_2CHO), 1.47–1.92 (8H, m, CH_2), 1.30 (3H, t, J = 7.1 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 176.3 (*C*=O), 102.3 (O*C*HO), 74.7 (*C*HOH), 65.2 (OCH_2CH_3), 64.0 (OCH_2), 60.7 (OCH_2), 49.5 (*Cq*), 41.3 (CH_2), 32.5 (CH_2), 31.3 (CH_2), 23.6 (CH_2), 22.3 (CH_2), 14.3 (CH_3); MS *m*/*z* 259 ($M + H^+$), 276 ($M + NH_4^+$).

1-[1,3]Dioxolan-2-ylmethylcyclohex-2-enecarboxylic acid ethyl ester (6)

Alcohol **5** (3.0 g, 11.6 mmol) was dissolved in pyridine (23.2 mL) and $MeSO_2Cl$ (2.7 mL, 35 mmol) was added at 0 °C. The reaction mixture was stirred for 30 min, allowed to warm up to ambient temperature and left stirring for 15 h. Cold H_2O and CH_2Cl_2 were then added, and the mixture was extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (heptane–EtOAc 9 : 1 to 4 : 1) gave the desired mesylate product (2.9 g, 76%) as a mixture of isomers (2 : 1). Major product (white crystals); mp 83–85 °C (CH_2Cl_2–heptane); ν_{max}/cm^{-1} 2872 (O–CH–O), 1731 (C=O), 1350 (O_2S–CH_3); δ_H (300 MHz, $CDCl_3$) 5.01 (1H, s, C*H*OSO_2CH_3), 4.92 (1H, t, J = 5.0 Hz, OC*H*O), 4.17 (2H, m, OCH_2CH_3), 3.80–3.95 (4H, m, OCH_2CH_2O), 2.98 (3H, s, SCH_3), 2.04–1.53 (10H, m, $5CH_2$), 1.29 (3H, t, J = 7.5 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 173.2 (*C*=O), 101.0 (O*C*HO), 82.6 (*C*HOSO_2), 64.3 (OCH_2CH_2O), 64.1 (OCH_2CH_2O), 60.4 (CH_3CH_2O), 47.1 (*Cq*), 38.1 (SCH_3), 36.1 (CH_2CHO), 26.5 (CH_2), 25.2 (CH_2), 19.5 (CH_2), 18.5 (CH_2), 13.5 (CH_3); MS *m*/*z* 353 ($M + NH_3$). Minor product (yellow oil); ν_{max}/cm^{-1} 2940 (OCHO), 1727 (C=O), 1353 (O_2SCH_3); δ_H (300 MHz, $CDCl_3$) 5.27 (1H, d, J = 4.0 Hz, C*H*OSO_2CH_3), 4.95 (1H, t, J = 5.0 Hz, OC*H*O), 4.14–4.24 (2H, dq, J = 6.5, 3.0 Hz, OCH_2CH_3), 3.80–3.98 (4H, m, OCH_2CH_2O), 3.07 (3H, s, SCH_3), 1.37–2.16 (10H, m, $5CH_2$), 1.29 (3H, t, J = 7.3 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 173.2 (*C*=O), 101.5 (O*C*HO), 81.3 (*C*HOSO_2), 65.0 (OCH_2CH_2O), 64.7 (OCH_2CH_2O), 60.6 (CH_3CH_2O), 48.3 (*Cq*), 39.2 (CH_2CHO), 38.8 (SCH_3), 36.7 (CH_2), 36.0 (CH_2), 21.7 (CH_2), 19.9 (CH_2), 14.0 (CH_3); MS *m*/*z* 353 ($M + NH_3$). A solution of the sulfonyl derivative (2.9 g, 8.62 mmol) and NaI (0.49 g, 3.5 mmol) in DBU (18.0 mL) was heated at 80 °C for 7 h. Saturated aq. NH_4Cl was added and the mixture was extracted with Et_2O, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (heptane–EtOAc 19 : 1) gave olefin **6** (1.8 g, 88%) as a colourless oil. ν_{max}/cm^{-1} 2867 (OCHO) 1728 (C=O), 733 (CH=CH, *cis*); δ_H (300 MHz, $CDCl_3$) 5.75–5.85 (2H, m, C*H*=C*H*), 4.93 (1H, t, J = 5 Hz, OC*H*O), 4.12 (2H, dq, J = 7.5, 3.6 Hz, OCH_2CH_3), 3.78–3.96 (4H, m, OCH_2CH_2O), 1.94–2.22 (2H, m, CH_2) 1.54–1.74 (6H, m, CH_2), 1.26 (3H, t, J = 7.0 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 175.7 (*C*=O), 129.3 (*C*H=CH), 128.9 (*C*H=CH), 102.3 (O*C*HO), 64.8 (OCH_2CH_2O), 64.7 (OCH_2CH_2O), 60.7 (OCH_2CH_3), 44.7 (*Cq*), 43.6 (CH_2CHO), 31.4 (CH_2), 24.8 (CH_2), 19.5 (CH_2), 14.3 (CH_3); MS *m*/*z* 241 ($M + H^+$).

General procedure for the preparation of thiosemicarbazones 8 and 23

A solution of HCl (10%) in EtOH (2.4 mL) was added to a solution of the dioxolane (1.0 mmol) dissolved in EtOH (9 mL). Thiosemicarbazide **7** (240 mg, 1.2 mmol) was added, and the mixture was left stirring at ambient temperature until the starting material had been consumed. The solvent was then removed *in vacuo*, H_2O was added and the mixture was extracted with Et_2O. A drop of H_2O was added, followed by copper sulfate, and the mixture was left stirring, until the hydrazine had been removed. The mixture was then filtered, washed with Et_2O, dried (Na_2SO_4) and the solvent removed *in vacuo* to give the desired hydrazide product. The hydrazide (1.0 mmol) was then dissolved in MeOH (8.5 mL $mmol^{-1}$) and sodium cyanoborohydride (182 mg, 2.9 mmol) was added. The solution was cooled to 0 °C and AcOH was added dropwise until the solution reached a pH between 4–5. The reaction mixture was then allowed to warm to ambient temperature and was left stirring for 20 h. During this time a further 2.5 eq. of sodium cyanoborohydride was added. EtOAc was added and the mixture was washed with H_2O, followed by brine, dried (Na_2SO_4), and the solvent removed *in vacuo* to give the desired thiosemicarbazone.

1-[2-(Methylsulfanylthiocarbonylphenylhydrazino)ethyl]-cyclohex-2-enecarboxylic acid ethyl ester (8). Crystallisation (CH_2Cl_2–heptane) gave the reduced product **8** (89%) as white crystals; mp 79–80 °C (CH_2Cl_2–heptane); ν_{max}/cm^{-1} 3202 (N–H), 3028 (Ph), 1720 (C=O), 1354 (SCH_3), 1058 (NCSS), 731 (CH=CH); δ_H (300 MHz, $CDCl_3$) 7.31–7.45 (5H, m, C*H*Ar), 5.73–5.79 (1H, dt, J = 10.6, 3.4 Hz, C*H*=CH), 5.63 (1H, d, J = 10.2 Hz, C*H*=CH), 4.08 (2H, dq, J = 7.2, 2.3 Hz, OCH_2CH_3), 2.86–2.92 (2H, m, $NHCH_2$), 2.54 (3H, s, SCH_3), 1.36–1.94 (7H, m, CH_2, N*H*), 1,19 (3H, t, J = 7.0 Hz, CH_3), 0.75–0.82 (2H, m, CH_2); δ_C (75 MHz, $CDCl_3$) 175.3 (*C*=O), 129.2, 129.0, 128.9, 127.5, (5*C*HAr, *C*H=*C*H), 60.5 (OCH_2CH_3), 45.3(*Cq*), 44.2 (CH_2NH), 36.9 (CH_2), 30.7 (CH_2), 24.7 (CH_2), 19.4 (CH_2), 20.0 (SCH_3), 14.1 (CH_3); MS *m*/*z* 287 (M − SCSMe), 379 ($M + H^+$).

Benzoic acid 4-ethoxycarbonyl-4-[2-(*N*′-methylsulfanylthiocarbonyl-*N*′-phenylhydrazino)ethyl]cyclohex-2-enyl ester (23). Purification by flash column chromatography (heptane–EtOAc 95 : 5) gave the reduced product **23** (91%) as a colourless

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oil. ν_{max}/cm^{-1} 3290 (N–H), 1714 (C=O, $CO_2CH_2CH_3$, BzO), 1353 (SCH_3), 1024 (N–N), 1058 (N–CS–S), 1024 (N–N), 735 (CH=CH); δ_H (300 MHz, $CDCl_3$) 78.03 (2H, d, J = 7.5 Hz, C*H*Ar), 7.34–7.55 (8H, m, C*H*Ar), 5.85–5.95 (2H, m, C*H*=C*H*), 5.45 (1H, s, BzOC*H*), 4.12–4.14 (2H, m, OCH_2CH_3), 2.95 (2H, s, CH_2NH), 2.54 (3H, s, SCH_3), 1.53–2.29 (5H, m, CH_2, N*H*), 1.20–1.27 (3H, dt, J = 7.5, 2.0 Hz, CH_3), 0.82–0.91 (2H, m, CH_2); δ_C (75 MHz, $CDCl_3$) 174.1 (CH_3CH_2OC=O), 165.8 (Ph*C*=O), 134.3, 133.2, 129.4, 129.2, 129.0, 127.8, 127.4, 126.4 (10*C*HAr, *C*H=*C*H), 130.2 (*C*Ar), 68.6 (BzO*C*H), 60.9 (OCH_2CH_3), 45.4 (CH_2N), 44.0 (*Cq*), 36.3 (CH_2), 27.7 (CH_2), 25.6 (CH_2), 20.4 (SCH_3), 15.2 (CH_3); MS m/z 499 ($M + H^+$).

General procedure for the preparation of acylated thiosemicarbazide products 9, 12–14, and 24

The hydrazide derivative (1.0 mmol) was dissolved in pyridine (2.0 mL), and the acid chloride (2.0 mmol) was added. The mixture was heated at 80 °C until the starting material had been consumed. The mixture was extracted with CH_2Cl_2, dried (Na_2SO_4) and the solvent was removed *in vacuo*. The oil obtained was dissolved in a mixture of H_2O–CH_2Cl_2, and $NaHCO_3$ was added, followed by a few drops of Et_3N and the reaction mixture was stirred for 12 h at ambient temperature to eliminate the anhydride formed during the acylation. The mixture was re-extracted with CH_2Cl_2, dried (Na_2SO_4), concentrated *in vacuo* and the product purified by flash column chromatography.

1-{2-[*N*-(4-Methoxybenzoyl)-*N*′-methylsulfanylthiocarbonyl-*N*′-phenylhydrazino]ethyl}cyclohex-2-enecarboxylic acid ethyl ester (9). Purification by flash column chromatography (heptane–EtOAc 19 : 1 to 4 : 1) gave desired acylated product **9** (93%) as a yellow oil. ν_{max}/cm^{-1} 3055 (Ph), 1727 (C=O, $CO_2CH_2CH_3$), 1674 (NC=O), 1606 (Ar–OCH_3), 1331 (SCH_3), 1062 (NC–S-S); δ_H (300 MHz, $CDCl_3$), 8.08 (1H, dd, J = 10.5, 8.7 Hz, C*H*Ar), 7.64 (2H, d, J = 8.0 Hz, C*H*Ar), 7.39 (2H, s, C*H*Ar), 6.91–6.99 (4H, m, C*H*Ar), 5.77–5.83 (1H, m, C*H*=CH), 5.60 (1H, s, C*H*=CH), 4.05–4.13 (2H, m, OCH_2CH_3), 3.87 (3H, s, OCH_3), 3.62–3.77 (2H, m, NCH_2), 2.60 (3H, s, SCH_3), 2.08–2.11 (8H, m, CH_2), 0.87 (3H, t, J = 7.0 Hz, OCH_2CH_3); δ_C (75 MHz, $CDCl_3$) 171.0 (C=O), 137.0, 133.0, 129.7, 129.6, 128.8 (*C*Ar), 114.3 (*C*H=CH), 113.9 (*C*H=CH), 60.9 (OCH_2CH_3), 58.6 (*Cq*), 55.8 (OCH_3), 45.5 (CH_2), 36.9 (CH_2), 30.6 (CH_2), 24.9 (CH_2), 20.4 (SCH_3), 19.6 (CH_2), 14.3 (OCH_2CH_3); MS m/z 287 (M − SCSMe), 514 ($M + H^+$). Anal. calcd for $C_{27}H_{32}O_4N_2S_2$: C, 63.25, H 6.29; found: C, 63.32, H, 6.46%.

