JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b02005 • Publication Date (Web): 23 Sep 2019

Secondary products from intramolecular cycloadditions of azidoalkyl enol ethers and azidoalkyl vinyl bromides. 1-Azadienes, their reactions with diphenylketene, and radical cyclizations to form bi- and tricyclic lactams.

John T. R. Liddon,[†] Peter J. Lindsay-Scott,[‡] and Jeremy Robertson*,[†]

[†] Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, OX1 3TA, UK.

[‡] Eli Lilly and Company Limited, Erl Wood Manor, Windlesham, Surrey, GU20 6PH, UK.

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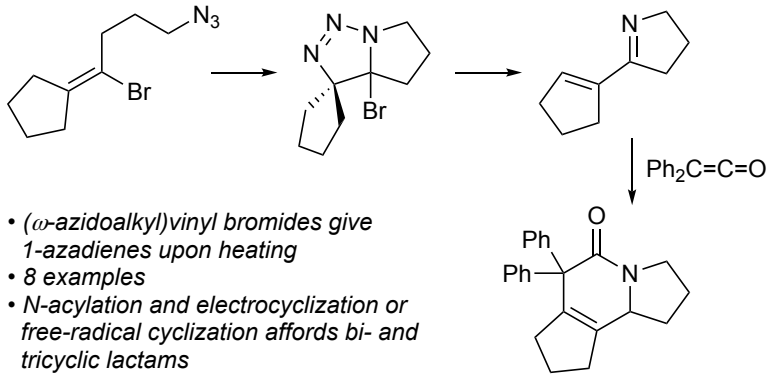


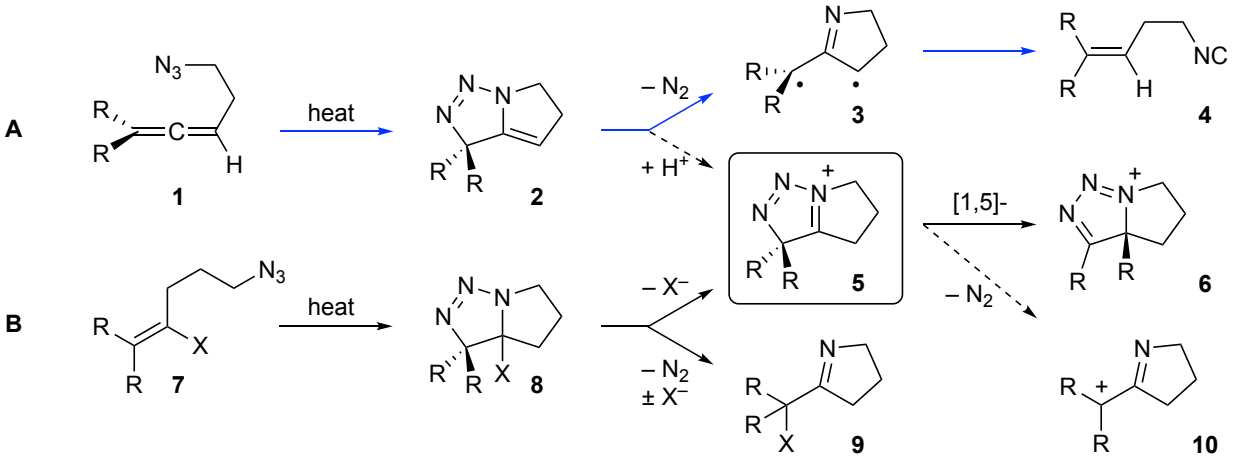
ABSTRACT

Azidoalkyl enol ethers undergo intramolecular 1,3-dipolar cycloaddition to generate stable triazolines; in contrast, the cycloadducts formed by heating analogous azidoalkyl vinyl bromides are unstable with respect to elimination of N_2 and HBr, affording 1-azadienes (2-alkenyl cyclic imines). These primary products may be isolated or treated directly with diphenylketene to produce bi- and tri-cyclic 3,4-dihydropyridin-2(1*H*)-ones; similar ring systems may also be produced from the azadienes by *N*-acylation and radical cyclization.

INTRODUCTION

Within a general research program aiming to develop new methods for assembling multicyclic alkaloids, we speculated that triazolium ions **5** (Scheme 1), formed by hypothetical protonation of triazolines **2**, might enter into potentially valuable chemistry centered on the addition of carbon-based nucleophiles either directly or following

alkyl shift (→ **6**). Loss of nitrogen from the triazolium ions was expected to be unfavourable, in view of the likely high energy of the so-formed 1-azaallyl cations **10**.[1] The intramolecular dipolar cycloaddition of (2-azidoethyl)allenes **1** (Scheme 1A) is an unsuitable route to the precursor triazolines **2** because the cycloadducts lose nitrogen directly to generate azatrimethylenemethane (ATMM) diyls **3** which, in turn, evolve into alkenyl isocyanides **4** unless tethered alkene or diene functionality is present to trap them rapidly.[2] The same triazolium ions **5** could potentially be generated by Lewis-acid mediated abstraction of X^- from triazolines **8** (Scheme 1B), formed by intramolecular azide cycloaddition onto a suitable heteroatom-bearing alkene **7**.[3] It was appreciated at the outset that triazolines **8** might, under the reaction conditions used for their formation, be susceptible to loss of nitrogen and migration of the X-group giving pyrrolines **9**. This paper summarizes the results of an evaluation of this approach, and selected transformations of the 1-azadienes produced from vinyl bromides **7** (X = Br) via pyrrolines **9** or equivalent species.



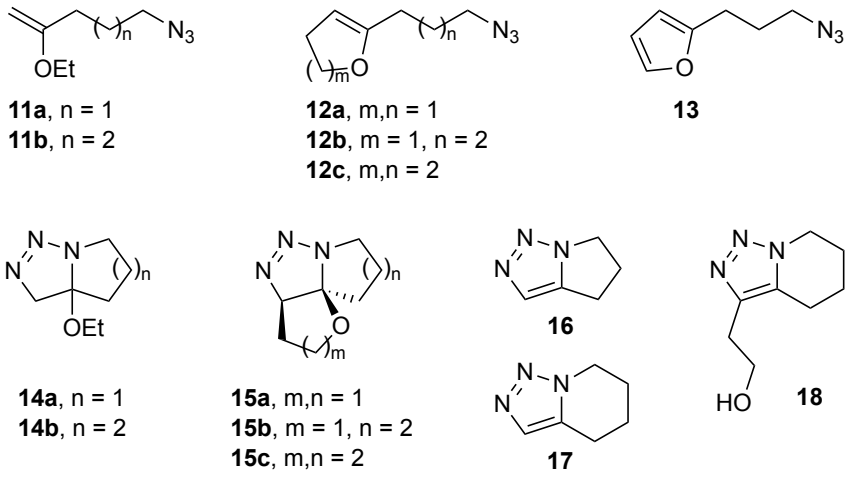
Scheme 1 A: Cycloaddition of (2-azidoethyl)allenes **1** leads to γ,δ-unsaturated isocyanides **4**; **B**: Cycloaddition of heteroatom-substituted (ω-azidoalkyl)alkenes **7** as a potential route to triazolium ions **5** and **6**.

RESULTS AND DISCUSSION

Enol ethers

With some limited precedent available on intramolecular azide + enol ether cycloadditions to give isolable adducts[4,5] an initial exploration of this idea focused on substrates **11–13** (Figure 1), easily prepared by deprotonation and alkylation[6] of ethyl vinyl ether, dihydrofuran, dihydropyran, or furan (Scheme S1). In general, the rate of azide + alkene cycloaddition varies dramatically with, inter alia, variation of the electronic character of the alkene component.[7] For example, the second order rate constant for the reaction of azidobenzene with *N*-(cyclopenten-1-yl)pyrrolidine is around 235,000× larger than that for the reaction with 1-ethoxycyclopentene;[8] accordingly, it was expected that the rate of reaction of substrates **11–13** would be low. In practice, heating the substrates in toluene at 130 °C (pressure tube), with K_2CO_3 present to minimize acid-mediated decomposition pathways, led to essentially complete conversion to bi- and tri-cyclic triazolines **14** and **15** over a period of 2–4 days, accompanied, in the reactions of **11**, by variable quantities of the triazoles **16**[9] and **17**[9,10] resulting from elimination of ethanol. The cycloadditions of the azidobutyl substrates **11b** and **12b** were somewhat slower than those of the corresponding azidopropyl substrates **11a** and **12a**, in line with a less unfavourable entropy of

activation in the latter pair. The dihydrofuranyl substrates **12a**,**b** reacted more rapidly than their simpler ethoxy counterparts **11**, presumably as a result of slight strain-activation. This advantage is absent in the dihydropyranyl substrate **12c** which, in combination with the longer linking chain, required 10 days for full consumption of the substrate, and a crude product of poor quality was obtained from which only a 20% yield of cycloadduct **15c** was isolated. The furanyl substrate **13**[11] merely decomposed unproductively at temperatures up to 170 °C.



11a, n = 1
11b, n = 2

12a, m,n = 1
12b, m = 1, n = 2
12c, m,n = 2

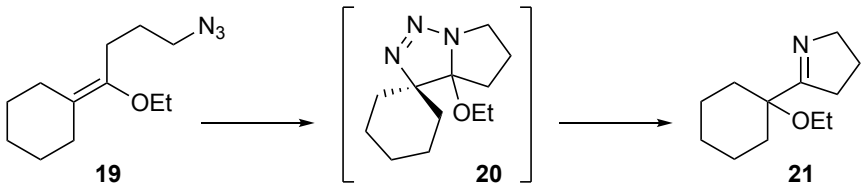
13

14a, n = 1
14b, n = 2

15a, m,n = 1
15b, m = 1, n = 2
15c, m,n = 2

Figure 1 (ω-Azidoalkyl)enol ethers (**11**–**13**), the products of their intramolecular cycloaddition (**14**,**15**), and triazoles formed by elimination (**16**–**18**).

Attempts to generate and trap iminium intermediates from hemiaminals **14** and **15b** resulted either in recovery of starting material (e.g. EtMgBr, –78 °C → RT; or Et_3Al) or aromatization (→ **16**–**18**; e.g. EtMgBr, THF, reflux; or allyltributylstannane + a variety of Lewis acids), with nucleophilic addition being unable to compete with rapid proton loss. In order to shut down the aromatization pathway, significant effort was expended on a search for an effective general route to substrates bearing two alkyl substituents at the distal end of the alkene. Eventually, a small, impure sample of cyclohexylidene substrate **19** was prepared via Johnson–Claisen rearrangement of the adduct of lithiated ethyl vinyl ether and cyclohexanone (Scheme S2).[12] With sufficient enol ether available for just a single experiment, the thermolysis was conducted in toluene-d_8 and the reaction progress was followed by NMR analysis. After 3.5 days at 130 °C, the major product of the reaction was assigned as pyrroline derivative **21** arising from overall loss of nitrogen and migration of the alkoxy group (Scheme 2; *cf.* **9**, Scheme 1). It appeared from this result that the combination of steric crowding and relatively favourable stabilization of any developing positive charge rendered the intermediate cycloadduct **20** unstable under the conditions of the reaction and, coupled with the difficulty of preparing suitable substrates, investigations on azidoalkyl enol ether cycloadditions were terminated.



Scheme 2 Intramolecular azide + alkene cycloaddition of fully-substituted enol ether **19** with loss of N_2 and accompanying 1,2-ethoxy-group shift.

Vinyl bromides

Without an efficient, general route available to fully-substituted enol ethers, focus switched to vinyl bromides since their preparation by bromination/dehydrobromination of the corresponding alkenes is straightforward.[13] Little is reported on the non-catalysed, purely thermal, cycloaddition of azides and simple vinyl bromides[14] and, to the best of our knowledge, intramolecular azide + vinyl bromide cycloadditions have not been studied. The results would therefore provide a comparison with analogous enol ethers as well as potentially providing access to triazolium ions as outlined in Scheme 1B.

Substrates **22a**–**f**,**i** (Figure 2, preparation: Schemes S3–S7) were chosen so as to provide meaningful comparison with the enol ethers already studied, and to probe the effect of structural variations in the substrate (tether length, electronic and strain effects on the alkene, conformational restriction). The hydroxy- and azido-methyl substrates **22g**,**h** were prepared in order to gain information on functional group compatibility with the cycloaddition conditions and to introduce an intermediate level of conformational restriction compared with the un- and *gem*-dimethyl-substituted substrates **22a** and **22f**, respectively.

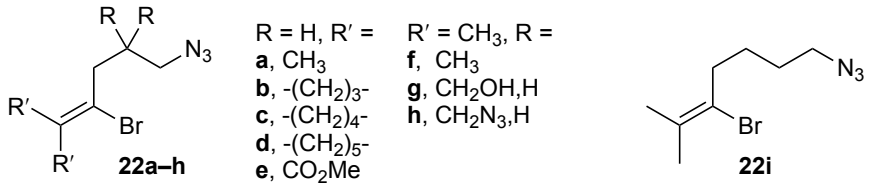
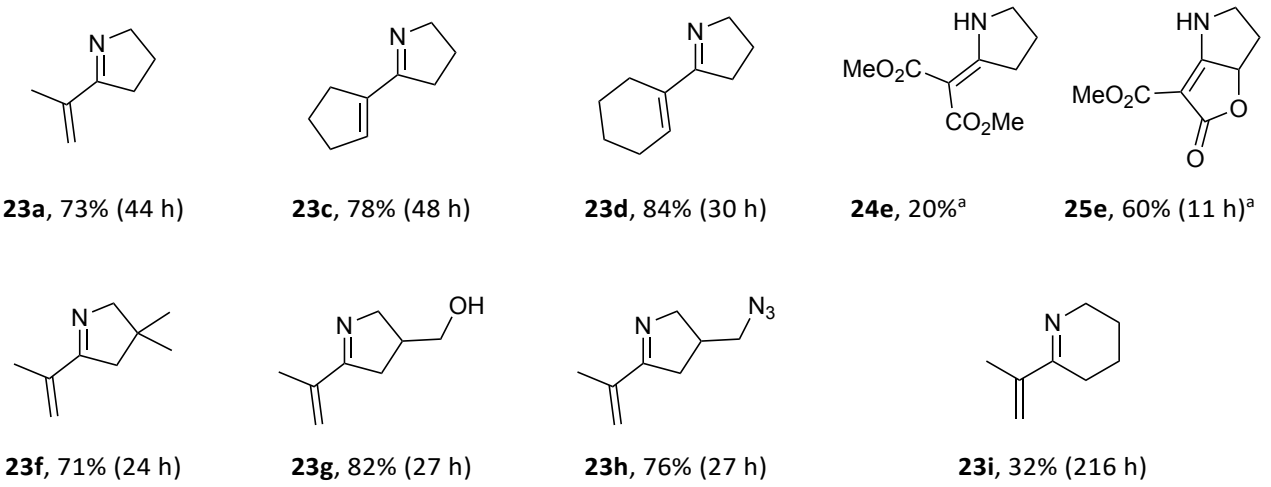


Figure 2 (ω-Azidoalkyl)vinyl bromide substrates.

A preliminary study of the reactivity of azidoalkyl vinyl bromides, using substrate **22a**, showed that the choice of solvent[15] (between available high-boiling deuterated solvents for an NMR study: DMSO-d_6, pyridine-d_5, toluene-d_8) had a merely marginal effect on reaction rate and, for ease of product isolation, toluene was chosen as in the enol ether work. Running the reactions in dilute solution (0.05–0.1 M) minimized the production of oligomeric products, and the formation of tarry deposits during the reaction was reduced by including a solid base to sequester the liberated HBr (see below), with a combination of K_2CO_3 (10.0 equiv.) and NaOH (2.0 equiv.) providing the cleanest product mixtures. Azide **22a** converted into products very slowly at 100 °C but at 150 °C the reaction progressed steadily and was complete after around 40 h. These reaction parameters were then employed in the thermolysis

of the remaining substrates **22b–i**, the corresponding products of which are shown in Figure 3 which also provides the approximate reaction times required for the starting material to be consumed (TLC).



