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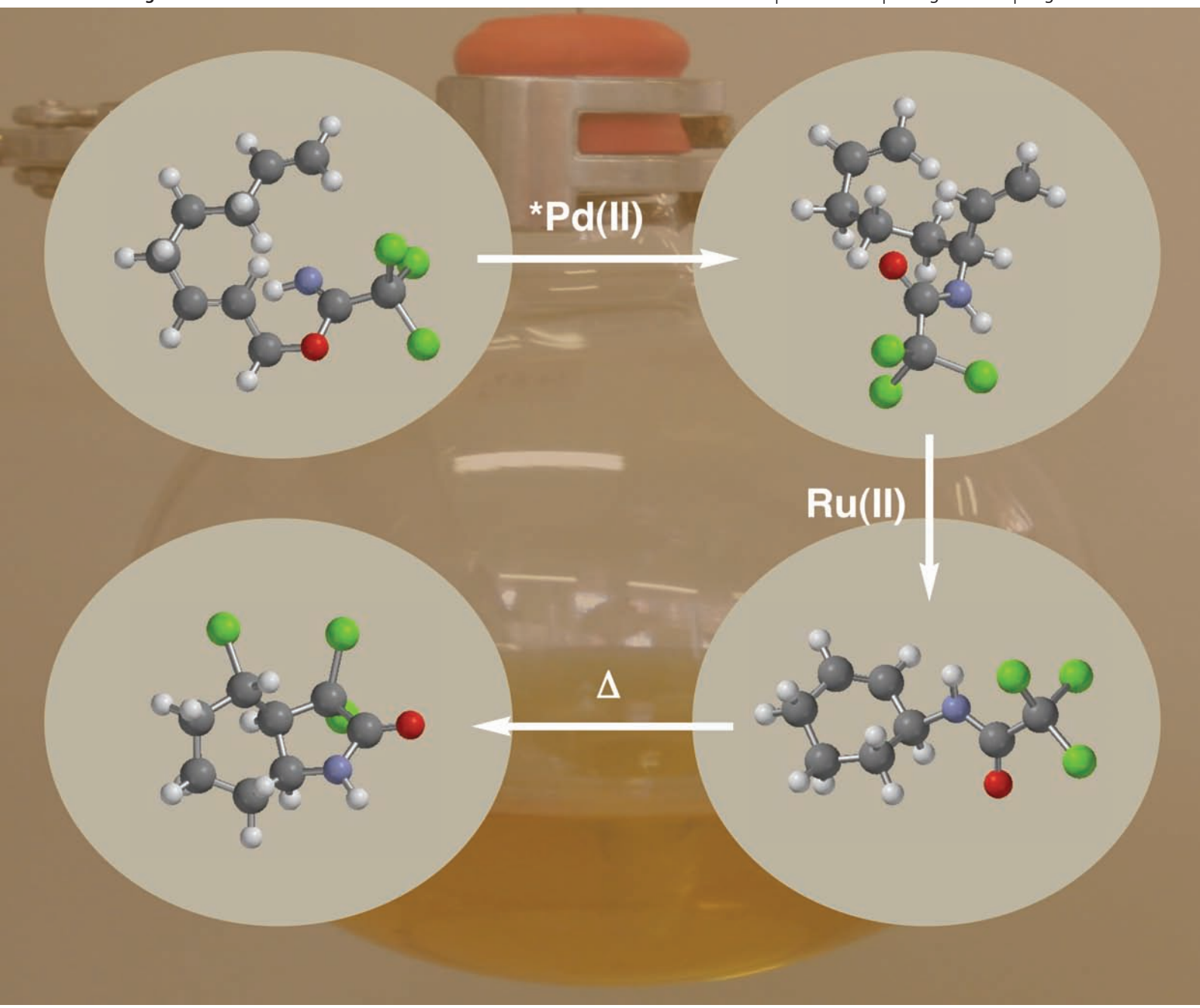

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FULL PAPER
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A three-step tandem process for the synthesis of bicyclic γ-lactams†

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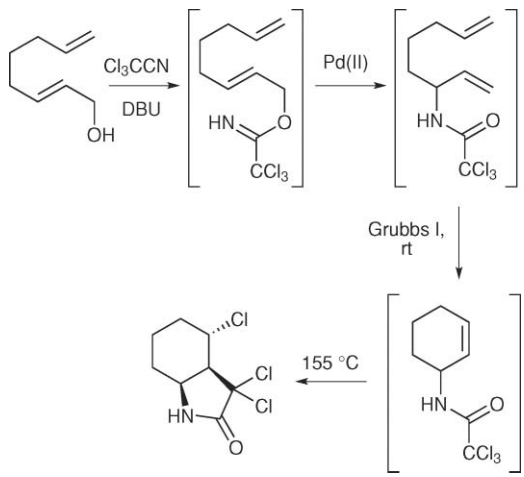
A one-pot, three-step tandem process has been developed for the direct synthesis of functionalised bicyclic [3.3.0], [4.3.0] and [5.3.0] γ-lactams from simple allylic trichloroacetimidates. The process involves a palladium(II) mediated Overman rearrangement followed by the use of Grubbs first generation complex which catalyzes both a ring closing metathesis reaction and a Kharasch cyclization. As well as exploring the scope of this process for the synthesis of a range of functionalised bicyclic γ-lactams, the use of chiral palladium(II) catalysts during the Overman rearrangement for the enantioselective synthesis of the bicyclic γ-lactams is also demonstrated.

Introduction

Tandem or cascade processes have become a powerful tool for performing several chemical reactions in only one operation often yielding products with significantly increased molecular complexity.[1,2] Furthermore, these processes circumvent the time-intensive and yield reducing isolation and purification of intermediates in conventional multiple-step syntheses and their general use results in a reduction in waste generation which has obvious benefits for the environment.[3] While a variety of transformations have been utilised for tandem processes, pericyclic or metathesis reactions have featured prominently.[1,4,5] This is mainly due to the highly selective and efficient nature of most pericyclic processes and the continued development of stable and commercially available ruthenium alkylidene complexes for metathesis reactions.

