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Tandem inverse electron demand Diels–Alder, retro-Diels–Alder and intramolecular Diels–Alder sequences: one-pot synthesis of diaza-polycycles

William J. Bromley,[a] Mairi Gibson,[b] Stuart Lang,[a] Steven A. Raw,[a,*] Adrian C. Whitwood[a] and Richard J. K. Taylor[a,*]

[a]*Department of Chemistry, University of York, Heslington, York YO10 5DD, UK*
[b]*Neurology & GI CEDD, GlaxoSmithKline R&D, New Frontiers Science Park, Harlow CM19 5AW, UK*

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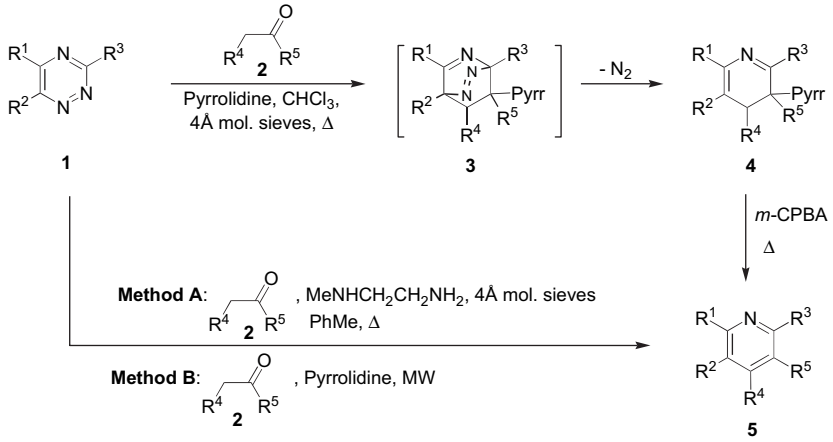
Abstract—A new and straightforward methodology is described for the construction of complex nitrogen-containing polycycles from substituted 1,2,4-triazines and enamines, prepared in situ from carbonyl components and allylic amines. The transformation proceeds via a pericyclic reaction cascade (inverse electron demand Diels–Alder then retro-Diels–Alder then intramolecular Diels–Alder) forming the polycyclic systems in good to excellent yield and with high diastereoselectivity in a one-pot procedure. The scope and limitations of the methodology are described as are preliminary studies to extend its synthetic utility.

1. Introduction

1,2,4-Triazine derivatives have a range of applications, for example, in medicine, agrochemistry and as ligands for metal ions.[1,2] However, from a synthetic chemistry standpoint, one of the most important roles of 1,2,4-triazines is as substrates for inverse electron demand Diels–Alder sequences, which can be employed to prepare a wide range of heterocyclic systems.[3,4] The use of this approach to prepare pyridines is particularly valuable[4,5] and we recently disclosed new variants of the inverse electron demand Diels–Alder reaction of substituted 1,2,4-triazines with enamines to prepare highly substituted pyridines (Scheme 1).[6]

Thus, using Boger's in situ enamine-formation protocol[4a] with polysubstituted triazines **1** and ketones **2** we established



Scheme 1.

Keywords: Substituted 1,2,4-triazines; Diels–Alder reactions; Inverse electron demand; IMDA; Cascade or tandem processes; Diaza-polycycles.
* Corresponding authors. Fax: +44 (0) 1904 434523; e-mail: rjkt1@york.ac.uk

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that the Diels–Alder/retro-Diels–Alder sequence via intermediate **3** proceeded smoothly but, perhaps unsurprisingly,[5] in situ elimination/aromatisation was not observed and dihydropyridines **4** were isolated in excellent yields; oxidation and Cope elimination[5a] were then employed to convert **4** into the required pyridines **5**. In order to overcome this limitation, we went on to design a novel tethered imine–enamine (TIE) methodology (Method A)[6a,b] for the direct conversion of 1,2,4-triazines **1** into highly substituted pyridines **5**, and then later developed a solvent-free microwave (MW) procedure (Method B),[6b,c] both of which gave successful results when applied to the one-pot preparation of highly substituted pyridines directly from triazines **1** and the appropriate ketones **2**. These tandem sequences involve enamine formation from ketone **2**, inverse electron demand Diels–Alder giving **3**, retro-Diels–Alder with loss of nitrogen giving **4** and then elimination/aromatisation producing pyridines **5**.

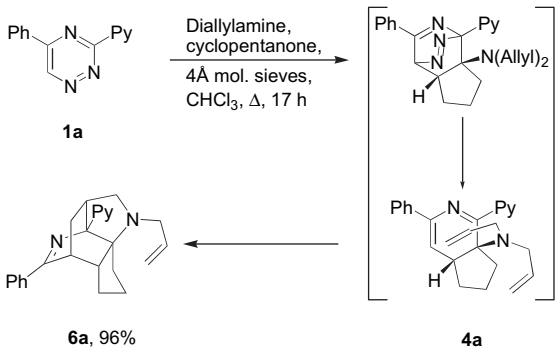
Given our long-standing interest in one-pot, tandem processes,[7] we became intrigued by the possibility that dihydropyridines of type **4**, generated from 1,2,4-triazines **1**, could be exploited in further reaction cascades. The *s-cis*-2-azabutadiene moiety found in dihydropyridines **4** is known to be a suitable substrate for Diels–Alder (DA) reactions,[3a,8] and we therefore envisaged preparing compound **4a** in which the amino substituent bears an internal dienophile (Scheme 2). Such a modification would be expected to promote a subsequent intramolecular Diels–Alder (IMDA) reaction giving polycyclic products **6**. Thus, in a one-pot process we would have enamine formation followed by (i) an inverse electron demand DA reaction, (ii) a retro-DA reaction, and (iii) an IMDA reaction.

If successful, such an approach would lead to a dramatic increase in molecular complexity: the planar triazine unit would be transformed into a tricyclic system **6** with the formation of four new C–C bonds and up to six new stereogenic centres, with potential control of diastereoselectivity. A preliminary communication describing the success of this novel approach to diaza-polycyclic systems has been published;[9] we now report the scope and limitations of this sequence together with additional examples and full experimental details.

2. Preliminary studies

In order to establish the viability of this procedure, we first investigated the reaction between the readily-available 1,2,4-triazine **1a**,[10] cyclopentanone and diallylamine (to generate the corresponding enamine in situ) as shown in Scheme 3.

When the reaction was carried out in chloroform at reflux overnight in the presence of powdered 4 Å molecular sieves, we were delighted to observe the formation of 7-allyl-12-phenyl-10-(2-pyridyl)-7,11-diazatetracyclo[7.3.1.$0^{2,6}$.$0^{6,10}$]-tridec-11-ene **6a** as a single diastereoisomer in a gratifying 96% isolated yield (Scheme 3).



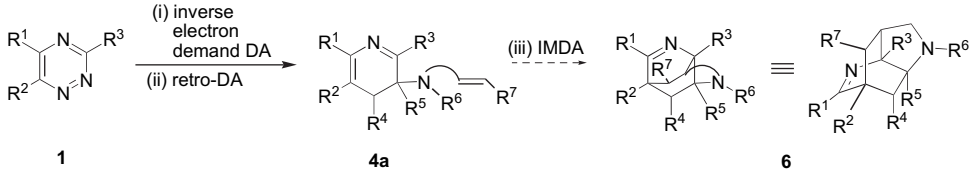
Scheme 3.

In this multi-step process, it should be noted that the use of a cyclic enamine (derived from cyclopentanone and diallylamine) produces a tetracyclic product (**6a**) with the formation of four new C–C bonds and five new stereogenic centres in a regio- and diastereo-selective process. The structure was elucidated by comprehensive 2-D NMR studies (COSY, NOESY and HSQC), which confirmed the expected regioselectivity of the initial enamine addition (preferential addition of the nucleophilic carbon of the enamine occurs at the C-6 centre of 5-phenyl-3-(2-pyridyl)-[1,2,4]triazine **1a**[6b]) and the diastereoselectivity of subsequent IMDA reaction. It should be noted that subsequent studies produced a crystalline product and an X-ray crystallography confirmed this structural assignment (see later).

3. Variation of the triazine unit

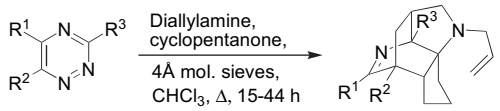
With the result shown in Scheme 3 in hand, we went on to study the scope of this chemistry, first with respect to the triazine **1** (Table 1). In all cases, the isolated yields were high and single diastereoisomers were observed (NMR analysis indicated that the regioselectivity seen in the enamine addition to **1a** was mirrored in other examples). As can be seen, this chemistry is not limited to highly substituted systems, with a variety of mono-, di- and tri-substituted triazines proving to be acceptable substrates (entries i–v).

The success with the mono-substituted triazine **1d** (entry iv) is particularly noteworthy as the dihydropyridine intermediate **4** obtained from this substrate would be expected to undergo reasonably facile elimination/aromatization,[4] but the IMDA process obviously occurs at a faster rate as no pyridine product was observed.



Scheme 2.

Table 1. Scope of the methodology with respect to the triazine



1 6

	Triazine	R^1	R^2	R^3	Isolated yield (%)
i	**1a**	Ph	H	2-Pyridyl	**6a**, 96[a]
ii	**1b**	2-Furyl	2-Furyl	2-Pyridyl	**6b**, 89[b]
iii	**1c**	Ph	H	CO_2Et	**6c**, 88
iv	**1d**	H	H	CO_2Et	**6d**, 89
v	**1e**	H	Ph	CO_2Et	**6e**, 95

[a] Isolated yield is 97% when performed under microwave conditions (see text).
[b] Isolated yield is 86% when performed under microwave conditions (see text).

In view of the fairly-long-reaction times needed for the thermal process, microwave acceleration was investigated for triazines **1a** and **1b** (entries i and ii). Microwave reactions were performed using a CEM Discover® Microwave synthesiser on 50 mg scale with standard proportions of amine, ketone, molecular sieves and solvent. However, even at 300 W and 90 °C, although high yields were obtained, the reaction times were still 4 h, which does not represent a significant improvement. Therefore, the conventional thermal procedure was employed in all subsequent synthetic studies.