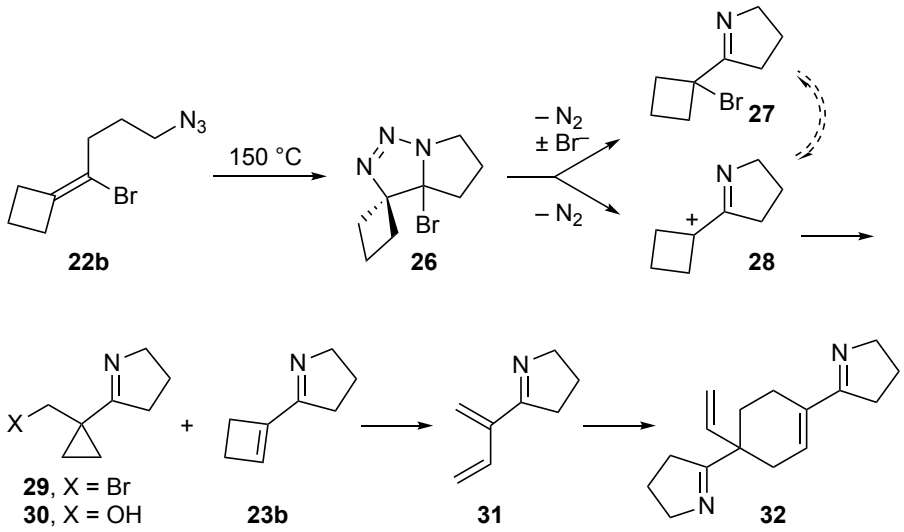
23a, 73% (44 h) **23c**, 78% (48 h) **23d**, 84% (30 h) **24e**, 20%[a] **25e**, 60% (11 h)[a]

23f, 71% (24 h) **23g**, 82% (27 h) **23h**, 76% (27 h) **23i**, 32% (216 h)

Figure 3 Products formed from the thermolysis of azidopropyl vinyl bromides **22a–i**. *Reaction conditions*: toluene, K_2CO_3, NaOH, 150 °C (pressure tube). Percentage yields refer to products isolated following column chromatography. The products from **22b** are shown in Scheme 3. [a] Reaction temperature = 100 °C.

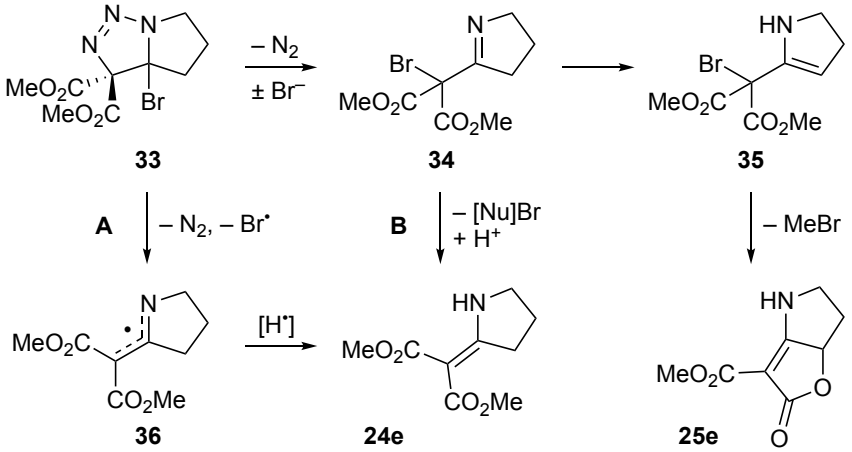
In all cases, the reaction temperature and time combined to ensure that the primary cycloadducts (**8**, X = Br, Scheme 1B) ejected N_2 and HBr to generate cyclic imines **23** in all cases, except where noted below. The relative rates of reactions of homologous substrates **22b–d** roughly parallel the rates of $NaBH_4$ reduction of the analogous ketones,[16] reflecting differential contributions of angle strain at the non-brominated alkene carbon and significant rehybridization at that center in the cycloaddition transition state. The cyclobutyl substrate **22b** reacted rapidly to give a complex product mixture from which three components (**27, 29, 30**, Scheme 3) were isolated and characterized. These products gave some insight into the nature of the reactions to form azadienes **23**, in particular the potential involvement of a cationic intermediate (**28**; *cf*. **10**, Scheme 1) en route to the azadienes. A fourth component, observed as a contaminant in some samples of alcohol **30** and not isolated as a pure compound, is tentatively assigned as cyclohexene derivative **32** on the basis of NMR spectroscopic and HRMS data; this is presumed to arise by electrocyclic ring-opening of intermediate **23b** and Diels–Alder dimerization.

As expected, the presence of the *gem*-dimethyl substituent in substrate **22f** led to a significant acceleration of the reaction,[17] supporting a rate-limiting cycloaddition step; even mono-substitution of the linking chain (in **22g**,**h**) led to an appreciably reduced reaction time compared to the unsubstituted analogue. Conversely, the extra conformational mobility offered by the additional methylene group linking the azide and vinyl bromide functionality in **22i** led to a dramatic reduction in the rate of reaction; various decomposition pathways became significant during the extended reaction time, lowering the yield of the azadiene **23i**.



Scheme 3 Minor products **27**, **29**, **30**, and **32** generated from the cyclobutylidene substrate **22b**.

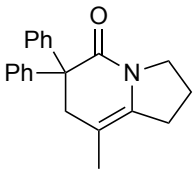
The malonyl derivative **22e** was prepared in the expectation that the electron-deficient alkene would react rapidly, possibly at a sufficiently low temperature to allow the primary cycloadduct **33** (Scheme 4) to be isolated, but also to block the final elimination reaction, potentially giving insight into the nature of the intermediates in the overall transformation. In the event, the reaction was complete within 11 h at 100 °C (*cf.* ~7% conversion of **22a** after 89 h at 100 °C) but, again, the cycloadduct **33** was not isolated under these conditions. Accepting that any discussion of the mechanism leading to the obtained products **24e**[18] and **25e** is purely speculative, it is conceivable that the major product **25e** arises from bromoimine intermediate **34** via tautomerization (→ **35**) and a process formally equivalent to an oxapentadienyl cation electrocyclization.[19] The minor component **24e** could arise from the same bromoimine intermediate by providing Br^+ to a suitable nucleophile present in the reaction mixture (pathway **B**) or, for example, by homolytic loss of N_2 and $Br^\bullet$ (→ **36**) then abstraction of a hydrogen atom (e.g. from the solvent) (pathway **A**). Compounds with the tetrahydrofuro[3,2-*b*]pyrrol-2-one core present in product **25e** are known, and generally prepared by intramolecular Wittig reaction of succinimide derivatives,[20] but **25e** appears to be the first reported *N*-unsubstituted example.



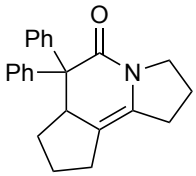
Scheme 4 Outline reaction pathways leading from primary cycloadduct **33** to enamides **24e** and **25e**.

1-Azadiene reactions

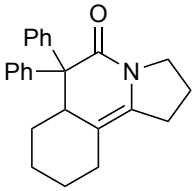
With two exceptions (**23d**[21] and **23i**[22]) the azadiene products are not reported in the literature and a survey of their reactivity[23] was undertaken.[24] Two aspects of this survey shall be described here, with the linking feature being the formation of 1-azabicyclo[4.3.0]nonane derivatives, the core ring system in, for example, the large class of indolizidine alkaloids.[25] First, it was found that azadiene **23a** showed little reactivity as a diene in attempted Diels–Alder cycloadditions with both electron-deficient and electron-rich potential dienophiles; however, an equivalent transformation proceeded efficiently upon treatment with diphenylketene.[26] For convenience, the reaction mixtures obtained from heating azides **22** were simply cooled to RT and diphenylketene added directly; the intermediate azadienes **23** reacted efficiently over a period of a few hours to generate the lactams shown in Figure 4. The isolated yields for this one-pot process were generally comparable to the yields obtained for the conversion of azides **22** to azadienes **23**.



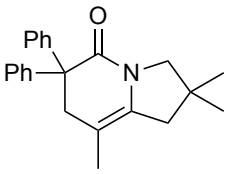
37a, 80%



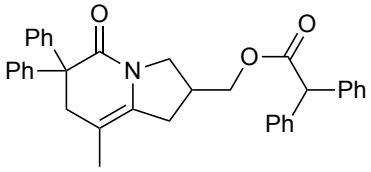
37c, 77%



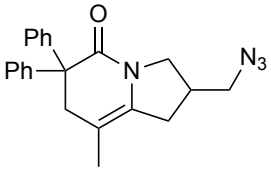
37d, 80%



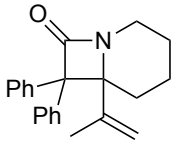
37f, 91%



37g, 74%



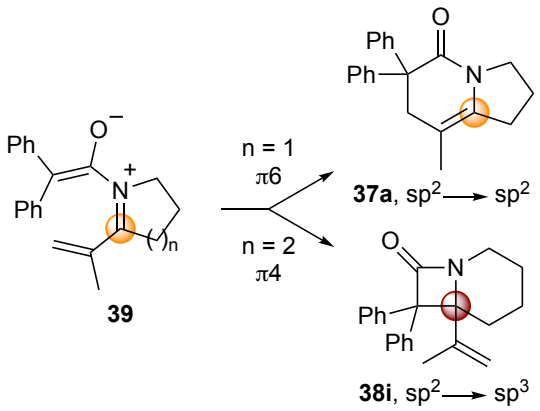
37h, 58%



38i, 35%

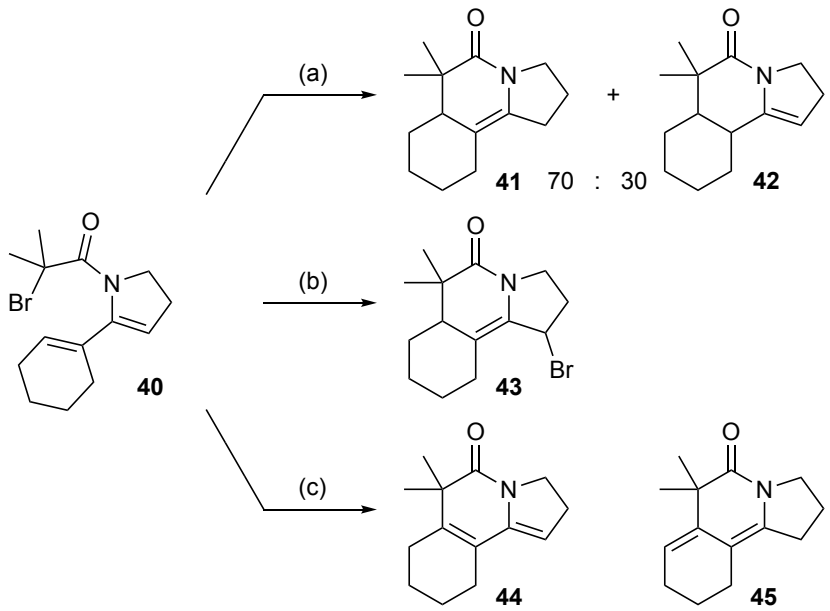
Figure 4 Products formed, and yields of purified product, from the one-pot thermolysis and subsequent trapping of azidoalkyl vinyl bromides **22**. *Reaction conditions*: toluene, K_2CO_3, NaOH, 150 °C (pressure tube) then $Ph_2C{=}C{=}O$, RT.

From Figure 4, the production of β-lactam **38i** appears anomalous; however, the few analogous reported reactions of this type, that concern only acyclic azadienes[27] tend to generate β-lactams kinetically which, upon heating, may rearrange to the δ-lactam isomers. Thus, in fact, the production of δ-lactams **37** at RT from the pyrroline azadienes deserves comment. On the basis that the reactions proceed via a stepwise acylation/(formal) electrocyclization process,[27a] the balance in favour of δ-lactam formation from zwitterion **39** (Scheme 5) may reflect the relative resistance to introduce a further sp^3-center into the five-membered heterocycle when compared to the ease with which six-membered rings accommodate full saturation. The production of δ-lactam products (from **39**, n = 1) maintains an sp^2-carbon adjacent to the nitrogen throughout the reactions with diphenylketene, whereas β-lactam formation would necessarily increase unfavourable eclipsing interactions in the transition state for formal electrocyclization.



Scheme 5 Divergent formal electrocylization modes from pyrroline- (n = 1) and piperideine- (n = 2) derived zwitterions.

The nucleophilicity of the azadienes **23** was harnessed for the production, by *N*-acylation,[28] of precursors for potential 6-*endo*-*trig* radical cyclization, the aim being to produce δ-lactams of the same form as those shown in Figure 4 but with potentially more flexibility. In a proof-of-principle study, α-bromoenamide **40** (Scheme 6), readily prepared from azadiene **23d**, was employed in three sets of conditions established for radical cyclization. First, classical reductive cyclization with the tributyltin hydride/AIBN combination produced a mixture of alkene regioisomers **41** and **42** arising from H-atom trapping at the termini of the allylic radical formed upon cyclization. However, under Cu(I)-mediated atom-transfer radical cyclization (ATRC) conditions,[29] using PMDTA as a tridentate ligand for the copper center,[30] the fragile allylic bromide **43** was isolated in excellent yield provided that chromatographic purification was carried out rapidly through a short silica plug. When the reaction was conducted with bidentate TMEDA employed as ligand,[31] slightly more forcing reaction conditions were necessary and diene **44** was obtained cleanly; here, chromatography required basic alumina in order to retain the integrity of the 2-amido-1,3-diene motif as the use of silica gel as column support led to diene isomerization, generating a roughly equimolar mixture of isomers **44** and **45**.



Scheme 6 Radical cyclizations from *N*-(α-bromoisobutyroyl)pyrroline **40**. *Reagents and conditions*: (a) Bu_3SnH, AIBN, toluene, 110 °C, 22 h (72%); (b) CuBr (30 mol%), PMDTA, CH_2Cl_2, RT, 0.25 h (90%); (c) CuBr (110 mol%), TMEDA, CH_2Cl_2, RT 40 °C, 2.5 h (**44**, 77% [92% based on 16% recovered starting material]).

CONCLUSION

This work originated from our group's interest in accessing azide/allene cycloadducts **2** (Scheme 1), expected to participate in diverse mechanistic pathways depending on the nature of subsequent reaction conditions and reagents added in situ. The isolable azide/enol ether cycloadducts **8** (X = OR) are potentially equivalent to cycloadducts **2** but these merely aromatized when induced to form derived iminium ions **5**. In substrates such as **19**, whose primary cycloadduct cannot readily aromatize, secondary products were obtained and the possibility of generating extended iminium ions could not be explored. Analogous vinyl bromide substrates showed similar reactivity in the cycloaddition step but the primary adducts were found not to survive the reaction conditions, losing molecular N_2 and either Br^- or $Br^\bullet$, with the formation of alkenyl pyrrolidines (1-azadienes) in most cases. The chemistry of these secondary products, as a group, has not been reported on previously and, as part of a wider study of their diversification,[24] this work demonstrates that (4+2) and (2+2) annulation modes can be achieved, following *N*-acylation, via both electrocyclic and free-radical mechanisms. The resulting indolizidine ring systems, and the cyclopenta- and cyclohexa-fused variants, are core components of a variety of alkaloids; there is therefore clear potential to harness the reactivity of 1-azadienes for the synthesis of specific natural products and their analogues.