Our own research efforts have resulted in the development of a highly efficient one-pot tandem process involving the Overman rearrangement of allylic trichloroacetimidates[6] followed by ring closing metathesis (RCM) of the resulting trichloroacetamide derived dienes to give functionalized carbocyclic amides of various ring sizes.[7] Asymmetric variants have also been developed and utilized in natural product synthesis.[7,8] The carbocyclic trichloroacetamides formed from this tandem process are excellent substrates for the ruthenium(II) catalyzed Kharasch cyclization which allows the preparation of γ-lactams *via* an atom transfer radical mechanism.[8a,9] As the second step of our tandem process and the Kharasch cyclization both use a ruthenium(II) catalyst, it was proposed that our original one-pot two-step tandem process could be extended to include the Kharasch cyclization (Scheme 1). Such a process would allow the direct one-pot synthesis of bicyclic γ-lactams from simple allylic alcohol precursors using a palladium(II) complex to catalyze the Overman rearrangement and a ruthenium(II) complex to effect both the RCM and Kharasch steps. Our confidence in developing such a process came from work reported by the research groups of Schmidt,[10] Snapper[11] and Quayle[12] which utilized ruthenium mediated tandem catalytic processes[13] for the preparation of γ-lactams and γ-lactones from trihaloacetamide and trihaloacetate derived dienes, respectively.



Scheme 1 Proposed one-pot tandem synthesis of bicyclic γ-lactams.

In this paper, we now report the development of a one-pot, three step tandem process for the diastereoselective synthesis of functionalised bicyclic [3.3.0], [4.3.0] and [5.3.0] γ-lactams. The use of chiral palladium(II) catalysts during the first step of this tandem process for the enantioselective synthesis of bicyclic [3.3.0] and [4.3.0] γ-lactams is also described.

Results and discussion

To fully examine the scope of the tandem process, a series of allylic alcohols were prepared in three steps (Scheme 2). A one-pot Swern oxidation and Horner–Wadsworth–Emmons (HWE) reaction[14,15] was used to generate (*E*)-α,β-unsaturated esters in good yields over the two steps from either commercially available or known alcohols.[16,17] Subsequent reduction of the (*E*)-α,β-unsaturated esters using DIBAL-H gave the desired allylic alcohols.

The development of the three-step tandem process was carried out using (2*E*)-octa-2,7-dien-1-ol (**1**) (Scheme 3). Allylic alcohol **1** was converted to the corresponding allylic trichloroacetimidate **2** using trichloroacetonitrile and a catalytic amount of DBU.[18]

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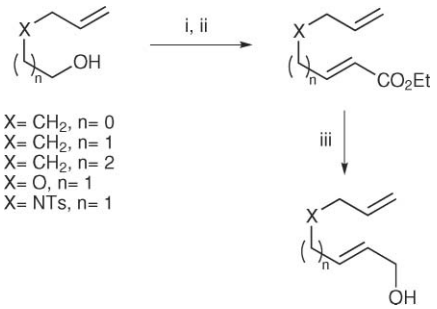
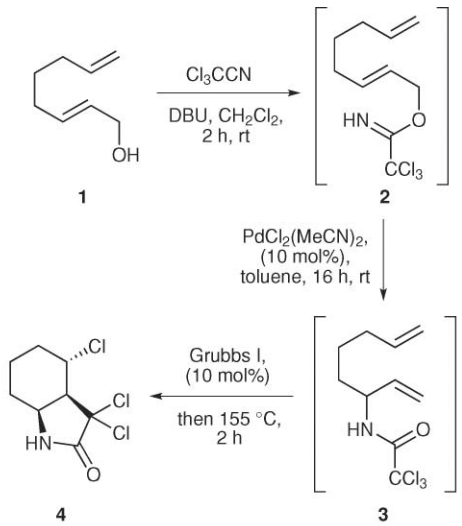
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra for **4**, **6**, **8**, **10** and **12** and all new compounds.



Scheme 2 *Reagents and conditions*: i. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; ii. DBU, LiCl, $(EtO)_2POCH_2CO_2Et$, MeCN, 50–79% over the two steps; iii. DIBAL-H, Et_2O, 76–90%.



entry	Reaction conditions for RCM	yield[a] (%) of **4** from **1**
1	1 h, 60 °C	59
2[b]	1 h, 60 °C	73
3	1 h, rt	71
4[c]	1 h, rt	87

[a] Isolated yields. [b] Grubbs first generation catalyst (5 mol%) was added at the Kharasch cyclisation stage. [c] 4Å molecular sieves were added.

Scheme 3 Optimisation of the one-pot reaction.

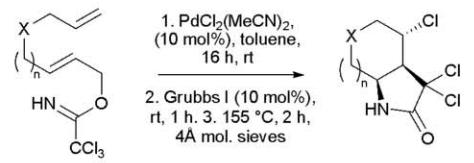
Without purification, allylic trichloroacetimidate **2** was subjected to an Overman rearrangement using bis(acetonitrile)palladium(II) chloride (10 mol%). Grubbs first generation catalyst[19] (10 mol%) was then added and the RCM step was heated to 60 °C (entry 1). The temperature was then increased to 155 °C to initiate the Kharasch cyclization step which led to the isolation of bicyclic [4.3.0] lactam **4** as a single diastereomer in 59% overall yield from allylic alcohol **1**.[20] A significant amount of the cyclic allylic trichloroacetamide (~30%), the product of the RCM step was also isolated, suggesting that the Grubbs first generation catalyst may have decomposed before completion of the Kharasch cyclization. To overcome this, an additional quantity of Grubbs first generation catalyst (5 mol%) was added at the start of the Kharasch cyclization (entry 2), resulting in an increased yield of 73% for lactam **4**. Instead of using additional Grubbs first generation catalyst, a similar yield of 71% could be achieved for lactam **4** using just 10 mol% of catalyst for both steps and by doing the RCM reaction at room temperature (entry 3). In this case only lactam **4** was isolated suggesting that the lower temperature used for the RCM step prolongs the lifetime of the Grubbs first generation catalyst allowing better overall conversion. The high temperatures used for the Kharasch cyclization can lead to the generation of hydrochloric acid resulting in partial decomposition of both starting materials and products. During previous studies on the Kharasch cyclization of cyclic allylic trichloroacetamides we have found that the addition of 4 Å molecular sieves as an acid scavenger[21] allowed the reproducible synthesis of bicyclic γ-lactams in high yields.[8a] Thus, the conditions used for entry 3 were further modified by the addition of 4 Å molecular sieves at the Kharasch cyclization step (entry 4) and this led to the isolation of lactam **4** in an excellent 87% yield from allylic alcohol **1**.