1-{2-[*N*-(3-Methylbenzoyl)-*N*′-methylsulfanylthiocarbonyl-*N*′-phenylhydrazino]ethyl}cyclohex-2-enecarboxylic acid ethyl ester (12). Purification by flash column chromatography (heptane–EtOAc 19 : 1 to 9 : 1) gave desired acylated product **12** (97%) as a yellow oil. ν_{max}/cm^{-1} 1723 (C=O, $CO_2CH_2CH_3$), 1683 (NC=O), 1063 (N–CS–S); δ_H (300 MHz, $CDCl_3$), 7.18–7.68 (9H, m, C*H*Ar), 5.77 (1H, m, C*H*=CH), 5.31 (1H, s, C*H*=CH), 3.99 (2H, m, OCH_2CH_3), 3.62 (2H, s, NCH_2), 2.63 (3H, s, SCH_3), 2.39 (3H, s, CH_3), 1.16–2.15 (8H, m, CH_2), 0.88–0.90 (3H, s, OCH_2CH_3); δ_C (75 MHz, $CDCl_3$) 174.7 (*C*=O), 141.8 (N*C*=O), 138.2 (*C*Ar), 134.6 (*C*Ar), 131.4, 130.2, 129.2, 128.2, 127.4, 126.7, 125.1, 123.8 (*C*HAr), 109.5 (*C*H=CH), 66.2 (OCH_2CH_3), 44.9 (*Cq*), 36.7 (CH_2), 30.2 (CH_2), 29.5 (CH_2), 24.5 (CH_2), 22.5 (CH_3), 21.2 (SCH_3), 19.2 (CH_2), 13.9 (OCH_2CH_3); MS m/z 498 ($M + H^+$). Anal. calcd for $C_{27}H_{32}N_2O_3S_2$: C, 65.29, H 6.49; found: C, 65.61, H, 6.86%.

1-{2-[*N*-(3-Methoxybenzoyl)-*N*′-methylsulfanylthiocarbonyl-*N*′-phenylhydrazino]ethyl}cyclohex-2-enecarboxylic acid ethyl ester (13). Purification by flash column chromatography (heptane–EtOAc 19 : 1) gave desired acylated product **13** (95%) as a yellow oil. ν_{max}/cm^{-1} 1723 2872 (OCH_3), 1718 (C=O, $CO_2CH_2CH_3$), 1675 (NC=O), 1063 (N–CS–S); δ_H (300 MHz, $CDCl_3$), 6.76–7.68 (9H, m, C*H*Ar), 5.76 (1H, s, C*H*=CH), 5.50 (1H, s, C*H*=CH), 3.98 (2H, s, OCH_2CH_3), 3.80 (3H, s, OCH_3), 3.64 (1H, s, NCH_2), 3.47 (1H, s, NCH_2), 2.59 (3H, s, SCH_3), 2.35–1.34 (8H, m, CH_2), 1.27 (3H, s, OCH_2CH_3); δ_C (75 MHz, $CDCl_3$) 188.2 (*C*=S), 174.8 (*C*=O), 159.4 (N–*C*=O), 135.9 (*C*Ar), 129.5, 129.3, 128.3, 127.1 (*C*HAr), 118.6 (*C*H=CH), 116.8 (*C*H=CH), 60.7 (OCH_2CH_3), 55.2 (OCH_3), 47.2 (*Cq*), 36.8 (CH_2), 30.3 (CH_2), 29.9 (CH_2), 24.6 (CH_2), 20.5 (SCH_3), 19.2 (CH_2), 14.0 (OCH_2CH_3); MS m/z 514 ($M + H^+$).

1-{2-[*N*′-Methylsulfanylthiocarbonyl-*N*′-phenyl-*N*-(3-trifluoromethylbenzoyl)hydrazino]ethyl}cyclohex-2-enecarboxylic acid ethyl ester (14). Purification by flash column chromatography (heptane–EtOAc 19 : 1) gave desired acylated product **14** (83%) as a yellow oil. ν_{max}/cm^{-1} 1722 (C=O, $CO_2CH_2CH_3$), 1678 (NC=O), 1266–1208 (Ar–CF_3), 1072 (N–CS–S); δ_H (300 MHz, $CDCl_3$) 6.66–7.78 (9H, m, C*H*Ar), 5.66 (1H, s, C*H*=CH), 5.33–5.42 (1H, m, C*H*=CH), 3.88–4.08 (2H, m, OCH_2CH_3), 3.31–3.55 (2H, m, NCH_2), 2.48 (3H, s, SCH_3), 0.76–2.27 (11H, m, $4CH_2$, OCH_2CH_3); δ_C (75 MHz, $CDCl_3$) 203.0 (*C*=S), 175.1 (*C*=O), 142.0 (*C*Ar), 141.2 (*C*Ar), 135.7 (*C*Ar), 131.1, 130.2, 129.4, 128.4, 127.9, 127.2, 126.7, 125.2, 123.8, 121.6 (9*C*HAr, *C*H=*C*H), 60.6 (OCH_2CH_3), 45.3 (*Cq*), 36.7 (CH_2), 31.6 (CH_2), 29.1 (CH_2), 24.5 (CH_2), 20.4 (SCH_3), 19.1 (CH_2), 14.9 (OCH_2CH_3); 552 ($M + H^+$).

Benzoic acid 4-ethoxycarbonyl-4-{2-[*N*-(4-methoxybenzoyl)-*N*′-methylsulfanylthiocarbonyl-*N*′-phenylhydrazino]ethyl}cyclohex-2-enyl ester (24). Purification by flash column chromatography (heptane–EtOAc 19 : 1 to 9 : 1) gave desired acylated product **24** (64%) as a pale yellow oil. ν_{max}/cm^{-1} 1720 (C=O, $CO_2CH_2CH_3$), 1670 (NC=O), 1268, 1024 (N–CS–S); δ_H (300 MHz, $CDCl_3$) 8.06–6.90 (14H, m, C*H*Ar), 5.89–5.96 (2H, m, C*H*=C*H*), 5.45 (1H, m, BzOC*H*), 4.10 (2H, s, OCH_2CH_3), 3.85 (3H, s, CH_3O), 3.79 (2H, s, NCH_2), 2.61 (3H, s, SCH_3), 1.55–2.26 (6H, m, CH_2), 1.23–1.26 (3H, s, OCH_2CH_3); δ_C (75 MHz, $CDCl_3$) 203.8 (*C*=S), 173.8 (*C*=O, $CO_2CH_2CH_3$), 166.0 (Ph*C*O_2), 161.9 (N*C*=O), 142.6 (*C*Ar), 133.0, 132.3, 130.3, 129.6, 129.5, 128.4, 126.9, 126.6 (14*C*HAr), 125.3 (*C*Ar), 114.1, 113.8, (*C*H=*C*H), 109.7 (–*C*–), 67.0 (*C*HOBz), 61.2 (OCH_2CH_3), 55.3 (OCH_3), 47.8 (NCH_2), 45.5 (*Cq*), 36.3 (CH_2), 27.6 (CH_2), 25.8 (CH_2), 21.4 (SCH_3), 14.0 (OCH_2CH_3); 552 ($M + H^+$). Anal. calcd for $C_{34}H_{36}O_6N_2S_2$: C, 64.54, H 5.73; found: C, 64.89, H, 5.93%.

Benzoic acid 4-(2-{*N*-[3-(2,2-dimethylpropionyloxy)-4-methoxybenzoyl]-*N*′-methylsulfanylthiocarbonyl-*N*′-phenylhydrazino}-ethyl)-4-ethoxycarbonylcyclohex-2-enyl ester (27)

To a solution of 4-hydroxy-4-methoxybenzoic acid (1.00 g, 6.0 mmol) in pyridine (18.0 mL), pivaloyl chloride (1.45 mL, 12.0 mmol) was added at 0 °C. The solution was allowed to warm to ambient temperature and stirred for 48 h. During this time a further 2 eq. of pivaloyl chloride were added. H_2O was then added until the mixture turned transparent and the reaction mixture was stirred for a further 12 h. Saturated aq. $NaHCO_3$ was added slowly and the mixture was extracted with Et_2O, dried (Na_2SO_4) and the solvent removed *in vacuo*. Crystallisation (CH_2Cl_2–heptane) gave 1,3-(2,2-dimethylpropionyloxy)-4-methoxybenzoic acid (1.24 g, 82%). To a solution of the acid (0.76 g, 3.0 mmol) dissolved in freshly distilled CH_2Cl_2 (6.0 mL), DMF (0.25 mL), followed by oxalyl chloride (1.30 mL, 15.0 mmol) were added at 0 °C. The reaction mixture was stirred for 2 h and the solvent was removed *in vacuo*. The acid chloride obtained was added slowly to hydrazide **23** (0.50 g, 1.0 mmol) in Et_2O (2.0 mL) and Et_3N (0.8 mL) at 0 °C, the reaction mixture was allowed to warm to ambient temperature and was stirred for 3 h. The mixture was then filtered, extracted with Et_2O and work-up was carried out as described for the general acylation procedure. Purification by flash column chromatography (heptane–EtOAc 9 : 1 to 4 : 1) gave desired acylated product **27** (50%) as a yellow mousse. ν_{max}/cm^{-1} 2930 (OCH_3), 1758 (O–C=O, *Pv*), 1727 ($CO_2CH_2CH_3$, BzO), 1655

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(N–C=O), 1069 (N–CS–S); δ_H (300 MHz, $CDCl_3$) 6.93–8.03 (13H, m, C*H*Ar), 5.90–5.97 (2H, m, C*H*=C*H*), 5.46 (1H, s, BzOC*H*), 4.11 (2H, q, J = 7.0 Hz, OCH_2CH$_3$), 3.89 (3H, s, CH_3O), 3.80 (2H, s, NCH_2), 2.59 (3H, s, SCH_3), 1.58–2.30 (6H, m, CH_2), 1.36 (9H, s, CH_3), 1.24 (3H, t, J = 6.8 Hz, OCH$_2$CH_3); δ_C (75 MHz, $CDCl_3$) 203.7 (*C*=S), 176.3 (*C*=O, $CO_2CH_2CH_3$), 170.2 (*C*=O, CO_2Pv), 166.0, (*C*=O, CO_2Ph), 156.6, (N*C*=O), 140.3 (*C*Ar), 132.9, 130.3, 129.6, 129.5, 128.3, 126.4, 125.1, 124.7 (13*C*HAr), 121.9 (*C*Ar), 121.2 (*C*Ar), 111.8 (*C*H=CH), 111.5 (*C*H=CH), 68,6 (*C*HOCOPh), 61.2 (O*C*H$_2$CH$_3$), 56.2 (O*C*H$_3$), 45.5 (*Cq*), 39.0 (*C*H$_2$), 36.1 (*C*H$_2$), 27.6 (3*C*H$_3$), 27.0 (*C*H$_2$), 25.7 (*C*H$_2$), 21.0 (S*C*H$_3$), 14.2 (OCH$_2$*C*H$_3$); MS *m*/*z* 734 (M + H$^+$), 751 (M + NH$_4^+$).

Benzoic acid 4-{2-[*N*-(3,4-dimethoxybenzoyl)-*N*′-methylsulfanylthiocarbonyl-*N*′-phenylhydrazino]ethyl}-4-ethoxycarbonylcyclohex-2-enyl ester (28)

To a solution of 3,4-dimethoxybenzoic acid (2.19 g, 12.0 mmol) dissolved in freshly distilled CH_2Cl_2 (24 mL), DMF (1.0 mL), followed by oxalyl chloride (5.2 mL, 60.0 mmol) were added at 0 °C. The reaction mixture was stirred for 2 h and the solvent was removed *in vacuo*. The acid chloride obtained was added slowly to hydrazide **23** in heptane (2.5 mL) and Et_3N (3.4 mL) at 0 °C, the reaction mixture was allowed to warm to ambient temperature and was stirred for 3 h. The mixture was then filtered, extracted with Et_2O and work-up was carried out as described for the general acylation procedure. Purification by flash column chromatography (heptane–EtOAc 4 : 1 to 1 : 1) gave desired acylated product **28** (71%) as a white mousse. ν_{max}/cm^{-1} 1715 (C=O, $CO_2CH_2CH_3$, Ph–CO–O), 1673 (N–C=O), 1606 (Ph–OCH$_3$), 1331 (SCH$_3$), 1067 (N–CS–S); δ_H (300 MHz, $CDCl_3$) 6.86–8.04 (13H, m, C*H*Ar), 5.97 (1H, s, C*H*=CH), 5.43 (1H, s, C*H*=CH) 5.48–5.43 (1H, m, BzOC*H*), 4.13 (2H, s, OCH_2CH$_3$), 3.86–3.94 (8H, m, 2CH_3O, NCH_2), 2.61 (3H, s, SCH_3), 1.42–2.29 (6H, m, CH_2), 1.26 (3H, s, OCH$_2$CH_3); δ_C (75 MHz, $CDCl_3$) 203.3 (*C*=S), 174.0 (*C*=O), 166.2 (166.0) (*C*=O, OBz), 151.6 (N*C*=O), 148.8 (*C*Ar), 134.1 (*C*HAr), 132.9 (*C*HAr), 130.4 (*C*Ar), 129.6–126.9 (11*C*HAr), 126.7 (*C*Ar), 110.8 (*C*H=*C*H), 68.7 (*C*HOBz), 61.2 (O*C*H$_2$CH$_3$), 56.0 (O*C*H$_3$), 55.8 (O*C*H$_3$), 48.1 (N*C*H$_2$), 45.7 (*C*q), 36.3 (*C*H$_2$), 39.7 (*C*H$_2$), 25.7 (*C*H$_2$), 21.1 (S*C*H$_3$), 14.2 (OCH$_2$*C*H$_3$); MS *m*/*z* 542 (M − OBz), 664 (M + H$^+$).

General procedure for the preparation of cyclised products 10, 11, 15–20, 25, 26, and 29–36

The hydrazide (2.0 mmol) was dissolved in chlorobenzene (10 mL) and the resulting solution was degassed under argon for 15 min. DLP (3.0 mmol) was dissolved in chlorobenzene (22 mL), and the solution was degassed under argon for 15 min. The solution containing the DLP (0.5 mmol) was added every 20 min until the starting material had been consumed.