4. Variation of carbonyl unit

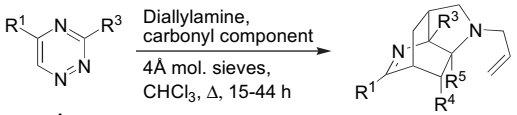
The scope of this method was next investigated with respect to the carbonyl unit (Table 2). Initially, 3-(ethoxycarbonyl)-5-phenyl-[1,2,4]triazine **1c** was treated with diallylamine and a range of cyclic ketones; thus, as well as cyclopentanone (entry i), which has already been discussed, cyclobutanone (entry ii) and cyclohexanone (entry iii) gave the tetracyclic products **6f** and **6g** in excellent yields, respectively. In addition, the use of the more complex bicyclic ketone, bicyclo[3.2.0]hept-2-en-6-one was explored and this gave the expected diazapentacyclic product **6h** in quantitative yield with complete diastereoselectivity (entry iv). As well as using cyclic ketones, reaction of triazine **1c** with pentanal was studied: again, the process was efficient and regioselective and only one diastereomer **6i** was obtained (entry v).[11] Other combinations were also explored. Thus, 5-phenyl-3-(2-pyridyl)-[1,2,4]triazine **1a** was treated with diallylamine and pentanal (entry vi) and 3-(ethoxycarbonyl)-[1,2,4]triazine **1d** was treated with diallylamine and cyclohexanone (entry vii) giving the expected products **6j**[11] and **6k**.

The above result using cyclobutanone (Table 2, entry ii) deserves further comment. We have recently shown that cyclobuta-annelated dihydropyridines such as **4b** undergo spontaneous electrocyclic ring expansion, providing a novel route to prepare 4,5-dihydroazocines such as **7a** (Scheme 4).[12] The reaction between triazine **1c**, cyclobutanone and diallylamine (Table 2, entry ii), shown in more detail in Scheme 5, was therefore of interest as the intermediate dihydropyridine **4c** could, in principle, undergo either type of pericyclic reaction, with electrocyclic ring expansion giving 4,5-dihydroazocine **7b** and IMDA cyclisation producing the tetracyclic system **6f**. As shown, the only product of this reaction was 6-allyl-9-(ethoxycarbonyl)-11-phenyl-6,10-diazatetracyclo [6.2.1.$0^{2,5}$.$0^{5,9}$]-dodec-10-ene **6f**, which was isolated in quantitative yield. Therefore, in this example, the [4+2]-cycloaddition of an internal dienophile is observed in preference to electrocyclic ring expansion.

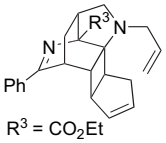
5. Variation of allylic amine

The third major variable in this process is the allylic amine and, so far, only cyclisations involving diallylamine have been discussed. We therefore examined the use of alternative allylic amines (Table 3). The first example (entry i) illustrates that amines containing a single vinyl unit (in contrast to the use of diallylamine) can be employed successfully and with high efficiency, and also that the IMDA dienophile can be conjugated to an (electron rich) aromatic unit. All the entries ii–vi utilise a more complex allyl unit, *N*-(methyl)geranylamine, which also proved to be an effective coupling

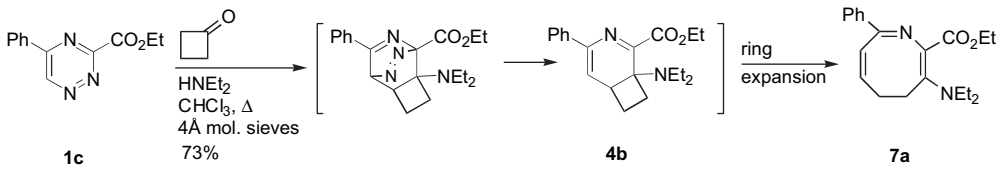
Table 2. Scope of methodology with respect to the carbonyl unit



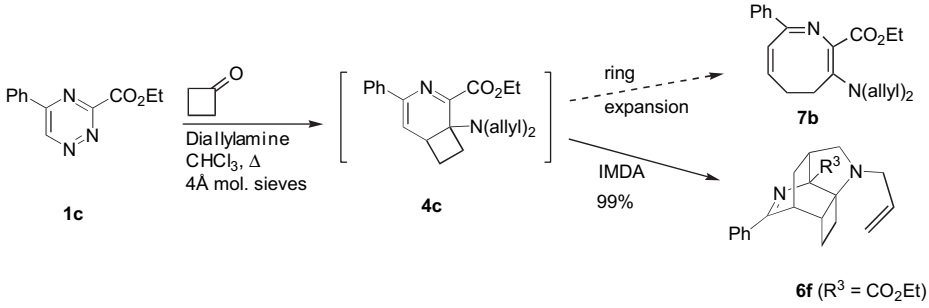
1 6

	Triazine	Ketone	R^4	R^5	Isolated yield (%)
i	**1c**; R^1=Ph, R^3=CO_2Et	Cyclopentanone	–$CH_2CH_2CH_2$–		**6c**, 88
ii	**1c**	Cyclobutanone	–CH_2CH_2–		**6f**, 99
iii	**1c**	Cyclohexanone	–$CH_2CH_2CH_2CH_2$–		**6g**, 87
iv	**1c**	Bicyclo[3.2.0]hept-2-en-6-one	 R^3 = CO_2Et		**6h**, 100
v	**1c**	$CH_3(CH_2)_3CHO$	*n*-Pr	H	**6i**,[11] 72[a]
vi	**1a**; R^1=Ph, R^3=Py	$CH_3(CH_2)_3CHO$	*n*-Pr	H	**6j**,[11] 93
vii	**1d**; R^1=H, R^3=CO_2Et	Cyclohexanone	–$CH_2CH_2CH_2CH_2$–		**6k**, 45

[a] Isolated yield is 75% when performed under microwave conditions (300 W, 90 °C, 4 h).



Scheme 4.

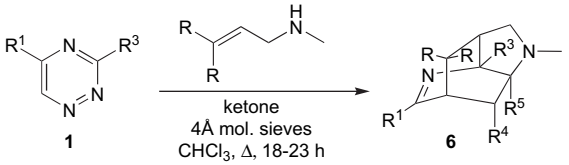


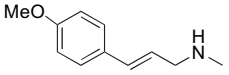
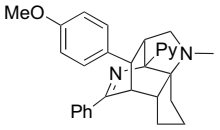
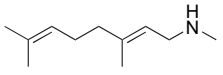
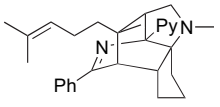
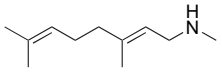
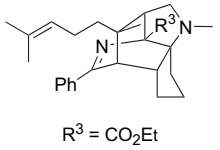
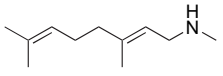
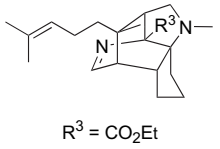
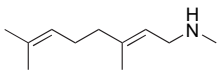
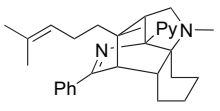
Scheme 5.

partner. It should be noted that the IMDA process occurs stereoselectively, as expected, leading to the '*exo*'-orientation of the methoxyphenyls and 4-methylpent-3-enyl substituents in all examples (and thus providing good evidence for a concerted process).

Perhaps the most important observation from this study was that the polycyclic system **6m** proved to be crystalline: as shown in Figure 1, X-ray crystallography confirmed all aspects of the earlier spectroscopic assignments (including the regiochemistry of the initial Diels–Alder reaction).

Table 3. Scope of the methodology with respect to the allylic amine



	Triazine; ketone	Amine	Product	Isolated yield (%)
i	**1a**; R^1=Ph, R^3=2-Py; cyclopentanone			**6l**, 88
ii	**1a**, R^1=Ph, R^3=2-Py; cyclopentanone			**6m**, 94
iii	**1c**, R^1=Ph, R^3=CO_2Et; cyclopentanone		 $R^3 = CO_2Et$	**6n**, 90
iv	**1d**, R^1=H, R^3=CO_2Et; cyclopentanone		 $R^3 = CO_2Et$	**6o**, 74
v	**1a**, R^1=Ph, R^3=2-Py; cyclohexanone			**6p**, 57

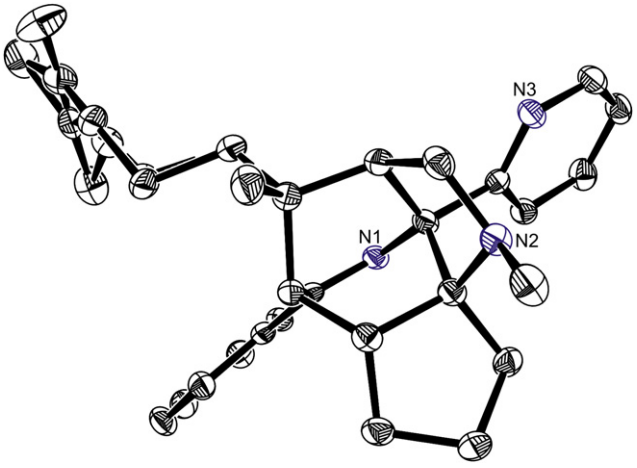
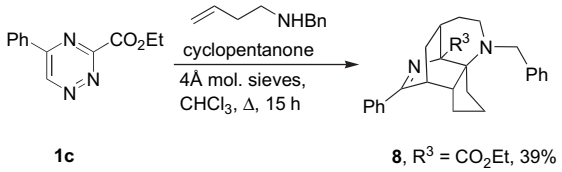


Figure 1. ORTEP diagram of **6m**. Hydrogen atoms have been omitted for clarity. Ellipsoids drawn at 50% probability. As shown, two orientations of the 4-methylpent-3-enyl unit were observed (see Section 9).