Experimental Section

General information: Except where stated, all reagents were purchased from commercial sources and used without further purification. "Petrol" refers to the fraction of light petroleum ether boiling in the

range 30–40 °C. "Ether" refers to diethyl ether. MTBE refers to methyl *tert*-butyl ether. Dry ether, dichloromethane and toluene were obtained from Grubbs canisters under argon. Tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone under a nitrogen atmosphere. Pyridine and triethylamine were distilled prior to use and stored over KOH. All reactions were performed using oven-dried glassware under an atmosphere of argon unless otherwise stated. Base-washed glassware was prepared by soaking with saturated aqueous NaOH solution, washing successively with water and acetone, then oven dried. Reactions were heated, where stated, using oil baths. Pressure tube reactions were carried out in ~4 inch "ACE glassware #15" thick-walled vessels with an approximate volume of 14 mL; tube threads were wrapped with PTFE tape and capped with PTFE screw tops complete with FETFE® O-ring seal (from Sigma-Aldrich). Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on Bruker AVII-500 (500/125 MHz), Bruker AVIII-400 (400/100 MHz), or Bruker AV-400 (400/100 MHz) spectrometers in deuterated solvents; all ^{13}C NMR spectra were proton-decoupled and are reported as such. Chemical shifts (δ_H and δ_C) are quoted in parts per million (ppm), referenced to the appropriate solvent peak. Peak multiplicities are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), sextet (sext), septet (sept), multiplet (m), apparent (app.) and broad (br). Coupling constants (*J*) are rounded to the nearest 0.5 Hz. Infrared spectra were recorded using a Bruker Tensor 27 FT-IR spectrometer. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}) and are described as strong (s), medium (m), weak (w) and broad (br). High-resolution mass spectra (HRMS) were recorded by the staff of the Chemistry Research Laboratory on a Bruker Daltonics MicroTOF spectrometer; mass to charge ratios (*m/z*) are reported in Daltons. Melting points were determined using a Griffin MFB-700-010U melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was carried out using Merck aluminum-backed DC60 F_{254} precoated plates (0.2 mm); spots were visualized by ultraviolet (UV) light (λ_{max} = 254 nm) and then stained with anisaldehyde or $KMnO_4$ dips as appropriate. Flash column chromatography was performed using Merck 60 silica gel (particle size 40–63 μm) and eluted

with the described solvent(s). The following starting materials were prepared according to literature procedures: 5-(3-chloropropyl)-2,3-dihydrofuran;[32] 1-(1-ethoxyvinyl)cyclohexan-1-ol;[33] 5-methylhex-4-en-1-ol;[34] 1-vinylcyclobutanol,[35] 1-vinylcyclopentanol;[36] 4-cyclohexylidenebutan-1-ol;[37] 2-(2-bromo-3-methylbut-2-en-1-yl)malonate;[38] 2,2,5-trimethylhex-4-en-1-ol;[39] 4-azidobutyroyl chloride.[40] Reaction schemes for the preparation of substrates, including a key to compound numbers, are included in the Supporting Information.

5-Chloro-2-ethoxypent-1-ene (S1); general procedure for the preparation of ω-(chloroalkyl)enol ethers S1–S5

To an oven-dried 50 mL round-bottomed flask under an atmosphere of argon was added ethyl vinyl ether (2.0 mL, 20.9 mmol) and freshly distilled THF (15 mL). The flask was cooled to –78 °C, and *tert*-butyllithium (19.0 mL, 1.6 M in pentane, 30.4 mmol) was added dropwise via syringe over 10 min causing an intense yellow coloration. The mixture was stirred at –78 °C for 1 h then warmed to 0 °C and stirred at this temperature for 2 h, during which time the solution changed color from yellow to brown. The mixture was then cooled to –78 °C, stirred for 1 h, and neat 1-bromo-3-chloropropane (1.0 mL, 10.1 mmol) was added dropwise, causing a light purple color that faded to colorless within seconds. The reaction mixture was stirred for 14 h while the cooling bath was allowed to warm from –78 °C to ~15 °C. The resulting white slurry was cooled to 0 °C, the reaction was quenched with brine (6 mL) and the aqueous layer extracted with ether (3 × 30 mL). The combined organic extracts were washed successively with water (5 mL) and brine (5 mL), then dried (Na_2SO_4) and concentrated under reduced pressure to yield a colorless oil (1.35 g, 90%) that was sufficiently pure to be used in the next reaction. An analytical sample was obtained by chromatography using basic alumina and eluting with 1% triethylamine/petrol. R_f 0.37 (petrol); ν_{max} 2980w, 1655m, 1276m, 1077s, 798s; δ_H (400 MHz, C_6D_6) 1.02 (3 H, t, J = 7.0 Hz), 1.77 (2 H, app. quin, J = 7.0 Hz), 2.13 (2 H, t, J = 7.0 Hz), 3.17 (2 H, t, J = 7.0 Hz), 3.38 (2 H, q, J = 7.0

Hz), 3.79 and 3.87 (2 × 1 H, 2 × d, J = 1.5 Hz); δ_C (100 MHz, C_6D_6) 14.5, 30.6, 32.7, 44.3, 62.7, 81.8, 161.8; HRMS (FI^+) *m/z*: [M^+] Calcd for $C_7H_{13}{}^{35}ClO$ 148.0649; Found 148.0658.

6-Chloro-2-ethoxyhex-1-ene (S2)

Obtained as a colorless oil (1.36 g, quantitative) from ethyl vinyl ether and 1-chloro-4-iodobutane. R_f 0.25 (petrol); ν_{max} 2934w, 2972w, 1653m, 1277m, 1081m, 796s, 652m; δ_H (400 MHz, C_6D_6) 1.06 (3 H, t, J = 7.0 Hz), 1.42–1.55 (4 H, m), 1.99 (2 H, t, J = 7.0 Hz), 3.08 (2 H, t, J = 6.5 Hz), 3.44 (2 H, q, J = 7.0 Hz), 3.82 and 3.86 (2 × 1 H, 2 × d, J = 1.5 Hz); δ_C (100 MHz, C_6D_6) 14.5, 24.9, 32.2, 34.7, 44.7, 62.7, 81.2, 163.0; HRMS (FI^+) *m/z*: [M^+] Calcd for $C_8H_{15}{}^{35}ClO$ 162.0806; Found 162.0813.

5-(3-Chloropropyl)-2,3-dihydrofuran (S3)[32]

Obtained as a pale yellow oil (1.07 g, quantitative) from dihydrofuran and 1-bromo-3-chloropropane. R_f 0.60 (ethyl acetate/petrol, 1:10); ν_{max} 2958w, 2862w, 1668m, 1003s, 930s, 724s, 651s; δ_H (400 MHz, C_6D_6) 1.71 (2 H, app. quin, J = 7.0 Hz), 2.10 (2 H, tq, J = 7.0, 1.0 Hz), 2.24 (2 H, tq, J = 9.0, 2.0 Hz), 3.13 (2 H, t, J = 6.0 Hz), 3.99 (2 H, t, J = 9.0 Hz), 4.40 (1 H, sept, J = 1.0 Hz); δ_C (100 MHz, C_6D_6) 25.4, 30.0, 30.2, 44.3, 69.8, 94.6, 157.7; HRMS (FI^+) *m/z*: [M^+] Calcd for $C_7H_{11}{}^{35}ClO$ 146.0493; Found 146.0502.

5-(4-Chlorobutyl)-2,3-dihydrofuran (S4)

Obtained as a pale yellow oil (824 mg, quantitative) from dihydrofuran and 1-chloro-4-iodobutane. R_f 0.20 (petrol); ν_{max} 2935s, 2861m, 1667s, 1005s, 725s; δ_H (400 MHz, C_6D_6) 1.41–1.49 (4 H, m), 1.93–1.97 (2 H, m), 2.28 (2 H, tq, J = 9.5, 2.0 Hz), 3.06 (2 H, t, J = 6.0 Hz), 4.05 (2 H, t, J = 9.5 Hz), 4.42 (1 H, app. sept, J = 1.0 Hz); δ_C (100 MHz, C_6D_6) 24.3, 27.4, 30.3, 32.3, 44.6, 69.8, 94.0, 158.8; HRMS (ESI^+) *m/z*: $[M+H]^+$ Calcd for $C_8H_{14}{}^{35}ClO$ 161.0728; Found 161.0725.

6-(4-Chlorobutyl)-3,4-dihydro-2H-pyran (S5)

Obtained as a pale yellow oil (1.08 g, quantitative) from dihydropyran and 1-chloro-4-iodobutane. R_f 0.80 (ethyl acetate/petrol, 1:1); ν_{max} 2932m, 2868w, 1675m, 1234m, 1062s, 762s, 649m; δ_H (400 MHz, C_6D_6) 1.40–1.51 (6 H, m), 1.75–1.80 (2 H, m), 1.90–1.92 (2 H, m), 3.08–3.12 (2 H, m), 3.72 (2 H, t, J = 5.0 Hz), 4.37 (1 H, t, J = 4.0 Hz); δ_C (100 MHz, C_6D_6) 20.6, 22.7, 24.6, 32.3, 33.9, 44.8, 66.0, 95.6, 154.3; HRMS (FI^+) *m/z*: [M^+] Calcd for $C_9H_{15}{}^{35}ClO$ 174.0806; Found 174.0804.

5-Azido-2-ethoxypent-1-ene (11a); general procedure for the preparation of azides 11a,b and 12a–c

To an oven-dried 50 mL round-bottomed flask was added chloride **S1** (211 mg, 1.42 mmol), NaN_3 (146 mg, 2.25 mmol) and DMSO (2.0 mL). The slurry was stirred under an atmosphere of argon at 50 °C for 21 h then cooled to RT; ether (50 mL) was added and the solution was washed successively with water (10 × 1 mL) and brine (1 mL). The organic layer was then dried (Na_2SO_4) and concentrated under reduced pressure to afford a yellow oil (160 mg, 73%) that was sufficiently pure to be used in the next reaction. R_f 0.37 (petrol); ν_{max} 2932w, 2092s, 1654m, 1271m, 1086m, 799m; δ_H (400 MHz, C_6D_6) 1.03 (3 H, t, J = 7.0 Hz), 1.53 (2 H, app. quin, J = 7.0 Hz), 2.00 (2 H, t, J = 7.0 Hz), 2.74 (2 H, t, J = 7.0 Hz), 3.39 (2 H, q, J = 7.0 Hz), 3.79 and 3.84 (2 × 1 H, 2 × d, J = 1.5 Hz); δ_C (100 MHz, C_6D_6) 14.5, 26.9, 32.5, 50.6, 62.8, 81.6, 162.1; HRMS (ESI^+) *m/z*: $[M+H]^+$ Calcd for $C_7H_{14}N_3O$ 156.1131; Found 156.0933.

6-Azido-2-ethoxyhex-1-ene (11b)

Obtained as a pale yellow oil (1.02 g, 84%) from chloride **S2**. R_f 0.25 (petrol); ν_{max} 2980w, 2091s, 1653m, 1094m, 796s; δ_H (400 MHz, C_6D_6) 1.07 (3 H, t, J = 7.0 Hz), 1.22 (2 H, app. quin, J = 7.0 Hz), 1.39 (2 H, app. quin, J = 7.5 Hz) 1.98 (2 H, t, J = 7.5 Hz), 2.65 (2 H, t, J = 7.0 Hz), 3.45 (2 H, q, J = 7.0 Hz), 3.83

and 3.87 (2 × 1 H, 2 × d, J = 1.0 Hz); δ_C (100 MHz, C_6D_6) 14.5, 24.7, 28.4, 34.9, 51.1, 62.7, 81.2, 163.0; HRMS (ESI$^+$) *m/z*: $[M+H]^+$ Calcd for $C_8H_{16}N_3O$ 170.1288; Found 170.1289.

5-(3-Azidopropyl)-2,3-dihydrofuran (12a)

Obtained as a yellow oil (178 mg, 55%) from chloride **S3**. R_f 0.60 (ethyl acetate/petrol, 1:10); ν_{max} 2933w, 2864w, 2095s, 1668w, 1258m, 1005m, 961m. δ_H (400 MHz, C_6D_6) 1.47 (2 H, app. quin, J = 7.0 Hz), 1.97 (2 H, tq, J = 7.0, 1.0 Hz), 2.25 (2 H, tq, J = 9.5, 2.0 Hz), 2.72 (2 H, t, J = 7.0 Hz), 4.01 (2 H, t, J = 9.5 Hz), 4.39 (1 H, sept, J = 1.0 Hz); δ_C (100 MHz, C_6D_6) 25.2, 26.3, 30.3, 50.7, 69.8, 94.5, 157.9; HRMS (FI$^+$) *m/z*: $[M^+]$ Calcd for $C_7H_{11}N_3O$ 153.0897; Found 153.0899.

5-(4-Azidobutyl)-2,3-dihydrofuran (12b)

Obtained as a pale yellow oil (497 mg, 84%) from chloride **S4**. R_f = 0.20 (petrol); ν_{max} 2941m, 2864m, 2091s, 1667m, 1005m, 723m; δ_H (400 MHz, C_6D_6) 1.17–1.24 (2 H, m), 1.30–1.38 (2 H, m), 1.94 (2 H, tq, J = 7.5, 1.0 Hz), 2.29 (2 H, tq, J = 9.5, 2.0 Hz), 2.63 (2 H, t, J = 7.0 Hz), 4.06 (2 H, t, J = 9.5 Hz), 4.43 (1 H, app. sept, J = 1.0 Hz); δ_C (100 MHz, C_6D_6) 24.0, 27.7, 28.5, 30.3, 51.1, 69.8, 94.0, 158.8; HRMS (ESI$^+$) *m/z*: $[M+H]^+$ Calcd for $C_8H_{14}N_3O$ 168.1131; Found 168.1131.

6-(4-Azidobutyl)-3,4-dihydro-2H-pyran (12c)

Obtained as a pale yellow oil (398 mg, 72%) from chloride **S5**. R_f 0.80 (ethyl acetate/petrol, 1:1); ν_{max} 2970m, 2867w, 2090s, 1739m, 1675m, 1233m, 1063m, 763m; δ_H (400 MHz, C_6D_6) 1.25 (2 H, app. quin, J = 7.0 Hz), 1.36–1.49 (4 H, m), 1.78–1.81 (2 H, m), 1.92 (2 H, t, J = 7.5 Hz), 2.68 (2 H, t, J = 7.0 Hz), 3.74 (2 H, t, J = 5.0 Hz), 4.39 (1 H, t, J = 4.0 Hz); δ_C (100 MHz, C_6D_6) 20.6, 22.8, 24.3, 28.4, 34.2, 51.2, 66.0, 95.6, 154.3; HRMS (FI$^+$) *m/z*: $[M^+]$ Calcd for $C_9H_{15}N_3O$ 181.1210; Found 181.1210.

3a-Ethoxy-3a,4,5,6-tetrahydro-3H-pyrrolo[1,2-c][1,2,3]triazole (14a); general procedure for thermolysis of azides 11 and 12

To an oven-dried 14 mL Ace pressure tube was added azide **11a** (467 mg, 3.01 mmol), dry toluene (8.0 mL), and solid K_2CO_3 (128 mg, 0.926 mmol). The vessel was flushed with argon, sealed with a PTFE screw cap with FETFE® O-ring and stirred at 130 °C for 96 h, during which time the white slurry became brown. The tube was cooled to RT and the solution was filtered then concentrated to yield a yellow oil (460 mg), revealed by ^{1}H-NMR spectroscopy to be a 4:1 mixture of the *title compound* (**14a**) and 5,6-dihydro-4*H*-pyrrolo[1,2-c][1,2,3]triazole (**16**).[9] An analytical sample of **14a** was obtained as a colorless oil by chromatography over basic alumina eluting with 1% triethylamine in 5% ether/petrol. R_f = 0.28 (ether/petrol, 1:1); ν_{max} 2971m, 1476w, 1443w, 1366m, 1216s, 1106s; δ_H (400 MHz, C_6D_6) 0.98 (3 H, t, *J* = 7.0 Hz), 1.03–1.18 (2 H, m), 1.43–1.53 (1 H, m), 1.76 (1 H, dt, *J* = 12.5, 6.5 Hz), 2.90–2.98 (1 H, m, *J* = 7.0 Hz), 3.12–3.23 (2 H, m), 3.45 (1 H, dt, *J* = 11.5, 6.0 Hz), 3.60 and 4.10 (2 × 1 H, 2 × d, *J* = 18.5 Hz); δ_C (100 MHz, C_6D_6) 15.5, 24.9, 36.9, 49.2, 57.9, 72.6, 101.0; HRMS (ESI$^+$) *m/z*: $[M+H]^+$ Calcd for $C_7H_{14}N_3O$ 156.1131; Found 156.1138. Data for **16**: R_f = 0.10 (ethyl acetate/petrol, 1:4); ν_{max} 2961m, 1654w, 1454w, 1438m, 1311m, 1224m, 1177m, 1094s, 724m; δ_H (400 MHz, $CDCl_3$) 2.80 (2 H, app. quin, *J* = 7.0 Hz), 2.92 (2 H, t, *J* = 7.0 Hz), 4.33 (2 H, t, *J* = 7.0 Hz), 7.39 (1 H, s); δ_C (100 MHz, $CDCl_3$) 20.7, 28.4, 46.3, 126.9, 142.0; HRMS (ESI$^+$) *m/z*: $[M+H]^+$ Calcd for $C_5H_8N_3$ 110.0713; Found 110.0710.