10-Methoxy-7-oxo-2,3,4,5,11b,11c-hexahydro-1*H*,7*H*-pyrrolo-[3,2,1-*de*]phenanthridine-3a-carboxylic acid ethyl ester (10) and (11). Purification by flash column chromatography (heptane–EtOAc 19 : 1 to 3 : 2) gave the major isomer **10** (79%) as white crystals; mp 146 °C; ν_{max}/cm^{-1} 2931 (OCH$_3$), 1726 (C=O, $CO_2CH_2CH_3$), 1636 (NC=O); δ_H (300 MHz, $CDCl_3$) 8.04 (1H, d, J = 8.1 Hz, C*H*Ar), 6.84–6.88 (1H, dd, J = 8.4 Hz, 2.0 Hz, C*H*Ar), 6.72 (1H, d, J = 2.1 Hz, C*H*Ar), 4.25 (2H, q, J = 7.1 Hz, OCH_2CH$_3$), 4.21 (1H, d, J = 4.8 Hz, NC*H*), 3.91 (1H, s, NCH_2), 3.81 (3H, s, CH_3O), 3.63–3.73 (1H, m, NCH_2), 3.06–3.13 (1H, ddd, J = 12.0, 7.5, 4.4 Hz, C*H*), 2.00–2.13 (2H, m, CH_2), 1.37–1.73 (4H, m, CH_2), 1.32 (3H, t, J = 7.1 Hz, OCH$_2$CH_3), 1.25–1.28 (m, 2H, CH_2); δ_C (75 MHz, $CDCl_3$) 173.9 (*C*=O), 163.5 (N*C*=O), 145.0 (*C*Ar), 129.8 (*C*HAr), 121.3 (*C*Ar), 122.4 (*C*HAr), 61.1 (O*C*H$_2$CH$_3$), 59.1 (N*C*H), 55.4 (O*C*H$_3$), 51.4 (*Cq*), 45.5 (N*C*H$_2$), 37.9 (*C*H), 33.3 (*C*H$_2$), 29.7 (*C*H$_2$), 28.8 (*C*H$_2$), 21.9 (*C*H$_2$), 14.3 (OCH$_2$*C*H$_3$); MS *m*/*z* 330 (M + H$^+$). Anal. calcd for $C_{19}H_{23}NO_4$: C, 69.27, H 7.04; found: C, 68.75, H, 7.14%. Minor isomer **11** (2%); δ_H (300 MHz, $CDCl_3$) 8.41 (1H, d, J = 8.8 Hz, C*H*Ar), 7.04–7.08 (1H, dd, J = 8.0, 2.5 Hz, C*H*Ar), 6.93 (1H, d, J = 2.3 Hz, C*H*Ar), 4.35 (2H, q, J = 7.5 Hz, OCH_2CH$_3$), 4.32 (1H, d, J = 7.0 Hz, NC*H*), 4.12–4.21 (1H, m, NCH_2), 3.93 (4H, s + m, OCH_3; NCH_2), 2.96–3.03 (1H, m, C*H*), 2.56–2.78 (2H, m, CH_2), 2.01–2.14 (2H, m, CH_2), 1.55–1.75 (2H, m, CH_2), 1.26 (3H, t, J = 7.5 Hz, OCH$_2$CH_3), 1.04–1.08 (2H, m, CH_2); δ_C (75 MHz, $CDCl_3$) 179.5 (*C*=O), 162.4 (N*C*=O), 143.4 (*C*Ar), 128.6 (*C*HAr), 125.9 (*C*Ar), 113.6 (*C*HAr), 62.5 (O*C*H$_2$CH$_3$), 52.8 (N*C*H), 55.2 (O*C*H$_3$), 52.0 (*Cq*), 44.5 (N*C*H$_2$), 39.0 (*C*H), 36.0 (*C*H$_2$), 34.8 (*C*H$_2$), 25.4 (*C*H$_2$), 21.8 (*C*H$_2$), 14.7 (OCH$_2$*C*H$_3$); MS *m*/*z* 330 (M + H$^+$).

9-Methyl-7-oxo-2,3,4,5,11b,11c-hexahydro-1*H*,7*H*-pyrrolo-[3,2,1-*de*]phenanthridine-3a-carboxylic acid ethyl ester (15) and 11-methyl-7-oxo-2,3,4,5,11b,11c-hexahydro-1*H*,7*H*-pyrrolo-[3,2,1-*de*]phenanthridine-3a-carboxylic acid ethyl ester (18). Purification by flash column chromatography (heptane–EtOAc 19 : 1 to 4 : 1) gave isomer **15** (35%) as white crystals; mp 103–105 °C; ν_{max}/cm^{-1} 1725 (C=O, $CO_2CH_2CH_3$), 1651 (NC=O); δ_H (300 MHz, $CDCl_3$) 7.82 (s, 1H, C*H*), 7.18 (1H, d, J = 7.5 Hz, C*H*Ar), 7.05 (1H, d, J = 8.4 Hz, C*H*Ar), 4.17 (2H, q, J = 6.8 Hz, OCH_2CH$_3$), 4.13 (1H, d, J = 4.8Hz, NC*H*), 3.80 (1H, t, J = 10.5 Hz, NCH_2), 3.58–3.68 (1H, m, NCH_2), 2.99–3.06 (1H, ddd, J = 13.0, 9.0, 4.5 Hz, C*H*), 2.31 (3H, s, CH_3), 1.33–2.11 (6H, m, CH_2), 1.25 (3H, t, J = 7.0 Hz, OCH$_2$CH_3), 1.19 (2H, s, CH_2); δ_C (75 MHz, $CDCl_3$) 173.9 (*C*=O), 163.7 (N*C*=O), 139.9 (*C*Ar), 136.8 (*C*Ar), 132.7 (*C*HAr), 128.1 (*C*HAr), 127.5 (*C*Ar), 127.3 (*C*HAr), 61.1 (O*C*H$_2$CH$_3$), 59.3 (N*C*H), 51.4 (*Cq*), 42.7 (N*C*H$_2$), 37.1 (*C*H), 33.2 (*C*H$_2$), 29.9 (*C*H$_2$), 28.8 (*C*H$_2$), 21.9 (*C*H$_2$), 18.5 (*C*H$_3$), 14.3 (OCH$_2$*C*H$_3$); MS *m*/*z* 314 (M + H$^+$). Anal. calcd for $C_{19}H_{23}NO_3$: C, 72.82, H, 7.40; found: C, 72.65, H, 7.51%. Isomer **18** (31%) as white crystals; mp 110–112 °C; ν_{max}/cm^{-1} 1725 ($CO_2CH_2CH_3$), 1651 (NC=O), 1592 (CH=CH); δ_H (300 MHz, $CDCl_3$) 7.99 (1H, d, J = 7.2 Hz, C*H*Ar), 7.22–7.32 (2H, dd, J = 15.0, 7.5 Hz, C*H*Ar), 4.25 (2H, q, J = 7.0 Hz, OCH_2CH$_3$), 4.18 (1H, d, J = 4.0 Hz, NC*H*), 3.85–3.92 (2H, m, NCH_2), 3.26–3.34 (1H, ddd, J = 12.5, 8.5, 4.3 Hz, C*H*), 2.38 (3H, s, CH_3), 1.43–2.19 (6H, m, CH_2), 1.33 (3H, t, J = 7.2 Hz, OCH$_2$CH_3), 1.19–1.24 (2H, s, CH_2); δ_C (75 MHz, $CDCl_3$) 173.0 (*C*=O), 163.7 (N*C*=O), 130.7 (*C*Ar), 134.5 (*C*Ar), 133.8 (*C*HAr), 128.7 (*C*HAr), 126.6 (*C*HAr), 125.9 (*C*HAr), 61.1 (O*C*H$_2$CH$_3$), 58.9 (*C*HN), 51.5 (*C4*), 42.6 (N*C*H$_2$), 34.1 (*C*H), 33.3 (*C*H$_2$), 28.9 (*C*H$_2$), 26.7 (*C*H$_2$), 21.9 (*C*H$_2$), 18.5 (*C*H$_3$), 14.3 (OCH$_2$*C*H$_3$); MS *m*/*z* 314 (M + H$^+$). Anal. calcd for $C_{19}H_{23}NO_3$: C, 72.82, H 7.40; found: C, 72.43, H, 7.21%.

9-Methoxy-7-oxo-2,3,4,5,11b,11c-hexahydro-1*H*,7*H*-pyrrolo-[3,2,1-*de*]phenanthridine-3a-carboxylic acid ethyl ester (16) and 11-methoxy-7-oxo-2,3,4,5,11b,11c-hexahydro-1*H*,7*H*-pyrrolo[3,2,1-*de*]phenanthridine-3a-carboxylic acid ethyl ester (19). Purification by flash column chromatography (heptane–EtOAc 19 : 1 to 7 : 3) gave the major isomer **16** (48%) as a pale yellow oil; ν_{max}/cm^{-1} 1726 (C=O, $CO_2CH_2CH_3$), 1646 (NC=O), 1605 (Ar–OCH$_3$); δ_H (300 MHz, $CDCl_3$) 7.78 (1H, d, J = 7.8 Hz, C*H*Ar), 7.28 (1H, t, J = 8.3 Hz, C*H*Ar), 6.98 (1H, d, J = 7.8 Hz, C*H*Ar), 4.23 (2H, q, J = 6.4 Hz, OCH_2CH$_3$), 4.14 (1H, d, J = 4.5Hz, NC*H*), 3.84–3.87 (4H, s + m, OCH_3 NC*H*), 3.67–3.74 (1H, m, NCH_2), 3.45–3.53 (1H, ddd, J = 12.0, 8.6 4.3 Hz, C*H*), 1.26–2.17 (6H, m, CH_2), 1.30 (3H, t, J = 6.3 Hz, OCH$_2$CH_3), 1.16 (2H, s, CH_2); δ_C (75 MHz, $CDCl_3$) 173.9 (*C*=O), 163.4 (N*C*=O), 155.7 (*C*Ar), 131.2 (*C*Ar), 129.4 (*C*Ar), 127.4 (*C*HAr), 120.9 (*C*HAr), 113.4 (*C*HAr), 61.0 (O*C*H$_2$CH$_3$), 59.0 (N*C*H), 55.5 (O*C*H$_3$), 51.5 (*Cq*), 42.6 (N*C*H$_2$), 33.4 (*C*H$_2$), 30.9 (*C*H), 28.8 (*C*H$_2$), 26.7 (*C*H$_2$), 21.8 (*C*H$_2$), 14.2 (OCH$_2$*C*H$_3$); MS *m*/*z* 330 (M + H$^+$). Anal. calcd for $C_{19}H_{23}NO_4$: C, 69.28, H 7.04; found: C, 68.82, H, 7.24%. Isomer **19** (27%) as a pale yellow oil; ν_{max}/cm^{-1} 1723 ($CO_2CH_2CH_3$), 1653 (N–C=O),

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1606 ($ArOCH_3$); δ_H (300 MHz, $CDCl_3$) 7.59 (1H, s, C*H*Ar), 7. 13 (2H, d, J = 8.4 Hz, C*H*Ar), 4.23 (2H, q, J = 7.2 Hz, OCH_2CH_3), 4.20 (1H, d, J = 3.9 Hz, NC*H*), 3.86–3.91 (4H, s + m, OCH_3, NCH_2), 3.63–3.74 (1H, m, NCH_2), 3.03–3.10 (1H, ddd, J = 13.0, 8.5, 4.2 Hz, C*H*), 1.40–2.17 (6H, m, CH_2), 1.30 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.14 (2H, s, CH_2); δ_C (75 MHz, $CDCl_3$) 174.1 (*C*=O), 163.3 (N*C*=O), 158.7 (*C*Ar), 135.0 (*C*Ar), 129.6 (*C*Ar), 128.4 (*C*HAr), 119.2 (*C*HAr), 111.1, (*C*HAr), 61.0 (OCH_2CH_3), 59.3 (*C*HN), 55.5 (OCH_3), 51.3 (*Cq*), 42.6 (NCH_2), 36.9 (*C*H) 33.2 (CH_2), 29.9 (CH_2), 28.7 (CH_2), 21.8 (CH_2), 14.2 (OCH_2CH_3); MS m/z 330 (M + H^+). Anal. calcd for $C_{19}H_{23}NO_4$: C, 69.28, H 7.04; found: C, 68.82, H, 7.24%.