6. Extensions of the cascade methodology

Having established the versatility of the original Diels–Alder, retro-Diels–Alder and IMDA sequence based exclusively on the use of allylic amines to effect the IMDA process, we carried out preliminary studies to explore the potential of related processes in which the intermediate dihydropyridines **4** undergo IMDA trapping with differently positioned dienophiles. Thus (Scheme 6), in the most obvious extension, a homoallylic amine, *N*-benzyl but-3-enylamine, was employed with triazine **1c** successfully giving the corresponding homologated diaza-tetracycle **8** in moderate yield.



Scheme 6.

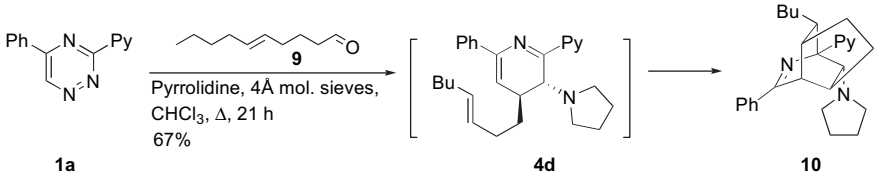
In the second example (Scheme 7), the dienophile is located in the carbonyl unit. Thus, the initial enamine was generated in situ from *trans*-5-decenal **9**[13] and pyrrolidine and after the initial Diels–Alder, retro-Diels–Alder sequence we assume that the intermediate alkenyl dihydropyridine **4d** undergoes IMDA cyclisation to produce the unusual[14] azatricycle **10** in 67% yield as a single diastereomer (the '*anti*'-arrangement of the pyrrolidine could not be assigned with certainty from the NMR data but seems likely as it would result from the *trans*-enamine derived from aldehyde **9**).

While the above yields still require optimisation, the examples in Schemes 6 and 7 demonstrate the potential of this cascade methodology for the preparation of other polycyclic systems.

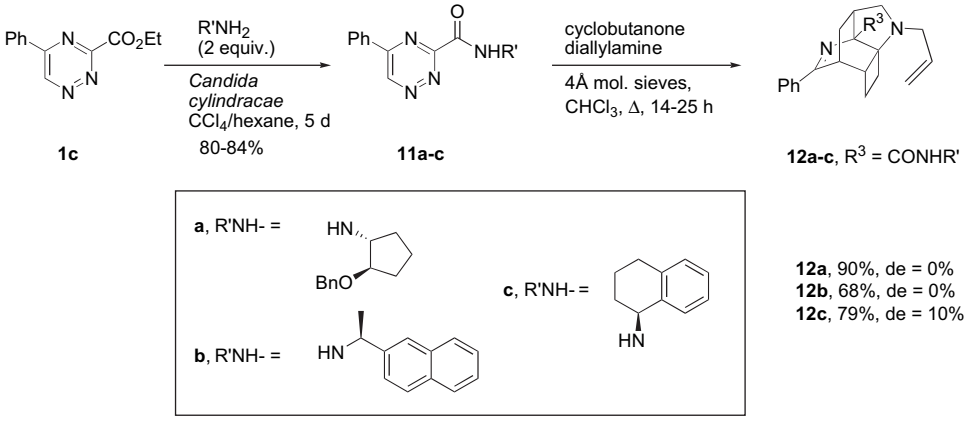
7. Use of chiral auxiliaries

Given the impressive amplification of molecular complexity inherent in these cascade processes, we were interested in the possibility of developing enantioselective variants. Thus far, only the use of chiral auxiliaries has been explored (Scheme 8).

Attempted hydrolysis of ester **1c**, or acid-catalysed transesterification using enantio-pure alcohols, proved unsuccessful



Scheme 7.



Scheme 8.

with no reaction occurring or decomposition of the triazine substrate being observed. We eventually utilised a procedure described[15] for a related triazine carboxylic ester, which involves lipase-catalysed amide formation and prepared the three novel enantiopure amides **11a–c** (Scheme 8).

All of the triazine amides **11a–c** underwent successful cascade reactions, under standard conditions, with diallylamine and cyclobutanone to give the tetracyclic products **12a–c**. Separation of the diastereomers proved impossible, and so the de's were calculated by integration of discrete signals in the ^{1}H NMR spectra. This itself was a non-trivial process, as the spectra were complex and were further complicated by the presence of amide rotamers. Disappointingly, only amide **11c**, derived from **1c** and (1*R*,2*R*)-2-benzyloxycyclopentylamine, gave a product **12c** with an appreciable de (10%). Although low, this result provides encouragement for further studies in this area and other chiral auxiliaries will be investigated as will the use of chiral enamines and chiral Lewis acid catalysts.

8. Summary

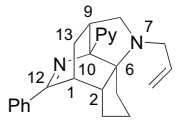
In summary, we have developed a new, one-pot route to complex nitrogen-containing polycycles, which commences from substituted 1,2,4-triazines and enamines (prepared in situ) and proceeds by way of a pericyclic cascade involving an inverse electron demand Diels–Alder, retro-Diels–Alder and IMDA sequence. The procedure is operationally straightforward (although chromatographic purification can be challenging) and is applicable to a wide range of triazines, carbonyl and amine components. The polycyclic products, which are usually formed in excellent yields and with high diastereoselectivity, represent unusual scaffolds, which may lend themselves to a variety of uses, for instance as ligands or chemotherapeutic scaffolds. We are currently exploring these aspects as well as further investigating enantioselective variants of the methodology.

9. Experimental

9.1. General details

NMR spectra were recorded on a Jeol EX-400 spectrometer using $CDCl_3$ as solvent unless otherwise stated. Tetramethylsilane or residual $CHCl_3$ was used as the internal standard. IR spectra were recorded on an ATI Mattson Genesis FTIR or ThermoNicolet IR 100 spectrometer. Low-resolution electron impact (EI) mass spectra were obtained on a Kratos MS 25 spectrometer, chemical ionisation (CI) data on a Micromass Autospec spectrometer, and high-resolution data on Kratos MS 25 or Bruker microTOF instruments. Melting points were determined on a GallenKamp melting point apparatus. Flash column chromatography was carried out using silica gel 35–70, which was purchased from Fluka. All reagents were purchased from commercial sources and were used without further purification unless stated in the text. PE is petroleum ether (bp 40–60 °C). The substituted 1,2,4-triazines **1**[10] and the amines used in Table 3 and Scheme 6[16] were prepared by literature procedures.

9.1.1. [1*R**,2*R**,6*S**,9*S**,10*S**]-7-Allyl-12-phenyl-10-(2-pyridyl)-7,11-diazatetracyclo[7.3.1.0^{2,6}.0^{6,10}]tridec-11-ene, 6a.



6a

To a solution of 5-phenyl-3-(2-pyridyl)-[1,2,4]triazine **1a**[10] (0.10 mmol, 0.023 g) in $CHCl_3$ (1.0 mL) were added powdered 4 Å molecular sieves (0.100 g), cyclopentanone (0.30 mmol, 0.027 mL) and diallylamine (0.30 mmol, 0.037 mL). The mixture was stirred at reflux for 17 h, cooled to rt, filtered through a cotton wool plug and concentrated in vacuo to give the crude product. Purification by flash chromatography on silica gel (1:1 PE/EtOAc to neat EtOAc) gave the *title compound* **6a** (0.035 g, 96%) as a colourless oil: R_f 0.0–0.2 (smear, EtOAc); ν_{max} (film) 3061, 2952, 2869, 2809, 1611, 1589, 1574, 1471, 1448, 1430, 1380, 1306, 1239, 918, 750, 695 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.91–1.03 (1H, m, H-3$_{endo}$), 1.26–1.41 (1H, m, H-4$_{exo}$), 1.41–1.54 (2H, m, H-4$_{endo}$, H-5$_{exo}$), 1.58–1.64 (1H, m, H-13a), 1.71–1.83 (2H, m, H-5$_{endo}$, H-13b), 1.87–1.98 (1H, m, H-3$_{exo}$), 2.10 (1H, d, *J* 9.5 Hz, H-8a), 2.38 (1H, br dd, *J* 7.9, 7.6 Hz, H-2), 2.62 (1H, br dd, *J* 9.5, 7.0 Hz, H-9), 2.88 (1H, dd, *J* 13.7, 7.0 Hz, allyl H-1a), 3.24–3.31 (1H, m, allyl H-1b), 3.54 (1H, br s, H-1), 3.89 (1H, dd, *J* 9.5, 7.0 Hz, H-8b), 5.00 (1H, d, *J* 10.1 Hz, allyl H-3a), 5.17 (1H, d, *J* 17.1 Hz, allyl H-3b), 5.77 (1H, dddd, *J* 17.1, 10.1, 7.0, 4.0 Hz, allyl H-2), 7.16 (1H, dd, *J* 7.6, 4.9 Hz, pyridyl H-5), 7.37–7.46 (3H, m, phenyl H-3,4,5), 7.68 (1H, dd, *J* 7.6, 7.6 Hz, pyridyl H-4), 7.92–7.97 (2H, m, phenyl H-2,6), 7.99 (1H, d, *J* 7.6 Hz, pyridyl H-3), 8.63 (1H, d, *J* 4.9 Hz, pyridyl H-6); δ_C (100 MHz, $CDCl_3$) 25.5 (CH_2), 32.2 (CH_2), 32.4 (CH_2), 35.8 (CH), 36.4 (CH), 37.7 (CH_2), 41.8 (CH), 52.6 (CH_2), 61.5 (CH_2), 75.0 (C), 79.1 (C), 115.6 (CH_2), 121.5 (CH), 124.1 (CH), 126.5 (CH), 128.6 (CH), 130.4 (CH), 135.1 (CH), 136.9 (CH), 137.7 (C), 148.1 (CH), 164.0 (C), 177.7 (C); *m*/*z* (CI) 370 (MH^+) [HRMS (CI) calcd for $C_{25}H_{28}N_3$ (MH^+) 370.2283. Found 370.2280 (−0.8 ppm error)].

