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The synthesis of β -enamino esters from the thermal, catalyst-free ring opening of aminocyclopropenones

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In an attempt to react aminocyclopropenones with cyclic imines in order to synthesise amido-substituted pyrrolizidine natural products, we found that aminocyclopropenones undergo a previously unreported stereospecific and regiospecific catalyst-free, thermal ring-opening reaction with alcohols to yield β -enamino esters (also known as vinylogous carbamates or aminoacrylates). We report 21 examples in 45 to 97% isolated yield. The reaction occurs *via* nucleophilic attack at the cyclopropenone carbonyl followed by regiospecific ring opening of the cyclopropenone with retention of alkene geometry. Preliminary studies with colon cancer cell line HCT116 show that a sub-set of these β -enamino esters have promising activity.

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Introduction

The reaction of cyclic imines 1 with cyclopropenones 2 is an established protocol for the synthesis of fused pyrrolones 3 (Scheme 1) and offers a key route for the synthesis of various alkaloid natural products and analogues.¹⁻⁹

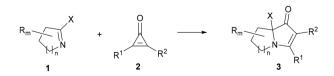
Building upon the pioneering work of Eicher,¹ our research group^{2–4} and those of Cui⁵ and Wood⁶ have shown that a variety of heterocycles such as pyrrolizidines³ and indolizidines² (*e.g.*, aza-sugar 4), pyrroloisoquinolines and indolizinoindoles (*e.g.*, indoles 5)^{1,2,5} and the aspergilline A precursor 6⁶ (Fig. 1) can be synthesised from the appropriate cyclic imine in this way. Other groups have used cyclopropenones in the synthesis of indolizinones, pyrroloisoquinolines and other fused systems by using dearomative cycloaddition to the carbon–nitrogen double bond of pyridines,⁷ isoquinolines⁷ and benzoxazoles,⁸ or *via* the *in situ* oxidation of tetrahydroisoquinolines with I₂-DMSO.⁹

One series of natural products that has attracted our attention is the amido-substituted pyrrolizidines (Fig. 2), a class of alkaloids that includes jenamidines A_1/A_2 7 (X = H) and B_1/B_2 8 (X = OH),^{2,3,10} NP25302 9,^{11,12} pyrrolizixenamides A-C 10,¹³

bohemamine D **11** and related natural products, ^{14–18} and the legonmycins **12**^{19,20} and the related fused azetidine natural products. ^{21,22} The natural products **7–12** are unusual in that they represent pyrrolizidines that are of bacterial rather than plant origin. ^{10–22} Compounds **10–12** show interesting activity against leukemic ^{10,12} and non-small cell cancer cell lines. ¹⁸

We anticipated that these amido-substituted pyrrolizidines might be accessed via the reaction of an amino-substituted cyclopropenone 14 with the appropriate cyclic imine (such as pyrroline 13, Scheme 2) and were particularly interested by the possibility that we would be able to simultaneously install the fused pyrrolidinone ring system and the bridgehead tertiary alcohol that are present in the natural products 8, 11 and 12 (see Fig. 2) as we had previously observed that oxidation at this bridgehead was facile, occurring spontaneously in air.^{2,3} Herein, we discuss the results of our initial attempts to investigate the approach that is summarised in Scheme 2, and describe how we found instead that the amino-substituted cyclopropenones 14 reacted by an alternative pathway to produce non-cyclic β-enamino esters 15 (Scheme 3) in high yields. β-Enamino esters are useful targets as they are attractive building blocks in synthetic chemistry²³⁻²⁸ with reactivity as electrophiles and nucleophiles, and have synthetic utility as pre-

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Scheme 1 The reaction of cyclopropenones with cyclic imines.

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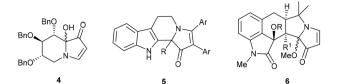


Fig. 1 Examples of fused pyrrolones accessed from cyclopropenones. $^{2-6}$

7 X = H, R¹ = H
8 X = OH, R¹ = H
9 X = Me, R¹ = Me
11 X = OH, R¹ = Me

$$R^2 = \int_{-\infty}^{\infty} OH$$

10 X = H, n = 3 - 5, R¹ = R² = H
12 X = OH, n = 1 or 2, R¹ = R² = Me

Fig. 2 Amido-substituted pyrrolizidine natural products.

Scheme 2 Proposed route to the amido-pyrrolizidine natural product core.

Scheme 3 Observed reaction – synthesis of β -enamino esters.

cursors for the synthesis of several classes of important aromatic heterocycles such as pyridines and fused pyridines, 23,24,26 pyrroles, $^{24-26}$ indoles, 24,26 quinolines, 23,25,26 pyrazines, oxazoles and imidazoles, 26 and saturated N-heterocycles containing additional O, N or S atoms. 27 β -Enamino esters have also been used as nucleophilic partners in Mitsunobu reactions allowing N-substitution, 27 have been used as substrates for addition–elimination reactions with other amines 23,25 thus allowing access to other β -enamino esters, and are used as starting materials for the synthesis of biologically relevant β -amino acids. 24,28

Results and discussion

In order to investigate the chemistry shown in Scheme 2, we needed to synthesise the amino-substituted cyclopropenones 14. Methods for the synthesis of the related aryl/alkyl-substi-

tuted cyclopropenones 2 (R¹/R² = alkyl/aryl) are readily available due to their use in alkaloid synthesis 1-9 as discussed above, and due to their widespread use in other processes, for example, reagents in cycloaddition/annulation reactions;²⁹⁻³¹ as precursors for butanolide synthesis;³² as fluorogenic reagents and photoactivatable probes in bioorthogonal ligation and imaging reactions;33-35 as catalysts for nucleophilic substitution reactions;36 as warheads with biological activity against breast cancer cell-lines;37 and further roles in synthetic and biological chemistry which are the subject of recent reviews. 38-41 2-Aminocyclopropen-1-ones 14, however, have attracted much less attention historically. 42-46 Recent contributions have come from the research group of Mishiro and Kunishima⁴⁷⁻⁵⁰ and have shown, for example, that 2-amino-3-(aryl)cyclopropen-1-ones (14, R³ = Ar) give arylynamines after photodecarbonylation. 47-49 2-Alkylamino-3-(aryl)-cyclopropen-1-ones have been shown by the same researchers to be strong inhibitors of the growth of HCT116 colon cancer cells via inhibition of the assembly bromodomain-containing protein 4 (BRD4).50

Our study started, as shown in Scheme 4, with the synthesis of the known (diisopropylamino)phenylcyclopropenone 18⁴⁷ using the established^{36,44,48} protocol of Friedel–Crafts reaction between tetrachlorocyclopropene and benzene. Hydrolysis of the Friedel–Crafts product gave the stable and isolable hydroxy (phenyl)cyclopropenone 16.³⁶ Chlorination of 16 with thionyl chloride gave the chlorinated intermediate 17 which was reacted immediately with diisopropylamine to give the desired product 18. We noted that failure to react intermediate 17 upon isolation resulted in its ready hydrolysis back to the hydroxycyclopropenone 16.

Pyrroline 13 (Scheme 5) was synthesised using procedures reported in our previous work. ^{2,3} All attempts to react pyrroline 13 with aminocyclopropenone 18 to give the desired aminosubstituted pyrrolizidine 19 were unsuccessful. However, when ethanol was used as the solvent, a single new product was observed by TLC analysis. Isolation and spectroscopic analysis of this product revealed it to be the previously unreported enamino ester 20a, formed as the isomer shown (see later for spectroscopic and other evidence).

It is known that 2,3-diaryl/dialkyl-substituted cyclopropenones 2 can be used as sources of alkenes in a variety of processes that involve attack at the cyclopropenone followed by ring opening.^{51–61} Several of these processes involve C–C bond

CI CI Ph—H CI CI
$$\frac{Ph-H}{AlCl_3}$$
 $\frac{Cl}{Ph}$ $\frac{Cl}{54\%}$ $\frac{O}{Ph}$ OH

SOCl₂ $\frac{O}{Ph}$ $\frac{iPr_2NH}{46\%}$ $\frac{O}{Ph}$ $\frac{NiPr_2}{18}$

Scheme 4 Synthesis of aminocyclopropenone 18:

Scheme 5 Attempted reaction of aminocyclopropenone 18 with cyclic imine 13.

formation using C-H or C-C activation in the presence of Ru/ Pd/Ag catalysts and additives. 51-54 More notably, other examples, shown in Scheme 6, involve heteroatom attack at the carbonyl of the cyclopropenone and the formation of esters and amides 21 after ring opening, 55-58 again requiring the presence of metal (Ag, Cu, Pd) catalysts. The use of triphenylphosphine in a metal-free catalytic ring opening reaction of cyclopropenones is a useful variant that has attracted recent attention, and is considered to proceed via the ketenyl phosphorus ylid 22 shown in Scheme 6.59-64 Isolated examples of the catalyst-free addition of just two nucleophiles (hydroxide⁶⁵ and methanol⁶⁶) to the carbonyl of a single type of cyclopropenone (diphenylcyclopropenone) followed by ring opening to give acrylates under thermal conditions have been reported (also shown in Scheme 6). 2-Methoxy-3-phenylcyclopropen-1one is also known to react with water at the carbonyl carbon and gives the ring-opened acrylic acid dervative. 67 The trisubstituted alkene products of these processes have proved to be useful for the synthesis of quinolones,58 as substrates for the synthesis of much sought after tetra-substituted alkenes after in situ Pd-catalysed C-H arylation, 59 and for elaboration into indenes, 61 benzazepines and phenanthrenes. 63

The examples of ring-opening shown in Scheme 6 all relate to aryl and alkyl-substituted cyclopropenones. In contrast, the literature on amino-substituted cyclopropenones contains only two examples of nucleophilic attack at the carbonyl followed by ring opening. Thus, as part of a study that focused upon the generation of ynamines by the photolytic decarbonylation

Scheme 6 Ring-opening reactions of aryl/alkyl cyclopropenones

Scheme 7 Ring-opening reactions of aminocyclopropenones.

of aminocyclopropenones, it was observed, as shown in Scheme 7, that the reaction of morpholinophenylcyclopropenone with methanol gave the methyl enamino ester, although no experimental detail was given. 44 The same authors reported the use of N-(pentafluorophenyl)aminophenylcyclopropenone (also shown in Scheme 7) for the generation of ynamines by photolytic decarbonylation, and obtained the enamino ester after reaction in methanolic acetone overnight. 45 With the prior work limited to just two aminocyclopropenones reacting with one alcohol (methanol) as a side reaction in studies focused upon photolytic decarbonylation, and also considering the importance of the enamino ester $^{23-28}$ and alkene $^{51-64}$ products, we thought it worthwhile to undertake a more detailed study focused upon the unexplored, facile, catalyst free, thermal process that we observed in Scheme 5.