3a-Ethoxy-3,3a,4,5,6,7-hexahydro[1,2,3]triazolo[1,5-a]pyridine (14b)

The crude product (69 mg), a yellow oil, was obtained from azide **11b** (70 mg, 0.43 mmol) and shown by ^{1}H NMR analysis to be a 6:4 mixture of the *title compound* (**14b**) and 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-a]pyridine (**17**).[9,10] An analytical sample of **14b** was obtained as a colorless oil by chromatography over basic alumina eluting with 1% triethylamine in 5% ether/petrol. R_f 0.33 (petrol/ether, 1:1); ν_{max} 2971w, 2943w, 1444w, 1316m, 1217m, 1046m, 904w; δ_H (400 MHz, C_6D_6)

0.90–0.98 (1 H, m) overlays 0.94 (3 H, t, *J* = 7.0 Hz), 1.10–1.27 (3 H, m), 1.66 (1 H, qt, *J* = 13.0, 4.0 Hz), 1.91 (1 H, dt, *J* = 13.0, 3.0 Hz), 2.71 and 2.79 (2 × 1 H, 2 × dq, *J* = 9.0, 7.0 Hz), 3.05 (1 H, td, *J* = 12.0, 4.0 Hz), 3.34 (1 H, d, *J* = 17.5 Hz), 3.90–3.94 (1 H, m), 3.99 (1 H, d, *J* = 17.5 Hz); δ_C (100 MHz, C_6D_6) 15.2, 20.7, 25.0, 34.7, 43.0, 58.1, 71.4, 88.0; HRMS (ESI^+) *m/z*: $[M+H]^+$ Calcd for $C_8H_{16}N_3O$ 170.1288; Found 170.1283. Data for **17**: R_f 0.10 (petrol/ethyl acetate, 4:1); ν_{max} 2950m, 2868w, 2095w, 1552w, 1431m, 1236s, 990s, 811m, 645m; δ_H (400 MHz, $CDCl_3$) 1.88–1.94 (2 H, m), 2.05–2.10 (2 H, m), 2.84 (2 H, t, *J* = 6.5 Hz), 4.37 (2 H, t, *J* = 6.0 Hz) 7.44 (1 H, s); δ_C (100 MHz, $CDCl_3$) 20.3 (two peaks), 22.9, 46.1, 130.9, 133.3.

2,3,3a,7,8,9-Hexahydrofuro[2,3-d]pyrrolo[1,2-c][1,2,3]triazole (15a)

The crude product (38 mg), a yellow oil, was obtained from azide **12a** (40 mg, 0.26 mmol). An analytical sample of **15a** was obtained as a colorless oil by chromatography over basic alumina eluting with 1% triethylamine in 5% ether/petrol. R_f 0.20 (petrol/ether, 1:1); ν_{max} 2951w, 2872w, 1491m, 1442m, 1121s, 1029s, 991s, 843m, 676m; δ_H (400 MHz, C_6D_6) 1.08–1.16 (1 H, m), 1.33–1.46 (2 H, m). 1.62–1.73 (1 H, m), 1.80–1.90 (2 H, m), 3.12–3.23 (2 H, m), 3.44–3.53 (2 H, m), 4.17 (1 H, d, *J* = 9.5 Hz); δ_C (100 MHz, C_6D_6) 25.5, 32.0, 33.5, 48.9, 65.2, 85.6, 108.0; HRMS (ESI^+) *m/z*: $[M+H–N_2]^+$ Calcd for $C_7H_{12}NO$ 126.0913; Found 126.0918.

3,3a,7,8,9,10-Hexahydro-2H-furo[3′,3′:4,5]triazolo[1,5-a]pyridine (15b)

The crude product (42 mg), a yellow oil, was obtained from azide **12b** (40 mg, 0.26 mmol). An analytical sample of **15b** was obtained as a colorless oil by chromatography over basic alumina eluting with 1% triethylamine in 5% ether/petrol. R_f = 0.19 (petrol ether, 1:1) ν_{max} 2946m, 2864w, 1440m, 1366s, 1216s, 1032m; δ_H (400 MHz, C_6D_6) 1.10–1.21 (3 H, m), 1.32 (1 H, dquin, *J* = 13.0, 3.5 Hz), 1.60–1.75 (3 H, m), 2.04 (1 H, dd, *J* = 12.0, 5.0 Hz), 3.14 (1 H, ddd, *J* = 12.0, 8.5, 5.0 Hz), 3.40 (1 H, td, *J* = 12.0, 4.5

Hz), 3.51 (1 H, ddd, J = 8.0, 7.5, 1.0 Hz), 3.94–3.98 (1 H, m), 4.09 (1 H, d, J = 8.0 Hz); δ_C (100 MHz, C_6D_6) 21.1, 25.3, 32.1, 32.9, 43.4, 65.8, 83.7, 95.1; HRMS (ESI^+) *m/z*: $[M+H]^+$ Calcd for $C_8H_{14}N_3O$ 168.1131; Found 168.1136.

12-Oxa-6,7,8-triazatricyclo[7.4.0.0^{1,6}]tridec-7-ene (15c)

The crude product (114 mg), a yellow waxy solid, was obtained from azide **12c** (147 mg, 0.81 mmol). The *title compound* (**15c**) was obtained pure, as a colorless oil, by chromatography over basic alumina, eluting with 1% triethylamine in 10% ether/petrol (30 mg, 20%). R_f 0.30 (petrol/ether, 1:1); ν_{max} 2942s, 2859m, 1445m, 1094m, 1033s, 942m, 808m; δ_H (400 MHz, C_6D_6) 0.93–1.03 (2 H, m), 1.23–1.30 (3 H, m), 1.39–1.51 (2 H, m), 1.57–1.69 (1 H, m), 1.73 (1 H, dt, J = 13.0, 3.0 Hz), 2.13–2.20 (1 H, m), 2.95–3.01 (1 H, m), 3.24–3.31 (2 H, m), 3.39–3.46 (1 H, m), 3.89–3.94 (1 H, m); δ_C (100 MHz, C_6D_6) 20.1, 21.2, 21.6, 24.9, 30.4, 43.0. 60.3, 76.5, 87.7; HRMS (ESI^+) *m/z*: $[M+H]^+$ Calcd for $C_9H_{16}N_3O$ 182.1288; Found 182.1285.

2-(4,5,6,7-Tetrahydro[1,2,3]triazolo[1,5-a]pyridin-3-yl)ethanol (18)

The title compound was obtained from a failed attempt to achieve iminium formation and allylation from cycloadduct **15b**. To an oven-dried 10 mL round-bottomed flask was added cycloadduct **15b** (19 mg, 0.11 mmol) and dry dichloromethane (2.0 mL); the flask was flushed with argon and the mixture cooled to –78 °C. Allyltributyl tin (38 μL, 0.12 mmol) was added via syringe, followed by TMSOTf (28 μL, 0.15 mmol) after 10 min. The reaction mixture was stirred for 16 h during which time the cooling bath was allowed to warm from –78 °C to ~12 °C; the reaction was quenched with saturated aqueous $NaHCO_3$ solution (1.0 mL), and extracted with dichloromethane (3 × 7 mL). The combined extracts were dried (K_2CO_3) and concentrated to yield a colorless oil with solid particles suspended within (62 mg). The solid was found to be insoluble in C_6D_6 but dissolved in $CDCl_3$, and was revealed to be the triazole **18**.

The crude triazole was passed through a silica gel column gradient eluting with ethyl acetate to methanol, yielding a the *title compound* as a colorless oil (7.0 mg, 38%). R_f 0.18 (petrol/ethyl acetate, 1:1); ν_{max} 3362br, 2949s, 2867m, 1574m, 1224m, 1052s, 668m; δ_H (400 MHz, $CDCl_3$) 1.89–1.95 (2 H, m), 2.03–2.09 (2 H, m), 2.75 (2 H, t, J = 6.5 Hz), 2.83 (2 H, t, J = 6.0 Hz), 3.97 (2 H, t, J = 6.0 Hz), 4.35 (2 H, t, J = 6.0 Hz); δ_C (100 MHz, $CDCl_3$) 19.9, 20.2, 22.8, 27.8, 46.4, 61.7 (the 4°-carbons were not observed in this weak NMR sample); HRMS (ESI^+) *m/z*: $[M+H]^+$ Calcd for $C_8H_{14}N_3O$ 168.1131; Found 168.1130.

Ethyl 4-cyclohexylidene-4-ethoxybutanoate (S6)

To an oven-dried 25 mL round-bottomed flask equipped with stirrer bar, distillation head and thermometer was added triethylorthoacetate (4.0 mL), 1-(1-ethoxyvinyl)cyclohexan-1-ol[33] (340 mg, 2.0 mmol), and a few crystals of hydroquinone. The set-up was flushed with argon, then placed into a pre-heated oil bath at 135 °C. Propionic acid (2 drops) was added at hourly intervals over 5 h, then the reaction mixture was heated for a further 16 h. Ethanol was observed distilling off at 78 °C. The mixture was cooled to RT, diluted with ether (70 mL) and washed successively with saturated aqueous NH_4Cl (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL). The organic layer was dried (Na_2SO_4) and concentrated onto basic alumina for purification over alumina eluting with 2% triethylamine in 5% ether/petrol (30 mg, 6%). R_f 0.66 (petrol/ether, 2:1); ν_{max} 2926m, 1735s, 1164m, 1112m, 1046m; δ_H (400 MHz, C_6D_6) 0.96 (3 H, t, J 7.5 Hz), 1.06 (3 H, t, J = 7.5 Hz), 1.41–1.49 (6 H, m), 2.00–2.07 (2 H, m), 2.29–2.34 (2 H, m), 2.42–2.48 (2 H, m), 2.52–2.57 (2 H, m), 3.42 (2 H, q, J = 7.5 Hz), 3.97 (2 H, q, J = 7.5 Hz); δ_C (100 MHz, C_6D_6) 14.3, 15.6, 22.9, 27.2, 27.7, 28.1, 28.5, 29.7, 32.9, 60.1, 64.9, 123.7, 145.1, 172.8; HRMS (ESI^+) *m/z*: $[M+Na]^+$ Calcd for $C_{14}H_{24}NaO_3$ 263.1618; Found 263.1621.[41]

(4-Azido-1-ethoxybutylidene)cyclohexane (19)

To an oven-dried 25 mL round-bottomed flask was added ester **S6** (30 mg, 0.12 mmol) and THF (1.0 mL), and the solution was stirred at 0 °C under argon. $LiAlH_4$ (0.20 mL, 1.0 M in THF, 0.20 mmol) was added at 0 °C, the reaction stirred for 2 h, and then quenched with saturated aqueous Rochelle's salt (1.0 mL). The layers were separated and the aqueous layer was extracted successively with ether (3 × 7 mL), the combined organic layers were washed with brine (3 mL), dried (Na_2SO_4), and then concentrated to yield an oil that was purified over basic alumina eluting with 2% triethylamine in 10% ether/petrol, yielding 4-cyclohexylidene-4-ethoxybutan-1-ol (**S7**) as a colorless oil (22 mg, 92%) that was taken directly into the next reaction. R_f 0.41 (petrol/ether, 2:1); δ_H (200 MHz, C_6D_6) 1.09 (3 H, t, J = 7.0 Hz), 1.30–1.78 (8 H, m), 2.00–2.11 (2 H, m), 2.19 (2 H, t, J = 7.0 Hz), 2.32–2.44 (2 H, m), 3.32–3.50 (4 H, m). To a 7.0 mL sample vial was added alcohol **S7** (20 mg, 0.10 mmol) in DMF (1.0 mL) and the solution was cooled to 0 °C under argon. Freshly recystallised carbon tetrabromide (66 mg, 0.20 mmol) and triphenylphosphine (52 mg, 0.20 mmol) were added, leading the colorless solution to become yellow. After 0.5 h at 0 °C, NaN_3 (26 mg, 0.40 mmol) was added and the reaction was stirred for 14 h, during which the ice bath warmed from 0 °C to 15 °C. The cloudy brown solution was extracted with petrol (8 × 3 mL) until no further product was observed by TLC analysis in the DMF layer. The combined petrol extracts were washed successively with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), then dried (Na_2SO_4) and concentrated to yield an oil that was purified over basic alumina eluting with 1% triethylamine and 5% ether/petrol, yielding the *title compound* as a colorless oil (13 mg, 58%). R_f 0.88 (petrol); δ_H (400 MHz, $CDCl_3$) 1.08 (3 H, t, J = 7.0 Hz), 1.42–1.52 (6 H, m), 1.99–2.12 (4 H, m), 2.34–2.36 (2 H, m), 2.83 (2 H, t, J = 6.5 Hz), 3.39 (2 H, q, J = 7.0 Hz); δ_C (100 MHz, C_6D_6) [from HSQC] 15.6, 23.8, 26.8, 27.2, 27.6, 28.2, 28.5, 29.6, 50.6, 64.6, 123.8, 144.9.

5-(1-Ethoxycyclohexyl)-3,4-dihydro-2H-pyrrole (21)

To an oven-dried 14 mL Ace pressure tube was added azide **19** (6.0 mg, 0.027 mmol) and toluene-d_8 (1.0 mL). The reaction vessel was flushed with argon, the thread sealed with PTFE tape, and the screw cap with FETFE® O-ring fitted; the whole was wrapped in cotton wool/aluminum foil and the colorless solution was stirred at 130 °C for 84 h. The tube was cooled to RT, the brown reaction solution was filtered through a sintered glass funnel, washing through with ether, and the solution concentrated onto silica for chromatography on silica gel, eluting with 10% → 40% ether/petrol. The volatile product was obtained as a 78% w/w solution in ether (~1.6 mg, ~30%). R_f 0.61 (ether); δ_H (400 MHz, $CDCl_3$) 1.19 (3 H, t, J = 7.0 Hz), 1.48–1.74 (8 H, m), 1.84–1.92 (4 H, m), 2.59 (2 H, tt, J = 8.0, 2.0 Hz), 3.21 (2 H, q, J = 7.0 Hz), 3.89 (2 H, tt, J = 7.5, 2.0 Hz); *m/z* (ESI^+) 196.2 (MH^+).

Ethyl 4-cyclobutylidenebutanoate (S8);[42] general procedure for Johnson–Claisen rearrangement

To an oven-dried 50 mL round-bottomed flask equipped with stirrer bar, distillation head and thermometer was added triethylorthoacetate (3.7 mL), 1-vinylcyclobutanol[35] (190 mg, 1.94 mmol), and a few crystals of hydroquinone. The set-up was flushed with argon, then placed into an oil bath pre-heated to 140 °C. Two drops of propionic acid were added and the mixture was stirred for 22 h. Ethanol was observed distilling off at 78 °C. Reaction completion was indicated by TLC. The mixture was cooled to RT, diluted with ether (50 mL) and washed successively with hydrochloric acid (0.1 M, 20 mL), saturated aqueous $NaHCO_3$ solution (10 mL), and brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated to afford an oil that was purified over silica gel, eluting with petrol, to yield a colorless oil (253 mg, 78%). R_f 0.60 (petrol/ether, 3:1); ν_{max} 1735s, 1164s; δ_H (400 MHz, $CDCl_3$) 1.26 (3 H, t, J = 7.0 Hz), 1.92 (2 H, app. quin, J = 8.0 Hz), 2.18 (2 H, app. q, J = 7.0 Hz), 2.31 (2 H, t, J = 7.0 Hz), 2.54–2.59 (4 H, m), 4.13 (2 H, q, J = 8.0 Hz), 4.98–5.05 (1 H, m); δ_C (100 MHz, $CDCl_3$) 14.4, 17.1, 23.7, 29.3,

31.0, 34.6, 60.3, 118.3, 141.7, 173.6; HRMS (FI^+) *m/z*: [M^+] Calcd for $C_{10}H_{16}O_2$ 168.1145; Found 168.1148.

Ethyl 4-cyclopentylidenebutanoate (S9)[43]

Application of the general procedure described above (for **S8**) afforded ester **S9** (1.25 g, 61% from 1-vinylcyclopentanol[36]) as a colorless oil. R_f 0.82 (petrol/ether, 3:1); ν_{max} 1736s; δ_H (400 MHz, $CDCl_3$) 1.26 (3 H, t, *J* = 7.0 Hz), 1.57–1.69 (4 H, m), 2.20 (4 H, app. q, *J* = 7.0 Hz), 2.28–2.36 (4 H, m), 4.11 (2 H, q, *J* = 7.0 Hz), 5.17–5.23 (1 H, m); δ_C (100 MHz, $CDCl_3$) 14.4, 25.3, 26.4, 26.5, 28.7, 33.7, 34.5, 60.3, 118.0, 144.9, 173.7; *m/z* (ESI^+) 205.1 (MNa^+), 183.1 (MH^+).