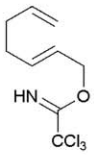
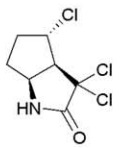
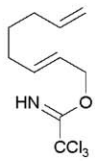
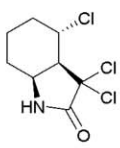
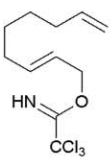
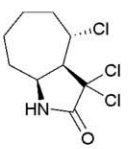
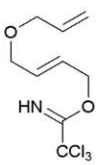
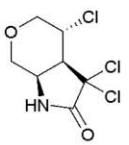
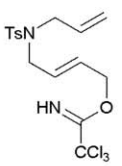
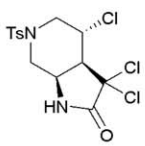
The optimized conditions were then used to explore the scope of the three-step tandem process (Table 1). Conversion of (2*E*)-hepta-2,6-dien-1-ol to the corresponding allylic trichloroacetimidate **5** followed by the three-step tandem sequence gave bicyclic [3.3.0] lactam **6** in 71% yield (entry 1). The bicyclic [5.3.0] lactam **8** was prepared in 60% yield over the four steps, however the RCM step required higher catalyst loading (25 mol%) and more forcing conditions than analogues **4** and **6** (entry 3). The bicyclic [4.3.0] lactams **10** and **12** containing ether and amine functionalities were also prepared using the one-pot tandem process but in only 36% and 19% overall yield, respectively. Inspection of the crude reaction material by NMR spectroscopy from these reaction processes indicated that the Overman rearrangement had not gone to completion. An increase in loading of the palladium catalyst and the use of longer reaction times and higher temperatures did not give any substantial improvement in the yields of **10** and **12**. The problems associated with the Overman rearrangement of allylic trichloroacetimidates **9** and **11** may be due to coordination of the palladium(II) catalyst with the heteroatom and the adjacent terminal alkene preventing effective activation and subsequent rearrangement of the allylic trichloroacetimidate moiety.[22] To overcome this problem, the rearrangement of allylic trichloroacetimidates **9** and **11** was done under thermal conditions resulting in a significant increase in the overall yields of the corresponding bicyclic lactams (entries 4 and 5).

Having examined the scope of the three-step tandem sequence, we were interested in developing an enantioselective variant. The groups of Richards and Overman have developed a series of chiral palladium(II) complexes such as (*S*)-COP–Cl **13**, which catalyze the rearrangement of allylic trichloroacetimidates in high yields and in excellent enantioselectivity.[18,23] These commercially available catalysts are finding increasingly more widespread application for the synthesis of chiral allylic amines.[24]

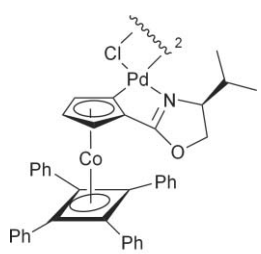
Rearrangement of allylic trichloroacetimidate **2** using either (*S*)-COP–Cl **13** or (*R*)-COP–Cl during the first step of the three-stage tandem process gave bicyclic [4.3.0] lactams **14** and **15** in 70% and 53% yield, respectively and both with high enantioselectivity (89% ee) (Table 2, entries 1 and 2).[25] The use of (*S*)-COP–Cl **13** for

Table 1 Synthesis of various bicyclic γ-lactams



entry	allylic imidate	bicyclic γ-lactam[a]	yield[b] (%) from allylic alcohol
1	 **5**	 **6**	71
2	 **2**	 **4**	87
3[c]	 **7**	 **8**	60
4[d]	 **9**	 **10**	52
5[d]	 **11**	 **12**	39

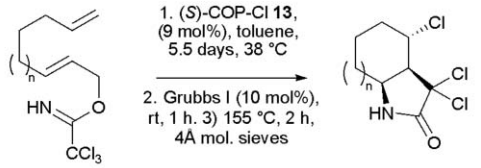
[a] All products were isolated as a single diastereomer. [b] Isolated yields. [c] More forcing conditions were required to complete the RCM step (25 mol% of Grubbs first generation catalyst, 50 °C 120 h). [d] Overman rearrangement was done under thermal conditions.

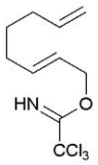
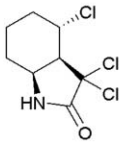
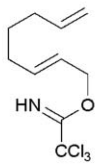
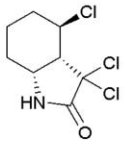
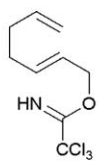
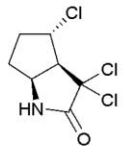


13 (*S*)-COP-Cl

the rearrangement of allylic trichloroacetimidate **5**, gave bicyclic [3.3.0] lactam **16** in 51% overall yield and in 94% ee (entry 3).[26]

Table 2 Development of the asymmetric tandem process



entry	allylic imidate	bicyclic γ-lactam	yield[a] (%) from allylic alcohol	ee (%)
1	 **2**	 **14**	70	89
2[b]	 **2**	 **15**	53	89
3	 **5**	 **16**	51	94

[a] Isolated yields. [b] Reaction done using (*R*)-COP-Cl.

Conclusions

In summary, a one-pot, three-step tandem process has been developed for the direct synthesis of functionalized bicyclic [3.3.0], [4.3.0] and [5.3.0] γ-lactams from simple allylic alcohol precursors. This process utilises a palladium catalyst to effect the Overman rearrangement with Grubbs first generation catalyst then used for the catalysis of both the RCM and Kharasch steps. Overall, the net result of the tandem process is the formation of two carbon-carbon bonds, a carbon-nitrogen bond and a carbon-chlorine bond and using chiral palladium(II) catalysts during the first step generates three contiguous stereogenic centres all in a single flask reaction. Further applications of this process will be reported in due course.

Experimental

All reagents and starting materials were obtained from commercial sources and used as received. All dry solvents were purified using a PureSolv 500 MD solvent purification system. All reactions were performed under an atmosphere of argon unless otherwise mentioned. Flash column chromatography was carried out using Fisher matrix silica 60. Macherey-Nagel aluminium-backed plates pre-coated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualised by staining with $KMnO_4$. ^1H NMR and ^{13}C NMR spectra were

recorded on a Bruker DPX 400 spectrometer with chemical shift values in ppm relative to tetramethylsilane as the standard. Assignment of ^{13}C NMR signals is based on DEPT experiments. Infrared spectra were recorded using Golden Gate apparatus on a JASCO FTIR 410 spectrometer and mass spectra were obtained using a JEOL JMS-700 spectrometer. Melting points were determined on a Reichert platform melting point apparatus. Optical rotations were determined as solutions irradiating with the sodium D line (λ = 589 nm) using an Autopol V polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}. The chiral HPLC methods were calibrated with their corresponding racemic mixtures. (*S*)-COP–Cl **13** refers to di-μ-chlorobis[η^5-(*S*)-(*ρR*)-2-(2′-(4′-methylethyl)oxazolinyl)cyclopentadienyl, 1-*C*, 3′-*N*)(η^4-tetraphenylcyclobutadiene)cobalt]dipalladium and (*R*)-COP–Cl and refers to di-μ-chlorobis[η^5-(*R*)-(*ρR*)-2-(2′-(4′-methylethyl)oxazolinyl)cyclopentadienyl, 1-*C*, 3′-*N*)(η^4-tetraphenylcyclobutadiene)cobalt]dipalladium.