We quickly found that the conversion of aminocyclopropenone **18** into the enamino ester **20a** could be carried out by heating compound **18** in neat ethanol or with ethanol in various solvents as shown in Table 1. The best conditions were found to be a solution of 5 equivalents of ethanol in chloroform at 80 °C for 18 hours (100% conversion of compound **18** into product **20a** was estimated by ¹H NMR, with 84% isolated yield after purification by chromatography).

Table 1 Optimising the reaction of cyclopropenone 18 with EtOH

Ph
$$N(Pr)_2$$
 EtOH EtO_2C Ph $N(Pr)_2$ 20a

Solvent	Equivalents of EtOH	Temp. (°C)	Time (h)	% Conversion for 18a to 20a (¹ H nmr) ^a
Neat	285	80	18	100
$CDCl_3$	100	80	18	100
$CDCl_3$	20	80	18	100
$CDCl_3$	10	80	18	100
$CDCl_3$	5	80	18	100
$CDCl_3$	4	80	18	99
$CDCl_3$	3	80	18	87
$CDCl_3$	2	80	18	73
$CDCl_3$	1	80	18	30
$CDCl_3$	5	70	18	68
$CDCl_3$	5	50	18	37
$CDCl_3$	5	20	18	5
$CDCl_3$	5	80	6	71
$CDCl_3$	5	80	1	11
D ₆ -DMSO	5	80	18	100^b
D ₃ -MeCN	5	80	18	80

 $[^]a$ Estimated by analysis of the crude reaction mass after the removal of the excess EtOH and reaction solvent. b The isolated yield (after purification by chromatography) fell by $\sim 20\%$ when DMSO was used as solvent.

The identity of compound 20a was inferred by analogy to the literature examples reported in Schemes 6 and 7, and by fully consistent mechanistic considerations and spectroscopic data, including 2D-NMR experiments. Thus, NOESY showed a strong correlation of the alkene CH with the methyl groups of the iso-propyl group, inferring that the alkene CH and NⁱPr₂ were close, hence discounting attack of the alcohol at C1 followed by C1-C3 cleavage that would form alkene isomer i (see Scheme 8). NOESY also showed a correlation of the phenyl protons with the methyl and CH protons of the iso-propyl group, indicating (E)-isomer 20a had formed rather than alkene ii or the (Z)-isomer of 20a, hence leading to our assignment of (E)-isomer 20a as the product. In the HMBC, the C=O showed coupling to the CH2 of the OEt group, inferring that EtOH had attacked the C1 carbonyl of the cyclopropenone (black arrows and structures in Scheme 8), rather than undergoing conjugate addition to either C2 or C3 of the alkene (blue arrows and structures in Scheme 8). No evidence of aldehyde peaks was seen in 1D or 2D NMR spectra, hence discounting addition to either C2 or C3 of the alkene followed by ring opening. Together, these observations indicated to us that ring opening had occurred by the route suggested in Scheme 8, i.e. attack at C1 followed by C1-C2 cleavage, leading to the enamino ester 20a rather than following the alternative ring opening pathway (red arrows and structures on Scheme 8) or conjugate addition pathway (blue arrows and structures on Scheme 8). To help confirm our assignment, we produced a spectroscopically identical compound to enamino ester 20a using an independent synthetic route as shown in Scheme 9, thus discounting the possible formation of alkene regioisomers i and ii, as well as discounting the formation of any products that arise from reaction at the alkene group of the cyclopropenone. Reactions with other substrates (see later) produced two known alkenes with spectroscopic data identical to the literature. All of this evidence, together with literature precedent relating to the structure of the alkenes produced by

the processes shown in Schemes 6 and 7 support the structural

Scheme 8 Suggested mechanism leading to observed product 20a.

Scheme 9 Independent confirmatory synthesis of compound 20a.

Table 2 Reactions of aminocyclopropenone 18 with alcohols

	O H	ROH (5 equiv.)	RO⟨O	н
	Ph N(ⁱ Pr) ₂	chloroform 80 °C, 18h	Ph	-≺ N(ⁱ Pr) ₂
	18	(see Table 2)	20k	o-n
Entry	ROH (5 equ 80 °C, 18 h	niv., chloroform,	% iso (after	lated yield of 20 purification)
b	МеОН		97	
c	ⁱ PrOH		79_	
d	^t BuOH		79 ^a	
e f	"BuOH	Н	76 74	
g	∕/OF	I	45	
h	OF	I	81	
i		ОН	80	
j	Me	ОН	57	
k	MeO MeO	ОН	87 ^a	
1		DH	51	
m) DH	77	
n	PhOH		94	
^a See te	ext and footnote.‡			

assignment, and strongly support the reaction pathway proposed in Scheme 8.

We next applied the optimised conditions (5 equivalents of alcohol in chloroform at 80 °C for 18 hours) to the reaction of a range of alcohols with aminocyclopropenone 18 as detailed in Table 2. The reaction worked with primary, secondary and tertiary alcohols, phenolic, benzylic, allylic and propargylic alcohols to give the enamino esters 20b–n with generally good to excellent isolated yields as shown in Table 2. All compounds gave spectroscopic data that was consistent with the assigned structures and were isolated in good purity as single isomers.‡

[‡]The NMR spectra for compounds **20d** and **20k** contain ~10% of an unidentified common aliphatic contaminant that was present in the batch of CDCl₃ used to collect NMR data for these samples after purification. The compounds could not subsequently be separated from this impurity.

Table 3 The reactivity of other aminocyclopropenones or other nucleophiles

$$R^1XH$$
 NR_2
 R^1XH
 R^1X
 R^1X
 NR_2

18 Ar = Ph, R = ⁱPr; **23** Ar = Ph, R = CH₂Ph; **24** Ar = Ph, R = Me; **25** Ar = 2,4-Me₂C₆H₄, R = ⁱPr; **26** Ar = 2,4-(OMe)₂C₆H₄, R = ⁱPr

20o-v see Table 3

Entry	Ar	R	R^1XH	% Yield 20
_	Ph	ⁱ Pr	Primary amine	No reaction
_	Ph	ⁱ Pr	Secondary amine	No reaction
_	Ph	ⁱ Pr	Valinol	No reaction
_	Ph	ⁱ Pr	H_2O	No reaction
_	Ph	ⁱ Pr	NaOH	No reaction
200	Ph	ⁱ Pr	PhSH	71
20p	Ph	Bn	EtOH	78
20q	Ph	Bn	PhOH	$\sim 60^a$
20r	Ph	Bn	OH N ₃	82
20s	Ph	Me	МеОН	89
20t	$2,4-Me_2C_6H_4$	ⁱ Pr	МеОН	73
20u	$2,4-Me_2C_6H_4$	ⁱ Pr	EtOH	92
20v	2,4-Me ₂ C ₆ H ₄	ⁱ Pr	ⁱ PrOH	54
_	$2,4-(OMe)_2C_6H_4$	ⁱ Pr	EtOH/MeOH	No reaction

^a Contained a small amount of phenol: see experimental and footnote therein.

It was notable, and in keeping with similar diisopropylamino compounds reported in the literature, ⁶⁸ that the isopropyl group gave very weak, broad signals in the ¹³C NMR spectra recorded for these compounds, and that occasionally the isopropyl signals were not distinguishable from the baseline.

In order to test the reaction scope, we also investigated other nucleophiles and other aminocyclopropenones as shown in Table 3. Thus, amines (aliphatic, benzylic or aryl), valinol, water or dilute sodium hydroxide gave no isolable products with aminocyclopropenone 18, leading only to complex mixtures under our standard conditions. Other conditions and the use of deactivated nitrogen sources such as TsNH2 were not explored. Thiophenol reacted to give the thioester 20o. 2-Dibenzylamino-3-phenylcyclopropen-1-one methylamino-3-phenylcyclopropen-1-one 2443 and 2-diisopropylamino-3-(2',4'-dimethylphenyl)cyclopropen-1-one 25^{47,49} reacted with alcohols to give the enamino esters 20p-25v, showing that variations in the nature of the aryl and dialkylamino groups could be made. Alkenes 20p69 and 20s25,70-72 have been reported previously where each was synthesised by routes quite different to ours and different to each other. In each case, our compounds had ¹H and ¹³C NMR spectra/data identical to those reported, 69,70 justifying the regiochemical, stereochemical and mechanistic arguments presented above in Scheme 8. In the case of compound 20p, we observed, as per the identical published spectrum,69 that the signal for the methylene of the benzyl group was very weak and broad in the ¹³C NMR spectrum, and almost indistinguishable from the baseline. This phenomenon was observed with the other N-benzyl compounds shown in Table 3, and also occurred with the methine and methyl signals in the ¹³C NMR spectra of the NⁱPr₂ compounds that appear in Table 3. In the case of known compound 20s, no literature spectrum was available, but the NMR data matched the published data. 25,70,72 2-Diisopropylamino-3-(2',4'-dimethoxyphenyl)cyclopropen-1one 26 was found to be unreactive towards ethanol and methanol, indicating that strongly electron donating groups on the aryl substituent are not tolerated, possibly due to their ability to lower the reactivity of the cyclopropenone carbonyl by electron donation. The 2-amino-3-arylevelopropenones 23-26^{43,47,49} used in Table 3 are known isolable compounds and were synthesised by adapting the route shown above in Scheme 4 to allow the use of substituted benzenes and other amines in the place of benzene and diisopropylamine. The synthesis of 2-dimethylamino-3-phenylcyclopropenone 24 required the use of dimethylaminotrimethylsilane rather than dimethylamine as the amine, a requirement also noted by other workers.43

In two final reactions, shown in Scheme 10, it was determined that the cyclopropenones 27 and 16, isolated as intermediates from the general aminocyclopropenone synthesis shown previously in Scheme 4, reacted with ethanol to give the alkenes 28 and 29, showing that other heteroatom-substituted cyclopropenones undergo reaction in the same way as aminocyclopropenones. The stable and known⁴⁹ intermediate 2-chloro-3-(2',4'-dimethoxyphenyl)cyclopropenone 27 used in this reaction was isolated after the hydrolysis of the intermediate Friedel-Crafts product (Scheme 4) obtained from 1,3dimethoxybenzene. The stability of this material was in contrast to that of 2-chloro-3-(phenyl)cyclopropenone 17 and this can be attributed to the ability of the electron donating methoxy groups to lower the reactivity of the cyclopropenone ring. Alkene 29 has been reported previously, is tautomeric with the thermodynamically less stable aldehyde and is known exist as the (Z)-isomer. 73,74 It is the same compound used in Scheme 9 and was identical to that material. The stereochemistry of the previously unreported chloroalkene 28 could not be determined, but the compound was a single stereoisomer. We are investigating the applications of these types of cyclopropenones and their alkene products further.