9.1.2. [1*R,2*R**,6*S**,9*S**,10*S**]-7-Allyl-1,12-di-(2-furyl)-10-(2-pyridyl)-7,11-diazatetracyclo[7.3.1.0^{2,6}.0^{6,10}]tridec-11-ene, 6b.** To a solution of 5,6-di-(2-furyl)-3-(2-pyridyl)-[1,2,4]triazine **1b**[10] (0.10 mmol, 0.029 g) in $CHCl_3$ (1.0 mL) were added powdered 4 Å molecular sieves (0.100 g), cyclopentanone (0.30 mmol, 0.027 mL) and diallylamine (0.30 mmol, 0.037 mL). The mixture was stirred at reflux for 17 h, cooled to rt, filtered through a cotton wool plug and concentrated in vacuo to give the crude product. Purification by flash chromatography on silica gel (2:1 CH_2Cl_2/EtOAc to neat EtOAc) gave the *title compound* **6b** (0.038 g, 89%) as a colourless oil: R_f 0.0–0.3 (smear, EtOAc); ν_{max} (film) 2957, 2869, 1587, 1468, 1433, 1302, 1216, 1157, 1024, 924, 753 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.98–1.11 (1H, m), 1.25–1.35 (1H, m), 1.35–1.49 (2H, m), 1.72 (1H, dd, *J* 12.8, 9.5 Hz), 1.98–2.14 (2H, m), 2.20 (1H, d, *J* 12.8 Hz), 2.26 (1H, d, *J* 9.8 Hz), 2.66 (1H, dd, *J* 9.5, 6.7 Hz), 2.91 (1H, dd, *J* 10.7, 7.3 Hz), 3.04 (1H, dd, *J* 13.7, 7.0 Hz), 3.32 (1H, d, *J* 13.7 Hz), 3.42 (1H, dd,

J 9.8, 6.7 Hz), 4.95 (1H, d, *J* 10.1 Hz), 5.10 (1H, d, *J* 17.1 Hz), 5.13 (1H, d, *J* 3.7 Hz), 5.67–5.79 (1H, m), 6.26 (1H, d, *J* 3.7, 1.8 Hz), 6.42–6.47 (2H, m), 7.16 (1H, ddd, *J* 7.3, 4.9, 1.2 Hz), 7.43 (1H, d, *J* 1.8 Hz), 7.45 (1H, d, *J* 1.8 Hz), 7.74 (1H, ddd, *J* 7.9, 7.3, 1.8 Hz), 8.29 (1H, ddd, *J* 7.9, 1.2, 0.9 Hz), 8.63 (1H, ddd, *J* 4.9, 1.8, 0.9 Hz); δ_C (100 MHz, $CDCl_3$) 25.4 (CH_2), 29.4 (CH_2), 35.1 (CH_2), 37.9 (CH), 44.3 (CH_2), 48.5 (CH), 52.1 (CH_2), 56.7 (C), 59.8 (CH_2), 65.5 (C), 79.6 (C), 109.1 (CH), 110.9 (CH), 111.5 (CH), 112.5 (CH), 115.3 (CH_2), 121.4 (CH), 122.7 (CH), 136.3 (CH), 137.3 (CH), 140.5 (CH), 143.9 (CH), 149.0 (CH), 151.4 (C), 155.1 (C), 162.9 (C), 165.0 (C); *m*/*z* (CI) 426 (MH^+) [HRMS (CI) calcd for $C_{27}H_{27}N_3O_2$ (MH^+) 426.2182. Found 426.2182 (−0.2 ppm error)].

9.1.3. [1*R,2*R**,6*S**,9*S**,10*S**]-7-Allyl-10-(ethoxycarbonyl)-12-phenyl-7,11-diazatetracyclo[7.3.1.0^{2,6}.0^{6,10}]-tridec-11-ene, 6c.** To a solution of 3-(ethoxycarbonyl)-5-phenyl-[1,2,4]triazine **1c**[10] (0.10 mmol, 0.023 g) in $CHCl_3$ (1.0 mL) were added powdered 4 Å molecular sieves (0.100 g), cyclopentanone (0.30 mmol, 0.027 mL) and diallylamine (0.30 mmol, 0.037 mL). The mixture was stirred at reflux for 44 h, cooled to rt, filtered through a cotton wool plug and concentrated in vacuo to give the crude product. Purification by flash chromatography on silica gel (9:1 CH_2Cl_2/EtOAc) gave the *title compound* **6c** (0.032 g, 88%) as a colourless oil: R_f 0.3 (9:1 CH_2Cl_2/EtOAc); ν_{max} (film) 2953, 2870, 1730, 1603, 1573, 1447, 1379, 1292, 1267, 1193, 1149, 1090, 917, 732, 694 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.80–0.95 (1H, m), 1.22–1.38 (1H, m), 1.33 (3H, t, *J* 7.2 Hz, CH_3), 1.41–1.51 (2H, m), 1.64 (1H, ddd, *J* 12.5, 9.5, 1.2 Hz), 1.72 (1H, dd, *J* 14.9, 8.2 Hz), 1.86–2.00 (1H, m), 1.96 (1H, d, *J* 9.5 Hz), 2.08 (1H, ddd, *J* 14.3, 13.7, 7.0 Hz), 2.16 (1H, ddd, *J* 10.4, 7.9, 2.4 Hz), 2.62 (1H, dd, *J* 8.2, 7.0 Hz), 2.78 (1H, dd, *J* 13.6, 7.5 Hz), 3.35 (1H, d, *J* 13.6 Hz), 3.42 (1H, br s), 3.62 (1H, dd, *J* 9.5, 7.0 Hz), 4.24–4.41 (2H, m), 5.03 (1H, d, *J* 10.1 Hz), 5.20 (1H, d, *J* 17.1 Hz), 5.73–5.86 (1H, m), 7.35–7.48 (3H, m), 7.80–7.90 (2H, m); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 25.5 (CH_2), 32.6 (CH_2), 32.9 (CH_2), 33.4 (CH), 36.1 (CH), 37.0 (CH_2), 41.0 (CH), 52.3 (CH_2), 60.6 (CH_2), 60.8 (CH_2), 75.4 (C), 78.8 (C), 115.7 (CH_2), 126.7 (CH), 128.6 (CH), 130.5 (CH), 136.8 (CH), 137.3 (C), 173.9 (C), 178.5 (C); *m*/*z* (CI) 365 (MH^+) [HRMS (CI) calcd for $C_{23}H_{29}N_2O_2$ (MH^+) 365.2229. Found 365.2231 (+0.5 ppm error)].

9.1.4. [1*R,2*R**,6*S**,9*S**,10*S**]-7-Allyl-10-(ethoxycarbonyl)-7,11-diazatetracyclo[7.3.1.0^{2,6}.0^{6,10}]tridec-11-ene, 6d.** To a solution of 3-(ethoxycarbonyl)-[1,2,4]triazine **1d**[10] (0.10 mmol, 0.015 g) in $CHCl_3$ (1.0 mL) were added powdered 4 Å molecular sieves (0.100 g), cyclopentanone (0.30 mmol, 0.027 mL) and diallylamine (0.30 mmol, 0.037 mL). The mixture was stirred at reflux for 15 h, cooled to rt, filtered through a cotton wool plug and concentrated in vacuo to give the crude product. Purification by flash chromatography on silica gel (39:1–19:1 CH_2Cl_2/MeOH) gave the *title compound* **6d** (0.025 g, 89%) as a yellow oil: R_f 0.3 (19:1 CH_2Cl_2/MeOH); ν_{max} (film) 2948, 2871, 1731, 1643, 1619, 1450, 1368, 1292, 1252, 1193, 1095, 1072, 919 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.85–0.98 (1H, m), 1.20–1.39 (2H, m), 1.30 (3H, t, *J* 7.0 Hz), 1.45–1.60 (2H, m), 1.68 (1H, dd, *J* 14.7, 6.7 Hz), 1.83–2.07 (3H, m), 1.87 (1H, d, *J* 9.5 Hz), 2.48 (1H, dd, *J* 8.9, 7.3 Hz), 2.71 (1H, dd, *J* 13.4, 7.3 Hz), 2.77 (1H, br s), 3.29 (1H, d, *J* 13.4 Hz), 3.58 (1H, dd, *J* 9.5, 7.3 Hz), 4.22 (1H, dq, *J* 11.0, 7.0 Hz), 4.34 (1H, dq, *J* 11.0, 7.0 Hz), 5.00 (1H, d, *J* 10.1 Hz), 5.16 (1H, d, *J* 16.8 Hz), 5.70–5.81 (1H, m), 8.42 (1H, d, *J* 4.0 Hz); δ_C (100 MHz, $CDCl_3$) 14.4 (CH_3), 25.2 (CH_2), 32.6 (CH), 32.8 (CH_2), 33.2 (CH_2), 36.2 (CH_2), 36.6 (CH), 40.9 (CH), 52.0 (CH_2), 60.5 (CH_2), 70.0 (CH_2), 74.7 (C), 78.7 (C), 115.8 (CH_2), 136.7 (CH), 173.3 (C), 175.6 (CH); *m*/*z* (CI) 289 (MH^+) [HRMS (CI) calcd for $C_{17}H_{25}N_2O_2$ (MH^+) 289.1916. Found 289.1915 (−0.3 ppm error)].