General procedure 1: One Pot Swern Oxidation/Horner–Wadsworth–Emmons reaction

To a stirred solution of oxalyl chloride (1.4 equiv.) in dichloromethane (60 mL) at −78 °C, was added dimethyl sulfoxide (2.5 equiv.). The reaction was stirred at −78 °C for 0.3 h before slow addition of the alcohol in dichloromethane (40 mL). After a further 0.3 h at −78 °C, triethylamine (5 equiv.) was added. The reaction mixture was stirred for a further 0.5 h then allowed to warm to room temperature and stirred for 2 h. The Horner–Wadsworth–Emmons solution was prepared by dissolving lithium chloride (1.8 equiv.) in acetonitrile (70 mL) followed by addition of triethyl phosphonoacetate (1.5 equiv.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.5 equiv.). The mixture was stirred at room temperature for 1 h. The Swern solution was concentrated *in vacuo* and the Horner–Wadsworth–Emmons solution was added to the crude residue before stirring at room temperature overnight. The reaction was quenched with saturated ammonium chloride solution (50 mL) and concentrated under reduced pressure to give an orange residue. The product was extracted using diethyl ether (4 × 50 mL), the organic layers combined, dried ($MgSO_4$) and concentrated to give a yellow oil. Purification was carried out by flash column chromatography using an eluent of petroleum ether/diethyl ether to afford the desired α,β-unsaturated ester.

General procedure 2: Reduction of α,β-unsaturated ester using DIBAL-H

α,β-Unsaturated ester (1 equiv.) was dissolved in diethyl ether (100 mL) and cooled to −78 °C. DIBAL-H (1 M in hexane, 2.2 equiv.) was added dropwise and the reaction mixture allowed to stir at −78 °C for 3 h. The reaction mixture was then allowed to warm to room temperature before stirring overnight. The reaction mixture was cooled to 0 °C and quenched with a saturated ammonium chloride solution (20 mL) before stirring rapidly for 1 h at room temperature to produce a white precipitate. The mixture was filtered through a short plug of Celite® and washed with diethyl ether (400 mL). The organic solvent was dried ($MgSO_4$) and concentrated *in vacuo*. Purification was carried out by flash column chromatography using an eluent of petroleum ether/diethyl ether to afford the desired allylic alcohol.

General procedure 3: Synthesis of allylic trichloroacetimidate followed by a one-pot Overman rearrangement/ring-closing metathesis/Kharasch cyclization

Allylic alcohol (1 equiv.) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. To the solution was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.5 equiv.) and trichloroacetonitrile (1.5 equiv.). The reaction mixture was allowed to warm to room temperature before stirring for 3 h. The reaction mixture was filtered through a short pad of silica gel and the filtrate concentrated *in vacuo* to give the allylic trichloroacetimidate, which was used without further purification. The allylic trichloroacetimidate was dissolved in toluene (10 mL) and transferred to a Schlenk tube containing bis(acetonitrile)palladium(II) chloride (10 mol%). The tube was then sealed under argon and the reaction mixture stirred at room temperature overnight. Grubbs first-generation catalyst (10 mol%) was added and after degassing of the solvent, the reaction mixture was stirred at room temperature. The reaction mixture was sealed under argon and stirred at 155 °C. The reaction mixture was cooled, filtered through a short pad of Celite® and washed with diethyl ether (150 mL). The solvent was removed *in vacuo* to give a brown residue. Purification was carried out by flash column chromatography using an eluent of petroleum ether/ethyl acetate to afford the desired bicyclic lactam.

Ethyl (2*E*)-2,6-heptadienoate[27]

Ethyl (2*E*)-2,6-heptadienoate was synthesised according to general procedure 1, using 4-penten-1-ol (1.00 g, 11.6 mmol). Flash column chromatography (petroleum ether/diethyl ether 95 : 5) afforded the desired compound (1.17 g, 65%) as a pale yellow oil. Spectroscopic data consistent with literature.[27] ν_{max}/cm^{-1} (neat) 2986 (CH), 1721 (CO), 1651 (C=C), 1265, 1173, 1042; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.18–2.26 (2H, m, 5-H_2), 2.27–2.35 (2H, m, 4-H_2), 4.19 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.99–5.09 (2H, m, 7-H_2), 5.75–5.86 (2H, m, 2-H and 6-H), 6.96 (1H, dt, *J* 15.6, 6.7 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 31.5 (CH_2), 32.1 (CH_2), 60.3 (CH_2), 115.6 (CH_2), 121.8 (CH), 137.2 (CH), 148.4 (CH), 166.7 (C); *m*/*z* (CI) 155.1075 (MH^+. $C_9H_{15}O_2$ requires 155.1072), 137 (16%), 107 (17), 73 (22).

Ethyl (2*E*)-2,7-octadienoate[28]

Ethyl (2*E*)-2,7-octadienoate was synthesised according to general procedure 1, using 5-hexen-1-ol (3.00 g, 30 mmol). Flash column chromatography (petroleum ether/diethyl ether 9 : 1) afforded the desired compound (3.96 g, 79%) as a pale yellow oil. Spectroscopic data consistent with literature.[28] ν_{max}/cm^{-1} (neat) 2978 (CH), 1721 (CO), 1651 (C=C), 1265, 1172, 1041; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.56 (2H, quin., *J* 7.2 Hz, 5-H_2), 2.05–2.13 (2H, m, 6-H_2), 2.18–2.26 (2H, m, 4-H_2), 4.19 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.95–5.06 (2H, m, 8-H_2), 5.73–5.84 (2H, m, 2-H and 7-H), 6.96 (1H, dt, *J* 15.7, 6.9 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 27.1 (CH_2), 31.5 (CH_2), 33.0 (CH_2), 60.1 (CH_2), 115.1 (CH_2), 121.5 (CH), 138.0 (CH), 148.8 (CH), 166.6 (C); *m*/*z* (CI) 169.1232 (MH^+. $C_{10}H_{17}O_2$ requires 169.1229), 141 (90%), 123 (75), 95 (100), 81 (53), 55 (32).