Mishiro and Kunishima found that 2-dialkylamino-3-(aryl)-cyclopropen-1-ones were strong inhibitors of the growth of HCT116 colon cancer cells.⁵⁰ We carried out preliminary studies with colon cancer cell line HCT116 in order to establish IC_{50} values for the aminocyclopropenone 18 and four of

Scheme 10 Reactions of cyclopropenones 27 and 16 with EtOH.

the enamino esters derived from it. We thought this would be of interest as this previous study⁵⁰ had compared 2-dialkylamino-3-(aryl)-cyclopropen-1-ones to simple amide analogues [ArC(O)NR₂], concluding that the cyclopropenone ring was essential for activity. Our results are shown in Table 4. Compounds 18, 20a, 20f, 20h and 20j were screened against colon cancer cell line HCT116 with cis-platin as a control.

As shown in Table 4, the 2-dialkylamino-3-phenyl-cyclopropen-1-one 18 showed the weakest cytotoxic activity and appeared not to be as potent as noted previously for other compounds in this class. ⁵⁰ It can also be seen from the results in Table 4 that the four enamino ester compounds showed micromolar cytotoxic activity that was more potent than that of compound 18, indicating that these enamino esters may warrant further biological evaluation. The possibility that the two classes of compounds form the same biological conjugate (shown as structure 30 in Scheme 11) is worthy of consideration given that they have similar electrophilic properties and H-bond acceptor capacity, and that a similar mode of reactivity has been noted previously with aryl/alkyl-substituted cyclopropenones. ^{37,41} We intend to study the biological activity of these enamino esters in more detail.

Although all but two of the β -enamino ester series **20a-v** that we have produced in this work are unreported, it is noteworthy that other non-cyclic β -enamino esters (also known as vinylogous carbamates or aminoacrylates), albeit produced by different pathways to the one we report, are a well-known and versatile class of compound. The most common route for the synthesis of β -enamino esters is the reaction of a **1**,3-dicarbonyl with an amine (as used in the confirmatory synthesis shown in Scheme 9). ^{24,74–77} This requires the synthesis of the appropriate **1**,3-dicarbonyls *via* reaction of an ester with an excess of alkyl formate in the presence of sodium hydride, and is generally utilised with only simple commercially available esters, so that an additional step is required for non-simple esters, resulting in a 3-step synthesis. ^{74,76,77} The process often gives rise to (E)/(Z) mixtures, although hindered amines tend

Table 4 $\,$ IC $_{50}$ Values for aminocyclopropenone 18 and enamino esters 20a, f, h and j

Compound	${ m IC}_{50}$ (µmol) for inhibition of HCT116 growth
18	117 ± 53
20a	23.7 ± 19
20f	33 ± 14
20h	72 ± 10
20j	13.9 ± 9
20j cis-platin	1.03 ± 0.36

Scheme 11 Proposed formation of biological conjugate 30.

to give the (E)-alkene. Our route is a simple process reacting alcohols with easily accessible amino-substituted cyclopropenones (two steps from commercially available materials), allows variation of the aryl and amine substituents on the aminocyclopropenone ring, gives good to high yields with a wide variety of readily available alcohols, and allows access to a range of previously unreported β-enamino esters in a regioand stereoselective manner. The other commonly used route for the synthesis of β-enamino esters is the reaction of dimethylformamide-dimethyl acetal (DMF-DMA)^{23,25,70,71,78} with active methylene compounds, a route that is restricted to dimethylamino-substituted β-enamino esters. Other dialkylformamide acetal derivatives are rarely used as they are not commercially available and require synthesis. This route also requires the synthesis of any non-simple esters that are used as the active methylene compounds. The DMF-DMA process also tends to use DMF as solvent at high temperature with long reaction times. Less common and less general routes for the synthesis of β-enamino esters include the rhodium catalysed decomposition of diazoketamines, 27,28 the copper-catalysed coupling of thioamides to diazocarbonyls, 72 the synthesis of diesters by reaction of dialkyl acetylenedicarboxylates with anilines, 79 nickel catalysed cross-couplings of organoboronic acids with isoxazoles,80 and the reaction of disubstituted β-enamino esters with bromodifluoroacetates to give α-keto ester substituted derivatives.81 The route that we report is an important contribution to a greater understanding of the reactivity of aminocyclopropenones, and offers a convenient and useful addition to the methods that are available for the synthesis of β-enamino esters, a class of molecule with high synthetic utility.

Conclusions

2-(Dialkylamino)-3-arylcyclopropen-1-ones have been shown to undergo a previously unreported thermal uncatalyzed ring opening reaction with alcohols to give synthetically useful β-enamino esters (vinylogous carbamates) in good yields in a regio- and stereospecific manner. This simple, catalyst-free reaction has parallels with the well-known transition metal or phosphine catalysed ring opening reactions of the more commonly available 2,3-diarylcyclopropenones. Some of the enamino esters that we have synthesised show interesting cytotoxic activity against colon cancer cell line HCT116. Further studies into the synthesis and reactivity of the 2-(dialkylamino)-3-arylcyclopropen-1-ones and precursors are underway.

Experimental

General information

Unless stated otherwise, reagents were purchased from Sigma-Aldrich, Acros, Alfa Aesar, Fisher Scientific or Fluorochem. Thin layer chromatography was performed on aluminium sheets coated with Merck silica gel 60 F254 with visualisation

at 254 nm and 365 nm UV light. Flash silica gel chromatography was performed using Silica 60 (40-63 microns) supplied by Sigma-Aldrich unless otherwise stated. All melting points were obtained using a Smart SMP10 melting point instrument. Nuclear magnetic resonance (NMR) spectroscopy was performed on a Bruker Avance 400 MHz NMR spectrometer (1H NMR at 400 MHz and 13C NMR at 100 MHz) or on a Bruker Avance 600 MHz NMR spectrometer (1H NMR at 600 MHz and ¹³C NMR at 150 MHz) with samples dissolved in the appropriate deuterated solvent as stated in parenthesis. Chemical shifts in ¹H NMR and ¹³C NMR are relative to either the deuterated solvent peak or the TMS peak and are reported as singlet (s), doublet (d), triplet (t), quartet (q) and combinations thereof, or multiplet (m). Coupling constants (1) are quoted in Hz and are averaged between coupling partners and quoted to the nearest 0.1 Hz. Mass spectrometry (MS) was performed using a Bruker MicroTOF-Q instrument with electrospray ionisation in the positive mode. FT-IR data was acquired using Thermo Electron Corporation Nicolet 380 FTIR with Smart Orbit diamond window instrument in transmittance mode with wavenumbers reported in cm⁻¹.

2-(Dialkylamino)-3-arylcyclopropen-1-ones 18 and 23-26 are known and were synthesised by adapting the published routes^{43,47,49} as described below. The intermediate 2-hydroxyand 2-chloro-3-aryl-cyclopropenones 16 and 27 are also known^{36,49} and were synthesised by adapting the published routes as described below. The enamino esters 20p69 and 20s^{25,70,71} have been reported previously each using a different route to that which we report. Enamino esters 20a-o, 20q, 20r, 20t-v and alkene 28 are unreported. Cyclic imine 13 was prepared as previously described.^{2,3} Compound 29 has been reported previously. 73,74 Copies of the ¹H and ¹³C NMR spectra for previously unreported compounds are available as SI.