4-Cyclobutylidenebutan-1-ol (S10); general procedure for ester reduction

To an oven-dried 10 mL round-bottomed flask was added ester **S8** (230 mg, 1.37 mmol) in THF (1.0 mL) and the solution was stirred at 0 °C under argon. $LiAlH_4$ (1.5 mL, 1.0 M in THF, 1.5 mmol) was added dropwise via syringe over 1 min, and the reaction was stirred for 13 h during which the ice bath warmed to 15 °C. The reaction was quenched carefully with saturated aqueous Rochelle's salt (1 mL) then brine (10 mL), and the mixture was extracted with ether (3 × 20 mL). The combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ solution (10 mL), then brine (10 mL), dried (Na_2SO_4), and concentrated to yield a colorless oil (168 mg, 97%). R_f 0.37 (petrol/ether, 1:1); ν_{max} 3327br; δ_H (400 MHz, $CDCl_3$) 1.60 (2 H, app. quin, *J* = 6.5 Hz), 1.89–1.99 (4 H, m), 2.61–2.66 (4 H, m), 3.64 (2 H, t, *J* = 6.5 Hz), 5.04–5.09 (1 H, m); δ_C (100 MHz, $CDCl_3$) 17.1, 24.5, 29.4, 31.0, 32.7, 62.9, 119.7, 140.9; HRMS (FI^+) *m/z*: [M^+] Calcd for $C_8H_{14}O$ 126.1039; Found 126.1041.

4-Cyclopentylidenebutan-1-ol (S11)

Application of the general procedure described above (for **S10**) afforded alcohol **S11** (851 mg, 92% from ester **S9**) as a colorless oil. R_f 0.32 (petrol/ether, 1:1); ν_{max} 3331br; δ_H (400 MHz, $CDCl_3$) 1.55–1.69 (6 H, m), 2.05 (2 H, app. q, J = 7.0 Hz), 2.16–2.23 (4 H, m), 3.64 (2 H, t, J = 6.5 Hz), 5.20–5.27 (1 H, m); δ_C (100 MHz, $CDCl_3$) 26.1, 26.5 (two peaks), 28.7, 32.7, 33.7, 62.9, 119.4, 144.1; *m/z* (ESI^+) 141.2 (MH^+).

6-Azido-2-methylhex-2-ene (S12);[34] general procedure for mesylation/azide displacement

To an oven-dried 100 mL round-bottomed flask was added 5-methylhex-4-en-1-ol[34] (948 mg, 8.30 mmol), ether (20 mL) and triethylamine (1.40 mL, 10.0 mmol) and the solution was cooled to 0 °C under argon. Methanesulfonyl chloride (0.80 mL, 10.3 mmol) was added dropwise via syringe over 5 min, causing a white precipitate to form. After 0.5 h, the reaction mixture was warmed to RT and stirred for 3 h. The reaction was quenched with brine (15 mL), and the separated aqueous layer extracted with ether (3 × 15 mL). The organic extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to yield a colorless oil (the mesylate) that was used directly in the next reaction. The crude mesylate was transferred to a 50 mL round-bottomed flask with DMSO (4 mL) and NaN_3 (1.0 g, 15.4 mmol), and the mixture was stirred at 35 °C for 18 h. The product was extracted into petrol (80 mL) and the petrol layer was washed with water (4 × 10 mL). The combined aqueous washes were extracted with petrol (3 × 10 mL), then the combined organic portions were dried ($MgSO_4$) and concentrated. The crude product was purified over silica gel, eluting with petrol to yield the title compound (**S12**) as a colorless oil (900 mg, 78% over the two steps). R_f 0.76 (petrol); ν_{max} 2093s; δ_H (400 MHz, $CDCl_3$) 1.62 (3 H, s), 1.64 (2 H, app. quin, J = 7.0 Hz), 1.71 (3 H, d, J = 1.0 Hz), 2.08 (2 H, app. q, J = 7.0 Hz), 3.27 (2 H, t, J = 7.0 Hz), 5.09 (1 H, t. hept, J = 7.0, 1.0 Hz); δ_C (100 MHz, $CDCl_3$) 17.8, 25.2, 25.8, 29.0, 51.1, 123.0, 133.0; HRMS (FI^+) *m/z*: [M^+] Calcd for $C_7H_{13}N_3$ 139.1104; Found 139.1106.

(4-Azidobutylidene)cyclobutane (S13)

Application of the general procedure described above (for **S12**) afforded azide **S13** (119 mg, 70% from alcohol **S10**) as a colorless oil. R_f 0.40 (petrol); ν_{max} 2093s; δ_H (400 MHz, $CDCl_3$) 1.62 (2 H, app. quin, J = 7.0 Hz), 1.90–2.00 (4 H, m), 2.61–2.67 (4 H, m), 3.26 (2 H, t, J = 7.0 Hz), 4.97–5.05 (1 H, m); δ_C (100 MHz, $CDCl_3$) 17.1, 25.1, 28.8, 29.4, 31.0, 51.0, 118.6, 141.6; HRMS (FI^+) *m/z*: [M^+] Calcd for $C_8H_{13}N_3$ 151.1104; Found 151.1113.

(4-Azidobutylidene)cyclopentane (S14)

Application of the general procedure described above (for **S12**) afforded azide **S14** as a colorless oil (711 mg, 77% from alcohol **S11**). R_f 0.38 (petrol); ν_{max} 2090s; δ_H (400 MHz, $CDCl_3$) 1.59–1.69 (6 H, m), 2.07 (2 H, qt, J = 7.5, 1.5 Hz), 2.16–2.25 (4 H, m), 3.27 (2 H, t, J = 7.0 Hz), 5.16–5.23 (1 H, m); δ_C (100 MHz, $CDCl_3$) 26.5 (two peaks), 26.7, 28.8 (two peaks), 33.7, 51.1, 118.4, 144.8; HRMS (FI^+) *m/z*: [M^+] Calcd for $C_9H_{15}N_3$ 165.1260; Found 165.1254.

6-Azido-3-bromo-2-methylhex-2-ene (22a); general procedure for bromination/dehydrobromination of trisubstituted alkenes

To an oven-dried 50 mL round-bottomed flask was added 6-azido-2-methylhex-2-ene **S12** (420 mg, 3.02 mmol) and petrol (10 mL), and the solution was cooled to 0 °C under argon. A solution of Br_2 (0.16 mL, 3.12 mmol) in petrol (0.5 mL) was added dropwise to the reaction via syringe over 15 min, causing an orange coloration that subsided and then persisted. The mixture was warmed to RT, stirred for 5 min, then cooled to 0 °C and quenched with saturated aqueous $Na_2S_2O_3$ solution (30 mL). After the orange color faded to colorless, the layers were separated and the aqueous extracted with petrol (3 × 30 mL), the combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), and concentrated to yield a

yellow oil. The crude product was transferred to a 50 mL round-bottomed flask with DMSO (1.0 mL) and stirred at RT under argon. Potassium *tert*-butoxide (4.5 mL, 1.0 M in *tert*-butanol, 4.5 mmol) was added dropwise via syringe pump over 20 min, causing the colorless solution to become brown, and stirring was continued for a further 14 h. The reaction mixture was concentrated to half its volume under vacuum to remove *tert*-butanol, then was diluted with saturated aqueous $NaHCO_3$ solution (20 mL). The solution was extracted with ether (4 × 20 mL), the combined organics were washed with brine (10 mL), dried ($MgSO_4$), and concentrated to yield a brown oil. The crude product was purified over silica gel, eluting with petrol to yield the *title compound* as a pale yellow oil (0.49 g, 74% over two steps). R_f 0.31 (petrol); ν_{max} 2092s; δ_H (400 MHz, $CDCl_3$) 1.80 (3 H, s), 1.85 (2 H, app. quin, J = 7.0 Hz), 1.89 (3 H, s), 2.60 (2 H, t, J = 7.0 Hz), 3.30 (2 H, t, J = 7.0 Hz); δ_C (100 MHz, $CDCl_3$) 20.5, 25.5, 27.5, 34.4, 50.3, 120.1, 131.8; HRMS (FI^+) *m/z*: [M^+] Calcd for $C_7H_{12}{}^{79}BrN_3$ 217.0209; Found 217.0131.

(4-Azido-1-bromobutylidene)cyclobutane (22b); alternative general procedure for bromination/dehydrobromination of trisubstituted alkenes

To an oven-dried 25 mL round-bottomed flask was added azide **S13** (330 mg, 2.18 mmol) and dichloromethane (6.0 mL), and the solution was cooled to 0 °C under argon. A solution of Br_2 (0.12 mL, 2.34 mmol) in petrol (1.0 mL) was added dropwise to the reaction via syringe over 1 min, causing an orange coloration that subsided and then persisted. The mixture was stirred at 0 °C for 5 min, then warmed to RT. After stirring for 0.5 h, the reaction mixture was concentrated under vaccum to yield an orange oil. To the crude dibromide was added THF (5.0 mL), and the solution was cooled to –78 °C under argon. KHMDS (7.2 mL, 0.91 M in THF, 6.6 mmol) was added dropwise via syringe pump over 20 min causing the clear orange solution to become dark brown, and the mixture was stirred for a further 14 h during which the cooling bath warmed from –78 °C to RT. The reaction was quenched with saturated aqueous NH_4Cl solution (50 mL) and the product was extracted into petrol (3 × 20 mL). The combined

organic extracts were washed successively with saturated aqueous $NaHCO_3$ solution (5 mL), brine (5 mL), then dried ($MgSO_4$), and concentrated to yield a brown oil. The crude product was purified over silica gel, eluting with petrol to yield a colorless oil (282 mg, 56% over two steps). R_f 0.31 (petrol); ν_{max} 2096s; δ_H (400 MHz, $CDCl_3$) 1.82 (2 H, app. quin, J = 7.0 Hz), 1.94 (2 H, app. quin, J = 7.0 Hz), 2.38 (2 H, tt, J = 7.0, 1.0 Hz), 2.60–2.69 (4 H, m), 3.30 (2 H, t, J = 7.0 Hz); δ_C (100 MHz, $CDCl_3$) 15.1, 27.0, 29.7, 32.2, 32.3, 115.1, 140.5; HRMS (FI^+) *m/z*: [M^+] Calcd for $C_8H_{12}{}^{79}BrN_3$ 229.0209; Found 229.0215

(4-Azido-1-bromobutylidene)cyclopentane (22c)

Application of the general procedure described above (for **22a**) afforded bromide **22c** (279 mg, 75% from azide **S14**) as a colorless oil. R_f 0.17 (petrol); ν_{max} 2094s; δ_H (400 MHz, $CDCl_3$) 1.69 (2 H, app. quin, J = 7.0 Hz), 1.78 (2 H, app. quin, J = 7.0 Hz), 1.85 (2 H, app. quin, J = 6.5 Hz), 2.30 (2 H, t, J = 7.0 Hz), 2.34 (2 H, t, J = 7.0 Hz), 2.53 (2 H, t, J = 7.0 Hz), 3.30 (2 H, t, J = 6.5 Hz); δ_C (100 MHz, $CDCl_3$) 26.1, 27.3, 28.0, 32.0, 35.2, 36.1, 50.3, 115.7, 144.3; HRMS (FI^+) *m/z*: [M–Br–N_2]$^+$ Calcd for $C_9H_{14}N$ 136.1121; Found 136.1135.

(4-Azidobutylidene)cyclohexane (S15) and (4-azido-1-bromobutylidene)cyclohexane (22d)

Application of the general procedure described above (for **S12**) afforded crude azide **S15** (from 4-cyclohexylidenebutan-1-ol[37]) as a pale brown oil that was taken directly into the next reaction. R_f 0.40 (petrol); ν_{max} 2092s; δ_H (400 MHz, $CDCl_3$) 1.47–1.58 (6 H, m), 1.63 (2 H, app. quin, J = 7.0 Hz), 2.06–2.14 (6 H, m), 3.27 (2 H, t, J = 7.0 Hz), 5.04 (1 H, t, J = 7.0); δ_C (100 MHz, $CDCl_3$) 24.2, 27.0, 28.0, 28.8 (two peaks), 29.3, 37.3, 51.0, 119.5, 141.3; HRMS (FI^+) *m/z*: [M–N_2]$^+$ Calcd for $C_{10}H_{17}N$ 151.1356; Found 151.1336. This crude azide was then taken through the general procedure described above (for **22a**) to yield the product as a pale yellow oil (11.0 g, 52% from 4-cyclohexylidenebutan-1-ol). R_f 0.21 (petrol); ν_{max} 2093s; δ_H (400 MHz, $CDCl_3$) 1.56 (6 H, br. s), 1.85 (2 H, app. quin, J = 7.0 Hz), 2.25–2.28

(2 H, m), 2.40 (2 H, br. s), 2.63 (2 H, t, J = 7.0 Hz), 3.30 (2 H, t, J = 6.5 Hz); δ_C (100 MHz, $CDCl_3$) 26.5, 27.4, 27.5, 28.0, 31.3, 34.0, 35.6, 50.2, 117.6, 139.4; HRMS (FI^+) *m/z*: [M^+] Calcd for $C_{10}H_{16}{}^{79}BrN_3$ 257.0522; Found 257.0543.

Dimethyl 2-(4-azido-1-hydroxybutylidene)malonate (S16)

To a 250 mL oven-dried round-bottomed flask was added anhydrous $MgCl_2$ (1.70 g, 17.9 mmol) and acetonitrile (100 mL) at 0 °C under argon. Dimethyl malonate (1.80 mL, 15.8 mmol) and triethylamine (4.40 mL, 31.6 mmol) were added dropwise, followed 10 min later by a solution of 4-azidobutyryl chloride[40] (3.48 g, 23.6 mmol) in acetonitrile (3.0 mL), dropwise over 45 min. The mixture was stirred at 0 °C for 1 h then warmed to ambient temperature, and, after 1 h stirring, quenched with water (150 mL) and extracted with ether (3 × 200 mL); the combined extracts were washed with brine (20 mL), dried ($MgSO_4$), concentrated, and purified on silica gel, eluting with 10% ether/petrol to yield the *title compound* as a *ca.* 60:40 mixture of keto/enol tautomers and as a pale yellow oil (2.66 g, 69%). R_f 0.40 (petrol/ether, 1:1); ν_{max} 2097s, 1722s, 1651m, 1602m; δ_H (400 MHz, $CDCl_3$) [keto/enol mixture] 1.87–1.97 (2 H, m), 2.55 (0.8 H, t, J = 7.5 Hz), 2.73 (1.2 H, t, J = 7.0 Hz), 3.32–3.37 (2 H, m), 3.79 (1.2 H, s), 3.81 (3.6 H, s), 3.82 (1.2 H, s), 4.51 (0.6 H, s), 13.50 (0.4 H, s); δ_C (100 MHz, $CDCl_3$) [keto/enol mixture] 22.9, 26.0, 31.1, 38.7, 50.4, 50.7, 52.3, 52.5, 53.4, 53.8, 65.0, 99.8, 165.0, 166.6, 171.6, 182.2, 197.9; HRMS (ESI^+) *m/z*: $[M+Na]^+$ Calcd for $C_9H_{13}N_3NaO_5$ 266.0747; Found 266.0755.