Ethyl (2*E*)-2,8-nonadienoate[29]

Ethyl (2*E*)-2,8-nonadienoate was synthesised according to general procedure 1, using 6-hepten-1-ol (1.00 g, 8.8 mmol). Flash column chromatography (petroleum ether/diethyl ether 97 : 3) afforded the desired compound (1.14 g, 71%) as a pale yellow oil. Spectroscopic data consistent with literature.[29] ν_{max}/cm^{-1} (neat) 2932 (CH), 1721 (CO), 1651 (C=C), 1265, 1180, 1042; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.37–1.53 (4H, m, 5-H_2 and 6-H_2), 2.06 (2H, q, *J* 6.9 Hz, 7-H_2), 2.21 (2H, q, *J* 6.9 Hz, 4-H_2), 4.18 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.92–5.04 (2H, m, 9-H_2), 5.73–5.85 (2H, m, 2-H and 8-H), 6.96 (1H, dt, *J* 15.6, 6.9 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 27.5 (CH_2), 28.4 (CH_2), 32.0 (CH_2), 33.5 (CH_2), 60.2 (CH_2), 114.6 (CH_2), 121.4 (CH), 138.6 (CH), 149.2 (CH), 166.8 (C); *m*/*z* (CI) 183.1382 (MH^+. $C_{11}H_{19}O_2$ requires 183.1385), 113 (8%), 97 (7), 81 (13), 71 (15).

Ethyl (2*E*)-4-allyloxybut-2-enoate

Ethyl (2*E*)-4-allyloxybut-2-enoate was synthesised according to general procedure 1, using ethylene glycol monoallyl ether (1.50 g, 14.7 mmol). Flash column chromatography (petroleum ether/diethyl ether 98 : 2) afforded the desired compound (1.26 g, 50%) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 2982 (CH), 1720 (CO), 1662 (C=C), 1447, 1386, 1302, 1178, 1040, 930; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.03 (2H, d, *J* 5.5 Hz, OCH_2CHCH_2), 4.15 (2H, dd, *J* 4.3, 1.9 Hz, 4-H_2), 4.20 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.21 (1H, d, *J* 10.4 Hz, OCH_2CHCHH), 5.31 (1H, d, *J* 17.2 Hz, OCH_2CHCHH), 5.85–5.97 (1H, m, OCH_2CHCH_2), 6.09 (1H, dt, *J* 15.7, 1.9 Hz, 2-H), 6.96 (1H, dt, *J* 15.7, 4.3 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 60.4 (CH_2), 68.6 (CH_2), 71.7 (CH_2), 117.4 (CH_2), 121.3 (CH), 134.2 (CH), 144.3 (CH), 166.4 (C); *m*/*z* (CI) 171.1022 (MH^+. $C_9H_{15}O_3$ requires 171.1021), 163 (6%), 131 (10), 125 (11), 115 (31), 69 (10).

Ethyl (2*E*)-4-[*N*-allyl-*N*-(*p*-toluenesulfonyl)amino]but-2-enoate

Ethyl (2*E*)-*N*-allyl-*N*-(*p*-toluenesulfonyl)but-2-enoate was synthesised according to general procedure 1, using *N*-allyl-*N*-(*p*-toluenesulfonyl)-2-aminoethanol (0.40 g, 1.56 mmol). Flash column chromatography (petroleum ether/diethyl ether 7 : 3) afforded the desired product (0.38 g, 75%) as a pale yellow oil. ν_{max}/cm^{-1} (NaCl) 2982 (CH), 2920 (CH), 1719 (CO), 1661 (C=C), 1598, 1347, 1161, 1039, 762; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.44 (3H, s, Ar-CH_3), 3.80 (2H, d, *J* 6.4 Hz, NCH_2CHCH_2), 3.92 (2H, d, *J* 5.6 Hz, 4-H_2), 4.18 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.10–5.19 (2H, m, NCH_2CHCH_2), 5.53–5.66 (1H, m, NCH_2CHCH_2), 5.90 (1H, d, *J* 15.6 Hz, 2-H), 6.70 (1H, dt, *J* 15.6, 5.6 Hz, 3-H), 7.31 (2H, d, *J* 8.0 Hz, 2 × Ar–H), 7.71 (2H, d, *J* 8.0 Hz, 2 × Ar–H); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 21.6 (CH_3), 47.3 (CH_2), 50.4 (CH_2), 60.6 (CH_2), 119.8 (CH_2), 124.0 (CH), 127.2 (2 × CH), 129.9 (2 × CH), 132.2 (CH), 136.8 (C), 142.3 (CH), 143.7 (C), 166.7 (C); *m*/*z* (FAB) 324.1275 (MH^+. $C_{16}H_{22}NO_4S$ requires 324.1270), 322 (24%), 278 (54), 224 (8), 168 (56), 155 (58), 122 (13), 91 (63), 85 (10).

(2*E*)-Hepta-2,6-dien-1-ol[27]

(2*E*)-Hepta-2,6-dien-1-ol was synthesised according to general procedure 2 using ethyl (2*E*)-2,6-heptadienoate (2.22 g, 14.4 mmol). Flash column chromatography (petroleum ether/diethyl ether 4 : 1) afforded the desired compound (1.43 g, 89%) as a colourless oil. Spectroscopic data consistent with literature.[27] ν_{max}/cm^{-1} (neat) 3325 (OH), 2924 (CH), 1643 (C=C), 1443, 1088, 972, 910; δ_H (400 MHz, $CDCl_3$) 1.35 (1H, br s, OH), 2.13–2.18 (4H, m, 4-H_2 and 5-H_2), 4.09 (2H, d, *J* 4.8 Hz, 1-H_2), 4.95–5.07 (2H, m 7-H_2), 5.62–5.75 (2H, m, 2-H and 3-H), 5.76–5.88 (1H, m, 6-H); δ_C (100 MHz, $CDCl_3$) 31.6 (CH_2), 33.3 (CH_2), 63.8 (CH_2), 114.9 (CH_2), 129.4 (CH), 132.4 (CH), 138.1 (CH); *m*/*z* (CI) 113.0964 (MH^+. $C_7H_{13}O$ requires 113.0966), 95 (100%), 81 (14), 73 (13).

(2*E*)-Octa-2,7-dien-1-ol (1)[28]

(2*E*)-Octa-2,7-dien-1-ol (**1**) was synthesised according to general procedure 2 using ethyl (2*E*)-2,7-octadienoate (3.88 g, 23.1 mmol). Flash column chromatography (petroleum ether/diethyl ether 1 : 1) afforded the desired compound (2.39 g, 82%) as a colourless oil. Spectroscopic data consistent with literature.[28] ν_{max}/cm^{-1} (neat) 3325 (OH), 2924 (CH), 1643 (C=C), 1435, 1087, 972, 910; δ_H (400 MHz, $CDCl_3$) 1.36 (1H, br s, OH), 1.49 (2H, quin, *J* 7.2 Hz, 5-H_2), 2.03–2.11 (4H, m, 4-H_2 and 6-H_2), 4.10 (2H, d, *J* 4.6 Hz, 1-H_2), 4.93–5.05 (2H, m, 8-H_2), 5.60–5.74 (2H, m, 2-H and 3-H), 5.80 (1H, ddt, *J* 17.0, 10.2, 6.7 Hz, 7-H); δ_C (100 MHz, $CDCl_3$) 28.3 (CH_2), 31.6 (CH_2), 33.2 (CH_2), 63.6 (CH_2), 114.6 (CH_2), 129.2 (CH), 132.9 (CH), 138.6 (CH); *m*/*z* (CI) 109.1009 (MH^+-H_2O. C_8H_{13} requires 109.1017), 95 (16%), 81 (12), 67 (47).