Synthetic procedures

2-Hydroxy-3-phenylcycloprop-2-en-1-one (16). Tetrachlorocyclopropene (3 mL, 27.8 mmol) was added to a stirring slurry of AlCl₃ (3.16 g, 27 mmol) in dichloromethane (50 mL) at 0 °C, and stirred for 10 minutes. Benzene (1.94 mL, 24.8 mmol) was added as a solution in dichloromethane (50 mL). The reaction was stirred overnight at room temperature. Water (30 mL) was added to the reaction and the mixture was extracted into dichloromethane (30 mL), washed with brine, dried with MgSO₄, and concentrated by rotary evaporation. The crude oil was dissolved in acetone (5 mL), and 30 g of crushed ice was added. The mixture was stirred at room temperature for 3 h and concentrated by rotary evaporation under reduced pressure. The crude solid was collected by filtration and washed with icecold diethyl ether to afford compound 16 as a pale-yellow solid (1.95 g, 13.4 mmol, 54%), m.p.: 119-121 °C. Known compound, literature m.p. not reported.³⁶ ¹H NMR (CDCl₃, 400 MHz) δ H 15.14 (br. s, 1H, OH), 7.79–7.77 (m, 2H, 2 × ArH), 7.52-7.49 (m, 3H, 3 × ArH). ¹³C NMR (CDCl₃, 100 MHz) δC 175.6 (qC), 148.7 (qC), 133.3 (qC), 131.8 (CH), 131.1 (CH), 129.2 (CH), 125.4 (qC). IR ν_{max} (thin film, cm⁻¹): 3340, 1597, 1488, 1173, 1060, 993, 922, 769. m/z (ESI+) calculated

for C₉H₆O₂ [M]⁺; 146.0368, observed 146.0366. Known compound.36

2-(Diisopropylamino)-3-phenylcycloprop-2-en-1-one (18). 1-Hydroxy-2-phenylcyclopropenone (800 mg, 5.6 mmol) was cooled to 0 °C and 8 drops of DMF were added, followed by thionyl chloride (16 mL). The reaction was stirred for 10 min at 0 °C, then at room temperature for 10 minutes. The excess thionyl chloride was removed by rotary evaporation under reduced pressure. The crude solid was dissolved in dichloromethane (20 mL) and the solution cooled to 0 °C, and diisopropylamine (708 mg, 7 mmol) was added. The reaction was stirred for 3 h and guenched with sat. ag. NH₄Cl (20 mL). The reaction mixture was extracted with dichloromethane (3 × 20 mL), washed with saturated brine, dried with MgSO4, and concentrated by rotary evaporation. The crude product was purified via column chromatography using graduated elution (PE: EtOAc 7:3 to 2:3) to afford the title compound as a pale brown oil (595 mg, 2.59 mmol, 46%), solidifying to a pale vellow solid, m.p.: 130-132 °C. Known compound, m.p. not previously reported. 36,47 ¹H NMR (CDCl₃, 400 MHz) δ H 7.59-7.57 (m, 2H, 2 × ArH), 7.43-7.39 (m, 2H, 2 × ArH), 7.36–7.32 (m, 1H, ArH), 4.20 (septet, 1H, J = 6.8 Hz, NCH), 3.64 (septet, 1H, J = 6.6 Hz, NCH), 1.40 (dd, 6H, J = 6.8 Hz, $N-CHC_2H_6$), 1.39 (dd, 6H, J = 6.6 Hz, $N-CHC_2H_6$). ¹³C NMR (CDCl₃, 100 MHz) δC 146.6 (qC), 140.8 (qC), 129.0 (CH), 128.9 (CH), 128.9 (CH), 125.1 (qC), 110.1 (qC), 54.9 (NCH), 47.9 (NCH), 23.6 (CH₃), 21.3 (CH₃). NMR data consistent with that reported previously.36,47

2-(Dibenzylamino)-3-phenylcycloprop-2-en-1-one (23). Prepared as per compound 18 using 1-hydroxy-2-phenylcyclopropenone (800 mg, 5.5 mmol), DMF (6 drops), thionyl chloride (8 mL), and dibenzylamine (2.7 mL, 14 mmol). The reaction was quenched with 0.1 M HCl (80 mL). The crude product was purified by column chromatography (25% EA in PE then 100% EA) to afford the desired compound as brown oil (100 mg, 0.43 mmol, 16%). ¹H NMR (CDCl₃, 400 MHz) δ H 7.57–7.54 (m, 2H, $2 \times ArH$), 7.42-7.30 (m, 13H, 13 × ArH), 4.63 (s, 2H, $N-CH_2$), 4.53 (s, 2H, NCH_2). ¹³C NMR (CDCl₃, 100 MHz) δC 146.08 (qC), 144.08 (qC), 135.31 (qC), 135.11 (qC), 129.43 (CH), 129.36 (CH), 129.20 (CH), 129.08 (CH), 128.99 (CH), 128.69 (CH), 128.44 (CH), 127.76 (CH), 124.26 (qC), 111.74 (qC), 55.78 (CH₂), 54.74 (CH₂). NMR data consistent with that reported previously.47,49

2-(Dimethylamino)-3-phenylcycloprop-2-en-1-one (24). Prepared as per compound 18 and 23 using 1-hydroxy-2-phenylcyclopropenone (800 mg, 5.5 mmol), DMF (6 drops), thionyl chloride (8 mL) and N,N-dimethylaminotrimethylsilane (1.29 g, 11 mmol). The reaction was quenched with 0.1 M HCl (80 mL). The crude product was purified by column chromatography (30% EA in PE then 100% EA) to afford the desired compound as a hygroscopic solid (143 mg, 0.83 mmol, 15%) that quickly decomposed to a yellow oil and needed to be used immediately upon isolation. The compound has been reported previously as an isolable and characterizable solid. 43

2-(Diisopropylamino)-3-(2,4-dimethylphenyl)cycloprop-2-en-**1-one** (25). Tetrachlorocyclopropene (4 mL, 29.6 mmol) was added to a stirred solution of AlCl₃ (5.9 g, 44.4 mmol) in MeNO₂ (20 mL) and DCM (50 mL) at 0 °C under an N₂ atmosphere. After 5 min, a solution of m-xylene (4 mL, 32.6 mmol) in DCM (30 mL) was added to the reaction mixture over 10 min and the whole was stirred for a further 2 h at 0 °C. The reaction mixture was guenched with ice-cooled water (80 mL), extracted with DCM, dried over MgSO4, filtered, and concentrated by rotary evaporation under reduced pressure. The residue was dissolved in acetone/water (80 mL/80 mL) at 0 °C and stirred for 1 h. Diisopropylamine (1.13 mL, 8.05 mmol) was added at 0 °C and the reaction was stirred for 30 min. The mixture was diluted with ethyl acetate (80 mL), washed with 1 M aqueous HCl (80 mL), water (80 mL), and brine (80 mL), dried over MgSO₄, filtered, and concentrated by rotary evaporation under reduced pressure. The crude product was purified by silica column chromatography (20% EA in PE then 50% EA in PE) to yield the desired compound as a pale-yellow solid (1.38 g, 5.36 mmol, 18%), m.p.: 130-132 °C (m.p. not previously reported). ¹H NMR (CDCl₃, 400 MHz) δ H 7.23 (d, J =7.8 Hz, 1H, ArH), 7.10 (s, 1H, ArH), 7.02 (d, J = 7.4 Hz, 1H, ArH), 4.23 (septet, J = 6.7 Hz, 1H, NCHC₂H₆), 3.63 (septet, J =6.6 Hz, 1H, NCHC₂H₆), 2.64 (s, 3H, ArCH₃), 2.35 (s, 3H, $ArCH_3$), 1.39 (2 × d, J = 7.3 Hz, 12H, 2 × $NCHC_2H_6$). ¹³C NMR (CDCl₃, 100 MHz) δC 146.27 (qC), 140.87 (qC), 139.51 (qC), 139.19 (qC), 131.44 (CH), 127.91 (CH), 127.24 (qC), 126.44 (CH), 122.72 (qC), 54.90 (NCH), 47.30 (NCH), 23.65 (CH₃), 21.33 (CH₃), 21.24 (CH₃), 20.98 (CH₃). The analytical data is consistent with that reported previously.⁴⁷

2-(Diisopropylamino)-3-(2,4-dimethoxyphenyl)cycloprop-2-en-**1-one (26).** To a stirring solution of 2-chloro-3-(2,4-dimethoxyphenyl)cycloprop-2-en-1-one 27 (100 mg, 0.45 mmol) in DCM (1 mL), a solution of diisopropylamine (0.15 mL, 1.07 mmol) in DCM (5 mL) was added and the reaction was stirred at 0 °C under N2 for 1 h. The reaction mixture was extracted with DCM (60 mL), washed with 0.1 M HCl (60 mL), H₂O (60 mL), brine (60 mL), dried over MgSO₄ and concentrated by rotary evaporation under reduced pressure to afford the title compound as a yellow oil (66.6 mg, 0.23 mmol, 51%). ¹H NMR $(CDCl_3, 400 \text{ MHz}) \delta H 7.43 (d, J = 8.5 \text{ Hz}, 1H, ArH), 6.46 (dd, J = 8.5 \text{ Hz})$ 8.6, 2.3 Hz, 1H, ArH), 6.42 (d, J = 2.3 Hz, 1H, ArH), 4.73 (br. s, 1H, NCH), 3.84 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃), 3.72 (br. s, 1H, NCH), 1.40 (d, J = 6.8 Hz, 6H, NCHC₂ H_6), 1.31 (d, J =6.8 Hz, 6H, NCHC₂ H_6). The analytical data is consistent with that reported previously.47

2-Chloro-3-(2,4-dimethoxyphenyl)cycloprop-2-en-1-one (27). Tetrachlorocyclopropene (4 mL, 29.6 mmol) was added to a stirring slurry of AlCl₃ (5.9 g, 44.4 mmol, 1.5 eq.) in DCM (32 mL) at 0 °C under N₂, and the mixture was stirred for 0.5 h. The mixture was cooled to -78 °C and 1,3-dimethoxybenzene (3.9 mL, 32.6 mmol) was added as a solution in DCM (48 mL), and the reaction was stirred at -78 °C for 1 h. The reaction was diluted with DCM (200 mL) and quenched with ice cooled water (100 mL). The reaction was warmed to 0 °C and stirred for 0.5 h. The reaction was extracted with DCM (100 mL), dried over MgSO₄, and concentrated by rotary evaporation under reduced pressure. The reaction mixture was pur-

ified using column chromatography (16% EA in PE to 33% EA in PE), to obtain the desired compound as a brown solid (2.1 g, 5.0 mmol, 17%), m.p.: 67–69 °C. Known compound, ⁴⁷ m.p. not previously reported. ¹**H NMR** (CDCl₃, 400 MHz) δ H 7.48 (d, J = 8.6 Hz, 1H, ArH), 6.51 (dd, J = 8.6, 2.2 Hz, 1H, ArH), 6.43 (d, J = 2.2 Hz, 1H, ArH), 3.89 (s, 3H, OCH₃), 3.87 (s, 3H, OCH₃). ¹³C NMR (CDCl₃, 100 MHz) δ C 165.04 (qC), 164.38 (qC), 149.21 (qC), 137.28 (CH), 106.14 (CH), 99.69 (qC), 98.30 (CH), 94.06 (qC), 88.35 (qC), 56.00 (OCH₃), 55.74 (OCH₃). The analytical data is consistent with that reported previously. ⁴⁷

Synthesis of enaminoesters (20): general procedure. 2-(Dialkylamino)-3-arylcycloprop-2-en-1-one (0.1 mmol) and the nucleophile (0.5 mmol) were dissolved in $CDCl_3$ (1 mL) and stirred at 80 °C for 18 h in a sealed tube. The reaction mixture was then purified via silica gel column chromatography using graduated elution with ethyl acetate and 60–40 petroleum ether to give the desired enamino esters.