Dimethyl 2-(4-azido-1-bromobutylidene)malonate (22e)

To a 50 mL oven-dried round-bottomed flask was added DMF (3.4 mL) and the solution was stirred at 0 °C under argon. PBr_3 (0.25 mL, 2.63 mmol) in ether (2.0 mL) was added dropwise over 40 min leading to a white precipitate to form. After 10 min, a solution of malonate derivative **S16** (200 mg, 0.822 mmol) in DMF (1.0 mL) was added over 25 min, washing in with further DMF (1.0 mL). An oven-dried reflux

condenser was attached under argon, and the reaction mixture was heated to 45 °C for 22 h, during which time the white precipitate became green. The flask was removed from the heat, quenched with brine (60 mL), extracted with ether (3 × 20 mL), and the combined extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The crude product was purified over silica gel, eluting with 6% ether/petrol, yielding a yellow oil (83 mg, 33%). R_f 0.50 (petrol/ether, 1:1); ν_{max} 2098s, 1729s, 1621m; δ_H (400 MHz, $CDCl_3$) 1.96 (2 H, app. quin, J = 7.0 Hz), 3.19 (2 H, app. t, J = 7.5 Hz), 3.38 (2 H, t, J = 7.0 Hz), 3.79 (3 H, s), 3.86 (3 H, s); δ_C (100 MHz, $CDCl_3$) 27.7, 36.3, 50.4, 52.9, 53.0, 129.9, 146.6, 162.2, 165.4; HRMS (ESI^+) *m/z*: $[M+Na]^+$ Calcd for $C_9H_{12}{}^{79}BrN_3NaO_4$ 327.9903; Found 327.9910.

6-Azido-2,5,5-trimethylhex-2-ene (S17)

To an oven-dried 25 mL round-bottomed flask was added 2,2,5-trimethylhex-4-en-1-ol[39] (500 mg, 3.52 mmol), pyridine (0.50 ml, 6.18 mmol) and dry dichloromethane (5.0 mL). The flask was cooled to –78 °C under argon and trifluoromethanesulfonic acid anhydride (0.88 mL, 5.23 mmol) was added dropwise; the mixture was stirred for 10 min, then the cold bath was removed to allow the mixture to reach RT during which time the solution turned from yellow to pink to purple. TLC analysis after 1.5 h revealed the reaction to be complete. The reaction was quenched with brine (50 mL), the mixture was extracted with ether (3 × 20 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (3 × 2 mL), then dried (Na_2SO_4) and concentrated to yield the product as a red oil that was used directly in the next step. The crude triflate was dissolved in DMF (2.0 mL) and stirred with NaN_3 (340 mg, 5.23 mmol) under argon at 30 °C overnight. The mixture was cooled to RT, diluted with ether (100 mL), and washed successively with water (10 × 1 mL) and brine (1 mL), then dried (Na_2SO_4) and concentrated to yield the product as an oil that was sufficiently pure to use in the next step (313 mg, 53% from the starting alcohol). R_f 0.58 (petrol); ν_{max} 2965m, 2928m, 2096s, 1470m, 1365m, 845w; δ_H (400 MHz, $CDCl_3$) 0.91 (6 H, s), 1.62 and 1.74 (2 × 3 H, 2 × s), 1.94 (2 H, d, J = 8.0 Hz), 3.09 (2 H, s), 5.14

(1 H, tt, J = 8.0, 1.5 Hz); δ_C (100 MHz, $CDCl_3$) 18.0, 25.0, 26.2, 36.5, 37.9, 62.3, 120.0, 134.2; HRMS (ESI^+) *m/z*: $[M+H–N_2]^+$ Calcd for $C_9H_{18}N$ 140.1434; Found 140.1434.

6-Azido-3-bromo-2,5,5-trimethylhex-2-ene (22f)

To an oven-dried 50 mL round-bottomed flask was added azide **S17** (1.12 g, 6.69 mmol) and dry dichloromethane (7.0 mL), and the flask was cooled to –78 °C under argon. A solution of Br_2 (0.34 mL, 6.64 mmol) in dichloromethane (1 mL) was added dropwise until the brown color remained. After stirring for 2 h, the cooling bath was removed and the flask was allowed to warm to RT for 0.5 h. The mixture was concentrated to an orange oil and purified over silica gel eluting with petrol, yielding 1-azido-4,5-dibromo-2,2,5-trimethylhexane as a yellow oil (470 mg, 21%). R_f 0.36 (petrol); ν_{max} 2964w, 2100s, 1457w, 1096m, 805w; δ_H (500 MHz, $CDCl_3$) 1.06 and 1.08 (2 × 3 H, 2 × s), 1.81 and 2.00 (2 × 3 H, 2 × s), 2.07 (1 H, dd, J = 16.0, 8.5 Hz), 2.50 (1 H, dd, J = 16.0, 1.0 Hz), 3.24 and 3.32 (2 × 1 H, 2 × d, J = 12.0 Hz), 4.30 (1 H, d, J = 8.5 Hz); δ_C (125 MHz, $CDCl_3$) 24.9, 25.5, 27.7, 35.2, 45.5, 59.8, 62.2, 69.5; HRMS (FI^+) *m/z*: $[M^+]$ Calcd for $C_9H_{17}{}^{79}Br^{81}BrN_3$ 326.9763; Found 326.9793. To an oven-dried 50 mL round-bottomed flask was added a sample of this dibromide (116 mg, 0.355 mmol) and dry THF (6.0 mL), and the flask was cooled to 0 °C under argon. KHMDS (4.0 mL, 0.5 M in toluene, 2.0 mmol) was added dropwise over 1 h, and the mixture was stirred for 14 h during which time the ice bath warmed to 10 °C. The reaction was quenched with brine (5 mL) and the mixture was extracted with petrol (3 × 20 mL); the combined organic extracts were washed sequentially with saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL), then dried (Na_2SO_4) and concentrated to yield a brown oil. The crude product was purified over silica gel eluting with petrol, yielding the *title compound* (**22f**) as a colorless oil (53 mg, 61%). R_f 0.40 (petrol); ν_{max} 2925m, 2101s, 1457w, 1389w, 802w; δ_H (400 MHz, $CDCl_3$) 1.01 (6 H, s), 1.78 and 1.91 (2 × 3 H, 2 × s), 2.60 (2 H, s), 3.25 (2 H, s); δ_C (100 MHz, $CDCl_3$) 21.8, 25.7, 26.1, 37.9, 46.1, 62.4, 117.1, 134.3; HRMS (FI^+) *m/z*: $[M^+]$ Calcd for $C_9H_{16}{}^{79}BrN_3$ 245.0522; Found 245.0535.

2-(2-Bromo-3-methylbut-2-en-1-yl)propane-1,3-diol (S18)

Application of the general procedure described above (for **S10**) afforded diol **S18** [780 mg, 78% from dimethyl 2-(2-bromo-3-methylbut-2-en-1-yl)malonate[38]] as a colorless oil after purification by chromatography on silica gel, eluting with a gradient of 50% ether/petrol to pure ether. R_f 0.36 (ether); ν_{max} 3269br; δ_H (400 MHz, $CDCl_3$) 1.62 (1 H, br s), 1.81 (3 H, s), 1.90 (3 H, s), 2.14–2.22 (2 H, m), 2.60 (2 H, d, *J* = 7.5 Hz), 3.70 (2 H, dd, *J* = 10.5, 6.0 Hz), 3.87 (2 H, dd, *J* = 10.5, 3.5 Hz); δ_C (100 MHz, $CDCl_3$) 20.8, 25.6, 35.9, 41.2, 65.0, 119.6, 132.4; HRMS (FI^+) *m/z*: [M^+] Calcd for $C_8H_{15}{}^{79}BrO_2$ 222.0250; Found 222.0254.

2-(Azidomethyl)-4-bromo-5-methylhex-4-en-1-ol (22g)

Application of the general procedure described above (for **S12**) afforded azide **22g** as a colorless oil (54 mg, 35% from diol **S18** using 1.0 molar equivalent of MsCl in the first step); the diazide (**22h**) was also obtained as a colorless oil (31 mg, 18%). Data for **22g**: R_f 0.28 (petrol/ether, 2:1); ν_{max} 3354br, 2095s; δ_H (500 MHz, $CDCl_3$) 1.82 (3 H, s), 1.91 (3 H, s), 2.19–2.26 (1 H, m), 2.51–2.62 (2 H, m), 3.40 (2 H, dd, *J* = 12.0, 6.0 Hz), 3.52 (2 H, dd, *J* = 12.0, 5.0 Hz), 3.63 (2 H, dd, *J* = 11.0, 6.0 Hz), 3.72 (2 H, dd, *J* = 11.0, 4.0 Hz); δ_C (125 MHz, $CDCl_3$) 20.8, 25.7, 36.6, 39.8, 52.0, 62.7, 119.0, 133.0; HRMS (ESI^+) *m/z*: $[M+H]^+$ Calcd for $C_8H_{15}{}^{79}BrN_3O$ 248.0393; Found 248.0424. Data for **22h**: R_f 0.94 (ether); ν_{max} 2091s; δ_H (400 MHz, $CDCl_3$) 1.82 (3 H, s), 1.91 (3 H, s), 2.22–2.32 (1 H, m), 2.54 (2 H, d, *J* = 7.5 Hz), 3.34 (2 H, dd, *J* = 12.0, 6.5 Hz), 3.46 (2 H, dd, *J* = 12.0, 5.0 Hz); δ_C (100 MHz, $CDCl_3$) 20.8, 25.7, 37.1, 37.7, 51.7, 118.1, 133.6; HRMS (FI^+) *m/z*: $[M–Br–N_2]^+$ Calcd for $C_8H_{13}N_4$ 165.1135; Found 165.1136.

6-Azido-5-(azidomethyl)-3-bromo-2-methylhex-2-ene (22h)

Application of the general procedure described above (for **S12**) afforded azide **22h** as a pale yellow oil (241 mg, 78% from diol **S18** using 2.2 molar equivalents of MsCl in the first step). Data as above.

7-Chloro-2-methylhept-2-ene (S19)

To an oven-dried 100 mL round-bottomed flask was added isopropyltriphenylphosphonium iodide (3.28 g, 7.59 mmol) and ether (40 mL), and the flask was cooled to 0 °C under argon. Butyllithium (4.70 mL, 1.60 M in pentane, 7.52 mmol) was added dropwise over 1 h, leading to an intense red coloration indicative of ylid formation. Stirring was continued for 2 h, then a solution of 5-chloropentanal (726 mg, 6.02 mmol) in ether (5.0 mL) was added dropwise via syringe pump over 40 min; the residue in the syringe was washed in with ether (2.0 mL), and the reaction mixture was stirred for 14 h, during which time the ice bath thawed to ~RT. The cream-colored reaction mixture was quenched with brine (70 mL) and filtered through Celite®, washing through with ether (60 mL). The phases were separated and the aqueous layer was extracted with ether (3 × 10 mL) and then dried ($MgSO_4$). The organic solution was concentrated onto silica gel and purified by eluting with petrol and the product-containing fractions collected. The combined fractions (~14 mL) were used directly in the next reaction, although an analytical sample was obtained by careful removal of the solvent. R_f 0.60 (petrol); ν_{max} 2928s, 1447m, 731s, 653s; δ_H (400 MHz, $CDCl_3$) 1.48 (2 H. app. quin, J = 7.5 Hz), 1.61 (3 H, s), 1.70 (3 H, s), 1.77 (2 H, app. quin, J = 7.0 Hz), 2.01 (2 H, app. q, J = 7.5 Hz), 3.53 (2 H, t, J = 7.0 Hz), 5.11 (1 H, app. tquin, J = 7.0, 1.0 Hz); δ_C (100 MHz, $CDCl_3$) 17.8, 25.8, 27.2, 27.3, 32.3, 45.2, 124.1, 132.1; HRMS (FI^+) *m/z*: [M^+] Calcd for $C_8H_{15}{}^{35}Cl$ 146.0857; Found 146.0862.

3-Bromo-7-chloro-2-methylhept-2-ene (S20)

Application of the general procedure described above (for **22a**) afforded bromide **S20** (604 mg, 44% overall from 5-chloropentanal) as a colorless oil. R_f 0.40 (petrol); ν_{max} 2864s, 1447m, 732s, 653s; δ_H

(400 MHz, $CDCl_3$) 1.64–1.82 (4 H, m) overlays 1.78 (3 H, s), 1.87 (3 H, s), 2.53 (2 H, t, J = 7.0 Hz), 3.56 (2 H, t, J = 6.5 Hz); δ_C (100 MHz, $CDCl_3$) 20.6, 25.5, 25.8, 31.6, 36.8, 45.0, 121.2, 130.9; HRMS (FI^+) *m/z*: [M^+] Calcd for $C_8H_{14}{}^{79}Br^{35}Cl$ 223.9962; Found 223.9969.

7-Azido-3-bromo-2-methylhept-2-ene (22i)

To an oven-dried 25 mL round-bottomed flask was added chloride **S20** (600 mg, 2.66 mmol), NaN_3 (346 mg, 5.32 mmol) and DMSO (4.0 mL), and the reaction mixture was stirred at 50 °C under argon for 24 h. The mixture was diluted with petrol (20 mL) and washed with water (3 × 5 mL). The combined aqueous washes were back-extracted with petrol (3 × 20 mL) and the combined organic portions were concentrated onto silica gel and purified by eluting with petrol to yield a colorless oil (528 mg, 86%). R_f 0.43 (petrol); ν_{max} 2092s; δ_H (400 MHz, $CDCl_3$) 1.57–1.66 (4 H, m), 1.78 (3 H, s), 1.88 (3 H, s), 2.53 (2 H, t, J = 6.5 Hz), 3.30 (2 H, t, J = 6.5 Hz); δ_C (100 MHz, $CDCl_3$) 20.6, 25.5, 25.6, 28.0, 37.0, 51.5, 121.2, 130.9; HRMS (FI^+) *m/z*: [M–Br–N_2]$^+$ Calcd for $C_8H_{14}N$ 124.1121; Found 124.1062.

5-(Prop-1-en-2-yl)-3,4-dihydro-2H-pyrrole (23a); general procedure for the thermolysis of azidoalkyl vinyl bromides 22

To an oven-dried 14 mL Ace pressure tube was added an ~0.05 M solution of azide **22a** (60 mg, 0.28 mmol) in toluene (5.5 mL), solid K_2CO_3 (381 mg, 2.76 mmol) and NaOH (20 mg, 0.50 mmol). The reaction vessel was flushed with argon, and the thread was sealed with PTFE tape and the PTFE screw-cap fitted with FETFE® O-ring. The whole tube was wrapped in cotton wool/aluminum foil, and the mixture was stirred at 150 °C for 44 h. Stirring was maintained vigorously to disperse the inorganic solids evenly throughout the solution. The vessel was removed from the oil bath, cooled to RT, and the solution was filtered through a sintered glass funnel, washing through with ether (20 mL), and concentrated to a toluene solution that was purified on silica gel, eluting with 0.1% triethylamine/petrol to 0.1%

triethylamine/10% ether/petrol. The volatile product was isolated as a yellow oil (22.5 mg, 73%). R_f 0.33 (ether); ν_{max} 1633s; δ_H (500 MHz, C_6D_6) 1.45 (2 H, app. quin, J = 7.5 Hz), 2.20 (3 H, app. s), 2.26 (2 H, tt, J = 8.0, 2.0 Hz), 3.85 (2 H, app. t, J = 7.5 Hz), 5.16 (1 H, app. s), 5.23 (1 H, s); δ_C (125 MHz, C_6D_6) 19.7, 23.1, 34.0, 61.9, 119.6, 142.2, 173.9; HRMS (ESI^+) *m/z*: $[M+H]^+$ Calcd for $C_7H_{12}N$ 110.0964; Found 110.0963.

5-Cyclopentenyl-3,4-dihydro-2H-pyrrole (23c)

Application of the general procedure described above (for **23a**) afforded cyclic imine **23c** (43 mg, 78% from azide **22c**) as a pale yellow oil. R_f 0.34 (1% MeOH in ether); ν_{max} 1680m, 1629m, 1590m, 1260s; δ_H (500 MHz, $CDCl_3$) 1.90 (2 H, app. quin, J = 7.5 Hz), 1.96 (2 H, app. quin, J = 7.5 Hz), 2.49–2.53 (2 H, m), 2.65–2.72 (4 H, m), 3.94 (2 H, t, J = 7.0 Hz), 6.19 (1 H, app. t, J = 2.0 Hz); δ_C (125 MHz, $CDCl_3$) 22.8, 23.4, 32.1, 33.7, 35.1, 61.4, 137.5, 141.1, 171.6; HRMS (ESI^+) *m/z*: $[M+H]^+$ Calcd for $C_9H_{14}N$ 136.1121; Found 136.1116.