(2*E*)-Nona-2,8-dien-1-ol[29]

(2*E*)-Nona-2,8-dien-1-ol was synthesised according to general procedure 2 using ethyl (2*E*)-2,8-nonadienoate (1.05 g, 5.77 mmol). Flash column chromatography (petroleum ether/diethyl ether 4 : 1) afforded the desired compound (0.73 g, 90%) as a colourless oil. Spectroscopic data consistent with literature.[29] ν_{max}/cm^{-1} (neat) 3341 (OH), 2924 (CH), 1643 (C=C), 1435, 1088, 972, 910; δ_H (400 MHz, $CDCl_3$) 1.33 (1H, br s, OH), 1.36–1.44 (4H, m, 5-H_2 and 6-H_2), 2.01–2.10 (4H, m, 4-H_2 and 7-H_2), 4.09 (2H, d, *J* 4.9 Hz, 1-H_2), 4.91–5.03 (2H, m, 9-H_2), 5.59–5.74 (2H, m, 2-H and 3-H), 5.80 (1H, ddt, *J* 17.0, 10.2, 6.7 Hz, 8-H); δ_C (100 MHz, $CDCl_3$) 28.4 (CH_2), 28.6 (CH_2), 32.1 (CH_2), 33.6 (CH_2), 68.9 (CH_2), 114.4 (CH_2), 129.0 (CH), 133.3 (CH), 138.9 (CH); *m*/*z* (CI) 123.1169 (MH^+-H_2O. C_9H_{15} requires 123.1174), 109 (16%), 95 (12), 81 (63), 67 (17).

(2*E*)-4-Allyloxybut-2-en-1-ol

(2*E*)-4-Allyloxybut-2-en-1-ol was synthesised according to general procedure 2 using ethyl (2*E*)-4-allyloxybut-2-enoate (0.79 g, 4.65 mmol). Flash column chromatography (petroleum ether/diethyl ether 4 : 1) afforded the desired compound (0.49 g, 76%) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 3433 (OH), 2855 (CH), 1645 (C=C), 1451, 1423, 1358, 1094, 1005; δ_H (400 MHz, $CDCl_3$) 1.49 (1H, br s, OH), 3.98–4.02 (4H, m, 4-H_2 and OCH_2CHCH_2), 4.16–4.18 (2H, m, 1-H_2), 5.17–5.22 (1H, m, OCH_2CHCHH), 5.26–5.32 (1H, m, OCH_2CHCHH), 5.79–5.97 (3H, m, 2-H, 3-H and OCH_2CHCH_2); δ_C (100 MHz, $CDCl_3$) 63.0 (CH_2), 70.0 (CH_2), 71.3 (CH_2), 117.2 (CH_2), 127.8 (CH), 132.2 (CH), 134.6 (CH); *m*/*z* (CI) 129.0918 (MH^+. $C_7H_{13}O_2$ requires 129.0916), 111 (98%), 93 (35), 79 (100), 71 (66).

(2*E*)-4-[*N*-(allyl)-*N*-(*p*-toluenesulfonyl)amino]but-2-en-1-ol

(2*E*)-4-[*N*-(Allyl)-*N*-(*p*-toluenesulfonyl)amino]but-2-en-1-ol was synthesised according to general procedure 2 using ethyl (2*E*)-4-[*N*-allyl-*N*-(*p*-toluenesulfonyl)amino]but-2-enoate (1.50 g, 4.64 mmol). Flash column chromatography (petroleum ether/diethyl ether 3 : 2) afforded the desired compound (1.01 g, 78%) as viscous oil. ν_{max}/cm^{-1} (NaCl) 3513 (OH), 2922 (CH), 1643 (C=C), 1597, 1443, 1338, 1158, 1091, 662; δ_H (400 MHz, $CDCl_3$) 1.79 (1H, br s, OH), 2.43 (3H, s, Ar-CH_3), 3.78–3.83 (4H, m, 4-H_2 and NCH_2CHCH_2), 4.08 (2H, d, *J* 4.9 Hz, 1-H_2), 5.11–5.19 (2H, m, NCH_2CHCH_2), 5.48–5.66 (2H, m, 3-H and NCH_2C*H*CH_2), 5.74 (1H, dt, *J* 15.4, 4.9 Hz, 2-H), 7.30 (2H, d, *J* 8.1 Hz, 2 × Ar–H), 7.70 (2H, d, *J* 8.1 Hz, 2 × Ar–H); δ_C (100 MHz, $CDCl_3$) 21.6 (CH_3), 48.2 (CH_2), 49.6 (CH_2), 62.7 (CH_2), 119.1 (CH_2), 125.7 (CH), 127.2 (2 × CH), 129.7 (2 × CH), 132.7 (CH), 133.7 (CH), 137.2 (C), 143.4 (C); *m*/*z* (CI) 282.1169 (MH^+. $C_{14}H_{20}NO_3S$ requires 282.1164), 264 (100%), 212 (11), 157 (8), 128 (6).

(1*S,5*S**,6*S**)-5,7,7-Trichloro-8-oxo-9-azabicyclo[4.3.0]nonane (4)[9b]**

(1*S**,5*S**,6*S**)-5,7,7-Trichloro-8-oxo-9-azabicyclo[4.3.0]nonane (**4**) was synthesised according to general procedure 3 using (2*E*)-octa-2,7-dien-1-ol (**1**) (0.10 g, 0.8 mmol). The reaction mixture was stirred with Grubbs first-generation catalyst (10 mol%) for 1 h at 60 °C followed by 3 h at 155 °C. Flash column chromatography (petroleum ether/ethyl acetate 7 : 3) afforded the desired compound (0.115 g, 59%) as a white solid. Spectroscopic data consistent with literature.[9b] mp 135–137 °C, lit.[9b] 142–143.5 °C; ν_{max}/cm^{-1} (neat) 3256 (NH), 2924 (CH), 1690 (CO), 1427, 1273, 741; δ_H (400 MHz, $CDCl_3$) 1.63–1.84 (3H, m, 3-H_2 and 4-*H*H), 1.91–2.01 (2H, m, 2-*H*H and 4-H*H*), 2.31–2.41 (1H, m, 2-H*H*), 3.34 (1H, dd, *J* 7.0, 3.7 Hz, 6-H), 3.99 (1H, apparent q, *J* 7.0 Hz, 1-H), 4.62 (1H, apparent q, *J* 3.7 Hz, 5-H), 7.30 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 17.5 (CH_2), 28.4 (CH_2), 32.2 (CH_2), 50.0 (CH), 55.2 (CH), 57.1 (CH), 82.5 (C), 168.5 (C); *m*/*z* (CI) 241.9908 (MH^+. $C_8H_{11}{}^{35}Cl_3NO$ requires 241.9906), 208 (100), 172 (32), 157 (71), 113 (24), 81 (43).