7-Oxo-9-trifluoromethyl-2,3,4,5,11b,11c-hexahydro-1*H*,7*H*-pyrrolo[3,2,1-*de*]phenanthridine-3a-carboxylic acid ethyl ester (17) and 7-oxo-11-trifluoromethyl-2,3,4,5,11b,11c-hexahydro-1*H*,7*H*-pyrrolo[3,2,1-*de*]phenanthridine-3a-carboxylic acid ethyl ester (20). Purification by flash column chromatography (heptane–EtOAc 19 : 1 to 7 : 3) gave the major isomer **17** (40%) as white crystals; mp 109–110 °C; ν_{max}/cm^{-1} 1727 (C=O, $CO_2CH_2CH_3$), 1662 (NC=O), 1165, 1124 (CF_3); δ_H (300 MHz, $CDCl_3$) 8.37 (1H, s, C*H*Ar), 7.71 (1H, d, J = 6.9 Hz, C*H*Ar), 7.38 (1H, d, J = 6.9 Hz, C*H*Ar), 4.26 (2H, q, J = 7.0 Hz, OCH_2CH_3), 4.23 (1H, d, J = 4.3 Hz, NC*H*), 3.88–3.95 (1H, m, NCH_2), 3.69–3.79 (1H, m, NCH_2), 3.27 (1H, ddd, J = 12.6, 8.1, 4.5Hz, C*H*), 1.45–2.17 (6H, m, CH_2), 1.32 (3H, t, J = 7.1 Hz, OCH_2CH_3), 1.27 (s, 2H, CH_2); δ_C (75 MHz, $CDCl_3$) 173.7 (*C*=O), 162.2 (N*C*=O), 146.4 (*C*Ar), 129.2 (*C*Ar), 128.4 (*C*HAr), 128.1 (*C*HAr), 125.0 (*C*HAr), 119.4 (*C*Ar), 61.3 (OCH_2CH_3), 58.9 (N*C*H), 51.3 (*Cq*), 42.8 (NCH_2), 37.4 (*C*H), 33.1 (CH_2), 29.6 (CH_2), 28.7 (CH_2), 21.7 (CH_2), 14.2 (OCH_2CH_3); MS m/z 368 (M + H^+). Anal. calcd for $C_{19}H_{20}F_3NO_3$: C, 62.12, H 5.49; found: C, 62.12, H, 5.52%. Isomer **20** (15%) as a colourless oil; ν_{max}/cm^{-1} 1728 (C=O, $CO_2CH_2CH_3$), 1651 (NC=O); δ_H (300 MHz, $CDCl_3$) 8.33 (1H, d, J = 8.0 Hz, C*H*Ar), 7.80 (1H, d, J = 7.5 Hz, C*H*Ar), 7.47 (1H, d, J = 7.8 Hz, C*H*Ar), 4.25 (2H, q, J = 7.2 Hz, OCH_2CH_3), 4.20 (1H, d, J = 4.0 Hz, NC*H*), 3.73–3.91 (4H, m, NCH_2), 3.57–3.65 (1H, ddd, J = 12.3, 8.3, 4.3 Hz, C*H*), 1.45–2.19 (6H, m, CH_2), 1.32 (3H, t, J = 7.0 Hz, OCH_2CH_3), 1.26 (2H, br s, CH_2); δ_C (75 MHz, $CDCl_3$) 174.6 (*C*=O), 161.7 (N–*C*=O), 141.3 (*C*Ar), 131.8 (*C*HAr), 130.9 (*C*Ar), 129.4 (*C*HAr), 128.2 (*C*Ar), 127.1 (*C*HAr), 61.4 (OCH_2CH_3), 58.9 (N*C*H), 51.5 (*Cq*), 42.8 (NCH_2), 34.7 (*C*H), 33.3 (CH_2), 28.8 (CH_2), 28.5 (CH_2), 22.1 (CH_2), 14.2 (OCH_2CH_3); MS m/z 368 (M + H^+).

1-Benzoyloxy-10-methoxy-7-oxo-2,3,4,5,7a,11a,11b,11c-octahydro-1*H*,7*H*-pyrrolo[3,2,1-*de*]phenanthridine-3a-carboxylic acid ethyl ester (25) and (26). Purification by flash column chromatography (heptane–EtOAc 9 : 1) gave the cyclised products (71%) in a 2 : 1 ratio. Major isomer **25** (45%) as a yellow mousse; ν_{max}/cm^{-1} 3583 (C=O, OBz), 1720 (C=O, $CO_2CH_2CH_3$), 1650 (NC=O); δ_H (300 MHz, $CDCl_3$) 6.76–8.02 (8H, m, C*H*Ar), 4.95–5.05 (1H, m, C*H*), 4.38 (1H, d, J = 4.5 Hz, NC*H*), 4.28 (2H, q, J = 7.5 Hz, OCH_2CH_3), 3.85–3.95 (1H, m, NCH_2), 3.66–3.78 (1H, m, NCH_2), 3.55 (3H, s, OCH_3), 3.32–3.38 (1H, dd, J = 10.5, 4.5 Hz, C*H*), 1.55–2.32 (6H, m, CH_2), 1.32 (3H, t, J = 7.0 Hz, OCH_2CH_3); δ_C (75 MHz, $CDCl_3$) 173.4 (*C*=O), 165.3 (C=O, $PhCO_2$), 163.3 (N*C*=O), 140.2 (*C*Ar), 133.1 (*C*HAr), 129.5 (*C*HAr), 128.4 (*C*HAr), 121.6 (*C*Ar), 114.2 (*C*HAr), 113.7 (*C*HAr), 73.5 (*C*H), 61.4 (OCH_2CH_3), 61.1 (N*C*H), 55.0 (OCH_3), 51.3 (*Cq*), 42.4 (NCH_2), 39.9 (*C*H), 32.8 (CH_2) 27.7 (CH_2), 27.6 (CH_2), 14.3 (OCH_2CH_3); 450 (M + H^+). Isomer **26** (26%) as a yellow mousse; ν_{max}/cm^{-1} 3576 (C=O, CO_2Ar), 1720 (C=O, $CO_2CH_2CH_3$), 1650 (N–C=O); δ_H (300 MHz, $CDCl_3$) 6.78–7.99 (8H, m, C*H*Ar), 5.36 (1H, s, C*H*), 4.36 (1H, d, J = 5.0 Hz, NC*H*), 4.30 (2H, q, J = 7.2 Hz, OCH_2CH_3), 3.93–3.97 (1H, m, NCH_2), 3.81 (3H, s, OCH_3), 3.73–3.78 (1H, m, NCH_2), 3.35 (1H, t, J = 4.8 Hz, C*H*), 1.64–2.27 (6H, m, CH_2), 1.33 (3H, t, J = 7.0 Hz, OCH_2CH_3); δ_C (75 MHz, $CDCl_3$) 173.7 (*C*=O), 165.7 ($PhCO_2$), 163.6 (N*C*=O), 139.5 (*C*Ar), 133.0 (*C*HAr), 130.1 (*C*HAr), 129.9 (*C*HAr), 129.3 (*C*HAr), 123.9 (*C*Ar), 113.2 (*C*HAr), 112.5 (*C*HAr), 70.9 (*C*H), 61.4 (OCH_2CH_3), 57.6 (N*C*H), 55.3 (OCH_3), 51.2 (*Cq*), 42.4 (NCH_2), 39.9 (*C*H), 33.1 (CH_2), 26.1 (CH_2), 22.6 (CH_2), 14.2 (OCH_2CH_3); MS m/z 450 (M + H^+).

1-Benzoyloxy-9-(2,2-dimethylpropionyloxy)-10-methoxy-7-oxo-2,3,4,5,11b,11c-hexahydro-1*H*,7*H*-pyrrolo[3,2,1-*de*]phenanthridine-3a-carboxylic acid ethyl ester (29) and (31), 1-benzoyloxy-11-(2,2-dimethylpropionyloxy)-10-methoxy-7-oxo-2,3,4,5,11b,11c-hexahydro-1*H*,7*H*-pyrrolo[3,2,1-*de*]phenanthridine-3a-carboxylic acid ethyl ester (33) and (35). Purification by flash column chromatography (heptane–EtOAc 19 : 1 to 3 : 2) gave two pairs of diastereoisomers in an overall yield of 65%. Isomer **29** (15%) as a pale yellow mousse; ν_{max}/cm^{-1} 2855 (CH_3), 1754 (C=O, *Pv*), 1723 (C=O, $CO_2CH_2CH_3$, *Bz*), 1654 (NC=O), 1397, 1368, 1267 (CH_3); δ_H (300 MHz, $CDCl_3$) 7.78 (2H, d, J = 7.6 Hz, C*H*Ar), 7.66 (1H, s, C*H*Ar), 7.49 (1H, t, J = 7.4 Hz, C*H*Ar), 7.39 (2H, t, J = 7.6 Hz, C*H*Ar), 6.82 (1H, s, C*H*Ar), 5.38 (1H, s, C*H*), 4.37 (1H, d, J = 5.2 Hz, NC*H*), 4.26 (2H, q, J = 7.3 Hz, OCH_2CH_3), 3.95–4.00 (1H, m, NCH_2), 3.84 (3H, s, OCH_3), 3.74–3.82 (1H, m, NCH_2), 3.45 (1H, t, J = 4.8 Hz, C*H*), 1.59–2.38 (6H, m, CH_2), 1.26–1.37 (12H, s + m, CH_3); δ_C (75 MHz, $CDCl_3$) 173.5 (*C*=O), 164.5 ($PhCO_2$), 162.7 (N*C*=O), 136.5 (*C*Ar), 133.2 (*C*Ar), 129.7 (*C*Ar), 128.6 (*C*Ar), 122.2 (*C*Ar), 110.6 (*C*HAr), 70.8 (*C*H), 61.5 (OCH_2CH_3), 57.8 (N*C*H), 56.2 (OCH_3), 51.3 (*Cq*), 42.5 (NCH_2), 39.9 (*C*H), 33.2 (CH_2), 29.8 (CH_2), 29.4 (*Cq*), 27.2 ($3CH_3$), 22.8 (CH_2), 14.2 (OCH_2CH_3); 550 (M + H^+). Anal. calcd for $C_{31}H_{35}NO_8$: C, 67.74, H 6.42; found: C, 68.12, H, 6.84%. Isomer **31** (21%) as white crystals; mp 213–216 °C; ν_{max}/cm^{-1} 2854 (OCH_3), 1759 (C=O, *Pv*), 1729 (C=O, $CO_2CH_2CH_3$, *Bz*), 1660 (NC=O), 1395, 1366, 1266 (CH_3); δ_H (300 MHz, $CDCl_3$) 8.20 (2H, d, J = 7.2 Hz, C*H*Ar), 7.72 (1H, s, C*H*Ar), 7.56 (H, t, J = 7.4 Hz, C*H*Ar), 7.43 (2H, t, J = 7.8 Hz, C*H*Ar), 6.79 (1H, s, C*H*Ar), 4.98–5.04 (1H, ddd, J = 10.8, 10.8, 4.0 Hz, C*H*), 4.46 (1H, d, J = 4.0 Hz, NC*H*), 4.24–4.30 (2H, dq, J = 7.2, 3.6 Hz, OCH_2CH_3), 3.83–3.92 (1H, m, NCH_2), 3.65–3.74 (1H, m, NCH_2), 3.44 (3H, s, OCH_3), 3.34–3.38 (1H, dd, J = 10.6, 4.4 Hz, C*H*), 2.27–2.31 (1H, m, CH_2), 2.11–2.17 (3H, m, CH_2), 1.81–1.88 (1H, m, CH_2), 1.60–1.69 (1H, m, CH_2), 1.25–1.39 (12H, s + m, OCH_2CH_3, $3CH_3$); δ_C (75 MHz, $CDCl_3$) 173.8 (*C*=O), 165.5 ($PhCO_2$), 163.2 (N*C*=O), 153.9 (*C*Ar), 140.2 (*C*Ar), 137.8 (*C*Ar), 133.8 (*C*HAr), 130.0 (*C*HAr), 128.9 (*C*HAr), 122.2 (–*C*–), 123.1 (*C*H), 113.0 (*C*H), 73.9 (*C*H), 61.9 (OCH_2CH_3), 61.5 (N*C*H), 56.1 (OCH_3), 51.8 (*Cq*), 42.9 (NCH_2), 42.5 (*C*H), 33.2 (CH_2), 30.2 (*Cq*), 29.2 (CH_2), 28.1 (CH_2), 27.6 ($3CH_3$), 14.8 (OCH_2CH_3); MS m/z 550 (M + H^+). Isomer **33** (17%) as an amorphous solid; mp 213–216 °C; ν_{max}/cm^{-1} 1758 (O–C=O, *Pv*), 1725 (C=O, $CO_2CH_2CH_3$, O*Bz*), 4(NC=O), 1366, 1319, 1267(CH_3); 1395, 1366, 1266 (CH_3); δ_H (300 MHz, $CDCl_3$) 6.78–8.04 (7H, m, C*H*Ar), 5.33 (1H, s, C*H*), 4.36 (1H, d, J = 4.8 Hz, NC*H*), 4.21–4.28 (2H, m, OCH_2CH_3), 3.98 (1H, t, J = 10.2 Hz, NCH_2), 3.78–3.82 (4H, m, OCH_3, NCH_2), 3.42 (1H, t, J = 4.9 Hz, C*H*), 1.90–2.23 (4H, m, CH_2), 1.23–1.45 (12H, m, CH_3), 0.82–0.94 (2H, m, CH_2); δ_C (75 MHz, $CDCl_3$) 189.7 (*C*=O), 173.2 (*C*=O), 166.3 ($PhCO_2$), 133.1 (*C*Ar), 132.9, 129.8, 128.5, 128.3, 127.0 (*C*HAr), 126.2 (*C*Ar), 111.1 (*C*HAr), 74.2 (*C*H), 69.4 (OCH_2CH_3), 61.4 (N*C*H), 56.2 (OCH_3), 51.0 (*Cq*), 43.0 (NCH_2), 42.5 (*C*H), 36.7 (CH_2), 34.8 (*Cq*), 32.7 (CH_2), 28.2 (CH_2), 27.2 ($3CH_3$), 14.4 (OCH_2CH_3); MS m/z 550 (M + H^+). Isomer **35** (13%) as white crystals; mp 217–220 °C; ν_{max}/cm^{-1} 1756 (O–C=O, *Pv*), 1727 ((C=O, $CO_2CH_2CH_3$, O*Bz*), 1657, 1613 (NC=O), 1366, 1281, 1325; δ_H (300 MHz, $CDCl_3$) 8.06 (1H, d, J = 7.6 Hz, C*H*Ar), 7.96 (1H, d, J = 8.6 Hz, C*H*Ar), 7.77 (1H, d, J = 8.4 Hz, C*H*Ar), 7.45–7.54 (1H, m, C*H*Ar), 7.34–7.41 (2H, m, C*H*Ar), 6.89 (1H, d,