5-Cyclohexenyl-3,4-dihydro-2H-pyrrole (23d)[44]

Application of the general procedure described above (for **23a**) afforded cyclic imine **23d** (73 mg, 84% from azide **22d**) as a pale yellow oil. R_f 0.40 (ether); ν_{max} 1642m; δ_H (400 MHz, $CDCl_3$) 1.61–1.71 (4 H, m), 1.86 (2 H, app. quin, J = 7.5 Hz), 2.16–2.21 (2 H, m), 2.36–2.42 (2 H, m), 2.65 (2 H, tt, J = 8.0, 1.5 Hz), 3.91 (2 H, t, J = 6.5 Hz), 6.26 (1 H, m); δ_C (100 MHz, $CDCl_3$) 22.2, 22.5, 22.6, 25.1, 26.1, 33.9, 61.2, 134.6, 135.0, 175.2; HRMS (FI^+) *m/z*: $[M^+]$ Calcd for $C_{10}H_{15}N$ 149.1199; Found 149.1199.

3,3-Dimethyl-5-(prop-1-en-2-yl)-3,4-dihydro-2H-pyrrole (23f)

Application of the general procedure described above (for **23a**) afforded cyclic imine **23f** (15 mg, 71% from azide **22f**) as a pale yellow oil. R_f 0.46 (petrol/ether, 1:1); ν_{max} 1591s; δ_H (500 MHz, C_6D_6) 0.84 (6

H, s), 2.20 (5 H, app. s), 3.66 (2 H, s), 5.16 (1 H, s), 5.24 (1 H, s); δ_C (125 MHz, C_6D_6) 19.4, 27.9, 38.4, 49.2, 75.2, 119.6, 142.4, 173.6; HRMS (ESI^+) *m/z*: $[M+H]^+$ Calcd for $C_9H_{16}N$ 138.1277; Found 138.1275.

[(5-(Prop-1-en-2-yl)-3,4-dihydro-2H-pyrrol-3-yl]methanol (23g)

Application of the general procedure described above (for **23a**) afforded cyclic imine **23g** (46 mg, 82% from azide **22g**) as a pale yellow oil. R_f 0.17 (ether); ν_{max} 3272br, 1596m; δ_H (500 MHz, $CDCl_3$) 2.00 (3 H, s), 2.54–2.63 (2 H, m), 2.81–2.87 (2 H, m), 3.49 and 3.53 (2 × 1 H, 2 × dd, *J* = 10.5, 6.5 Hz), 3.78 (1 H, dd, *J* = 16.5, 4.0 Hz), 4.04 (1 H, app. dd, *J* = 16.5, 7.0 Hz), 5.42 and 5.46 (2 × 1 H, 2 × s); δ_C (125 MHz, $CDCl_3$) 19.3, 37.6, 39.2, 64.0, 65.4, 121.5, 140.7, 174.7; HRMS (ESI^+) *m/z*: $[M+H]^+$ Calcd for $C_8H_{14}NO$ 140.1070; Found 140.1065.

3-(Azidomethyl)-5-(prop-1-en-2-yl)-3,4-dihydro-2H-pyrrole (23h)

Application of the general procedure described above (for **23a**) afforded cyclic imine **23h** (32 mg, 76% from azide **22h**) as a pale yellow oil. R_f 0.65 (ether); ν_{max} 2095s; δ_H (400 MHz, $CDCl_3$) 2.02 (3 H, s), 2.54–2.68 (2 H, m), 2.91 (1 H, app. qt, *J* = 7.5, 1.5 Hz), 3.24 (1 H, dd, *J* = 12.0, 7.5 Hz), 3.32 (1 H, dd, *J* = 12.0, 6.5 Hz), 3.76 (1 H, dd, *J* = 17.0, 4.5 Hz), 4.11 (1 H, dd, *J* = 17.0, 8.0 Hz), 5.42 and 5.49 (2 × 1 H, 2 × s); δ_C (100 MHz, $CDCl_3$) 19.3, 36.9, 38.5, 55.1, 64.8, 121.5, 140.7, 174.1; HRMS (ESI^+) *m/z*: $[M+H]^+$ Calcd for $C_8H_{13}N_4$ 165.1135; Found 165.1134.

6-(Prop-1-en-2-yl)-2,3,4,5-tetrahydropyridine (23i)[22]

Application of the general procedure described above (for **23a**) afforded cyclic imine **23i** (17 mg, 32% from azide **22h**) as a colorless oil. R_f 0.10 (ether); ν_{max} 2096m, 1767s, 1725s, 1695s, 1619s; δ_H (500 MHz, C_6D_6) 1.17–1.22 (2 H, m), 1.26–1.31 (2 H, m), 2.02 (2 H, tt, *J* = 6.5, 2.0 Hz), 2.17 (3 H, s), 3.70

(2 H, app. t, J = 5.5 Hz), 5.23 and 5.25 (2 × 1 H, 2 × s); δ_C (125 MHz, C_6D_6) 20.0 (two peaks), 22.2, 25.3, 50.0, 115.4, 146.8, 165.3; HRMS (ESI$^+$) *m/z*: $[M+H]^+$ Calcd for $C_8H_{14}N$ 124.1121; Found 124.1119.

Dimethyl 2-(pyrrolidin-2-ylidene)malonate (24e)[18] and methyl 2-oxo-4,5,6,6a-tetrahydro-2H-furo[3,2-b]pyrrole-3-carboxylate (25e)

Application of the general procedure described above (for **23a**) using azide **22e**, with heating at 100 °C for 11 h, led to the formation of a white solid while the solution became yellow. The pressure tube was removed from the oil bath, cooled to RT, and the reaction mixture was filtered to collect the solid precipitate which was dried at ~1 mmHg and identified as the bicyclic product **25e** (24 mg, 60%). Meanwhile, the filtrate was concentrated and purified on silica gel, eluting with a gradient of petrol to 25% ether/petrol, yielding the enamide **24e** (9 mg, 20%) as a red oil. Data for **24e**: R_f 0.34 (ether); ν_{max} 3308br, 1642s, 1573s; δ_H (500 MHz, $CDCl_3$) 2.05 (2 H, app. quin, J = 7.5 Hz), 3.13 (2 H, t, J = 8.0 Hz), 3.62 (2 H, t, J = 7.5 Hz), 3.73 (3 H, s), 3.75 (3 H, s), 9.66 (1 H, br); δ_C (125 MHz, $CDCl_3$) 21.8, 34.6, 47.7, 51.1, 51.3, 86.8, 168.2, 170.4, 174.1; *m/z* (ESI+) 222.1 (MNa^+), 200.1 (MH^+). Data for **25e**: M.p 235 °C; R_f 0.13 (ether/methanol, 8:1); ν_{max} 3165br, 1739m, 1702m, 1636s; δ_H (400 MHz, $CDCl_3$) 2.13 (1 H, tddd, J = 11.5, 11.0, 8.5 Hz), 2.61 (1 H, ddd, J = 11.5, 7.0, 4.5 Hz), 3.83 (3 H, s), 3.86–4.00 (2 H, m), 5.00 (1 H, dd, J = 12.0, 7.0 Hz), 6.86 (1 H, br); δ_C (125 MHz, $CDCl_3$) 32.5, 50.7, 51.7, 77.6, 85.9, 164.0, 170.8, 180.8; HRMS (ESI$^+$) *m/z*: $[M+Na]^+$ Calcd for $C_8H_9NNaO_4$ 206.0424; Found 206.0429.

5-(1-Bromocyclobutyl)-3,4-dihydro-2H-pyrrole (27), 5-[1-(bromomethyl)cyclopropyl]-3,4-dihydro-2H-pyrrole (29), [1-(3,4-dihydro-2H-pyrrol-5-yl)cyclopropyl]methanol (30), and 5,5′-(4-vinylcyclohex-1-ene-1,4-diyl)bis(3,4-dihydro-2H-pyrrole) (32)

Application of the general procedure described above (for **23a**) using azide **22b** gave product mixtures containing variable quantities of secondary products **27**, **29**, **30**, and **32**, each of which was typically

isolated in less than 10% yield. Data for **27**: R_f 0.78 (ether); ν_{max} 1627m; δ_H (500 MHz, $CDCl_3$) 1.86 (1 H, dtt, *J* = 10.5, 8.5, 6.5 Hz), 1.99 (2 H, app. quin, *J* = 7.5 Hz), 2.23–2.32 (1 H, m), 2.58–2.74 (2 H, m), 2.74–2.79 (2 H, m), 2.89–2.96 (2 H, m), 3.93 (2 H, tt, *J* = 7.0, 2.0 Hz); δ_C (125 MHz, $CDCl_3$) 17.1, 23.4, 33.3, 37.9 (two peaks), 61.1, 178.2; HRMS (ESI^+) *m/z*: $[M+H]^+$ Calcd for $C_8H_{13}{}^{79}BrN$ 202.0226; Found 202.0224. Data for **29**: R_f 0.55 (ether); ν_{max} 1629m; δ_H (500 MHz, C_6D_6) 0.53 (2 H, dt, *J* = 7.0, 4.5 Hz), 1.09 (2 H, dt, *J* = 7.0, 4.5 Hz), 1.40 (2 H, app. quin. *J* = 7.5 Hz), 1.95 (2 H, tt, *J* = 8.0, 2.0 Hz), 3.36 (2 H, s), 3.71 (2 H, tt, *J* = 7.0, 2.0 Hz); δ_C (125 MHz, C_6D_6) 17.8, 23.1, 26.2, 34.0, 40.5, 61.2, 175.7; HRMS (ESI^+) *m/z*: $[M+H]^+$ Calcd for $C_8H_{13}{}^{79}BrN$ 202.0226; Found 202.0228. Data for **30**: R_f 0.18 (5% methanol/ether); ν_{max} 3334br, 1621m; δ_H (500 MHz, $CDCl_3$) 0.84 (2 H, dt, *J* = 6.5, 4.5 Hz), 0.99 (2 H, dt, *J* = 6.5, 4.5 Hz), 1.83 (2 H, app. quin, *J* = 7.0 Hz), 2.23 (2 H, tt, *J* = 7.5, 1.5 Hz), 3.65 (2 H, s), 3.85 (2 H, tt, *J* = 7.0, 1.5 Hz); δ_C (125 MHz, $CDCl_3$) 11.8, 22.1, 26.2, 33.3, 61.0, 68.6, 180.9; HRMS (ESI^+) *m/z*: $[M+Na]^+$ Calcd for $C_8H_{13}NNaO$ 162.0889; Found 162.0889. Data for **32** (only observed as a contaminant of incompletely-separated alcohol **30**): R_f 0.28 (methanol/ether, 1:10); δ_H (500 MHz, C_6D_6) 1.39–1.46 (4 H, m), 1.78 (1 H, ddd, *J* = 13.5, 8.0, 5.5 Hz), 1.97 (1 H, ddd, *J* = 13.0, 6.5, 6.5 Hz), 2.16 (2 H, tq, *J* = 8.0, 2.0 Hz), 2.27 (2 H, tt, *J* = 8.0, 2.0 Hz) overlays 2.25–2.28 (1 H, m), 2.60–2.69 (1 H, m), 2.81–2.87 (1 H, m), 3.02 (1 H, br d, *J* = 18.5 Hz), 3.68 (2 H, tq, *J* = 7.0, 1.5 Hz), 3.86 (2 H, app. t, *J* = 7.0 Hz), 4.95–5.00 (2 H, m), 5.74 (1 H, dd, *J* = 17.5, 10.5 Hz), 6.03 (1 H, t, *J* = 4.0 Hz); δ_C (125 MHz, C_6D_6) 22.8, 23.1, 23.2, 30.4, 33.2, 33.8, 34.1, 44.8, 61.0, 61.5, 113.7, 1131.8, 134.8, 143.2, 173.4, 178.9; HRMS (ESI^+) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{22}N_2Na$ 265.1675; Found 265.1667.

8-Methyl-6,6-diphenyl-2,3,6,7-tetrahydroindolizin-5(1H)-one (37a); general procedure for the thermolysis of azidoalkyl vinyl bromides 22, and one-pot formal cycloaddition with diphenylketene

The general procedure described above (for **23a**) was followed with azide **22a** (100 mg, 0.459 mmol) until the point where the heated vessel is removed from the oil bath and cooled to RT. The PTFE screw

cap was removed and replaced with a suba cap, the headspace was flushed with argon, and a solution of diphenylketene (266 mg, 1.37 mmol) in toluene (2.0 mL) was added dropwise over 50 min, causing the yellow solution to become bright yellow. After stirring for 15 h, the cloudy solution was filtered through a sintered glass funnel, washing through with ether (30 mL); the filtrate was concentrated onto silica, and the residue was purified on silica gel, eluting with a gradient of 0.5% triethylamine/petrol to 0.5% triethylamine/25% ether/petrol. The lactam product was isolated as a white crystalline solid (112 mg, 80%). M.p 156–160 °C; R_f 0.28 (petrol/ether, 1:1); ν_{max} 2964w, 1651s, 1395m, 1260m, 1021m, 800m, 728s; δ_H (400 MHz, C_6D_6) 1.11 (2 H, app. quin, J = 7.0 Hz), 1.49 (3 H, app. quin, J = 1.0 Hz), 1.80 (2 H, ddd, J = 7.5, 3.5, 2.0 Hz), 2.67 (2 H, oct, J = 1.0 Hz), 3.52 (2 H, app. t, J = 7.0 Hz), 7.05 (2 H, tt, J = 7.5, 1.0 Hz), 7.13–7.18 (4 H, m), 7.38–7.41 (4 H, m); δ_C (100 MHz, C_6D_6) 17.5, 21.9, 27.1, 42.7, 46.5, 57.3, 103.4, 126.9, 128.2, 129.1, 133.7, 144.1, 169.2; HRMS (ESI^+) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{21}NNaO$ 326.1515; Found 326.1500.

6,6-Diphenyl-2,3,6a,7,8,9-hexahydro-1H-cyclopenta[g]indolizin-5(6H)-one (37c)

Application of the general procedure described above (for **37a**) afforded lactam **37c** (52 mg, 77% from azide **22c**) as a pale orange amorphous solid. M.p 159–161 °C; R_f 0.20 (petrol/ether, 1:1); ν_{max} 1645s; δ_H (500 MHz, C_6D_6) 1.21–1.36 (3 H, m), 1.50–1.59 (2 H, m), 1.75 (1 H, app. dq, J = 11.5, 6.5 Hz), 1.97–2.01 (2 H, m), 2.02–2.09 (1 H, m), 2.16 (1 H, dd, J = 16.0, 8.0 Hz), 3.37–3.42 (1 H, m), 3.45–3.56 (2 H, m), 7.03 (1 H, app. t, J = 7.0 Hz), 7.10 (2 H, app. t, J = 7.5 Hz), 7.13 (1 H, app. t, J = 7.0 Hz), 7.22 (2 H, app. t, J = 7.5 Hz), 7.35 (2 H, app. d, J = 8.0 Hz), 7.52 (2 H, app. d, J = 8.0 Hz); δ_C (125 MHz, C_6D_6) 22.5, 26.0, 27.4, 28.1, 28.4, 46.5, 50.4, 60.1, 114.3, 126.5, 127.1, 127.8, 128.4, 129.5, 130.5, 130.8, 140.5, 145.5, 169.7; HRMS (ESI^+) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{23}NNaO$ 352.1672; Found 352.1673.

6,6-Diphenyl-2,3,6,6a,7,8,9,10-octahydropyrrolo[2,1-a]isoquinolin-5(1H)-one (37d)

Application of the general procedure described above (for **37a**) afforded lactam **37d** (54 mg, 80% from azide **22d**) as a low-density white solid foam. M.p 51–53 °C; R_f 0.28 (petrol/ether, 1:1); ν_{max} 1651s; δ_H (400 MHz, C_6D_6) 0.92–1.18 (6 H, m), 1.51–1.54 (1 H, m), 1.60–1.63 (1 H, m), 1.87–2.00 (3 H, m), 2.19–2.23 (1 H, m), 2.68 (1 H, app. d, *J* = 11.5 Hz), 3.34 (1 H, ddd, *J* = 11.5, 8.0, 5.5 Hz), 3.52 (1 H, ddd, *J* = 11.5, 7.5, 7.0 Hz), 7.05 (2 H, tq, *J* = 7.5, 1.5 Hz), 7.13–7.18 (4 H, m), 7.46 (2 H, app. d, *J* = 7.5 Hz), 7.75 (2 H, app. d, *J* = 7.5 Hz); δ_C (100 MHz, C_6D_6) 21.5, 27.1, 27.4, 29.2, 30.9, 31.7, 46.7, 49.6, 59.8, 112.6, 126.3, 127.4, 127.6, 129.3, 129.6, 131.0, 143.8, 144.6, 168.1 [one Ph resonance obscured]; HRMS (ESI^+) *m/z*: $[M+Na]^+$ Calcd for $C_{24}H_{25}NNaO$ 366.1828; Found 366.1812.