(1*S,5*S**,6*S**)-5,7,7-Trichloro-8-oxo-9-azabicyclo[4.3.0]nonane (4)[9b]**

(1*S**,5*S**,6*S**)-5,7,7-Trichloro-8-oxo-9-azabicyclo[4.3.0]nonane (**4**) was synthesised according to general procedure 3 using (2*E*)-octa-2,7-dien-1-ol (**1**) (0.10 g, 0.8 mmol). The reaction mixture was stirred with Grubbs first-generation catalyst (10 mol%) for 1 h at 60 °C. A further quantity of Grubbs first-generation catalyst (5 mol%) was added to the reaction before stirring for 2 h at 155 °C. Flash column chromatography (petroleum ether/ethyl acetate 7 : 3) afforded the desired compound (0.141 g, 73%) as a white solid. Spectroscopic data as described above.

(1*S,5*S**,6*S**)-5,7,7-Trichloro-8-oxo-9-azabicyclo[4.3.0]nonane (4)[9b]**

(1*S**,5*S**,6*S**)-5,7,7-Trichloro-8-oxo-9-azabicyclo[4.3.0]nonane (**4**) was synthesised according to general procedure 3 using (2*E*)-octa-2,7-dien-1-ol (**1**) (0.10 g, 0.8 mmol). The reaction mixture was stirred with Grubbs first-generation catalyst (10 mol%) for 1 h at room temperature followed by 2 h at 155 °C. Flash column chromatography (petroleum ether/ethyl acetate 7 : 3) afforded the desired compound (0.138 g, 71%) as a white solid. Spectroscopic data as described above.

(1*S,5*S**,6*S**)-5,7,7-Trichloro-8-oxo-9-azabicyclo[4.3.0]nonane (4)[9b]**

(1*S**,5*S**,6*S**)-5,7,7-Trichloro-8-oxo-9-azabicyclo[4.3.0]nonane (**4**) was synthesised according to general procedure 3 using (2*E*)-octa-2,7-dien-1-ol (**1**) (0.10 g, 0.8 mmol). The reaction mixture was stirred with Grubbs first-generation catalyst (10 mol%) and 4 Å molecular sieves (1.00 g) for 1 h at room temperature, before sealing under argon and stirring for 2 h at 155 °C. Flash column chromatography (petroleum ether/ethyl acetate 7 : 3) afforded the desired compound (0.17 g, 87%) as a white solid. Spectroscopic data as described above.

(1*S,4*S**,5*S**)-4,6,6-Trichloro-7-oxo-8-azabicyclo[3.3.0]octane (6)[11b]**

(1*S**,4*S**,5*S**)-4,6,6-Trichloro-7-oxo-8-azabicyclo[3.3.0]octane (**6**) was synthesised according to general procedure 3 using (2*E*)-hepta-2,6-dien-1-ol (0.10 g, 0.9 mmol). The reaction mixture was stirred with Grubbs first-generation catalyst (10 mol%) and 4 Å molecular sieves (1.00 g) for 1 h at room temperature, before sealing under argon and stirring for 4 h at 155 °C. Flash column chromatography (petroleum ether/ethyl acetate 7 : 3) afforded the desired compound (0.14 g, 71%) as a white solid. Spectroscopic data consistent with literature.[11b] mp: 172–174 °C, lit.[11b] 175–176 °C; ν_{max}/cm^{-1} (neat) 3264 (NH), 2932 (CH), 1690 (CO), 1427, 1273, 1049, 741; δ_H (400 MHz, $CDCl_3$) 1.87–1.95 (1H, m, 2-*H*H), 2.00–2.09 (1H, m, 2-H*H*), 2.18–2.36 (2H, m, 3-H_2), 3.66 (1H, dd, *J* 6.4, 3.4 Hz, 5-H), 4.41–4.46 (1H, m, 1-H), 4.59–4.64 (1H, m, 4-H), 7.75 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 30.6 (CH_2), 34.7 (CH_2), 56.6 (CH), 61.0 (CH), 65.8 (CH), 83.1 (C), 169.0 (C); *m*/*z* (EI) 226.9679 (M^+. $C_7H_8{}^{35}Cl_3NO$ requires 226.9671), 192 (12%), 151 (96), 149 (100), 113 (71), 77 (56).

(1*S,6*S**,7*S**)-6,8,8-Trichloro-9-oxo-10-azabicyclo[5.3.0]decane (8)[11b]**

(1*S**,6*S**,7*S**)-6,8,8-Trichloro-9-oxo-10-azabicyclo[5.3.0]decane (**8**) was synthesised according to general procedure 3 (at a concentration of 0.009 M) using (2*E*)-octa-2,7-dien-1-ol (0.05 g, 0.36 mmol). The reaction was stirred with Grubbs first-generation catalyst (10 mol%) for 48 h at 50 °C. A second quantity of Grubbs first-generation catalyst (5 mol%) was then added and the reaction stirred for a further 24 h at 50 °C. A third quantity of Grubbs first-generation catalyst (5 mol%) was added and the reaction stirred for a further 24 h at 50 °C. A final quantity of Grubbs first-generation catalyst (5 mol%) was added and the reaction stirred for a final 24 h at 50 °C. To the cooled reaction, 4 Å molecular sieves (1.00 g) were added before sealing under argon and stirring at 155 °C for 2 h. Flash column chromatography (petroleum ether/ethyl acetate 7 : 3) afforded the desired compound (0.06 g, 60%) as a white solid. Spectroscopic data consistent with literature.[11b] mp 208–210 °C, lit.[11b] 206–208 °C; ν_{max}/cm^{-1} (neat) 3194 (NH), 2932 (CH), 1705 (CO), 1443, 1281, 1026, 849, 772; δ_H (400 MHz, $CDCl_3$) 1.22–1.35 (1H, m, 3-*H*H), 1.45–1.59 (1H, m, 4-*H*H), 1.73–1.84 (2H, m,

2-H_2), 1.85–1.97 (2H, m, 3-H*H* and 4-H*H*), 1.98–2.09 (1H, m, 5-*H*H), 2.32–2.40 (1H, m, 5-H*H*), 3.41 (1H, dd, *J* 10.1, 8.3 Hz, 7-H), 3.75–3.82 (1H, m, 1-H), 4.47–4.53 (1H, m, 6-H), 7.69 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 27.4 (CH_2), 29.0 (CH_2), 31.7 (CH_2), 38.7 (CH_2). 57.1 (CH), 59.0 (CH), 60.2 (CH), 83.9 (C), 168.8 (C); *m*/*z* (CI) 256.0063 (MH^+. $C_9H_{13}{}^{35}Cl_3NO$ requires 256.0063), 222 (49), 186 (12), 152 (26), 107 (41), 91 (6).