9.1.5. [1*R,2*R**,6*S**,9*S**,10*S**]-7-Allyl-10-(ethoxycarbonyl)-1-phenyl-7,11-diazotetracylo[7.3.1.0^{2,6}.0^{6,10}]tridec-11-ene, 6e.** To a solution of 3-(ethoxycarbonyl)-6-phenyl-[1,2,4]triazine **1e**[10] (0.09 mmol, 0.020 g) in $CHCl_3$ (2.0 mL) were added powdered 4 Å molecular sieves (0.080 g), cyclopentanone (0.17 mmol, 0.020 mL) and diallylamine (0.17 mmol, 0.015 mL). The mixture was stirred at reflux for 16 h, cooled to rt, filtered through a cotton wool plug and concentrated in vacuo to give the crude product. Purification by flash chromatography on silica gel (99:1–24:1 $CHCl_3$/MeOH) gave the *title compound* **6e** (0.030 g, 95%) as a pale oil: R_f 0.4 (24:1 CH_2Cl_2/MeOH); ν_{max} (film) 3053, 2959, 2927, 2873, 2854, 1732, 1642, 1446, 1420, 1265, 1203, 1075, 738 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.80–0.92 (1H, m), 1.24–1.28 (1H, m), 1.37 (3H, t, *J* 7.0 Hz), 1.41–1.44 (1H, m), 1.64–1.83 (4H, m), 1.94 (1H, dd, *J* 14.3 Hz), 2.02–2.06 (1H, m), 2.13 (1H, d, *J* 10.4 Hz), 2.63 (1H, dd, *J* 10.1, 8.24 Hz), 2.96 (1H, dd, *J* 13.7, 7.3 Hz), 3.36 (1H, d, *J* 13.7), 3.42 (1H, dd, *J* 10.4, 6.4 Hz), 4.33–4.39 (2H, m, CO_2CH_2), 5.03 (1H, d, *J* 9.8 Hz), 5.19 (1H, d, *J* 17.1 Hz), 5.76–5.83 (1H, m), 7.28 (1H, t, *J* 7.3 Hz), 7.35–7.40 (2H, m), 7.63–7.66 (2H, m), 8.35 (1H, s); δ_C (100 MHz, $CDCl_3$) 14.4 (CH_3), 25.2 (CH_2), 28.5 (CH_2), 29.7 (CH_2), 33.9 (CH_2), 40.0 (CH), 41.9 (CH_2), 47.3 (CH), 52.1 (CH_2), 58.4 (C), 59.7 (CH_2), 61.3 (CH_2), 66.3 (C), 115.7 (CH_2), 126.5 (CH), 128.1 (CH), 128.9 (CH), 136.7 (CH), 141.5 (C), 172.9 (CH), 174.5 (C); *m*/*z* (CI) 365 (MH^+) [HRMS (CI) calcd for $C_{23}H_{29}N_2O_2$ (MH^+) 365.2229. Found 365.2224 (+0.5 ppm error)].

9.1.6. [1*R,2*R**,5*S**,8*S**,9*S**]-6-Allyl-9-(ethoxycarbonyl)-11-phenyl-6,10-diazatetracyclo[6.2.1.0^{2,5}.0^{5,9}]dodec-10-ene, 6f.** To a solution of 3-(ethoxycarbonyl)-5-phenyl-[1,2,4]triazine **1c**[10] (0.10 mmol, 0.023 g) in $CHCl_3$ (1.0 mL) were added powdered 4 Å molecular sieves (0.100 g), cyclobutanone (0.30 mmol, 0.022 mL) and diallylamine (0.30 mmol, 0.037 mL). The mixture was stirred at reflux for 22 h, cooled to rt, filtered through a cotton wool plug and concentrated in vacuo to give the crude product. Purification by flash chromatography on silica gel (CH_2Cl_2 to 19:1 CH_2Cl_2/EtOAc) gave the *title compound* **6f** (0.035 g, 99%) as a colourless oil: R_f 0.35 (9:1 CH_2Cl_2/EtOAc); ν_{max} (film) 2969, 2869, 1730, 1651, 1573, 1446, 1383, 1296, 1142, 1096, 694 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.00–1.14 (1H, m), 1.31 (3H, t, *J* 7.3 Hz), 1.42 (1H, dd, *J* 13.1, 2.4 Hz), 1.62–1.73 (1H, m), 1.76 (1H, ddd, *J* 13.1, 9.8, 1.2 Hz), 2.10 (1H, d, *J* 9.8 Hz), 2.27 (1H, ddd, *J* 13.4, 11.6, 8.2 Hz), 2.53 (1H, dd, *J* 9.8, 6.7 Hz), 2.63 (1H, ddd, *J* 13.4, 10.7, 5.2 Hz), 2.74–2.83 (1H, m), 2.95 (1H, dd, *J* 14.0, 7.0 Hz), 3.39 (1H, br s), 3.58 (1H, dd, *J* 9.8, 6.7 Hz), 3.56–3.64 (1H, m), 4.23–4.39 (2H, m), 5.05 (1H, d, *J* 10.1 Hz), 5.11 (1H, d, *J* 17.1 Hz), 5.76–5.88 (1H, m),

7.36–7.47 (3H, m), 7.82–7.91 (2H, m); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 18.0 (CH_2), 24.1 (CH_2), 32.8 (CH), 34.8 (2×CH), 36.8 (CH_2), 52.7 (CH_2), 60.8 (CH_2), 61.2 (CH_2), 71.5 (C), 74.4 (C), 115.7 (CH_2), 126.8 (CH), 128.6 (CH), 130.5 (CH), 136.8 (CH), 137.5 (C), 173.8 (C), 178.3 (C); *m/z* (CI) 351 (MH^+) [HRMS (CI) calcd for $C_{22}H_{27}N_2O_3$ (MH^+) 351.2073. Found 351.2074 (+0.3 ppm error)].

9.1.7. [1*R,2*R**,7*S**,10*S**,11*S**]-8-Allyl-11-(ethoxycarbonyl)-13-phenyl-8,12-diazatetracyclo[8.3.1.0^{2,7}.0^{7,11}]-tetradec-12-ene, 6g.** To a solution of 3-(ethoxycarbonyl)-5-phenyl-[1,2,4]triazine **1c**[10] (0.11 mmol, 0.026 g) in $CHCl_3$ (1.0 mL) were added powdered 4 Å molecular sieves (0.100 g), cyclohexanone (0.34 mmol, 0.035 mL) and diallylamine (0.34 mmol, 0.042 mL). The mixture was stirred at reflux for 38 h, cooled to rt, filtered through a cotton wool plug and concentrated in vacuo to give the crude product. Purification by flash chromatography on silica gel (9:1 CH_2Cl_2/EtOAc to neat EtOAc) gave the *title compound* **6g** (0.037 g, 87%) as a colourless oil: R_f 0.0–0.1 (smear, EtOAc); ν_{max} (film) 2936, 2870, 1730, 1606, 1573, 1447, 1383, 1252, 1104, 1071, 921, 735, 695 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.96–1.08 (1H, m), 1.17–1.41 (2H, m), 1.49–1.72 (7H, m), 1.98 (1H, m), 2.16 (1H, d, *J* 9.5 Hz), 2.49 (1H, ddd, *J* 9.5, 7.0, 7.0 Hz), 3.00 (1H, dd, *J* 13.7, 7.0 Hz), 3.23 (1H, br s), 3.48 (1H, d, *J* 13.7 Hz), 3.72 (1H, dd, *J* 9.5, 7.0 Hz), 4.25–4.41 (2H, m), 5.04 (1H, d, *J* 10.1 Hz), 5.23 (1H, d, *J* 17.1 Hz), 5.75–5.88 (1H, m), 7.36–7.45 (3H, m), 7.85–7.90 (2H, m); δ_C (100 MHz, $CDCl_3$) 14.4 (CH_3), 17.8 (CH_2), 19.1 (CH_2), 25.7 (CH_2), 27.0 (CH_2), 34.4 (CH), 37.9 (CH_2), 38.0 (CH), 38.7 (CH), 52.8 (CH_2), 61.9 (CH_2), 69.9 (C), 77.2 (C), 115.4 (CH_2), 126.6 (CH), 128.6 (CH), 130.5 (CH), 137.0 (C), 137.2 (CH), 173.4 (C), 177.5 (C); *m/z* (CI) 379 (MH^+) [HRMS (CI) calcd for $C_{24}H_{31}N_2O_2$ (MH^+) 379.2386. Found 379.2384 (−0.4 ppm error)].

9.1.8. [1*R,2*R**,3*S**,7*S**,8*S**,11*S**,12*S**]-9-Allyl-12-(ethoxycarbonyl)-14-phenyl-9,13-diazapentacyclo[9.3.1.0^{2,8}.0^{3,7}.0^{8,12}]pentadecadi-4,13-ene, 6h.** To a solution of 3-(ethoxycarbonyl)-5-phenyl-[1,2,4]triazine **1c**[10] (0.10 mmol, 0.023 g) in $CHCl_3$ (1.0 mL) were added powdered 4 Å molecular sieves (0.100 g), bicyclo[3.2.0]hept-2-en-6-one (0.30 mmol, 0.032 mL) and diallylamine (0.30 mmol, 0.037 mL). The mixture was stirred at reflux for 21 h, cooled to rt, filtered through a cotton wool plug and concentrated in vacuo to give the crude product. Purification by flash chromatography on silica gel (CH_2Cl_2 to 19:1 CH_2Cl_2/EtOAc) gave the *title compound* **6h** (0.039 g, 100%) as a colourless oil: R_f 0.4 (19:1 CH_2Cl_2/EtOAc); ν_{max} (film) 2975, 2921, 2852, 1731, 1446, 1381, 1291, 1260, 1134, 1094, 915, 756, 730, 694 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.0 Hz), 1.38 (1H, br d, *J* 13.1 Hz), 1.76 (1H, ddd, *J* 13.1, 10.4, 1.8 Hz), 1.96 (1H, d, *J* 10.1 Hz), 2.36–2.51 (4H, m), 2.66 (1H, br d, *J* 17.4 Hz), 2.80 (1H, dd, *J* 15.6, 6.4 Hz), 3.45–3.54 (1H, m), 3.48 (1H, br s, H-1), 3.63 (1H, dd, *J* 7.7, 7.0 Hz), 3.71 (1H, dd, *J* 10.1, 6.1 Hz), 4.27 (1H, dq, *J* 10.7, 7.0 Hz), 4.41 (1H, dq, *J* 10.7, 7.0 Hz), 5.02 (1H, br d, *J* 10.4 Hz), 5.22 (1H, br d, *J* 17.1 Hz), 5.64–5.70 (1H, m), 7.39–7.48 (3H, m), 7.87–7.96 (2H, m); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 32.9 (CH), 33.8 (CH_2), 34.5 (CH), 36.4 (CH_2), 41.9 (CH), 44.4 (CH), 46.3 (CH), 56.6 (CH_2), 60.7 (CH_2), 63.3 (CH_2), 72.1 (C), 75.5 (C), 114.8 (CH_2), 126.7 (CH), 128.6 (CH), 130.6 (CH), 132.7 (CH), 132.8 (CH), 136.9 (CH), 137.5 (C), 173.8 (C), 178.4 (C); *m/z* (CI) 389 (MH^+) [HRMS (CI) calcd for $C_{25}H_{29}N_2O_2$ (MH^+) 389.2229. Found 389.2227 (−0.5 ppm error)].