Ethyl (*E*)-3-(diisopropylamino)-2-phenylacrylate (20a). Prepared according to the general procedure, using 2-(diisopropylamino)-3-phenylcycloprop-2-en-1-one and ethanol to afford the title compound as a brown solid (23.1 mg, 0.084 mmol, 84%), m.p.: 62–64 °C. ¹H NMR (CDCl₃, 400 MHz) δH 7.75 (s, 1H, C=CH), 7.32–7.25 (m, 2H, 2 × ArH), 7.23–7.20 (m, 3H, 3 × ArH), 4.12 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 3.49 (septet, J = 6.6 Hz, 2H, 2 × NCHC₂H₆), 1.19 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 1.08 (br. s, 12H, 2 × NCHC₂H₆). ¹³C NMR (CDCl₃, 100 MHz) δC 170.39 (qC), 143.25 (CH), 138.42 (qC), 131.16 (CH), 127.78 (CH), 126.25 (CH), 98.24 (qC), 59.39 (OCH₂), 47.17 (broad, NCH), 21.74 (broad, CH₃), 14.65 (CH₃). IR ν_{max} (thin film, cm⁻¹): 2976, 1734, 1676, 1571, 1495, 1459, 1369, 1298, 1246, 1180. m/z (ESI+) calculated for C₁₇H₂₆NO₂ [M + H]⁺; 276.1958, observed 276.1961.

Methyl (*E*)-3-(diisopropylamino)-2-phenylacrylate (20b). Prepared according to the general procedure, using 2-(diisopropylamino)-3-phenylcycloprop-2-en-1-one and MeOH to afford the title compound as a yellow solid (25.4 mg, 0.097 mmol, 97%), m.p.: 99–101 °C. ¹H NMR (CDCl₃, 400 MHz) δH 7.74 (s, 1H, C=CH), 7.31–7.26 (m, 2H, 2 × ArH), 7.24–7.18 (m, 3H, 3 × ArH), 3.61 (s, 3H, OCH₃), 3.47 (septet, J = 6.6 Hz, 2H, 2 × NCHC₂H₆), 1.06 (br. s, 12H, 2 × NCHC₂H₆). ¹³C NMR (CDCl₃, 100 MHz) δC 170.89 (qC), 143.52 (CH), 138.31 (qC), 131.15 (CH), 127.91 (CH), 126.43 (CH), 97.84 (qC), 51.18 (OCH₃), 47.20 (broad, NCH), 21.68 (broad, CH₃). IR ν _{max} (thin film, cm⁻¹): 2971, 1675, 1590, 1496, 1465, 1455, 1433, 1370, 1308, 1260, 1190. m/z (ESI+) calculated for C₁₆H₂₄NO₂ [M + H]⁺; 262.1802, observed 262.1802.

Isopropyl (*E*)-3-(diisopropylamino)-2-phenylacrylate (20c). Prepared according to the general procedure, using 2-(diisopropylamino)-3-phenylcycloprop-2-en-1-one and isopropanol to afford the title compound as a brown solid (22.9 mg, 0.079 mmol, 79%), m.p.: 125–127 °C. ¹H NMR (CDCl₃, 400 MHz) δH 7.71 (s, 1H, C=CH), 7.29–7.25 (m, 2H, 2 × ArH), 7.21–7.17 (m, 3H, 3 × ArH), 4.99 (septet, J = 6.2 Hz, 1H, OCH(CH₃)₂), 3.47 (septet, J = 6.7 Hz, 2H, 2 × NCHC₂H₆), 1.15 (d, J = 6.2 Hz, 6H, OCH(CH₃)₂), 1.06 (br. s, 12H, 2 × NCHC₂H₆). ¹³C NMR (CDCl₃, 100 MHz) δC 169.94 (qC), 142.98 (CH),

138.52 (qC), 131.16 (CH), 127.64 (CH), 126.06 (CH), 98.66 (qC), 66.22 (OCH), 47.21 (weak, broad, NCH), 22.15 (CH₃), 21.76 (weak, broad, CH₃). IR ν_{max} (thin film, cm⁻¹): 2980, 2932, 2874, 1731, 1666, 1593, 1495, 1465, 1432, 1371, 1336, 1299. m/z (ESI+) calculated for $C_{18}H_{28}NO_2$ [M + H]⁺; 290.2115, observed 290.2116.

tert-Butyl (E)-3-(diisopropylamino)-2-phenylacrylate (20d)‡. Prepared according to the general procedure, using 2-(diisopropylamino)-3-phenylcycloprop-2-en-1-one and tert-butanol to afford the title compound as a colourless oil (24 mg, 0.079 mmol, 79%). ¹H NMR (CDCl₃, 400 MHz) δ H 7.64 (s, 1H, C=CH), 7.27-7.24 (m, 2H, $2 \times ArH$), 7.19-7.16 (m, 3H, $3 \times C$ ArH), 3.47 (septet, J = 6.6 Hz, 2H, $2 \times NCHC_2H_6$), 1.39 (s, 9H, OC_4H_9), 1.06 (br. s, 12H, 2 × $NCHC_2H_6$). ¹³C NMR (CDCl₃, 100 MHz) δC 169.96 (qC), 142.46 (CH), 138.88 (qC), 131.10 (CH), 127.58 (CH), 125.89 (CH), 99.80 (qC), 78.22 (qC), 47.00 (weak, broad, NCH), 28.52 (CH₃), 21.87 (weak, broad, CH₃). IR ν_{max} (thin film, cm⁻¹): 2976, 1683, 1597, 1576, 1460, 1369, 1297, 1248, 1216, 1179, 1145. m/z (ESI+) calculated for $C_{19}H_{30}NO_2[M + H]^+$; 304.2271, observed 304.2270.

Butyl (E)-3-(diisopropylamino)-2-phenylacrylate (20e). Prepared according to the general procedure, using 2-(diisopropylamino)-3-phenylcycloprop-2-en-1-one and n-butanol to afford the title compound as a colourless oil (23 mg, 0.076 mmol, 76%). ¹H NMR (CDCl₃, 400 MHz) δ H 7.73 (s, 1H, C=CH), 7.29-7.25 (m, 2H, $2 \times ArH$), 7.22-7.17 (m, 3H, $3 \times ArH$), 4.04 (t, $I = 6.6 \text{ Hz}, 2H, OCH_2CH_2$, 3.49 (septet, $I = 6.7 \text{ Hz}, 2H, 2 \times$ $NCHC_2H_6$), 1.52 (m, 2H, CH_2), 1.28 (m, 2H, CH_2), 1.06 (br. s, 12H, $2 \times \text{NCHC}_2H_6$), 0.86 (t, J = 7.4 Hz, 3H, CH_3). ¹³C NMR $(CDCl_3, 100 \text{ MHz}) \delta C 170.46 (qC), 143.14 (CH), 138.43 (qC),$ 131.15 (CH), 127.73 (CH), 126.21 (CH), 98.27 (qC), 63.30 (OCH₂), 47.11 (weak, broad, NCH), 31.02 (CH₂), 21.94 (weak, broad, CH₃), 19.25 (CH₂), 13.76 (CH₃). IR ν_{max} (thin film, cm⁻¹) 2935, 1734, 1689, 1660, 1599, 1252, 1215, 1176, 1148. *m*/ z (ESI+) calculated for $C_{19}H_{30}NO_2 [M + H]^+$; 304.2271, observed 304.2270.

2-Chloroethyl (E)-3-(diisopropylamino)-2-phenylacrylate (20f). Prepared according to the general procedure, using 2-(diisopropylamino)-3-phenylcycloprop-2-en-1-one and 2-chloroethanol to afford the title compound as a yellow solid (23 mg, 0.074 mmol, 74%), m.p.: 72–75 °C. 1 H NMR (CDCl $_{3}$, 400 MHz) δ H 7.79 (s, 1H, C=CH), 7.33-7.26 (m, 2H, 2 × ArH), 7.24-7.22 (m, 3H, 3 × ArH), 4.31 (t, J = 6.0 Hz, 2H, OCH₂), 3.65 (t, J =6.0 Hz, 2H, CH_2Cl), 3.53 (septet, J = 6.6 Hz, 2H, $2 \times NCHC_2H_6$), 1.09 (br. s, 12H, 2 × NCHC₂ H_6). ¹³C NMR (CDCl₃, 100 MHz) δ C 169.60 (qC), 143.97 (CH), 137.92 (qC), 131.16 (CH), 127.88 (CH), 126.46 (CH), 97.42 (qC), 63.07 (OCH₂), 42.34 (CH₂Cl). IR ν_{max} (thin film, cm⁻¹): 2934, 1667, 1589, 1450, 1301, 1261. m/z (ESI+) calculated for $C_{17}H_{24}NClO_2Na [M + Na]^+$; 332.1388, observed 332.1395.