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J = 8.6 Hz, C*H*Ar), 4.92 (1H, t, J = 10.0 Hz, C*H*), 4.31 (1H, d, J = 4.0 Hz, NC*H*), 4.17–4.26 (2H, m, OCH_2CH$_3$), 3.93–3.88 (1H, m, NCH_2), 3.68–3.86 (4H, m, OCH_2, NCH_2), 3.45 (1H, dd, J = 10.6, 3.6 Hz, C*H*), 1.60–2.26 (4H, m, CH_2), 1.27–1.42 (12H, m, CH_3), 0.85–0.88 (2H, m, CH_2); δ_C (75 MHz, CDCl$_3$) 188.2 (*C*=O), 173.5 (*C*O$_2$CH$_2$CH$_3$), 162.8 (N*C*=O), 154.1 (*C*Ar), 133.1 (*C*Ar), 129.8 (*C*Ar), 129.7 (*C*Ar), 128.6 (*C*HAr), 126.3 (*C*Ar), 111.1 (*C*HAr), 69.4 (*C*H), 61.4 (O*C*H$_2$CH$_3$), 57.5 (N*C*H), 56.1 (O*C*H$_3$), 51.2 (*Cq*), 42.4 (N*C*H$_2$), 39.6 (*Cq*), 36.8 (*C*H), 33.1 (*C*H$_2$), 28.2 (*C*H$_2$), 27.3 (3*C*H$_3$), 22.9 (*C*H$_2$), 14.4 (OCH$_2$*C*H$_3$); MS m/z 550 (M + H$^+$). Anal. calcd for C$_{31}$H$_{35}$NO$_8$: C, 67.74, H 6.42; found: C, 67.51, H, 6.51%.

1-Benzoyloxy-9,10-dimethoxy-7-oxo-2,3,4,5,11b,11c-hexahydro-1*H*,7*H*-pyrrolo[3,2,1-*de*]phenanthridine-3a-carboxylic acid ethyl ester (30) and (32), 1-benzoyloxy-10,11-dimethoxy-7-oxo-2,3,4,5,11b,11c-hexahydro-1*H*,7*H*-pyrrolo[3,2,1-*de*]phenanthridine-3a-carboxylic acid ethyl ester (34) and (36). Purification by flash column chromatography (heptane–EtOAc 9 : 1 to 3 : 7) gave two pairs of diastereoisomers in an overall yield of 86%. Isomer **30** (31%) as a white mousse; ν_{max}/cm^{-1} 2926, 1726 (C=O, CO$_2$CH$_2$CH$_3$), 1651 (NC=O); δ_H (300 MHz, CDCl$_3$) 77.79 (2H, d, J = 7.2 Hz, C*H*Ar), 7.55 (1H, s, C*H*Ar), 7.37–7.50 (3H, m, C*H*Ar), 6.75 (1H, s, C*H*Ar), 5.38 (1H, s, C*H*), 4.36 (1H, d, J = 5.0 Hz, NC*H*), 4.29 (2H, q, J = 7.2 Hz, OCH_2CH$_3$), 3.99–3.95 (1H, m, NCH_2), 3.92 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.66–3.82 (1H, m, NCH_2), 3.41 (1H, t, J = 4.5 Hz, C*H*), 2.29–1.65 (4H, m, CH_2), 1.35 (3H, t, J = 7.2 Hz, OCH_2CH$_3$), 1.27 (2H, s, CH_2); δ_C (75 MHz, CDCl$_3$) 173.9 (*C*=O), 165.8 (Ph*C*O$_2$), 163.7 (N*C*=O), 152.0 (*C*Ar), 145.5 (*C*Ar), 133.1 (*C*HAr), 130.9 (*C*Ar), 129.7 (*C*HAr), 128.5 (*C*HAr), 124.1 (*C*Ar), 109.8 (*C*HAr), 109.7 (*C*HAr), 70.8 (*C*H), 61.4 (O*C*H$_2$CH$_3$), 57.9 (N*C*H), 56.2 (O*C*H$_3$), 56.1 (O*C*H$_3$), 51.3 (*Cq*), 42.6 (N*C*H$_2$), 39.6 (*C*H), 33.2 (*C*H$_2$), 27.8 (*C*H$_2$), 26.2 (*C*H$_2$), 14.4 (OCH$_2$*C*H$_3$); 480 (M + H$^+$). Anal. calcd for C$_{27}$H$_{29}$NO$_7$: C, 67.63, H 6.10; found: C, 68.07, H, 6.22%. Isomer **32** (47%) as a white mousse; ν_{max}/cm^{-1} 1726 (C=O, CO$_2$CH$_2$CH$_3$), 1651 (NC=O), 1266 (CH$_3$); δ_H (300 MHz, CDCl$_3$) 8.04 (2H, d, J = 7.2 Hz, C*H*Ar), 7.61 (1H, s, C*H*Ar), 7.40–7.57 (3H, m, C*H*Ar), 6.71 (1H, s, C*H*Ar), 5.03 (1H, ddd, J = 10.8, 10.8, 4.3 Hz, C*H*), 4.45 (1H, d, J = 4.5 Hz, NC*H*), 4.28 (2H, q, J = 7.2 Hz, OCH_2CH$_3$), 3.95–4.11 (2H, m, NCH_2), 3.91 (3H, s, OCH_3), 3.50 (3H, s, OCH_3), 3.30 (1H, dd, J = 10.8, 4.7 Hz, C*H*), 1.69–2.25 (4H, m, CH_2), 1.36 (3H, t, J = 7.2 Hz, OCH$_2$CH_3), 1.36 (2H, s, CH_2); δ_C (75 MHz, CDCl$_3$) 173.6 (*C*=O), 165.2 (Ph*C*O$_2$), 163.4 (N*C*=O), 151.3 (*C*Ar), 148.6 (*C*Ar), 133.2 (*C*HAr), 131.9 (*C*Ar), 129.7 (*C*HAr), 128.5 (*C*HAr), 121.6 (*C*Ar), 115.5 (*C*HAr), 110.2 (*C*HAr), 73.9 (*C*H), 61.5 (O*C*H$_2$CH$_3$), 58.0 (N*C*H), 56.1 (O*C*H$_3$), 55.5 (O*C*H$_3$), 51.5 (*Cq*), 42.5 (N*C*H$_2$), 41.8 (*C*H), 32.9 (*C*H$_2$), 29.8 (*C*H$_2$), 22.8 (*C*H$_2$), 14.2 (OCH$_2$*C*H$_3$); MS m/z 480 (M + H$^+$). Isomer **34** (6%) as an amorphous solid; mp 213–216 °C; ν_{max}/cm^{-1} 2928, 1727 (C=O, CO$_2$CH$_2$CH$_3$), 1652 (NC=O), 1602, 1267; δ_H (300 MHz, CDCl$_3$) 8.03 (2H, d, J = 7.2 Hz, C*H*Ar), 7.77 (1H, d, J = 8.0 Hz, C*H*Ar), 7.35–7.59 (3H, m, C*H*Ar), 6.69 (1H, d, J = 9.5 Hz, C*H*Ar), 5.37 (1H, s, C*H*), 4.34 (1H, d, J = 5.5 Hz, NC*H*), 4.26 (2H, q, J = 6.7 Hz, OCH_2CH$_3$), 3.65–3.99 (9H, m, NCH_2, 2OCH_3, C*H*), 2.15–1.32 (m, 6H, CH_2), 0.86 (3H, t, J = 6.8 Hz, OCH$_2$CH_3); MS m/z 480 (M + H$^+$). Isomer **36** (2%) as a white mousse; ν_{max}/cm^{-1} 3405 (C=O, *Bz*), 1720 (C=O, CO$_2$CH$_2$CH$_3$), 1653 (NC=O); δ_H (300 MHz, CDCl$_3$) 173.5 (*C*=O), 166.3 (Ph*C*O$_2$), 163.2 (N*C*=O), 155.5 (*C*Ar), 146.6 (*C*Ar), 132.8 (*C*HAr), 132.1 (*C*Ar), 130.5 (*C*Ar), 129.9 (*C*HAr), 128.3 (*C*HAr), 124.5 (*C*HAr), 122.5 (*C*Ar), 111.7 (*C*HAr), 74.4 (*C*H), 61.9 (O*C*H$_3$), 61.4 (O*C*H$_2$CH$_3$), 61.1 (N*C*H), 55.9 (O*C*H$_3$), 51.3 (*Cq*), 42.5 (N*C*H$_2$), 35.9 (*C*H), 33.1 (*C*H$_2$), 28.2 (*C*H$_2$), 27.9 (*C*H$_2$), 14.3 (OCH$_2$*C*H$_3$); MS m/z 480 (M + H$^+$). Anal. calcd for C$_{27}$H$_{29}$NO$_7$: C, 67.63, H 6.10; found: C, 67.37, H, 6.11%.

1-(1,3-Dioxolan-2-ylmethyl)-4-hydroxycyclohex-2-enecarboxylic acid ethyl ester (21)

Formic acid (0.87 mL, 23.05 mmol) was added to a solution of selenium dioxide (1.48 g, 23.05 mmol) in dioxane (23 mL). Olefin **6** (2.77 g, 11.53 mmol) in dioxane (11.6 mL) was added dropwise and the reaction mixture was heated under reflux for 7 h. The reaction mixture was allowed to cool to ambient temperature and then filtered through Celite. H$_2$O was then added to the filtrate and the mixture was extracted with Et$_2$O, dried (Na$_2$SO$_4$) and the solvent removed *in vacuo*. Purification by flash column chromatography (heptane–EtOAc 19 : 1 to 7 : 3) gave alcohol **21** (63%) as a colourless oil. ν_{max}/cm^{-1} 3434 (OH), 1726 (C=O), 944 (O–CH–O); δ_H (300 MHz, CDCl$_3$) 6.05 (1H, s, CH=C*H*), 5.85 (2H, m, C*H*OH, CHC*H*=CH), 4.91 (1H, t, J = 4.8 Hz, OC*H*O), 4.15 (2H, dq, J = 7.2, 3.6 Hz, OCH_2CH$_3$), 3.77–3.95 (4H, m, OCH_2CH_2O), 1.55–2.33 (6H, m, 3CH_2), 1.26 (3H, t, J = 7.2 Hz, CH_3CH$_2$O); δ_C (75 MHz, CDCl$_3$) 174.8 (*C*=O), 132.1, 129.3 (*C*H=*C*H), 131.3, 129.6 (*C*H=*C*H), 101.9, 101.8 (O*C*HO), 65.9 (*C*HOH), 64.7 (O*C*H$_2$CH$_2$O), 64.6 (O*C*H$_2$–CH$_2$O), 60.9 (O*C*H$_2$CH$_3$), 44.8 (*Cq*), 42.9 (*C*H$_2$CHO), 29.5 (*C*H$_2$), 28.8 (*C*H$_2$), 14.1 (OCH$_2$*C*H$_3$); MS m/z 239 (M − H$_2$O), 257 (M + H$^+$ − H$_2$O), 274 (M + NH$_4^+$ − H$_2$O).