9.1.9. [1*R,2*R**,3*S**,6*S**,7*S**]-4-Allyl-7-(ethoxycarbonyl)-9-phenyl-2-*n*propyl-4,8-diazatricyclo[4.3.1.0^{3,7}]dec-8-ene, 6i.** To a solution of 3-(ethoxycarbonyl)-5-phenyl-[1,2,4]triazine **1c**[10] (0.21 mmol, 0.050 g) in $CHCl_3$ (2.0 mL) were added powdered 4 Å molecular sieves (0.100 g), valeraldehyde (0.47 mmol, 0.050 mL) and diallylamine (0.49 mmol, 0.060 mL). The mixture was stirred at reflux for 24 h, cooled to rt, filtered through a cotton wool plug and concentrated in vacuo to give the crude product. Purification by flash chromatography on silica gel (199:1 $CHCl_3$/MeOH), concentrated in vacuo and then further flash chromatography on silica gel (9:1–7:3 PE/EtOAc) gave the *title compound* **6i** (0.034 g, 93%) as a colourless oil: R_f 0.6 (1:1 PE/EtOAc); ν_{max} (film) 2959, 2928, 1732, 1604, 1572, 1463, 1446, 1380, 1299, 1254, 1134, 1096, 1080, 910, 733, 693 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.79 (3H, t, *J* 7.4 Hz), 0.90–1.10 (2H, m), 1.21–1.33 (2H, m), 1.34 (3H, t, *J* 7.0 Hz), 1.56–1.60 (1H, m), 1.67–1.74 (1H, m), 1.85–1.89 (1H, m), 2.47 (1H, d, *J* 9.2 Hz), 2.59 (1H, br dd, *J* 9.8, 5.2 Hz), 3.06 (1H, br s), 3.11 (1H, dd, *J* 9.4, 5.2 Hz), 3.20–3.33 (3H, m), 4.29–4.35 (2H, m), 5.05 (1H, d, *J* 10.1 Hz), 5.20 (1H, d, *J* 17.4 Hz), 5.77–5.87 (1H, m), 7.35–7.45 (3H, m), 7.84–7.86 (2H, m); δ_C (100 MHz, $CDCl_3$) 13.9 (CH_3), 14.2 (CH_3), 20.5 (CH_2), 34.7 (CH_2), 35.5 (CH), 35.8 (CH_2), 36.1 (CH), 41.9 (CH), 55.9 (CH_2), 59.0 (C), 61.0 (CH_2), 65.6 (CH), 74.4 (C), 116.0 (CH_2), 126.3 (CH), 128.4 (CH), 130.4 (CH), 136.6 (CH), 136.7 (C), 174.3 (C), 177.7 (C). *m/z* (ESI) 367.2373 (MH^+) [HRMS (ESI) calcd for $C_{23}H_{31}N_2O_2$ (MH^+) 367.2380. Found 367.2373 (−1.86 ppm error)].

9.1.10. [1*R,2*R**,3*S**,6*S**,7*S**]-4-Allyl-9-phenyl-2-*n*propyl-7-(2-pyridyl)-4,8-diazatricyclo[4.3.1.0^{3,7}]dec-8-ene, 6j.** To a solution of 5-phenyl-3-(2-pyridyl)-[1,2,4]triazine **1a**[10] (0.10 mmol, 0.023 g) in $CHCl_3$ (1.0 mL) were added powdered 4 Å molecular sieves (0.100 g), valeraldehyde (0.30 mmol, 0.032 mL) and diallylamine (0.30 mmol, 0.037 mL). The mixture was stirred at reflux for 44 h, cooled to rt, filtered through a cotton wool plug and concentrated in vacuo to give the crude product. Purification by flash chromatography on silica gel (2:1 CH_2Cl_2/EtOAc to neat EtOAc) gave the *title compound* **6j** (0.034 g, 93%) as a colourless oil: R_f 0.2–0.3 (smear, EtOAc); ν_{max} (film) 2958, 2926, 2870, 1605, 1591, 1572, 1471, 1446, 1430, 1380, 912, 786, 731, 693 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.81 (3H, t, *J* 7.3 Hz), 0.96–1.17 (2H, m), 1.21–1.47 (2H, m), 1.75 (1H, ddd, *J* 12.8, 2.4, 2.4 Hz), 1.88 (1H, ddd, *J* 12.8, 10.4, 2.4 Hz), 2.05 (1H, dt, *J* 2.4, 7.3 Hz), 2.57 (1H, d, *J* 9.2 Hz), 2.73 (1H, br dd, *J* 10.4, 4.9 Hz), 2.88 (1H, dd, *J* 9.2, 4.9 Hz), 3.16–3.25 (3H, m), 3.43 (1H, br s), 4.99 (1H, d, *J* 10.1 Hz), 5.06 (1H, d, *J* 17.1 Hz), 5.71–5.85 (1H, m), 7.20 (1H, dd, *J* 7.0, 4.9 Hz), 7.33–7.45 (3H, m), 7.65 (1H, d, *J* 7.9 Hz), 7.73 (1H, dd, *J* 7.9, 7.0 Hz), 7.82–7.93 (2H, m), 8.62 (1H, br d, *J* 4.9 Hz); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 20.8 (CH_2), 35.0 (CH_2), 36.2 (CH), 36.3 (CH_2), 38.6 (CH), 44.9 (CH), 56.7 (CH_2), 58.9 (CH_2), 67.2 (CH), 74.5 (C), 115.8 (CH_2), 121.9 (CH), 122.7 (CH), 126.4 (CH), 128.5 (CH), 130.2 (CH), 136.4 (CH), 137.4 (CH),

137.5 (C), 148.2 (CH), 165.2 (C), 176.9 (C); *m/z* (CI) 372 (MH^+) [HRMS (CI) calcd for $C_{25}H_{30}N_3$ (MH^+) 372.2440. Found 372.2436 (−1.1 ppm error)].

9.1.11. [1*R,2*R**,7*S**,10*S**,11*S**]-8-Allyl-11-(ethoxycarbonyl)-8,12-diazatetracyclo[8.3.1.0^{2,7}.0^{7,11}]tetradec-12-ene, 6k.** To a solution of 3-(ethoxycarbonyl)-5-phenyl-[1,2,4]triazine **1d**[10] (0.41 mmol, 0.063 g) in $CHCl_3$ (1.5 mL) were added powdered 4 Å molecular sieves (0.100 g), cyclohexanone (0.48 mmol, 0.050 mL) and diallylamine (0.49 mmol, 0.060 mL). The mixture was stirred at reflux for 18 h, cooled to rt, filtered through a cotton wool plug and concentrated in vacuo to give the crude product. Purification by flash chromatography on silica gel ($CHCl_3$ to 99:1 $CHCl_3$/MeOH), concentrated in vacuo and then further flash chromatography on silica gel (Et_2O) gave the *title compound* **6k** (0.056 g, 45%) as a colourless oil: R_f 0.7 ($CHCl_3$/MeOH 24:1); ν_{max} (film) 2935, 2872, 1730, 1643, 1622, 1463, 1454, 1369, 1304, 1282, 1252, 1231, 1173, 1122, 1106, 1069 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.00–1.10 (1H, m), 1.29–1.38 (5H, m), 1.40–1.45 (1H, m), 1.49–1.63 (6H, m), 1.82–1.86 (1H, m), 2.06 (1H, d, *J* 9.5 Hz), 2.32 (1H, dd, *J* 8.8, 7.8 Hz), 2.52 (1H, m), 2.91 (1H, dd, *J* 14.0, 7.0 Hz), 3.41 (1H, d, *J* 14.0 Hz), 3.67 (1H, dd, *J* 9.5, 7.0 Hz), 4.20–4.35 (2H, m), 4.99 (1H, d, *J* 10.0 Hz), 5.17 (1H, d, *J* 17.1 Hz), 5.72–5.82 (1H, m), 8.45 (1H, d, *J* 4.3 Hz); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 17.3 (CH_2), 19.1 (CH_2), 25.3 (CH_2), 27.0 (CH_2), 33.3 (CH), 36.8 (CH_2), 38.4 (CH), 38.5 (CH), 52.4 (CH_2), 60.8 (CH_2), 61.9 (CH_2), 69.9 (C), 76.2 (C), 115.2 (CH_2), 136.9 (CH), 172.8 (C), 173.9 (CH); *m/z* (CI) 303 (MH^+) [HRMS (CI) calcd for $C_{18}H_{27}N_2O_2$ (MH^+) 303.2072. Found 303.2071 (−0.5 ppm error)].