Allyl (E)-3-(diisopropylamino)-2-phenylacrylate (20g). Prepared according to the general procedure, using 2-(diisopropylamino)-3-phenylcycloprop-2-en-1-one and allyl alcohol to afford the title compound as a thick yellow oil (13 mg, 0.045 mmol, 45%). ¹H NMR (CDCl₃, 400 MHz) δ H 7.76 (s, 1H, C=CH), 7.31-7.23 (m, 2H, 2 \times ArH), 7.23-7.20 (m, 3H, 3 \times

ArH), 5.92-5.83 (m, 1H, CH=CH₂), 5.14-5.05 (m, 2H, $CH=CH_2$), 4.57-4.55 (m, 2H, CH_2), 3.49 (septet, J = 6.6 Hz, 2H, $2 \times NCHC_2H_6$, 1.06 (br. s, 12H, $2 \times NCHC_2H_6$). ¹³C NMR (CDCl₃, 100 MHz) δ C 169.96 (qC), 143.57 (CH), 138.26 (qC), 133.71 (CH), 131.19 (CH), 127.85 (CH), 126.36 (CH), 115.79 (CH₂), 97.87 (qC), 63.99 (CH₂), 47.15 (weak, broad, NCH), 21.87 (weak, broad, CH₃). IR ν_{max} (thin film, cm⁻¹): 2975, 1683, 1596, 1574, 1497, 1432, 1370, 1300, 1249, 1215, 1180, 1143. m/ z (ESI+) calculated for $C_{18}H_{26}NO_2 [M + H]^+$; 288.1958, observed 288.1958.

Propargyl (E)-3-(diisopropylamino)-2-phenylacrylate (20h). Prepared according to the general procedure, using 2-(diisopropylamino)-3-phenylcycloprop-2-en-1-one and propargyl alcohol to afford the title compound as a yellow solid (23 mg, 0.081 mmol, 81%), m.p.: 72-75 °C. ¹H NMR (CDCl₃, 400 MHz) δ H 7.79 (s, 1H, C=CH), 7.34-7.27 (m, 2H, 2 × ArH), 7.25-7.22 (m, 3H, 3 × ArH), 4.66 (d, J = 2.4 Hz, 2H, CH₂), 3.51 (septet, J =6.6 Hz, 2H, $2 \times NCHC_2H_6$), 2.37 (t, J = 2.4 Hz, 1H, C=CH), 1.09 (br. s, 12H, 2 × NCHC₂ H_6). ¹³C NMR (CDCl₃, 100 MHz) δ C 169.33 (qC), 144.27 (CH), 137.83 (qC), 131.20 (CH), 127.93 (CH), 126.51 (CH), 97.26 (qC), 79.59 (qC), 73.23 (CH), 51.02 (CH₂), 47.35 (very weak, broad, NCH), 21.88 (very weak, broad, CH₃). IR ν_{max} (thin film, cm⁻¹): 3295, 2979, 1673, 1563, 1456, 1367, 1244, 1178, 1070. m/z (ESI+) calculated for C₁₈H₂₄NO₂ [M + H]⁺; 286.1802, observed 286.1802.

4-Methylbenzyl (E)-3-(diisopropylamino)-2-phenylacrylate (20i). Prepared according to the general procedure, using 2-(diisopropylamino)-3-phenylcycloprop-2-en-1-one and 4-methylbenzyl alcohol to afford the title compound as a yellow oil (28 mg, 0.080 mmol, 80%). ¹H NMR (CDCl₃, 400 MHz) δ H 7.75 (s, 1H, C=CH), 7.31-7.26 (m, 2H, $2 \times ArH$), 7.23-7.20 (m, 3H, $3 \times ArH$), 7.12 (dd, J = 8.2 Hz, 5.4 Hz, 4H, $2 \times ArH$), 7.08 (dd, J =8.2 Hz, 5.4 Hz, 4H, $2 \times ArH$), 5.08 (s, 2H, CH_2), 3.49 (septet, J =6.6 Hz, 2H, $2 \times NCHC_2H_6$), 2.31 (s, 3H, CH_3), 1.05 (br. s, 12H, $2 \times \text{NCHC}_2H_6$). ¹³C NMR (CDCl₃, 100 MHz) δ C 170.06 (qC), 143.57 (CH), 138.31 (qC), 136.80 (qC), 134.94 (qC), 131.22 (CH), 128.87 (CH), 127.84 (CH), 127.19 (CH), 126.34 (CH), 97.99 (qC), 64.89 (CH₂), 47.23 (weak, broad, NCH), 22.02 (weak, broad, CH₃), 21.14 (CH₃). IR ν_{max} (thin film, cm⁻¹): 2976, 1733, 1687, 1596, 1548, 1450, 1379, 1265, 1194, 1173. m/z (ESI+) calculated for $C_{23}H_{30}NO_2$ [M + H]⁺; 352.2271, observed 352.2271.

4-Methoxybenzyl (E)-3-(diisopropylamino)-2-phenylacrylate (20j). Prepared according to the general procedure, using 2-(diisopropylamino)-3-phenylcycloprop-2-en-1-one and 4-methoxybenzyl alcohol to afford the title compound as a pale-yellow solid (21 mg, 0.057 mmol, 57%), m.p.: 81-84 °C. ¹H NMR $(CDCl_3, 400 \text{ MHz}) \delta H 7.77 \text{ (s, 1H, C=CH)}, 7.33-7.29 \text{ (m, 2H, C=CH)}$ $2 \times ArH$), 7.25-7.18 (m, 5H, 5 × ArH), 6.84 (d, J = 8.6 Hz, 2H, $2 \times ArH$), 5.07 (s, 2H, CH₂), 3.81 (s, 3H, OCH₃), 3.51 (septet, J =6.6 Hz, 2H, $2 \times NCHC_2H_6$), 1.07 (br. s, 12H, $2 \times NCHC_2H_6$). ¹³C NMR (CDCl₃, 100 MHz) δC 170.07 (qC), 158.86 (qC), 143.54 (CH), 138.32 (qC), 131.20 (CH), 130.14 (qC), 128.83 (CH), 127.83 (CH), 126.33 (qC), 113.59 (CH), 90.03 (qC), 64.73 (OCH₂), 55.24 (1C, OCH₃), 22.1 (weak, broad, CH₃). IR ν_{max} (thin film, cm⁻¹): 2980, 1665, 1589, 1516, 1464, 1439, 1371, 1307, 1246, 1173, 1142, 1028. m/z (ESI+) calculated for $C_{23}H_{30}NO_3 [M + H]^+$; 368.2220, observed 368.2235.

3-Methoxybenzyl (E)-3-(diisopropylamino)-2-phenylacrylate (20k). Prepared according to the general procedure, using 2-(diisopropylamino)-3-phenylcycloprop-2-en-1-one and 3-methoxybenzyl alcohol to afford the title compound as a pale-yellow oil (32 mg, 0.087 mmol, 87%). 1 H NMR (CDCl₃, 400 MHz) δH 7.78 (s, 1H, C=CH), 7.31-7.26 (m, 3H, $2 \times ArH$), 7.24-7.21 (m, 2H, $2 \times ArH$), 7.19 (d, 1H, J = 8.0 Hz, ArH), 6.79 (d, 1H, J =7.6 Hz, ArH), 6.75 (dd, 1H, J = 8.2 Hz, 2.4 Hz, ArH), 6.70 (s, 1H, ArH), 5.10 (s, 2H, CH₂), 3.71 (s, 3H, OCH₃), 3.50 (septet, J =6.6 Hz, 2H, $2 \times NCHC_2H_6$), 1.06 (br. s, 12H, $2 \times NCHC_2H_6$). ¹³C **NMR** (CDCl₃, 100 MHz) δ C 170.03 (qC), 159.57 (qC) 143.25 (CH), 139.52 (qC), 138.32 (qC), 131.26 (CH), 129.17 (CH), 127.89 (CH), 126.40 (CH), 119.00 (CH), 113.31 (CH), 111.58 (CH), 97.82 (qC), 64.74 (CH₂), 55.17 (OCH₃), 47.35 (weak, broad, NCH), 21.83 (weak, broad, CH₃). IR ν_{max} (thin film, cm⁻¹): 2940, 1738, 1690, 1597, 1461, 1270, 1195, 1175. m/z (ESI+) calculated for $C_{23}H_{30}NO_3 [M + H]^+$; 368.2220, observed 368.2220.

2-Aminobenzyl (E)-3-(diisopropylamino)-2-phenylacrylate (201). Prepared according to the general procedure, using 2-(diisopropylamino)-3-phenylcycloprop-2-en-1-one and 2-aminobenzyl alcohol to afford the title compound as a white solid (18 mg, 0.051 mmol, 51%), m.p.: 119–121 °C. ¹H NMR (CDCl₃, 400 MHz) δ H 7.75 (s, 1H, C=CH), 7.33-7.28 (m, 1H, ArH), 7.26-7.19 (m, 3H, 3 × ArH), 7.15 (dd, J = 7.4 Hz, 1.2 Hz, 1H, ArH), 7.10 (ddd, J = 8.0 Hz, 1.5 Hz, 1.5 Hz, 1H, ArH), 6.70 (ddd, J = 7.4 Hz, 1.0 Hz, 1.0 Hz, 1H, ArH), 6.62 (dd, <math>J = 8.0 Hz,0.6 Hz, 1H, ArH), 5.09 (s, 2H, CH₂), 3.87 (br. s, 2H, NH₂), 3.51 (septet, J = 6.5 Hz, 2H, $2 \times NCHC_2H_6$), 1.07 (br. s, 12H, $2 \times$ $NCHC_2H_6$). ¹³C NMR (CDCl₃, 100 MHz) δ C 170.02 (qC), 146.32 (qC), 143.80 (CH), 138.34 (qC), 131.14 (CH), 130.66 (CH), 129.15 (CH), 128.00 (CH), 126.49 (CH), 122.01 (qC), 117.93 (CH), 115.89 (CH), 97.57 (qC), 67.79 (OCH₂), 47.25 (broad, NCH), 21.71 (broad, CH₃). IR ν_{max} (thin film, cm⁻¹): 2976, 1734, 1676, 1571, 1495, 1459, 1369, 1298, 1246, 1180. m/z (ESI+) calculated for $C_{22}H_{29}N_2O_2 [M + H]^+$; 353.2224, observed 353.2221.