Benzoic acid 4-(1,3-dioxolan-2-ylmethyl)-4-ethoxycarbonylcyclohex-2-enyl ester (22)

A solution of alcohol **21** (0.50 g, 1.95 mmol) in pyridine (10.0 mL) was cooled to 0 °C and benzoyl chloride (1.1 mL, 9.70 mmol) was added slowly. The reaction mixture was then allowed to warm to ambient temperature and left stirring for 1 h. After this time the solvent was removed *in vacuo*, CH$_2$Cl$_2$ was then added, followed by NaHCO$_3$ and the mixture was stirred at ambient temperature for 1 h to remove the mixed anhydride and acid formed. The mixture was then extracted with CH$_2$Cl$_2$, dried (Na$_2$SO$_4$) and the solvent removed *in vacuo*. Purification by flash column chromatography (heptane–EtOAc 19 : 1 to 4 : 1) gave the benzoyl protected isomers **22** (74%) as white crystals in a 2 : 1 ratio. Major isomer (63%); ν_{max}/cm^{-1} 2886 (O–CH–O), 1716 (C=OCO$_2$CH$_2$CH$_3$, OBz), 716 (CH=CH; *cis*); δ_H (300 MHz, CDCl$_3$) 8174.4 (O=*C*OCH$_2$CH$_3$), 166.2 (Ph*C*=O), 133.7, 132.9, 127.7 (5*C*HAr), 130.4 (*C*Ar), 129.7 (*C*H=CH), 128.3 (CH=*C*H), 101.9 (O*C*HO), 68.7 (*C*HOBz), 64.8 (O*C*H$_2$CH$_2$O), 64.7 (OCH$_2$*C*H$_2$O), 61.0 (O*C*H$_2$CH$_3$), 44.7 (*Cq*), 42.7 (*C*H$_2$CHO), 28.4 (*C*H$_2$), 25.7 (*C*H$_2$), 14.2 (*C*H$_3$); δ_C (75 MHz, CDCl$_3$) 174.8 (*C*=O), 132.1, 129.3 (*C*H=CH), 131.3, 129.6 (*C*H=CH), 101.9, 101.8 (O*C*HO), 65.9 (*C*HOH), 64.7 (O*C*H$_2$CH$_2$O), 64.6 (OCH$_2$*C*H$_2$O), 60.9 (O*C*H$_2$CH$_3$), 44.8 (*Cq*), 42.9 (*C*H$_2$CHO), 29.5 (*C*H$_2$), 28.8 (*C*H$_2$), 14.1 (OCH$_2$–*C*H$_3$); MS m/z 239 (M − BzO), 256 (M − OBz + NH$_3$). Minor isomer (37%); ν_{max}/cm^{-1} 2888 (O–CH–O), 1716 (C=O, CO$_2$CH$_2$CH$_3$, OBz), 716 (CH=CH; *cis*); δ_H (300 MHz, CDCl$_3$) 8.03 (2H, d, J = 7.2 Hz, C*H*Ar), 7.56 (1H, t, J = 7.7 Hz, C*H*Ar), 7.43 (2H, t, J = 7.2 Hz, C*H*Ar), 6.10 (1H, d, J = 10.0 Hz, C*H*=CH), 5.91 (1H, dd, J = 10.3, 4.0 Hz, CH=C*H*CHOBz), 5.44 (1H, q, J = 4.2 Hz, C*H*OBz), 4.98 (1H, t, J = 4.5Hz, OC*H*O), 4.12–4.22 (2H, dq, J = 7.2, 2.5 Hz, OCH_2CH$_3$), 3.78–3.98 (4H, m, OCH_2CH_2O), 1.88–2.27 (6H, m, 3CH_2), 1.27 (3H, t, J = 7.0 Hz, OCH$_2$CH_3); δ_C (75 MHz, CDCl$_3$) 174.3 (*C*=O), 166.2 (*C*=O, Bz), 134.7, 132.9, 126.2 (5*C*HAr), 130.6 (*C*Ar), 129.7 (*C*H=CH), 128.4 (*C*H=CH), 102.1 (O*C*HO), 67.3 (*C*HOCOPh), 64.9 (O*C*H$_2$), 64.7 (O*C*H$_2$), 61.0 (O*C*H$_2$CH$_3$), 44.9 (*Cq*), 42.9 (*C*H$_2$CHO), 27.5 (*C*H$_2$), 25.6 (*C*H$_2$), 14.2 (*C*H$_3$); MS m/z 239 (M − Bz), 256 (M + NH$_3$ − Bz).

10-Methoxy-3a-(pyridin-2-ylsulfanyl)-2,3,4,5,11b,11c-hexahydro-1*H*,7*H*-pyrrolo[3,2,1-*de*]phenanthridine-7-(2*H*)-one (40)

Ester **10** (100 mg, 0.30 mmol) was added to a solution of NaOH in EtOH (0.03 M, 1.3 mL) and the reaction mixture

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was stirred at ambient temperature for 30 h. The solvent was then removed *in vacuo* and the residue was dissolved in H_2O and then acidified with 6 M HCl, until the saponified product precipitated. The crystals obtained were filtered and dried *in vacuo*. To a solution of the acid formed (40 mg, 0.12 mmol) in freshly distilled CH_2Cl_2 (0.24 mL), a drop of DMF followed by oxalyl chloride (0.05 mL, 0.60 mmol) were added at 0 °C. The reaction mixture was stirred for 2 h and the solvent was removed *in vacuo*. *N*-hydroxypyridine (21 mg, 0.14 mmol) and DMAP (3 mg, 0.02 mmol) were dissolved in a mixture of cyclohexane–toluene (1 : 1, 0.6 mL) and the mixture was heated under reflux for 10 min. To this mixture a solution of the acid chloride in a mixture of cyclohexane–toluene (1 : 1, 0.6 mL) was added *via* cannula and the reaction mixture was heated under reflux for 2 h. The reaction mixture was then allowed to warm to room temperature, filtered over Celite and the solvent removed *in vacuo*. Purification by flash column chromatography (petroleum ether–EtOAc 1 : 19) gave the Barton derivative **40** (24 mg, 55%) as a yellow mousse. δ_H (300 MHz, DMSO-d_6) 8.46–8.47 (1H, d, $J = 4.8$ Hz, NC*H*), 8.01–8.04 (1H, d, $J = 8.8$ Hz, C*H*Ar), 7.52–7.56 (1H, dt, $J = 7.9$, 2.4 Hz, C*H*), 7.33–7.35 (1H, d, $J = 8.4$ Hz, C*H*), 7.08–7.11 (1H, dt, $J = 7.6$, 2.4 Hz, C*H*), 6.84–6.86 (1H, dd, $J = 8.4$, 2.4 Hz, C*H*Ar), 6.73 (1H, d, $J = 2.4$ Hz, C*H*Ar), 4.18–4.19 (1H, d, $J = 4.0$ Hz, NC*H*), 3.82–3.88 (4H, s + m, OCH_3, NC*H*), 3.62–3.70 (1H, m, NC*H*), 3.09–3.14 (1H, m, C*H*), 2.44–2.60 (2H, m, CH_2), 2.09–2.13 (1H, m, CH_2), 1.82–1.89 (1H, m, CH_2), 1.55–1.73 (2H, m, CH_2), 1.25–1.41 (ddd, $J = 16.0$, 13.2, 3.2 Hz, 2H, CH_2); δ_C (75 MHz, DMSO-d_6) 163.5 (N*C*=O), 156.8 (*C*NAr), 149.9 (*C*NAr), 144.9 (MeO*C*Ar), 136.5 (*C*HAr), 130.2 (*C*HAr), 126.8 (*C*HAr), 121.6 (*C*HAr), 112.6 (*C*HAr), 112.4 (*C*HAr), 70.6 (*Cq*), 60.8 (N*C*H), 55.5 (O*C*H$_3$), 42.6 (N*C*H$_2$), (*C*H), 36.7 (*C*H$_2$), 30.5 (*C*H$_2$), 29.8 (*C*H$_2$), 21.2 (*C*H$_2$); MS *m*/*z* 367 (M + H$^+$).

1-(1,3-Dioxolan-2-ylmethyl)-2,5-cyclohexadiene-1-carboxylic acid (44)

A solution of benzoic acid (12.2 g, 100.0 mmol) in THF (100 mL) was added to ammonia (~500 mL) at −78 °C. Lithium metal (~2.0 g) was then added in small portions until the solution turned blue, and maintained this colour. The solution was left stirring at −78 °C for 30 min, after which a few drops of isoprene were added until the solution turned from blue to yellow. 2-Bromomethyl-1,3-dioxolane (21 mL, 186.0 mmol) was added and the solution was left for 1 h at −78 °C, then allowed to reflux in a water bath for 1 h, followed by the addition of ammonium chloride (~15 g). The ammonia was allowed to evaporate, after which, the mixture was partitioned between EtOAc and H_2O and the layers were separated. The water layer was acidified with HCl (2 M) and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. Purification by flash column chromatography (petroleum ether–EtOAc 9 : 1 to 7 : 3) gave acid **44** (16.5 g, 76%) as white crystals; mp 72–73 °C; ν_{max}/cm^{-1} 2817–3035 (CO$_2$H), 1702 (C=O); δ_H (400 MHz, $CDCl_3$) 9.75 (1H, br, CO$_2$*H*), 5.90–5.94 (2H, m, C*H*=CH), 5.80–5.83 (2H, m, C*H*=CH), 4.93 (1H, t, $J = 4.8$ Hz, OC*H*O), 3.89–3.95 (2H, m, OCH_2), 3.78–3.84 (2H, m, OCH_2), 2.67 (2H, s, CH_2), 2.11 (2H, d, $J = 4.8$ Hz, CH_2OCHO); δ_C (100 MHz, $CDCl_3$) 179.6 (*C*=O), 126.3 (2*C*H=CH), 125.8 (2*C*H=CH), 101.8 (*C*H), 64.4 (2O*C*H$_2$), 45.2 (*Cq*), 43.2 (*C*H$_2$CO$_2$*C*H$_2$), 25.6 (*C*H$_2$CH=CH); MS (CI, NH_3) *m*/*z* 211 (M + H$^+$), 228 (M + NH$_4^+$); HRMS calcd for $C_{11}H_{15}NO_4$ 211.0970 found 211.0977. Anal. calcd for $C_{11}H_{14}O_4$: C, 62.85, H 6.71; found: C, 62.89, H, 6.67%.

1-(1,3-Dioxolan-2-ylmethyl)-2,5-cyclohexadienyltetrahydro-1*H*-1-pyrrolylmethanone (45)

To a solution of acid **44** (8.3 g, 39.3 mmol), pyrrolidine (4.1 mL, 51.1 mmol), and diphenyl phosphonylaziate (10.1 mL, 47.2 mmol) in DMF (80 mL), Et_3N (12.8 mL, 88.7 mmol) was added dropwise over 15 min at 0 °C. The reaction mixture was stirred at 0 °C for 3 h, diluted with Et_2O, washed with brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. Purification by flash column chromatography (EtOAc–petroleum ether 1 : 9 to 1 : 1) gave the desired amide **45** (9.1 g, 88%) as white crystals; mp 56–58 °C; ν_{max}/cm^{-1} 1622 (C=O), 1411, 1389 (NC=O); δ_H (400 MHz, $CDCl_3$) 5.89 (2H, d, $J = 10.0$ Hz, C*H*=CH), 5.60 (2H, d, $J = 9.6$ Hz, C*H*=CH), 4.92 (1H, t, $J = 4.4$ Hz, OC*H*O), 3.91–3.94 (2H, m, OCH_2), 3.71–3.78 (2H, m, OCH_2), 3.46–3.49 (4H, m, CH_2CH$_2$), 2.70 (2H, m, CH_2), 2.19 (2H, d, $J = 4.0$ Hz, CH_2OCHO), 1.71–1.83 (4H, m, NCH_2CH$_2$); δ_C (100 MHz, $CDCl_3$) 170.6 (NC=O), 127.2 (2*C*H=CH), 125.3 (2*C*H=CH), 103.1 (*C*H), 64.5 (2O*C*H$_2$), 48.2 (N*C*H$_2$), 46.2 (N*C*H$_2$), 43.6 (*C*H$_2$CO$_2$*C*H$_2$), 27.0 (*C*H$_2$CH=CH), 26.1 (NCH$_2$*C*H$_2$), 23.3 (*Cq*); MS (CI, NH_3) *m*/*z* 263 (M$^+$), 264 (M + H$^+$); HRMS calcd for $C_{15}H_{22}NO_3$ 264.1600 found 264.1594. Anal. calcd for $C_{15}H_{21}NO_3$: C, 68.42, H 8.04; found: C, 68.37, H, 8.00%.

1-(1,3-Dioxolan-2-ylmethyl)-8-iodo-6-oxabicyclo[3.2.1]oct-2-en-7-one (46)

Iodine (15.0 g, 58.9 mmol) was added in one portion to a mixture of amide **45** (6.0 g, 20.3 mmol) in THF–H_2O (1 : 1, 150 mL). The reaction mixture was stirred for 14 h at ambient temperature, diluted with EtOAc, washed with sodium thiosulfite, followed by brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. Purification by flash column chromatography (EtOAc–petroleum ether 1 : 9) gave iodolactone **46** (5.3 g, 73%) as a white solid; mp 113–115 °C; ν_{max}/cm^{-1} 1777 (C=O); δ_H (400 MHz, $CDCl_3$) 5.85 (1H, d, $J = 9.2$ Hz, C*H*=CH), 5.43 (1H, d, $J = 9.2$ Hz, C*H*=CH), 5.09 (1H, t, $J = 5.0$ Hz, OC*H*O), 4.83 (1H, d, $J = 5.6$ Hz, OC*H*), 4.75 (1H, m, C*H*I), 3.93–4.04 (2H, m, OCH_2), 3.79–3.89 (2H, m, OCH_2), 2.83 (1H, dd, $J = 19.4$, 2.2 Hz, CH_2), 2.55 (1H, dd, $J = 19.4$, 2.2 Hz, CH_2), 2.29 (1H, dd, $J = 14.6$, 5.0 Hz, CH_2OCHO), 1.95 (1H, dd, $J = 14.6$, 5.0 Hz, CH_2OCHO); δ_C (100 MHz, $CDCl_3$) 171.4 (C=O), 129.8 (2*C*H=CH), 126.9 (2*C*H=CH), 101.0 (*C*HCO$_2$CH$_2$), 76.5 (*C*HOCI), 65.1 (O*C*H$_2$), 64.4 (O*C*H$_2$), 46.7 (*Cq*), 33.7 (*C*H$_2$CO$_2$*C*H$_2$), 30.1 (*C*H$_2$CH=CH), 24.5 (CHO*C*I); MS (CI, NH_3) *m*/*z* 336 (M$^+$), 337 (M + H$^+$), 354 (M + NH$_4^+$); HRMS calcd for $C_{11}H_{14}O_4I$ 336.9937 found 336.9921. Anal. calcd for $C_{11}H_{13}IO_4$: C, 39.31, H 3.90; found: C, 39.40, H, 3.84%.