9.1.12. [1*S,2*R**,6*S**,9*S**,10*R**,13*R**]-13-(4-methoxyphenyl)-7-methyl-12-phenyl-10-(2-pyridyl)-7,11-diazatetracyclo[7.3.1.0^{2,6}.0^{6,10}]tridec-11-ene, 6l.** To a solution of 5-phenyl-3-(2-pyridyl)-[1,2,4]triazine **1a**[10] (0.07 mmol, 0.016 g) in $CHCl_3$ (1.0 mL) were added powdered 4 Å molecular sieves (0.100 g), cyclopentanone (0.14 mmol, 0.012 mL) and [3-(4-methoxyphenyl)allyl]methylamine[16b] (0.14 mmol, 0.025 g). The mixture was stirred at reflux for 20 h, cooled to rt, filtered through a cotton wool plug and concentrated in vacuo to give the crude product. Purification by flash chromatography on silica gel (EtOAc) gave the *title compound* **6l** (0.027 g, 88%) as a colourless solid: R_f 0.0–0.1 (smear, EtOAc); mp >155 °C (decomp.); ν_{max} (Nujol) 1611, 1587, 1510, 1307, 1245, 1177, 1109, 1030, 825, 742 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.82–0.95 (1H, m), 1.23–1.36 (1H, m), 1.36–1.47 (2H, m), 1.68–1.86 (2H, m), 2.14–2.28 (1H, m), 2.19 (3H, s), 2.48 (1H, br t, *J* 7.3 Hz), 2.96 (1H, d, *J* 2.4 Hz), 3.03 (1H, d, *J* 6.7 Hz), 3.52 (1H, br t, *J* 3.1 Hz), 3.57 (3H, s), 4.11 (1H, dd, *J* 9.4, 6.7 Hz), 6.53 (2H, d, *J* 8.7 Hz), 6.84 (2H, d, *J* 8.7 Hz), 7.07–7.22 (4H, m), 7.26–7.33 (2H, m), 7.67 (1H, ddd, *J* 7.9, 1.8, 0.9 Hz), 7.93 (1H, d, *J* 7.9 Hz), 8.56 (1H, dd, *J* 4.9, 0.9 Hz); δ_C (100 MHz, $CDCl_3$) 25.4 (CH_2), 29.8 (CH_2), 31.9 (CH_2), 32.1 (CH_2), 36.0 (CH_3), 43.9 (CH), 45.7 (CH), 55.3 (CH_3), 55.7 (C), 64.5 (CH_2), 75.3 (C), 79.3 (C), 113.6 (CH), 121.9 (CH), 124.7 (CH), 126.2 (CH), 128.2 (CH), 128.9 (CH), 129.8 (CH), 135.5 (CH), 136.1 (C), 139.2 (C), 148.1 (CH), 157.9 (C), 163.9 (C), 176.7 (C); *m/z* (CI) 450 (MH^+) [HRMS (CI) calcd for $C_{30}H_{32}N_3O$ (MH^+) 450.2545. Found 450.2544 (−0.4 ppm error)].

9.1.13. [1*S,2*R**,6*S**,9*S**,10*R**,13*R**]-7,13-Dimethyl-13-(4-methylpent-3-enyl)-12-phenyl-10-(2-pyridyl)-7,11-diazatetracyclo[7.3.1.0^{2,6}.0^{6,10}]tridec-11-ene, 6m.** To a solution of 5-phenyl-3-(2-pyridyl)-[1,2,4]triazine **1a**[10] (0.10 mmol, 0.023 g) in $CHCl_3$ (1.0 mL) were added powdered 4 Å molecular sieves (0.100 g), cyclopentanone (0.20 mmol, 0.018 mL) and *N*-methylgeranylamine[16a] (0.20 mmol, 0.033 g). The mixture was stirred at reflux for 21 h, cooled to rt, filtered through a cotton wool plug and concentrated in vacuo to give the crude product. Purification by flash chromatography on silica gel (EtOAc) gave the *title compound* **6m** (0.041 g, 94%) as a colourless solid: R_f 0.0–0.1 (smear, EtOAc); mp 138–140 °C; ν_{max} (Nujol) 2768, 1613, 1574, 1307, 1234, 1196, 1048, 972, 833, 782 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.81–0.91 (1H, m), 0.92–1.18 (2H, m), 1.14 (3H, s), 1.21–1.53 (3H, m), 1.25 (3H, s), 1.48 (3H, s), 1.62–1.93 (4H, m), 2.24 (3H, s), 2.30 (1H, d, *J* 7.0 Hz), 2.35–2.50 (2H, m), 3.12 (1H, d, *J* 2.4 Hz), 3.71 (1H, dd, *J* 10.1, 7.0 Hz), 4.69 (1H, br t, *J* 6.4 Hz), 7.17 (1H, ddd, *J* 7.3, 4.9, 0.9 Hz), 7.38–7.46 (3H, m), 7.69 (1H, ddd, *J* 7.3, 1.8, 0.9 Hz), 7.92–8.02 (3H, m), 8.61 (1H, br d, *J* 4.9 Hz); δ_C (100 MHz, $CDCl_3$) 17.4 (CH_3), 21.5 (CH_3), 22.9 (CH_2), 25.7 (CH_3), 25.7 (CH_2), 32.0 (CH_2), 32.1 (CH_2), 36.0 (CH_3), 38.2 (CH), 41.2 (C), 42.3 (CH_2), 46.0 (CH), 47.0 (CH), 54.3 (CH_2), 76.6 (C), 80.2 (C), 121.7 (CH), 124.5 (CH), 124.6 (CH), 126.5 (CH), 128.6 (CH), 130.2 (CH), 130.9 (C), 135.3 (CH), 138.8 (C), 147.9 (CH), 164.5 (C), 176.7 (C); *m/z* (CI) 440 (MH^+) [HRMS (CI) calcd for $C_{30}H_{38}N_3$ (MH^+) 440.3066. Found 440.3063 (−0.6 ppm error)].

The X-ray crystal structure data is shown in Table 4.[17] The structure showed disorder in the orientation of the 4-methylpent-3-enyl unit, which was satisfactorily modelled using a two site model the relative occupancy of which refined

Table 4. Crystal data and structure refinement for product **6m** (CCDC 244632)[17]

Empirical formula	$C_{30}H_{37}N_3$
Formula weight	439.63
Temperature	115(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	*P*2(1)2(1)2(1)
Unit cell dimensions	*a*=7.4661(12) Å; α=90° *b*=11.4751(17) Å; β=90° *c*=28.238(4) Å; γ=90°
Volume	2419.3(6) $Å^3$
Z	4
Density (calculated)	1.207 Mg/m^3
Absorption coefficient	0.071 mm^{-1}
F(000)	952
Crystal size	0.41×0.16×0.04 mm^3
Theta range for data collection	1.92–25.01°
Index ranges	$-8\leq h\leq 8$, $-13\leq k\leq 11$, $-33\leq l\leq 33$
Reflections collected	13,220
Independent reflections	4251 [*R*(int)=0.0448]
Completeness to theta=25.01°	99.9%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000 and 0.815
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4251/135/350
Goodness-of-fit on F^2	1.000
Final *R* indices [*I*>2sigma(*I*)]	*R*1=0.0351, *wR*2=0.0745
R indices (all data)	*R*1=0.0510, *wR*2=0.0807
Absolute structure parameter	1(2)
Largest diff. peak and hole	0.196 and −0.150 $eÅ^{-3}$

to 7:3. Due to considerable overlap of the two positions of the 4-methylpent-3-enyl unit, restraints were required to ensure sensible bond lengths and angles as follows: the four terminal C–CH_3 bond lengths, the C=C bonds and the =C–CH_2 bond lengths were restrained to be equal.

9.1.14. [1*S,2*R**,6*S**,9*S**,10*R**,13*R**]-7,13-Dimethyl-10-(ethoxycarbonyl)-13-(4-methylpent-3-enyl)-12-phenyl-7,11-diazatetracyclo[7.3.1.0^{2,6}.0^{6,10}]tridec-11-ene, 6n.** To a solution of 3-(ethoxycarbonyl)-5-phenyl-[1,2,4]triazine **1c**[10] (0.10 mmol, 0.023 g) in $CHCl_3$ (1.0 mL) were added powdered 4 Å molecular sieves (0.100 g), cyclopentanone (0.20 mmol, 0.018 mL) and *N*-methylgeranylamine[16a] (0.20 mmol, 0.033 g). The mixture was stirred at reflux for 21 h, cooled to rt, filtered through a cotton wool plug and concentrated in vacuo to give the crude product. Purification by flash chromatography on silica gel (9:1–1:1 CH_2Cl_2/EtOAc) gave the *title compound* **6n** (0.039 g, 90%) as a colourless solid: R_f 0.0–0.1 (smear, 9:1 CH_2Cl_2/EtOAc); mp 87–89 °C; ν_{max} (Nujol) 1728, 1604, 1574, 1288, 1267, 1195, 1153, 1084, 1028, 702 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.80–1.11 (3H, m), 1.05 (3H, s), 1.25 (3H, s), 1.30–1.34 (4H, m), 1.38–1.47 (1H, m), 1.50 (3H, s), 1.55–1.67 (1H, m), 1.68–1.79 (2H, m), 1.80–1.90 (1H, m), 1.93–2.06 (1H, m), 2.14–2.35 (3H, m), 2.24 (3H, s), 3.01 (1H, d, *J* 2.4 Hz), 3.32 (1H, dd, *J* 10.4, 7.0 Hz), 4.24–4.42 (2H, m), 4.69 (1H, t, *J* 7.1 Hz), 7.32–7.47 (3H, m), 7.80–7.92 (2H, m); δ_C (100 MHz, $CDCl_3$) 14.4 (CH_3), 17.4 (CH_3), 21.0 (CH_3), 22.9 (CH_2), 25.6 (CH_2), 25.7 (CH_3), 32.2 (CH_2), 32.7 (CH_2), 35.5 (CH_3), 37.8 (CH), 41.6 (C), 42.2 (CH_2), 43.6 (CH), 47.1 (CH), 53.4 (CH_2), 60.9 (CH_2), 77.1 (C), 79.3 (C), 124.2 (CH), 126.7 (CH), 128.6 (CH), 130.4 (CH), 131.2 (C), 138.7 (C), 174.1 (C), 177.6 (C); *m*/*z* (CI) 435 (MH^+) [HRMS (CI) calcd for $C_{28}H_{39}N_2O_2$ (MH^+) 435.3012. Found 435.3008 (–0.9 ppm error)].