2-Azidobenzyl (E)-3-(diisopropylamino)-2-phenylacrylate (20m). Prepared according to the general procedure, using 2-(diisopropylamino)-3-phenylcycloprop-2-en-1-one and 2-azidobenzyl alcohol to afford the title compound as a brown solid (29 mg, 0.077 mmol, 77%), m.p.: 125-127 °C. ¹H NMR (CDCl₃, 400 MHz) δ H 7.77 (s, 1H, C=CH), 7.32-7.21 (m, 6H, 6 × ArH), 7.11 (dd, J = 7.9 Hz, 7.9 Hz, 2H, ArH), 7.03 (ddd, J = 7.5 Hz, 0.9 Hz, 0.9 Hz, 1H, ArH), 5.07 (s, 2H, CH_2), 3.51 (septet, J =6.5 Hz, 2H, $2 \times \text{NC}HC_2H_6$), 1.06 (br. s, 12H, $2 \times \text{NC}HC_2H_6$). ¹³C **NMR** (CDCl₃, 100 MHz) δ C 169.87 (qC), 143.74 (CH), 138.23 (qC), 137.32 (qC), 131.22 (CH), 129.25 (qC), 128.55 (CH), 128.39 (CH), 127.88 (CH), 126.43 (CH), 124.63 (CH), 117.80 (CH), 97.75 (qC), 60.72 (OCH₂), 47.30 (weak, broad, NCH), 22.00 (broad, CH₃). IR ν_{max} (thin film, cm⁻¹): 2851, 2126, 1731, 1681, 1594, 1492, 1450, 1379. m/z (ESI+) calculated for $C_{22}H_{27}N_4O_2[M+H]^+$; 379.2129, observed 379.2129.

Phenyl (*E*)-3-(diisopropylamino)-2-phenylacrylate (20n). Prepared according to the general procedure, using 2-(diiso-

propylamino)-3-phenylcycloprop-2-en-1-one and phenol to afford the title compound as a white waxy solid (30 mg, 0.094 mmol, 94%). ¹H NMR (CDCl₃, 400 MHz) δH 7.88 (s, 1H, C=CH), 7.32–7.22 (m, 7H, 7 × ArH), 7.11 (t, J = 7.4 Hz, 1H, 1 × ArH), 7.05 (d, 2H, J = 7.6 Hz, 2 × ArH), 3.58 (bs, 2H, 2 × NCHC₂H₆), 1.12 (bs, 12H, 2 × NCHC₂H₆). ¹³C NMR (CDCl₃, 100 MHz) δC 169.05 (qC), 152.12 (qC), 144.90 (CH), 137.88 (qC), 131.24 (CH), 128.88 (CH), 127.98 (CH), 126.59 (CH), 124.56 (CH), 122.16 (CH), 97.11 (qC). IR $\nu_{\rm max}$ (thin film, cm⁻¹): 3378, 2980, 1666, 1590, 1557, 1485, 1456, 1261, 1194, 1140. m/z (ESI+) calculated for C₂₁H₂₅NO₂Na [M + Na]⁺; 346.1778, observed 346.1785.

Phenyl (*E*)-3-(diisopropylamino)-2-phenylprop-2-enethioate (200). Prepared according to the general procedure, using 2-(diisopropylamino)-3-phenylcycloprop-2-en-1-one and thiophenol to afford the title compound as a yellow oil (24 mg, 0.071 mmol, 71%). ¹H NMR (CDCl₃, 400 MHz) δH 7.80 (s, 1H, C=CH), 7.41–7.37 (m, 7H, 7 × ArH), 7.35–7.29 (m, 3H, 3 × ArH), 3.52 (bs, 2H, 2 × NCHC₂H₆), 1.05 (bs, 12H, 2 × NCHC₂H₆). ¹³C NMR (CDCl₃, 100 MHz) δC 188.54 (qC), 142.02 (CH), 137.04 (qC), 135.26 (CH), 132.84 (CH), 131.08 (qC), 128.55 (CH), 128.28 (CH), 128.24 (CH), 127.95 (CH), 107.01 (qC), 48.94 (very weak, very broad, NCH), 20.60 (very weak, very broad, CH₃). IR ν_{max} (thin film, cm⁻¹): 2976, 1651, 1549, 1477, 1457, 1386, 1305, 1219, 1110. m/z (ESI+) calculated for C₂₁H₂₆NOS [M + H]⁺; 340.1735, observed 340.1738.

Ethyl (E)-3-(dibenzylamino)-2-phenylacrylate (20p). Prepared according to the general procedure, using 2-(dibenzylamino)-3phenylcycloprop-2-en-1-one and ethanol to afford the title compound as yellow oil (29 mg, 0.078 mmol, 78%). ¹H NMR (CDCl₃, 400 MHz) δ H 7.95 (s, 1H, C=CH), 7.33-7.25 (m, 6H, $6 \times ArH$), 7.16-7.06 (m, 9H, 9 × ArH), 4.14 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.04 (bs, 4H, 2 × $NCH_2C_6H_5$), 1.18 (t, J = 7.1 Hz, 3H, OCH₂CH₃). ¹³C NMR (CDCl₃, 100 MHz) δ C 170.27 (qC), 148.75 (CH), 136.78 (qC), 136.14 (qC), 131.59 (CH), 128.65 (CH), 127.63 (CH), 127.57 (CH), 127.46 (CH), 126.54 (CH), 100.70 (qC), 59.79 (OCH₂), 55.10 (very weak, broad, NCH₂), 14.59 (CH₃). IR ν_{max} (thin film, cm⁻¹): 2989, 1684, 1593, 1389, 1275, 1200, 1140, 1133. m/z (ESI+) calculated for C₂₅H₂₆NO₂ [M + H]⁺; 372.1958, observed 372.1958. Previously reported by other workers using a different route. 69 NMR data is consistent with that reported for this compound previously.⁶⁹

Phenyl (*E*)-3-(dibenzylamino)-2-phenylacrylate (20q)§. Prepared according to the general procedure, using 2-(dibenzylamino)-3-phenylcycloprop-2-en-1-one and phenol to afford the title compound as a colourless oil (35 mg, 0.083 mmol, ~60% as the sample contains ~20% phenol by 1 H NMR). 1 H NMR (CDCl₃, 400 MHz) δH 8.12 (s, 1H, C=CH), 7.35–7.27 (m, 8H, 8 × ArH), 7.25–7.17 (m, 3H, 3 × ArH), 7.16–7.14 (m, 3H, 3 × ArH), 7.12–7.06 (m, 6H, 6 × ArH), 4.04 (br. s, 4H, 2 × NCH₂C₆H₅); phenol was seen as small triplet and doublet just below 7 ppm

§ This material could not be completely separated from the excess of phenol used despite repeated attempts. The yield is estimated from the total amount of material obtained and the ratio of phenol to compound **20q** in the proton NMR.

with the OH at ~ 5.3 ppm ($\sim 20\%$). ¹³C NMR (CDCl₃, 100 MHz) δC 168.99 (qC), 155.76 (qC, PhOH), 151.84 (qC), 150.24 (CH), 136.38 (qC), 135.63 (qC), 131.69 (CH), 129.59 (CH, PhOH), 129.05 (CH), 128.75 (CH), 127.84 (CH), 127.75 (CH), 127.49 (CH), 126.88 (CH), 124.88 (CH), 122.07 (CH), 120.50 (CH, PhOH), 115.32 (CH, PhOH), 99.51 (qC). IR ν_{max} (thin film, cm⁻¹): 2976, 1734, 1676, 1571, 1495, 1459, 1369, 1298, 1246, 1180. m/z (ESI+) calculated for $C_{29}H_{26}NO_2 [M + H]^+$; 420.1958, observed 420.1967.

2-Azidobenzyl (E)-3-(dibenzylamino)-2-phenylacrylate (20r). Prepared according to the general procedure, using 2-(dibenzylamino)-3-phenylcycloprop-2-en-1-one and 2-azidobenzyl alcohol to afford the title compound as a brown solid (39 mg, 0.082 mmol, 82%), m.p.: 110-112 °C. ¹H NMR (CDCl₃, 400 MHz) δ H 7.99 (s, 1H, C=CH), 7.33-7.27 (m, 7H, 7 × ArH), 7.17-7.11 (m, 7H, $7 \times ArH$), 7.08-7.02 (m, 5H, $5 \times ArH$), 5.11 (s, 2H, CH_2), 4.06 (bs, 4H, 2 × $NCH_2C_6H_5$). ¹³C NMR (CDCl₃, 100 MHz) δ C 169.84 (qC), 149.12 (CH), 137.51 (qC), 136.60 (qC), 135.94 (qC), 131.63 (CH), 128.78 (qC), 128.67 (CH), 128.59 (CH), 127.69 (CH), 127.62 (CH), 127.45 (CH), 126.69 (CH), 124.66 (CH), 117.86 (CH), 100.17 (qC), 61.09 (OCH₂). IR ν_{max} (thin film, cm⁻¹): 2973, 2125, 1684, 1593, 1494, 1453, 1377, 1295, 1229, 1129. m/z (ESI+) calculated for C₃₀H₂₇N₄O₂ $[M + H]^+$; 475.2129, observed 475.2135.

Methyl (E)-3-(dimethylamino)-2-(phenyl)acrylate (20s). Prepared according to the general procedure, using 2-(dimethylamino)-3-phenylcycloprop-2-en-1-one (0.1000 g), and methanol (0.5 mL) in chloroform (5 mL) to afford the title compound as a viscous yellow oil (0.1050 g, 89%). ¹H NMR (CDCl₃, 400 MHz) δ H 7.56 (s, 1H, C=CH), 7.30-7.24 (m, 2H, 2 × ArH), 7.23-7.17 (m, 3H, $3 \times ArH$), 3.62 (s, 3H, OCH₃), 2.66 (s, 6H, N(CH₃)₂). ¹³C **NMR** (CDCl₃, 100 MHz) δ C 170.62 (qC), 149.29 (CH), 136.54 (qC), 132.11 (CH), 127.35 (CH), 126.26 (CH), 98.97 (qC), 51.16 (CH₃), 43.02 (CH₃). Previously reported by other workers using a different route.25,70,71 NMR data is consistent with that reported previously and was identical to a sample produced using the reported route.