General procedure for the preparation of thiosemicarbazones 48 and 49

A solution of the acetal (1.0 mmol) in formic acid–water (9 : 1; 10 mL) was stirred at 0 °C for 8–10 h. After this time, the mixture was diluted with CH_2Cl_2, washed with H_2O, followed by saturated aq. $NaHCO_3$ and brine, dried (Na_2SO_4), and the solvent removed *in vacuo* to give the corresponding aldehyde. The aldehyde was dissolved in MeOH–AcOH (1 : 1, 0.1 mmol mL^{-1}) and hydrazide **7** (0.22 g, 1.1 mmol) was added. The resulting solution was left stirring at ambient temperature for 2–12 h and the solvent was removed *in vacuo*. The crude mixture was dissolved in EtOAc and washed with H_2O followed by saturated aq. $NaHCO_3$ and brine, dried (Na_2SO_4), and the solvent removed *in vacuo*.

8-Iodo-6-oxabicyclo[3.2.1]-1-[2-(methylsulfanylthiocarbonyl-phenylhydrazono)ethyl]oct-2-en-7-one (48). Purification by flash column chromatography (EtOAc–petroleum ether 1 : 9) gave the desired thiosemicarbazone derivative **48** (86%) as a white solid; mp 65–67 °C; ν_{max}/cm^{-1} 1779 (C=O), 1590 (C=N), 1323 (SCH$_3$), 1220, 1075 (N–CS–S); δ_H (400 MHz, $CDCl_3$) 7.45–7.53 (3H, m, C*H*Ar), 7.16 (2H, d, $J = 7.5$ Hz, C*H*Ar), 6.80 (1H, t, $J = 4.4$ Hz, N=C*H*), 5.91 (1H, dt, $J = 9.6$, 4.4 Hz, C*H*=CH), 5.43 (1H, d, $J = 9.2$ Hz, C*H*=CH), 5.25 (1H, d, $J = 5.6$ Hz, OC*H*), 4.85 (1H, d, $J = 1.2$ Hz, C*H*I), 2.65 (3H, s, SCH_3), 2.57–2.85 (4H, m, 2CH_2); δ_C (100 MHz, $CDCl_3$) 202.2 (C=S), 170.8 (C=O), 142.5 (*C*Ar), 138.4, 130.2, 129.4, 128.7,

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128.5, 127.4 (5 *C*HAr, *C*H=*C*H), 76.5 (*C*HOCI), 47.6 (*Cq*), 32.1 (CH_2CH=N), 30.0 (CH_2CH=CH), 23.6 (CHO*C*I), 18.9 (SCH_3); MS (CI, NH_3) *m/z* 473 (M + H^+); HRMS calcd for $C_{17}H_{18}N_2O_2S_2I$ 472.9854 found 472.9838. Anal. calcd for $C_{17}H_{17}N_2O_2S_2I$: C, 43.23, H 3.63; found: C, 43.02, H, 3.68%.

1-[2-(Methylsulfanylthiocarbonylphenylhydrazono)ethyl]-6-oxabicyclo[3.2.1]oct-2-en-7-one (49). Purification by flash column chromatography (Et_2O–petroleum ether 1 : 1) gave the desired thiosemicarbazone derivative **49** (77%) as an oil. ν_{max}/cm^{-1} 1778 (C=O), 1590 (C=N), 1323 (SCH_3), 1219, 1075 (N–CS–S); δ_H (400 MHz, $CDCl_3$) 7.46–7.56 (3H, m, C*H*Ar), 7.14 (2H, d, *J* = 7.4 Hz, C*H*Ar), 6.79 (1H, t, *J* = 5.0 Hz, N=C*H*), 5.76 (2H, m, C*H*=CH), 4.87 (1H, dd, *J* = 6.0, 1.2 Hz, OC*H*), 2.67 (1H, m, CHCH_2CHO), 2.59 (3H, s, SCH_3), 2.43–2.47 (2H, m, CH_2), 2.43–2.45 (1H, m, CH_2), 2.10 (1H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 202.2 (*C*=S), 177.0 (*C*=O), 143.9 (*C*H=N), 138.6 (*C*Ar), 130.2, 129.4, 128.6, 126.7 (5 *C*HAr, *C*H=*C*H), 74.6 (*C*HOCH$_2$), 43.7 (*Cq*), 37.1 (CH_2CH=N), 34.4 (CH_2CH=CH), 31.3 (CHOCH_2), 18.8 (SCH_3); MS (CI, NH_3) *m/z* 346 (M^+), 347 (M + H^+); HRMS calcd for $C_{17}H_{19}N_2O_2S_2$ 347.0888 found 347.0896.

General procedure for the preparation of hydrazides 50 and 51

The thiosemicarbazone derivative (1.0 mmol) was dissolved in MeOH (10 mL $mmol^{-1}$) and sodium cyanoborohydride (2.5 mmol) was added. The solution was cooled to 0 °C and AcOH was added dropwise until the solution reached a pH between 4–5. The reaction mixture was then allowed to warm up to ambient temperature and was left stirring for 12–20 h. During this time a further 2.5 eq. of sodium cyanoborohydride was added. EtOAc was added and the mixture was washed with H_2O, followed by brine, dried (Na_2SO_4), and the solvent removed *in vacuo* to give the corresponding reduced hydrazide product.

8-Iodo-6-oxabicyclo[3.2.1]-1-[2-(*N*′-methylsulfanylthiocarbonyl-*N*′-phenylhydrazino)ethyl]oct-2-en-7-one (50). Purification by flash column chromatography (EtOAc–petroleum ether 1 : 9 to 3 : 7) gave the desired reduced hydrazide product **50** (91%) as a yellow oil. ν_{max}/cm^{-1} 3202 (N–H), 1779 (C=O), 1354 (SCH_3), 1060 (N–CS–S); δ_H (400 MHz, $CDCl_3$) 7.42–7.46 (3H, m, C*H*Ar), 7.35 (2H, d, *J* = 6.8 Hz, C*H*Ar), 5.82 (1H, d, *J* = 8.8 Hz, C*H*=CH), 5.36 (1H, d, *J* = 9.2 Hz, C*H*=CH), 4.63 (1H, br, OC*H*), 4.40 (1H, br, C*H*I), 3.10 (1H, br, N*H*), 2.99 (2H, br, CH_2), 2.63 (2H, m, CH_2), 2.61 (3H, s, SCH_3), 2.15–2.23 (1H, m, CH_2), 1.77–1.83 (1H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 129.3, 129.2, 129.0, 128.7, 127.4, 126.5 (6 *C*Ar, *C*H=*C*H), 76.0 (*C*HOCI), 47.2 (*Cq*), 43.0 (CH_2CH_2NH), 29.7 (CH_2CH_2NH), 26.8 (CH_2CH=CH), 22.8 (CHO*C*I), 20.5 (SCH_3); MS (CI, NH_3) *m/z* 475 (M + H^+); HRMS calcd for $C_{17}H_{20}N_2O_2S_2I$ 475.0011 found 475.0003.

1-[2-(*N*′-Methylsulfanylthiocarbonyl-*N*′-phenylhydrazino)-ethyl]-6-oxabicyclo[3.2.1]oct-2-en-7-one (51). Purification by flash column chromatography (EtOAc–petroleum ether 3 : 7) gave the desired reduced hydrazide product **51** (84%) as a yellow oil. ν_{max}/cm^{-1} 3209 (N–H), 1775 (C=O), 1350 (SCH_3); δ_H (400 MHz, $CDCl_3$) 7.43–7.50 (3H, m, C*H*Ar), 7.34 (2H, d, *J* = 6.8 Hz, C*H*Ar), 5.67–5.71 (2H, m, C*H*=CH), 4.78 (1H, d, *J* = 7.2 Hz, OC*H*), 3.07 (1H, br, CH_2), 2.96 (1H, br, CH_2), 2.55 (3H, s, SCH_3), 2.41 (1H, s, CH_2), 2.04 (1H, br, N*H*), 1.87–1.9 (4H, m, 2CH_2); δ_C (100 MHz, $CDCl_3$) 177.7 (C=O), 131.0, 129.2, 127.3, 126.6 (6 *C*Ar, *C*H=*C*H), 74.1 (*C*HOCH$_2$), 44.0 (CH_2CH_2NH), 43.6 (*Cq*), 36.5 (CH_2CH_2NH), 31.2 (CH_2CH=CH), 29.3 (CHOCH_2), 20.0 (SCH_3); MS (CI, NH_3) *m/z* 349 (M + H^+); HRMS calcd for $C_{17}H_{21}N_2O_2S_2$ 349.1044 found 349.1046.

General procedure for acylation of hydrazides 52, 53 and 58

The hydrazide derivative (0.01 g, 1.0 mmol) was dissolved in pyridine (1.7 mL $mmol^{-1}$), and 4-methoxybenzoyl chloride (0.85 g, 5.0 mmol) followed by DMAP (0.01 g, 0.1 mmol) were added. The mixture was heated at 80 °C for 12 h and the solvent was then removed *in vacuo*.

8-Iodo-6-oxabicyclo[3.2.1]-1-{2-[*N*-(4-methoxybenzoyl)-*N*′-methylsulfanylthiocarbonyl-*N*′-phenylhydrazino]ethyl}oct-2-en-7-one (52). Purification by flash column chromatography (EtOAc–petroleum ether 1 : 9 to 100% EtOAc) gave the desired acylated hydrazide **52** (63%) as a yellow oil. ν_{max}/cm^{-1} 1778 (C=O), 1668 (N–C=O), 1606 (Ar–OCH_3), 1306, 1063; δ_H (400 MHz, $CDCl_3$) 7.90 (1H, br, C*H*Ar), 7.72 (2H, d, *J* = 8.0 Hz, C*H*Ar), 7.45 (4H, br, C*H*Ar), 6.98 (2H, d, *J* = 6.4 Hz, C*H*Ar), 5.90 (1H, br, C*H*=CH), 5.49 (1H, br, CH=C*H*), 4.60 (1H, br, CH_2), 3.88 (3H, s, OCH_3), 2.52–2.85 (2H, m, CH_2), 2.65 (3H, s, SCH_3), 2.64 (2H, m, CH_2), 2.20 (2H, s, CH_2); δ_C (100 MHz, $CDCl_3$) 162.0 (*C*=O), 132.2, 129.5, 129.1, 128.2, 127.2, 126.5, 114.0, 113.7 (12 *C*Ar, *C*H=*C*H), 76.3 (*C*HOCI), 55.4 (ArOCH_3), 47.4 (*Cq*), 30.9 (CH_2CH_2NH), 30.0 (CH_2CH_2NH), 27.8 (CH_2CH=CH), 22.8 (CHO*C*I), 20.6 (SCH_3); MS (CI, NH_3) *m/z* 608 (M^+); 609 (M + H^+); HRMS calcd for $C_{25}H_{26}N_2O_4S_2I$ 609.0379 found 609.0380.

1-{2-[*N*-(4-Methoxybenzoyl)-*N*′-methylsulfanylthiocarbonyl-*N*′-phenylhydrazino]ethyl}-6-oxabicyclo[3.2.1]oct-2-en-7-one (53). Purification by flash column chromatography (EtOAc–petroleum ether 1 : 9 to 100% EtOAc) gave the desired acylated hydrazide **53** (82%) as a white solid. ν_{max}/cm^{-1} 1771 (C=O), 1670 (N–C=O), 1606 (Ar–OCH_3), 1304, 1063; δ_H (400 MHz, $CDCl_3$) 7.66 (2H, d, *J* = 6.8 Hz, C*H*Ar), 7.32 (5H, br, C*H*Ar), 6.68 (2H, d, *J* = 6.8 Hz, C*H*Ar), 5.74 (1H, br, C*H*=CH), 4.79 (1H, br, CH=C*H*), 3.87–3.91 (1H, m, CH_2), 3.86 (3H, s, OCH_3), 3.70–3.73 (1H, m, CH_2), 2.61 (3H, s, SCH_3), 2.17 (2H, m, CH_2), 2.04–2.10 (2H, br, CH_2); δ_C (100 MHz, $CDCl_3$) 161.6 (*C*=O), 130.2, 129.2, 127.1, 113.5 (12 *C*Ar, *C*H=*C*H), 74.1 (*C*HOCH$_2$), 55.1 (ArOCH_3), 47.0 (*Cq*), 36.5 (CH_2CH_2NH), 36.3 (CH_2CH_2N), 31.2 (CH_2CH=CH), 29.6 (CHOCH_2), 20.0 (SCH_3); MS (CI, NH_3) *m/z* 483 (M + H^+), 500 (M + NH_4^+); HRMS calcd for $C_{25}H_{27}N_2O_4S_2$ 483.1412 found 483.1400.