2,2,8-Trimethyl-6,6-diphenyl-2,3,6,7-tetrahydroindolizin-5(1H)-one (37f)

Application of the general procedure described above (for **37a**) afforded lactam **37f** (63 mg, 91% from azide **22f**) as a yellow viscous oil. R_f 0.60 (petrol/ether, 1:1); ν_{max} 2957w, 1658s, 1397m, 1035w, 698s; δ_H (400 MHz, C_6D_6) 0.57 (6 H, s), 1.52 (3 H, s), 1.71 (2 H, s), 2.70 (2 H, s), 3.35 (2 H, s), 7.06 (2 H, tt, *J* = 7.5, 1.0 Hz), 7.14–7.18 (4 H, m), 7.40–7.42 (4 H, m); δ_C (100 MHz, C_6D_6) 17.5, 26.0, 35.8, 41.8, 42.7, 57.1, 58.8, 104.5, 126.9, 128.2, 129.1, 133.9, 143.9, 169.4; HRMS (ESI^+) *m/z*: $[M+Na]^+$ Calcd for $C_{23}H_{25}NNaO$ 354.1828; Found 354.1821.

(8-Methyl-5-oxo-6,6-diphenyl-1,2,3,5,6,7-hexahydroindolizin-2-yl)methyl 2,2-diphenylacetate (37g)

Application of the general procedure described above (for **37a**) afforded lactam **37g** (60 mg, 74% from azide **22g**) as a yellow oil. R_f 0.40 (petrol/ether, 1:1); ν_{max} 1735s, 1655m; δ_H (500 MHz, $CDCl_3$) 1.70 (3 H, s), 2.12 (1 H, d, *J* = 11.0 Hz), 2.45–2.55 (2 H, m), 2.88 (2 H, s), 3.49 (1 H, dd, *J* = 12.0, 5.5 Hz), 3.79 (1 H, dd, *J* = 12.0, 7.0 Hz), 3.90 (1 H, dd, *J* = 11.0, 7.5 Hz), 3.99 (1 H, dd, *J* = 11.0, 6.5 Hz), 5.01 (1 H, s), 7.11–7.35 (20 H, m); δ_C (125 MHz, $CDCl_3$) 17.7, 30.1, 34.6, 42.1, 48.7, 56.9, 57.1, 66.0, 106.0, 126.9,

127.0, 127.5, 128.1, 128.2, 128.4, 128.5, 128.7, 128.8, 131.8, 138.5, 142.5, 142.9, 169.9, 172.4 [some Ph resonances obscured]; HRMS (ESI^+) *m/z*: $[M+Na]^+$ Calcd for $C_{36}H_{33}NNaO_3$ 550.2353; Found 550.2334.

2-(Azidomethyl)-8-methyl-6,6-diphenyl-2,3,6,7-tetrahydroindolizin-5(1H)-one (37h)

Application of the general procedure described above (for **37a**) afforded lactam **37h** (38 mg, 58% from azide **22h**) as a yellow oil. R_f 0.34 (petrol/ether, 1:1); ν_{max} 2097s, 1655m; δ_H (400 MHz, $CDCl_3$) 1.76 (3 H, s), 2.27 (1 H, dd, *J* = 15.5, 4.0 Hz), 2.36–2.46 (1 H, m), 3.56–3.63 (1 H, m), 2.86 and 2.92 (2 × 1 H, 2 × d, *J* = 17.0 Hz), 3.06 (1 H, dd, *J* = 12.5, 7.5 Hz), 3.12 (1 H, dd, *J* = 12.5, 7.0 Hz), 3.55 (1 H, dd, *J* = 12.0, 5.0 Hz), 3.83 (1 H, dd, *J* = 12.0, 7.0 Hz), 7.12–7.32 (10 H, m); δ_C (100 MHz, $CDCl_3$) 17.8, 31.0, 35.5, 42.2, 49.2, 53.7, 56.8, 106.2, 126.9, 127.1, 128.1, 128.2, 128.4, 128.5, 131.7, 142.0, 143.2, 170.0; HRMS (ESI^+) found 381.1679, $C_{22}H_{24}N_4ONa$ (MNa^+) requires 381.1686. HRMS (ESI^+) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{22}N_4NaO$ 381.1686; Found 381.1679.

7,7-Diphenyl-6-(prop-1-en-2-yl)-1-azabicyclo[4.2.0]octan-8-one (38i)

Application of the general procedure described above (for **37a**) afforded lactam **37i** (24 mg, 35% from azide **22i**) as a white solid. M.p 105–107 °C; R_f 0.41 (petrol/ether, 2:1); ν_{max} 1746s; δ_H (500 MHz, C_6D_6) 0.81–1.14 (4 H, m), 1.22 (1 H, dt, *J* = 13.0, 3.0 Hz), 1.27 (3 H, s), 1.92 (1 H, d, *J* = 12.5 Hz), 2.43 (1 H, br s), 3.86 (1 H, dd, *J* = 13.5, 6.0 Hz), 4.77 (1 H, br s), 4.80 (1 H, br s), 6.93–6.96 (1 H, m), 7.00–7.04 (2 H, m), 7.08 (1 H, app. t, *J* = 7.5 Hz), 7.21 (2 H, app. t, *J* = 7.5 Hz), 7.50 (2 H, br s), 7.91 (2 H, br s); δ_C (125 MHz, C_6D_6) 20.3, 20.4, 24.7, 33.9, 37.5, 70.3, 77.2, 116.4, 127.1 (2 peaks), 128.4, 128.6, 129.2, 138.8, 139.6, 145.8, 168.9 [one Ph resonance obscured]; HRMS (ESI^+) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{23}NNaO$ 340.1672; Found 340.1661.

2-Bromo-1-(5-cyclohexenyl-2,3-dihydro-1H-pyrrol-1-yl)-2-methylpropan-1-one (40)

To a 14 mL sample vial was added cyclic imine **23d** (640 mg, 4.29 mmol), toluene (10 mL), and 4 Å molecular sieves (1.0 g), and the mixture was stirred under argon at 0 °C. Pyridine (380 μL, 4.70 mmol) and α-bromoisobutyryl bromide (550 μL, 4.45 mmol) were added to the solution, which became turgid and immobile before regaining mobility after 5 min. After 10 min, the solution was warmed to RT and stirred for a further 1 h. The reaction mixture was filtered through a sintered glass funnel, washing through with petrol, and the filtrate was concentrated under vacuum to a toluene solution. The solution was quickly purified by silica gel chromatography, eluting with a gradient of 0.5% triethylamine/petrol to 0.5% triethylamine/20% ether/petrol, yielding the *title compound* as a white solid (1.16 g, 91%). M.p 89–91 °C; R_f 0.65 (ether); ν_{max} 1643s, 1624s, 1388s; δ_H (400 MHz, C_6D_6) 1.55 (2 H, dddd, J = 12.5, 6.0, 2.5, 2.5 Hz), 1.70 (2 H, dddd, J = 12.0, 6.0, 3.0, 3.0 Hz), 1.78 (6 H, s), 2.00 (2 H, td, J = 7.5, 3.0 Hz), 2.03–2.07 (2 H, m), 2.17–2.22 (2 H, m), 3.86 (2 H, t, J = 8.0 Hz), 5.07 (1 H, t, J = 3.0 Hz), 5.83 (1 H, app. sept, J = 2.0 Hz); δ_C (100 MHz, C_6D_6) 22.6, 22.9, 25.7, 27.7, 29.4, 32.2, 52.0, 59.2, 111.4, 124.2, 132.6, 149.7, 168.4; HRMS (ESI^+) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{21}{}^{79}BrNO$ 298.0801; Found 298.0800.

6,6-Dimethyl-2,3,6,6a,7,8,9,10-octahydropyrrolo[2,1-a]isoquinolin-5(1H)-one (41) and 6,6-dimethyl-2,6,6a,7,8,9,10,10a-octahydropyrrolo[2,1-a]isoquinolin-5(3H)-one (42)

To an oven-dried two-neck 100 mL round-bottomed flask was added a solution of bromoester **40** (200 mg, 0.671 mmol) in degassed toluene (27 mL), and the solution was heated to 100 °C. A solution of tributyltin hydride (0.235 mL, 0.873 mmol) and AIBN (11.0 mg, 67.0 μmol) in degassed toluene (20 mL) was added dropwise over 1 h, and the mixture was heated at reflux for 22 h. The flask was removed from the oil bath and stirred with saturated aqueous KF solution (40 mL) for 3 h. The mixture was extracted with dichloromethane (3 × 20 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated to yield a solid that was purified over silica gel, eluting with a gradient of 0.5% triethylamine/petrol to 0.5% triethylamine/20% ether/petrol. The isomeric products **41** and **42** were

isolated as a yellow oil in a ratio of 2.3:1 (106 mg, 72%). Partial separation of the isomers was achieved by further chromatography for characterization. Data for **41**: R_f 0.40 (ether/petrol, 2:1); ν_{max} 1658s, 1641s, 1408s; δ_H (500 MHz, C_6D_6) 0.94–1.03 (1 H, m), 1.05–1.11 (2 H, m), 1.17 (3 H, s), 1.25 (2 H, app. quin, J = 7.0 Hz), 1.32 (3 H, s), 1.54–1.67 (3 H, m), 1.74 (1 H, tdq, J = 14.0, 5.0, 1.5 Hz), 1.82 (1 H, app. dsext, J = 12.0, 2.0 Hz), 1.95–2.09 (2 H, m), 2.13–2.18 (1 H, m), 3.47 and 3.55 (2 × 1 H, 2 × dt, J = 11.5, 7.0 Hz); δ_C (125 MHz, C_6D_6) 20.7, 21.9, 25.7, 26.5, 27.2, 27.4, 27.9, 29.5, 41.1, 46.1, 47.9, 108.9, 130.4, 172.6; HRMS (ESI^+) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{22}NO$ 220.1696; Found 220.1693. Partial data for **42** (that was not obtained free from **41**): R_f 0.39 (ether/petrol, 2:1); δ_H (500 MHz, C_6D_6) 1.01 and 1.32 (2 × 3 H, 2 × s), 3.73 (1 H, ddd, J = 12.5, 11.5, 7.5 Hz), 3.87 (1 H, ddd, J = 12.5, 11.0, 6.5 Hz), 4.43 (1 H, app. q, J = 2.5 Hz).

1-Bromo-6,6-dimethyl-2,3,6,6a,7,8,9,10-octahydropyrrolo[2,1-a]isoquinolin-5(1H)-one (43)

To a 7 mL sample vial was added bromoester **40** (100 mg, 0.335 mmol), CuBr (15.0 mg, 0.105 mmol), and degassed dichloromethane (2.5 mL), and the insoluble mixture was stirred at RT under argon. Pentamethyldiethylenetriamine (PMDTA) (21 μL, 0.101 mmol) was added to the mixture, which which instantly turned a clear green color that darkened over 15 min. The reaction mixture was filtered through a pipette of silica gel and concentrated to yield a pale yellow oil, a 1:1.3 mixture of inseparable diastereoisomers (90 mg, 90%). The product was unstable to column chromatography with either silica gel or alumina due to the lability of the allylic bromide functionality towards dehydrobromination leading to diene **44**. R_f 0.24 (petrol/ether, 2:1); ν_{max} 1605s; δ_H (400 MHz, $CDCl_3$) 1.01, 1.04, 1.14 and 1.17 (4 × ~1.5 H, 4 × s), 1.07–1.46 (~3 H, m), 1.69–1.83 (~2 H, m), 1.87–2.04 (~3 H, m), 2.19–2.32 (~2 H, m), 2.53 (~1 H, app. t, J = 7.0 Hz), 3.61–3.75 (~1 H, m), 3.90–4.06 (~1 H, m), 5.12 (~0.5 H, d, J = 4.5 Hz), 5.18 (~0.5 H, d, J = 5.0 Hz); δ_C (100 MHz, $CDCl_3$) 19.9, 20.4, 25.4, 25.6, 25.7, 25.9, 26.0, 27.2 (two

peaks), 27.9, 29.2, 29.8, 34.6, 34.7, 40.6, 40.9, 43.7, 43.8, 47.0, 47.1, 47.8, 48.0, 117.0, 117.3, 131.3, 131.6, 173.0, 173.3; HRMS (ESI^+) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{21}{}^{79}BrNO$ 298.0801; Found 298.0796.

6,6-Dimethyl-2,3,7,8,9,10-hexahydropyrrolo[2,1-a]isoquinolin-5(6H)-one (44)

To a 10 mL oven-dried round-bottomed flask was added bromoester **40** (100 mg, 0.335 mmol), CuBr (53.0 mg, 0.369 mmol), and degassed dichloromethane (2.5 mL), and the insoluble mixture was stirred at RT under argon. Tetramethylethylenediamine (TMEDA) (56 μL, 0.37 mmol) was added to the mixture, which instantly became clear and colorless; after 10 min further stirring, a green tint appeared in the solution. The reaction mixture was heated to reflux for 2.5 h, during which the mixture became brown; the cooled reaction mixture was filtered through a plug of silica gel and concentrated to yield an oil. The oil was purified over basic alumina, eluting with a gradient of 2.5% triethylamine/petrol to 2.5% triethylamine/40% ether/petrol, separating recovered starting material (**40**) from the product, a yellow oil (56 mg, 77%; 92% based on recovered **40**, 16 mg, 16%). R_f 0.43 (ether); ν_{max} 1720m, 1666s; δ_H (400 MHz, C_6D_6) 1.36–1.40 (4 H, m) overlaying 1.35 (6 H, s), 1.75–1.81 (2 H, m), 1.96–2.01 (2 H, m), 2.09–2.15 (2 H, m), 3.80 (2 H, app. t, J = 9.0 Hz), 4.56 (1 H, t, J = 3.0 Hz); δ_C (100 MHz, C_6D_6) 22.3, 23.1, 24.6, 24.7, 25.7, 27.4, 44.4, 45.2, 102.4, 118.3, 140.9, 141.0, 170.5; HRMS (ESI^+) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{20}NO$ 218.1539; Found 298.1538.

6,6-Dimethyl-2,3,6,8,9,10-hexahydropyrrolo[2,1-a]isoquinolin-5(1H)-one (45)

When tricyclic lactam **44** was purified on silica gel in the absence of triethylamine, or when dissolved in $CDCl_3$, partial isomerization occurred to give lactam **45** in ~1:1 ratio with **44**; this isomer was isolated by chromatography for characterization. R_f 0.33 (ether); ν_{max} 1660s, 1410m; δ_H (500 MHz, C_6D_6) 1.19 (2 H, app. quin, J = 7.0 Hz), 1.51 (6 H, s), 1.57 (2 H, app. quin, J = 6.0 Hz), 1.99–2.05 (4 H, m), 2.11 (2 H, tt, J = 6.5, 1.0 Hz), 3.47 (2 H, t, J = 7.0 Hz), 5.44 (1 H, t, J = 4.0 Hz); δ_C (125 MHz, C_6D_6) 21.5, 22.9,

26.1, 26.3, 27.6, 27.8, 44.1, 46.3, 119.3, 124.1, 131.9, 141.5, 172.9; HRMS (ESI^+) *m/z*: $[M+Na]^+$ Calcd for $C_{14}H_{19}NNaO$ 240.1359; Found 240.1358.

ASSOCIATED CONTENT

Supporting information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.@@@@@@.

Reaction schemes for preparation of substrates, and copies of ^1H and ^{13}C NMR spectra.

AUTHOR INFORMATION

Corresponding author

* E-mail: jeremy.robertson@chem.ox.ac.uk

ORCID

John T. R. Liddon: 0000-0002-5287-9817

Peter J. Lindsay-Scott: 0000-0002-4721-3594

Jeremy Robertson: 0000-0002-6809-8265

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors are grateful to the Engineering and Physical Sciences Research Council, UK, and Eli Lilly for a studentship (to J.T.R.L.), and Prof. T. D. W. Claridge, University of Oxford, and his staff for NMR services.

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