Methyl (E)-3-(diisopropylamino)-2-(2,4-dimethylphenyl)acrylate (20t). Prepared according to the general procedure, using 2-(diisopropylamino)-3-(2,4-dimethylphenyl)cycloprop-2-en-1one and methanol to afford the title compound as a yellow solid (21.1 mg, 0.073 mmol, 73%), m.p.: 103–106 °C. ¹H NMR $(CDCl_3, 400 \text{ MHz}) \delta H 7.76 \text{ (s, 1H, C=C}H), 6.99-6.91 \text{ (m, 3H, C=C}H)$ $3 \times ArH$), 3.60 (s, 3H, OCH₃), 3.45 (septet, J = 6.6 Hz, 2H, 2×10^{-2} $NCHC_2H_6$), 2.31 (s, 3H, ArC H_3), 2.15 (s, 3H, ArC H_3), 1.06 (br. s, 12H, 2 × NCHC₂ H_6). ¹³C NMR (CDCl₃, 100 MHz) δ C 170.98 (qC), 143.45 (CH), 137.82 (qC), 136.38 (qC), 134.29 (qC), 131.11 (CH), 130.34 (CH), 126.29 (CH), 96.28 (qC), 51.15 (OCH₃), 46.97 (very weak, broad, NCH), 22.70 (weak, very broad, N(CH $(CH_3)_2)_2$, 21.24 (CH₃), 20.01 (CH₃). IR ν_{max} (thin film, cm⁻¹): 2974, 1664, 1581, 1486, 1477, 1442, 1431, 1308, 1283, 1195. m/z (ESI+) calculated for $C_{18}H_{28}NO_2$ [M + H]⁺; 290.2115, observed 290.2126.

Ethyl (E)-3-(diisopropylamino)-2-(2,4-dimethylphenyl)acrylate (20u). Prepared according to the general procedure, using 2-(diisopropylamino)-3-(2,4-dimethylphenyl)cycloprop-2-en-1one and ethanol to afford the title compound as a yellow solid (28 mg, 0.092 mmol, 92%), m.p.: 60-63 °C. ¹H NMR (CDCl₃, 400 MHz) δ H 7.75 (s, 1H, C=CH), 6.98-6.90 (m, 3H, 3 × ArH), 4.19-4.11 (m, 1H, OCH_2CH_3), 4.06-3.98 (m, 1H, OCH_2CH_3), 3.44 (septet, J = 6.7 Hz, 2H, $2 \times NCHC_2H_6$), 2.30 (s, 3H, ArC H_3), 2.15 (s, 3H, ArC H_3), 1.15 (t, I = 7.1 Hz, 3H, OCH₂C H_3), 1.05 (br. s, 12H, 2 × NCHC₂ H_6). ¹³C NMR (CDCl₃, 100 MHz) δ C 170.41 (qC), 143.19 (CH), 137.77 (qC), 136.18 (qC), 134.44 (qC), 131.09 (CH), 130.23 (CH), 126.18 (CH), 96.72 (qC), 59.21 (OCH₂), 46.92 (very weak, broad, NCH), 22.05 (weak, broad, CH₃), 21.23 (CH₃), 20.00 (CH₃), 14.73 (CH₃). IR ν_{max} (thin film, cm⁻¹): 2975, 1673, 1569, 1503, 1454, 1369, 1245, 1184, 1163, 1142, 1114, 1046. m/z (ESI+) calculated for $C_{19}H_{30}NO_2$ [M + H]⁺; 304.2271, observed 304.2268.

(E)-3-(diisopropylamino)-2-(2,4-dimethylphenyl) Isopropyl acrylate (20v). Prepared according to the general procedure, using 2-(diisopropylamino)-3-(2,4-dimethylphenyl)cycloprop-2en-1-one and isopropanol to afford the title compound (17 mg, 0.054 mmol, 54%) as a pale yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ H 7.72 (s, 1H, C=CH), 6.96-6.88 (m, 3H, 3 × ArH), 4.98 (septet, J = 6.2 Hz, 1H, OCH), 3.45 (septet, J = 6.7 Hz, 2H, $2 \times NCHC_2H_6$, 2.30 (s, 3H, ArCH₃), 2.14 (s, 3H, ArCH₃), 1.13 (d, J = 6.2 Hz, 3H, OCHC H_3), 1.11 (d, J = 6.2 Hz, 3H, OCHC H_3), 1.05 (bs, 12H, 2 × NCHC₂ H_6). ¹³C NMR (CDCl₃, 150 MHz) δ C 170.00 (qC), 142.85 (CH), 137.71 (qC), 135.93 (qC), 134.58 (qC), 131.07 (CH), 130.07 (CH), 126.04 (CH), 97.21 (qC), 65.93 (OCH), 46.62 (very weak, broad, NCH), 22.16 (CH₃), 22.07 (CH_3) , 21.71 (very weak, CH_3), 21.21 (CH_3) , 19.99 (CH_3) . IR ν_{max} (thin film, cm⁻¹): 2974, 1666, 1592, 1464, 1434, 1369, 1304, 1258, 1174, 1143, 1108, 1086. m/z (ESI+) calculated for $C_{20}H_{32}NO_2 [M + H]^+$; 318.2428, observed 318.2441.

Ethyl 3-chloro-2-(2,4-dimethoxyphenyl)acrylate (28). Prepared from 2-chloro-3-(2,4-dimethoxyphenyl)cycloprop-2-en-1-one 27 and ethanol according to the procedure used for compounds 20. The reaction mixture was concentrated in reduced pressure to remove the solvents and afford the title compound as a light brown oil (38 mg, 0.082 mmol, 82%). ¹H NMR (CDCl₃, 400 MHz) δ H 7.23 (d, J = 8.5 Hz, 1H, ArH), 6.53 (dd, J = 8.5 Hz, 2.3 Hz, 1H, ArH), 6.48 (d, J = 2.3 Hz, 1H, ArH), 6.37 (s, 1H, C=CH), 4.06 (q, 2H, J = 7.1 Hz, OCH₂CH₃), 3.85 (s, 3H, OCH₃), 3.82 (s, 3H, OC H_3), 1.15 (t, 3H, J = 7.1 Hz, OC H_2 C H_3). ¹³C NMR (CDCl₃, 100 MHz) δ C 163.94 (qC), 162.16 (qC), 157.29 (qC), 146.35 (qC), 130.58 (CH), 121.44 (CH), 119.05 (qC), 104.42 (CH), 98.51 (CH), 60.26 (OCH₂), 55.65 (OCH₃), 55.41 (OCH₃), 14.02 (CH₃). IR ν_{max} (thin film, cm⁻¹): 2938, 2839, 1721, 1602, 1576, 1503, 1456, 1438, 1416, 1303, 1282, 1261, 1208. m/z (ESI+) calculated for $C_{13}H_{16}ClO_4 [M + H]^+$; 271.0732, observed 271.0732.

Ethyl (Z)-3-hydroxy-2-phenylacrylate (29). Method 1: according to the general procedure for compounds 20, using 2-hydroxy-3-phenylcycloprop-2-en-1-one and ethanol to afford the title compound as a light brown oil (158 mg, 0.82 mmol, 82%). Method 2: ethyl phenylacetate (1.5 g, 9.15 mmol) was added to a stirring solution of ethyl formate (4.74 g, 64.0 mmol) in THF (15 ml). NaH (60% dispersion in mineral oil, 0.73 g, 18.3 mmol) at 0 °C was slowly added to the reaction

mixture and the resulting mixture was stirred at room temperature for 3 h. The resulting mixture was poured into ice-cold water (50 mL) and adjusted to pH 5 using 1 M HCl. The reaction mixture was extracted with dichloromethane (2 × 25 mL), washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure to yield title compound as an orange oil (1.7 g, 8.84 mmol, 97%). ¹H NMR (CDCl₃, 400 MHz) δ H 12.15 (d, J = 12.6 Hz, 1H, CHOH), 7.38–7.28 (m, 6H, 5 × ArH + OH), 4.32 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 1.32 (t, J = 7.1 Hz, 3H, OCH₂CH₃). The analytical data is consistent with the literature. ^{73,74}

Cell line studies

HCT116 Human Colon Carcinoma cells (American Type Culture Collection) were cultured in DMEM (Dulbecco's Modified Eagle Medium) supplemented with 10% foetal bovine serum, 1% sodium pyruvate and 1% L-glutamine and incubated at 37 °C and 5% CO2. The cells were plated onto 96-well plates (CytoOne) at a density of 1×10^4 cells per mL. The 96-well plates were incubated at 37 °C, 5% CO₂ for 24 h. After 24 h elapsed, the cells received various concentrations $(10^{-4}-10^{-11} \text{ M})$ of cis-platin, the synthesised compounds in ethanol, or ethanol as the vehicle. The concentration of ethanol did not exceed 1% and preliminary experiments showed that 1% ethanol did not induce any cytotoxicity in the cells. The plates were left in the incubator for 96 h at 37 °C in 5% CO₂. After 96 h had elapsed, the supernatant was removed from the plate and MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] (10%) was added to the wells and the plate was then incubated at 37 °C for 4 h in 5% CO2. The formation of formazan crystals was determined using a Magellan Infinite F50 microplate reader after dissolving the crystals in DMSO (Fisher). Cell viability was expressed as a relative percentage of the absorbance measured at 540 nm in control and treated cells. Data were determined as the mean ± standard error of mean, and each experiment was repeated four times, and each concentration of compound was tested in triplicate on the 96-well plate.

Author contributions

BT and CL carried out all original synthetic experimental work under the supervision of KH. MS carried out confirmatory and alternative syntheses under the supervision of KH. BT carried out biological experimental work under the supervision of FJ. KH and BT conceived and designed the chemistry reactions. KH, BT and FJ conceived and designed the biological experimentation. KH conceived the ideas and wrote the manuscript. All authors approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

Data availability

The data supporting this article are included in the experimental section of the published article and as part of the SI. Supplementary information: copies of NMR spectra for previously unreported compounds. See DOI: https://doi.org/10.1039/d5ob01290b.

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