Methyl-1-{2-[*N*-(4-methoxybenzoyl)-*N*′-methylsulfanylthiocarbonyl-*N*′-phenylhydrazono]ethyl}-2,5-cyclohexadiene carboxylate (58). Purification by flash column chromatography (EtOAc–petroleum ether 1 : 9 to 100% EtOAc) gave the desired acylated hydrazide **55** (82%) as an oil. ν_{max}/cm^{-1} 1729 (C=O), 1672 (N–C=O), 1605 (Ar–OCH_3); δ_H (400 MHz, $CDCl_3$) 7.65 (2H, d, *J* = 8.0 Hz, C*H*Ar), 7.42 (5H, br, C*H*Ar), 6.95 (2H, d, *J* = 8.4 Hz, C*H*Ar), 5.89 (2H, br, C*H*=CH), 5.66 (2H, br, CH=C*H*), 3.65 (2H, br, CH_2), 3.89 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 2.64 (3H, s, SCH_3), 2.59 (2H, br, CH_2), 2.24 (2H, br, CH_2); δ_C (100 MHz, $CDCl_3$) 174.2 (*C*=O), 161.9 (N*C*=O), 132.3 (*Cq*Ar), 129.6, 129.4, 128.4, 126.9, 126.8, 125.8, 113.8 (11 *C*Ar, 2CH=*C*H), 55.4 (ArOCH_3), 52.4 (CO_2CH_3), 46.4 (*Cq*), 35.8 (CH_2CH_2N), 26.0 (CH_2CH=CH), 20.3 (SCH_3); MS (CI, NH_3) *m/z* 497 (M + H^+); HRMS calcd for $C_{26}H_{29}N_2O_4S_2$ 497.1569 found 497.1549.

1-(1,3-Dioxolan-2-ylmethyl)-6-oxabicyclo[3.2.1]oct-2-en-7-one (47)

Iodolactone **46** (334 mg, 0.99 mmol) was dissolved in benzene (15 mL) and the mixture was degassed under argon for 15 min. Tri-*n*-butyltin hydride (0.34 mL, 1.10 mmol) and AIBN (12 mg, 0.08 mmol) were then added and the mixture was heated under reflux for 1.5 h. The solvent was removed *in vacuo* and purification by flash column chromatography (100% petroleum ether to petroleum ether–Et_2O 1 : 1) gave the desired lactone **47** (192 mg, 92%) as a colourless oil. ν_{max}/cm^{-1} 1770 (C=O); δ_H (400 MHz, $CDCl_3$) 5.83 (1H, d, *J* = 8.0 Hz, C*H*=CH),

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5.73 (1H, d, J = 8.0 Hz, C*H*=CH), 4.99 (1H, t, J = 5.0 Hz, OC*H*O), 4.81–4.83 (1H, m, C*H*O), 3.95–3.97 (2H, m, OCH_2), 3.83–3.86 (2H, m, OCH_2), 2.43 (2H, s, CH_2), 2.39 (1H, t, J = 5.6 Hz, CH_2), 2.23 (1H, dd, J = 14.5, 4.9 Hz, CH_2), 2.05 (1H, d, J = 11.6 Hz, CH_2), 1.99 (1H, dd, J = 14.5, 4.9 Hz, CH_2); δ_C (100 MHz, $CDCl_3$) 177.1 (*C*=O), 131.1 (*C*H=CH), 126.1 (*C*H=CH), 101.8 (*C*HCO$_2$CH$_2$), 74.4 (*C*HOCH$_2$), 64.5 (CHO*C*H$_2$), 64.4 (CHO*C*H$_2$), 42.5 (*Cq*), 37.5 (*C*H$_2$CHCO$_2$), 35.9 (*C*H$_2$CH=CH), 31.1 (CHOCH$_2$); MS m/z 211 (M + H$^+$), 228 (M + NH$_4^+$).

6-Bromo-2a-(1,3-dioxolan-2ylmethyl)-2a,5,6,6a-tetrahydro-2*H*-1-benzoxet-2-one (55)

NBS (196 mg, 1.1 mmol) was added to acid **44** (210 mg, 1.0 mmol) in DMF (10 mL) at ambient temperature. The mixture was left stirring for 3 h, after which EtOAc was added and the mixture was washed with water, followed by brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. Purification by flash column chromatography (EtOAc–petroleum ether 1 : 9) gave lactone **55** (263 mg, 91%) as a colourless oil. ν_{max}/cm^{-1} 1826 (C=O); δ_H (400 MHz, $CDCl_3$) 6.00 (1H, dt, J = 9.2, 4.0 Hz, C*H*=CH), 5.74 (1H, d, J = 10.4 Hz, C*H*=CH), 5.12 (1H, d, J = 2.8 Hz, OC*H*), 5.10 (1H, t, J = 4.8 Hz, OC*H*O), 4.55 (1H, dt, J = 6.4, 3.2 Hz, C*H*Br), 3.98–4.60 (2H, m, OCH_2), 3.88–3.91 (2H, m, OCH_2), 2.70–2.72 (2H, m, CH_2), 2.30 (1H, dd, J = 14.8, 4.6 Hz, CH_2OCHO), 2.24 (1H, dd, J = 14.8, 4.8 Hz, CH_2OCHO); δ_C (100 MHz, $CDCl_3$) 168.2 (C=O), 126.7 (*C*H=CH), 123.3 (*C*H=CH), 101.1 (*C*HCO$_2$CH$_2$), 74.8 (*C*HOCBr), 64.7 (O*C*H$_2$), 64.4 (O*C*H$_2$), 55.6 (*Cq*), 41.0 (*C*H$_2$CO$_2$*C*H$_2$), 36.1 (*C*H$_2$CH=CH), 27.4 (CHO*C*I); MS 289, 291 (M + H$^+$).

Methyl-1-[2-(*N*′-methylsulfanylthiocarbonyl-*N*′-phenylhydrazino)ethyl]-2,5-cyclohexadiene carboxylate (57)

DBU (12.8 mL, 85.0 mmol), followed by methyl iodide (6.5 mL, 105.0 mmol) were added to a solution of acid **46** (14.9 g, 70.6 mmol) in THF (150 mL). The mixture was left stirring for 3 h at ambient temperature, after which it was diluted with EtOAc and washed with saturated aqueous NH_4Cl, followed by brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. This gave the desired ester (15.7 g, 100%) as a colourless oil, without need for further purification. ν_{max}/cm^{-1} 1732 (C=O), 1434; δ_H (400 MHz, $CDCl_3$) 5.89–5.91 (2H, m, C*H*=CH), 5.82–5.85 (2H, m, C*H*=CH), 4.90 (1H, t, J = 4.8 Hz, OC*H*O), 3.92–3.95 (2H, m, OCH_2), 3.78–3.82 (2H, m, OCH_2), 2.70 (2H, s, CO$_2$CH_3), 2.66–2.67 (2H, m, CH_2), 2.10 (2H, d, J = 4.0 Hz, CH_2OCHO); δ_C (100 MHz, $CDCl_3$) 174.5 (C=O), 127.1 (*C*H=CH), 125.5 (*C*H=CH), 102.0 (*C*HCO$_2$CH$_2$), 64.7 (2O*C*H$_2$), 52.3 (CO$_2$*C*H$_3$), 45.6 (*Cq*), 43.9 (*C*H$_2$CH), 25.9 (*C*H$_2$CH=CH); MS (CI, NH_3) m/z 225 (M + H$^+$), 242 (M + NH$_4^+$); HRMS calcd for $C_{10}H_{15}N_3O_3$ 225.1113 found 225.1119. Hydrolysis of the acetal and condensation with hydrazide **7**, was carried out as described for thiosemicarbazones **48** and **49**, and the following reduction as for hydrazides **50** and **51**. Purification by flash column chromatography (petroleum ether–EtOAc 9 : 1) gave the hydrazone **58** (80%, over 3 steps) as an oil. ν_{max}/cm^{-1} 3286, 3199 (N–H), 1729 (C=O), 1593, 1351 (SCH$_3$); δ_H (400 MHz, $CDCl_3$) 7.47–7.53 (3H, m, C*H*Ar), 7.36 (2H, d, J = 7.2 Hz, C*H*Ar), 5.89–5.93 (2H, m, C*H*=CH), 5.73 (2H, d, J = 10.4 Hz, CH=C*H*), 3.72 (3H, s, CO$_2$CH_3), 2.41 (2H, t, J = 7.6 Hz, CH_2), 2.65 (2H, br, CH_2), 2.56 (3H, s, SCH_3), 1.98 (2H, t, J = 7.6 Hz, CH_2); δ_C (100 MHz, $CDCl_3$) 174.6 (C=O), 129.4, 129.2, 127.6, 126.5, 126.4 (6 *C*Ar, 2*C*H=*C*H), 52.3 (CO$_2$*C*H$_3$), 46.7 (CH$_2$*C*H$_2$NH), 44.4 (*C*H$_2$CH$_2$NH), 36.7 (*Cq*), 26.1 (*C*H$_2$CH=CH), 20.2 (S*C*H$_3$); MS (CI, NH_3) m/z 363 (M + H$^+$); HRMS calcd for $C_{18}H_{23}N_2O_2S_2$ 363.1201 found 363.1205.

General procedure for the preparation of cyclised products 54, 59

The thiosemicarbazide derivative (1.0 mmol) was dissolved in chlorobenzene (10 mL) and the solution was heated under reflux and degassed under argon for 15 min. DLP (0.1 g, 0.25 mmol) was then added every 20 min, whilst heating under reflux, until consumption of starting material was observed by TLC (generally, this required the addition 1.5–2.0 mmol of DLP). The solvent was removed *in vacuo* and purification by column flash column chromatography gave the desired cyclised product.

4-Methoxy-14-oxa-9-azapentacyclo[7.7.1.1.0.0]octadeca-2,4,6-triene-8,13-dione (54). Purification by flash column chromatography (EtOAc–petroleum ether 1 : 9 to 100% EtOAc) gave the desired cyclised product **54** (60%) as colourless crystals; mp 245–247 °C; ν_{max}/cm^{-1} 2930 (OCH$_3$), 1779 (C=O, CO$_2$CH$_2$CH$_3$), 1646, 1604 (NC=O); δ_H (400 MHz, $CDCl_3$) 8.10 (1H, d, J = 8.8 Hz, C*H*Ar), 6.88 (1H, dd, J = 8.8, 2.4 Hz, C*H*Ar), 6.63 (1H, s, C*H*Ar), 4.89 (1H, t, J = 5.0 Hz, C*H*O), 3.97 (1H, d, J = 8.0 Hz, NC*H*), 3.85 (3H, s, OCH_3), 3.79 (2H, dd, J = 10.2, 4.6 Hz, NCH_2), 3.53 (1H, dt, J = 14.0, 8.8 Hz, C*H*), 2.45–2.51 (1H, m, CH_2), 2.24–2.37 (2H, m, CH_2), 1.91–1.98 (2H, m, CH_2), 1.45–1.51 (1H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 173.7 (CH$_3$O*C*=O), 161.7 (*C*Ar), 160.9 (N*C*=O), 139.8 (*C*Ar), 129.4 (*C*HAr), 119.1 (*C*Ar), 111.9 (*C*HAr), 111.5 (*C*HAr), 74.8 (*C*HOCH$_2$), 57.7 (N*C*H), 54.4 (ArO*C*H$_3$), 49.8 (*Cq*), 42.3 (N*C*H$_2$), 34.4 (CHO*C*H$_2$), 33.3 (NCH$_2$*C*H$_2$), 28.7 (CH*C*H$_2$CHO), 27.0 (NCH*C*H); MS (CI, NH_3) m/z 300 (M + H$^+$); HRMS calcd for $C_{17}H_{18}NO_4$ 300.1236 found 300.1230.

Methyl 10-methoxy-7-oxo-3a,4,5,7,11b,11c-hexahydro-1*H*-pyrrolo[3,2,1-*de*]phenanthridine-3a-carboxylate (59). Purification by flash column chromatography (EtOAc–petroleum ether 1 : 9 to 100% EtOAc) gave the desired cyclised product **59** (59%) as a white solid; mp 113–114 °C; ν_{max}/cm^{-1} 2950 (OCH$_3$), 1731 (C=O, CO$_2$CH$_2$CH$_3$), 1645, 1606 (NC=O); δ_H (400 MHz, $CDCl_3$) 8.01 (1H, d, J = 8.6 Hz, C*H*Ar), 6.88 (1H, dd, J = 8.6, 2.4 Hz, C*H*Ar), 6.75 (1H, s, C*H*Ar), 5.97 (1H, m, CH=C*H*), 5.70 (1H, d, J = 10.0 Hz, CH=C*H*), 4.37 (1H, d, J = 8.0 Hz, NC*H*), 3.90–3.95 (1H, m, C*H*), 3.87 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.41–3.49 (1H, m, CH_2), 3.16–3.21 (1H, m, CH_2), 2.25–2.38 (2H, m, CH_2), 2.15–2.20 (1H, m, CH_2), 1.97–2.00 (1H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 173.0 (CH$_3$O*C*=O), 163.3 (*C*Ar), 162.2 (N*C*=O), 145.4 (*C*Ar), 130.1 (*C*H=CH), 129.6 (*C*HAr), 124.9 (*C*H=CH), 121.8 (*C*Ar), 112.3 (*C*HAr), 112.1 (*C*HAr), 59.0 (*Cq*), 58.7 (N*C*H), 55.4 (ArO*C*H$_3$), 52.5 (CO$_2$*C*H$_3$), 42.5 (*C*H$_2$CH=CH), 34.5 (N*C*H$_2$), 33.3 (NCH$_2$*C*H$_2$), 28.2 (NCH*C*H); MS (CI, NH_3) m/z 314 (M + H$^+$); HRMS calcd for $C_{18}H_{20}NO_4$ 314.1392 found 314.1397.

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