9.1.15. [1*S,2*R**,6*S**,9*S**,10*R**,13*R**]-7,13-Dimethyl-10-(ethoxycarbonyl)-13-(4-methylpent-3-enyl)-7,11-diazatetracyclo[7.3.1.0^{2,6}.0^{6,10}]tridec-11-ene, 6o.** To a solution of 3-(ethoxycarbonyl)-[1,2,4]triazine **1d**[10] (1.83 mmol, 0.280 g) in $CHCl_3$ (4.0 mL) were added powdered 4 Å molecular sieves (0.300 g), cyclopentanone (2.94 mmol, 0.246 mL) and *N*-methylgeranylamine[16a] (2.94 mmol, 0.491 g). The mixture was stirred at reflux for 18 h, cooled to rt, filtered through a cotton wool plug and concentrated in vacuo to give the crude product. Purification by flash chromatography on silica gel (249:1–247:3 CH_2Cl_2/MeOH) gave the *title compound* **6o** (0.478 g, 74%) as a pale yellow oil: R_f 0.3 (19:1 CH_2Cl_2/MeOH); ν_{max} (film) 2962, 2931, 2870, 1731, 1453, 1378, 1282, 1264, 1087, 1069, 1023, 801 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.85–1.05 (2H, m), 0.97 (3H, s), 1.12 (1H, ddd, *J* 13.4, 11.9, 5.8 Hz), 1.20–1.37 (1H, m), 1.32 (3H, t, *J* 7.3 Hz), 1.45–1.54 (1H, m), 1.56 (3H, s), 1.61–1.73 (1H, m), 1.63 (3H, s), 1.78–2.03 (4H, m), 2.04–2.13 (1H, m), 2.10 (1H, d, *J* 7.3 Hz), 2.15–2.26 (1H, m), 2.19 (3H, s), 2.42 (1H, br s), 3.28 (1H, dd, *J* 10.7, 7.3 Hz), 4.24 (1H, dq, *J* 11.0, 7.3 Hz), 4.36 (1H, dq, *J* 11.0, 7.3 Hz), 4.97 (1H, br t, *J* 7.0 Hz), 8.41 (1H, d, *J* 3.7 Hz); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 17.7 (CH_3), 20.8 (CH_3), 23.1 (CH_2), 25.3 (CH_2), 25.7 (CH_3), 32.5 (CH_2), 33.0 (CH_2), 35.2 (CH_3), 37.2 (CH), 40.8 (C), 42.3 (CH_2), 44.6 (CH), 47.1 (CH), 53.2 (CH_2), 61.2 (CH_2), 76.3 (C), 79.3 (C), 124.1 (CH), 131.7 (C), 173.5 (C), 175.8 (CH); *m*/*z* (CI) 359 (MH^+) [HRMS (CI) calcd for $C_{22}H_{35}N_2O_2$ (MH^+) 359.2699. Found 359.2695 (−0.9 ppm error)].

9.1.16. [1*S,2*R**,7*S**,10*S**,11*R**,14*R**]-8,14-Dimethyl-14-(4-methylpent-3-enyl)-13-phenyl-11-(2-pyridyl)-8,12-diazatetracyclo[8.3.1.0^{2,7}.0^{7,11}]tetradec-12-ene, 6p.** To a solution of 5-phenyl-3-(2-pyridyl)-[1,2,4]triazine **1a**[10] (0.22 mmol, 0.051 g) in $CHCl_3$ (3.0 mL) were added powdered 4 Å molecular sieves (0.120 g), cyclohexanone (0.44 mmol, 0.045 mL) and *N*-methylgeranylamine[16a] (0.44 mmol, 0.074 g). The mixture was stirred at reflux for 23 h, cooled to rt, filtered and concentrated in vacuo to give the crude product. Purification by flash chromatography on silica gel (2:1 PE/EtOAc) concentrated in vacuo and then further flash chromatography on silica gel (199:1–99:1 CH_2Cl_2/MeOH) gave the *title compound* **6p** (0.056 g, 57%) as a colourless solid: R_f 0.3 (24:1 CH_2Cl_2/MeOH); mp 116–118 °C; ν_{max} (Nujol) 3018, 2930, 2860, 1448, 1378, 1292, 1215, 1165, 1026, 756, 667, 637 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.09–1.12 (1H, m), 1.35 (3H, s), 1.40–1.49 (4H, m), 1.48 (3H, s), 1.65–1.75 (6H, m), 1.98–2.16 (4H, m), 2.31–2.33 (1H, m), 2.38–2.41 (1H, m), 2.66 (3H, s, NCH_3), 2.98–3.01 (1H, m), 3.46 (1H, d, *J* 12.5 Hz), 4.94 (1H, d, *J* 5.8 Hz), 5.04 (1H, t, *J* 7.0 Hz), 7.22–7.26 (5H, m), 7.67 (1H, dt, *J* 7.6, 1.8 Hz), 7.86 (2H, t, *J* 7.6 Hz), 8.48 (1H, d, *J* 4.9 Hz); δ_C (100 MHz, $CDCl_3$) 17.5 (CH_3), 22.66 (CH_2), 22.69 (CH_3), 23.4 (CH_2), 25.2 (CH_2), 25.6 (CH), 28.4 (CH_2), 29.6, (C), 31.8 (CH_2), 32.4 (CH_3), 38.8 (C), 40.1 (CH_3), 40.8 (CH), 44.5 (CH_2), 52.5 (CH_2), 58.6 (CH), 59.9 (C), 123.4 (CH), 123.9 (CH), 124.1 (CH), 126.1 (CH), 126.2 (CH), 127.2 (CH), 131.7 (CH), 131.8 (C), 134.6 (C), 136.4 (CH), 143.6 (C), 146.9 (CH), 158.4 (C), 161.6 (C); *m*/*z* (CI) 454 (MH^+) [HRMS (CI) calcd for $C_{31}H_{40}N_3$ (MH^+) 454.3217. Found 454.3205 (−2.51 ppm error)].

9.1.17. [1*S,2*R**,6*S**,9*S**,10*R**,14*R**]-7-Benzyl-11-(ethoxycarbonyl)-13-phenyl-7,12-diazatetracyclo[8,3,1,0^{2,6},0^{6,11}]tetradec-12-ene, 8.** To a solution of 3-(ethoxycarbonyl)-5-phenyl-[1,2,4]triazine **1c**[10] (0.32 mmol, 0.074 g) in $CHCl_3$ (3.0 mL) were added powdered 4 Å molecular sieves (0.140 g), cyclopentanone (0.50 mmol, 0.045 mL) and *N*-benzylbut-3-en-1-amine[16b] (0.50 mmol, 0.080 g). The mixture was stirred at reflux for 15 h, cooled to rt, filtered through a cotton wool plug and concentrated in vacuo to give the crude product. Purification by flash chromatography on silica gel (9:1 PE/EtOAc) gave the *title compound* **8** (0.055 g, 39%) as a colourless oil: R_f 0.4 (24:1 CH_2Cl_2/MeOH); ν_{max} (film) 2953, 2870, 1730, 1603, 1573, 1447, 1379, 1292, 1267, 1193, 1149, 1090, 917, 732, 694 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.90–1.0 (1H, m), 1.17–1.48 (7H, m), 1.96–2.07 (3H, m), 2.14–2.21 (1H, m), 2.28–2.41 (4H, m), 2.90 (1H, d, *J* 13.5 Hz), 3.42 (1H, s), 4.01 (1H, d, *J* 13.5 Hz), 4.33 (2H, q, *J* 7.0 Hz), 7.20–7.32 (3H, m), 7.37–7.44 (5H, m), 7.90 (2H, dd, *J* 7.3, 1.5 Hz); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 25.4 (CH_2), 27.1 (CH_2), 28.2 (CH_2), 30.4 (CH), 33.1 (CH_2), 36.4 (CH_2), 37.5 (CH), 39.3 (CH), 41.6 (CH_2), 54.4 (CH_2), 60.6 (CH_2), 71.8 (C), 72.7 (C), 126.53 (CH), 126.55 (CH), 128.07 (CH), 128.13 (CH), 128.5 (CH), 130.4 (CH), 137.6 (C), 141.5 (C), 174.1 (C), 177.1 (C); *m*/*z* (ESI) 429.2549 (MH^+) [HRMS (ESI) calcd for $C_{28}H_{33}N_2O_2$ (MH^+) 429.2537. Found 429.2549 (+2.80 ppm error)].

9.1.18. [1*S,2*R**,3*S**,6*S**,7*R**,10*R**]-10-″Butyl-8-phenyl-1-(2-pyridyl)-2-(1-pyrrolidinyl)-9-azatricyclo[4.3.1.0^{3,7}]-dec-8-ene, 10.** To a solution of 5-phenyl-3-(2-pyridyl)-[1,2,4]triazine **1a**[10] (0.10 mmol, 0.023 g) in $CHCl_3$ (1.0 mL) were added powdered 4 Å molecular sieves (0.100 g), *trans*-5-decenal **9**[13] (0.30 mmol, 0.046 g) and pyrrolidine (0.30 mmol, 0.025 mL). The mixture was stirred at reflux for 21 h, cooled to rt, filtered through a cotton wool plug and concentrated in vacuo to give the crude product. Purification by flash chromatography on silica gel (4:1 CH_2Cl_2/EtOAc to neat EtOAc) gave the *title compound* **10** (0.027 g, 67%) as a very pale yellow oil: R_f 0.0–0.1 (smear, EtOAc); ν_{max} (film) 2929, 2871, 2856, 1608, 1589, 1573, 1466, 1447, 1434, 1377, 754, 693 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.44–0.57 (1H, m), 0.62–0.78 (1H, m), 0.66 (3H, t, *J* 7.0 Hz), 0.80–1.16 (5H, m), 1.20–1.39 (3H, m), 1.70–1.88 (3H, m), 1.93–2.13 (6H, m), 2.30 (2H, br s), 3.34 (1H, t, *J* 4.2 Hz), 3.49 (1H, br s), 7.13 (1H, br dd, *J* 7.6, 4.9 Hz), 7.42–7.50 (3H, m), 7.69 (1H, dd, *J* 7.9, 7.6 Hz), 7.96–8.05 (2H, m), 8.44 (1H, d, *J* 7.9 Hz), 8.64 (1H, d, *J* 4.9 Hz); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 22.5 (CH_2), 23.5 (CH_2), 29.4 (CH_2), 29.8 (C), 30.5 (CH_2), 32.1 (CH_2), 32.3 (CH_2), 42.4 (CH), 44.8 (CH)×2, 49.9 (CH_2), 53.6 (CH), 73.1 (CH), 120.8 (CH), 123.5 (CH), 126.3 (CH), 128.6 (CH), 130.0 (CH), 135.6 (CH), 138.5 (C), 148.8 (CH), 168.2 (C), 171.7 (C); *m*/*z* (CI) 414 (MH^+) [HRMS (CI) calcd for $C_{28}H_{36}N_3$ (MH^+) 414.2909. Found 414.2906 (−0.8 ppm error)].

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17. CCDC 244632 contains the supplementary crystallographic data for compound **6m**. These can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or by emailing to www.ccdc.cam.ac.uk.