(1*R**,5*R**,6*S**)-3-Oxa-5,7,7-trichloro-8-oxo-9-azabicyclo[4.3.0]nonane (10)

(1*R**,5*R**,6*S**)-3-Oxa-5,7,7-trichloro-8-oxo-9-azabicyclo[4.3.0]-nonane (**10**) was synthesised according to general procedure 3 using (2*E*)-4-allyloxybut-2-en-1-ol (0.10 g, 0.78 mmol). The allylic trichloroacetimidate was dissolved in toluene and stirred with potassium carbonate (0.03 g, 0.22 mmol) in a sealed tube at 140 °C for 72 h. Grubbs first-generation catalyst (10 mol%) was added and after degassing of the solvent, the reaction mixture was stirred at room temperature for 3 h. A second quantity of Grubbs first-generation catalyst (5 mol%) was added and the reaction stirred for a further 1 h at room temperature. 4 Å Molecular sieves (1.00 g) were then added, the reaction sealed under argon and heated at 155 °C for 3 h. Flash column chromatography (petroleum ether/ethyl acetate 7 : 3) afforded the desired bicyclic lactam (0.10 g, 52%) as a white solid. mp 188–190 °C; ν_{max}/cm^{-1} (neat) 3139 (NH), 2864 (CH), 1752 (CO), 1711, 1367, 1096, 1033, 909, 834, 763; δ_H (400 MHz, $CDCl_3$) 3.21 (1H, dd, *J* 8.0, 5.3 Hz, 6-H), 3.42 (1H, dd, *J* 12.0, 9.3 Hz, 4-*H*H), 3.77 (1H, dd, *J* 12.9, 2.8 Hz, 2-*H*H), 3.98–4.05 (1H, m, 5-H), 4.05–4.11 (2H, m, 1-H and 2-H*H*), 4.16 (1H, dd, *J* 12.0, 5.3 Hz, 4-H*H*), 7.59 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 50.1 (CH), 51.1 (CH), 56.7 (CH), 67.3 (CH_2), 70.7 (CH_2), 84.0 (C), 168.7 (C); *m*/*z* (CI) 243.9695 (MH^+. $C_7H_9{}^{35}Cl_3NO_2$ requires 243.9699), 210 (68%), 174 (38), 140 (18), 107 (42).

(1*R**,5*R**,6*S**)-3-(*p*-Toluenesulfonyl)-5,7,7-trichloro-8-oxo-3,9-diazabicyclo[4.3.0]nonane (12)

(1*R**,5*R**,6*S**)-3-(*p*-Toluenesulfonyl)-5,7,7-trichloro-8-oxo-3,9-diazabicyclo[4.3.0]nonane (**12**) was synthesised according to general procedure 3 using (2*E*)-4-[*N*-(allyl)-*N*-(*p*-toluenesulfonyl)-amino]but-2-en-1-ol (0.10 g, 0.36 mmol). The allylic trichloroacetimidate was dissolved in toluene and stirred with potassium carbonate (0.03 g, 0.22 mmol) in a sealed tube at 140 °C for 136 h. Grubbs first-generation catalyst (15 mol%) was added and after degassing the solvent, the reaction mixture was stirred at room temperature for 1 h. 4 Å Molecular sieves (1.00 g) were then added, the reaction sealed under argon and stirred at 155 °C for 3 h. Flash column chromatography (petroleum ether/ethyl acetate 7 : 3) afforded the desired bicyclic lactam (0.06 g, 39%) as a white solid. mp 184–186 °C; ν_{max}/cm^{-1} (neat) 3193 (NH), 2915 (CH), 2898 (CH), 1740 (CO), 1712, 1343, 1237, 1171, 1090, 869, 744; δ_H (400 MHz, $CDCl_3$) 2.45 (3H, s, Ar-CH_3), 3.11 (1H, dd, *J* 13.0, 7.4 Hz, 4-*H*H), 3.18 (1H, apparent t, *J* 5.8 Hz, 6-H), 3.28 (1H, dd, *J* 13.0, 4.2 Hz, 2-*H*H), 3.48 (1H, dd, *J* 13.0, 5.8 Hz, 2-H*H*), 3.81 (1H, dd, *J* 13.0, 4.3 Hz, 4-H*H*), 4.16–4.21 (1H, m, 1-H), 4.27–4.33 (1H, m, 5-H), 7.06 (1H, br s, NH), 7.36 (2H, d, *J* 8.2 Hz, 2 × Ar–H), 7.67 (2H, d, *J* 8.2 Hz, 2 × Ar–H); δ_C (100 MHz, $CDCl_3$) 21.6 (CH_3), 46.5 (CH_2), 49.3 (CH), 50.8 (CH_2), 51.4 (CH), 56.4 (CH), 82.6 (C), 127.5 (2 × CH), 130.2 (2 × CH), 133.4 (C), 144.6 (C), 167.5 (C); *m*/*z* (FAB) 398.9912 (MH^+. $C_{14}H_{16}{}^{35}Cl_2{}^{37}ClN_2O_3S$ requires 398.9919), 363 (6%), 307 (7), 243 (5), 155 (89), 137 (100), 121 (14), 109 (11).

(1*S*,5*S*,6*S*)-5,7,7-Trichloro-8-oxo-9-azabicyclo[4.3.0]nonane (14)

(1*S*,5*S*,6*S*)-5,7,7-Trichloro-8-oxo-9-azabicyclo[4.3.0]nonane (**14**) was synthesised according to general procedure 3 using (2*E*)-octa-2,7-dien-1-ol (**1**) (0.10 g, 0.8 mmol). The reaction was stirred with (*S*)-COP–Cl (3 mol%) for 36 h at 38 °C. A second quantity of (*S*)-COP–Cl (3 mol%) was added and the solution stirred at 38 °C for 72 h. A final quantity of (*S*)-COP–Cl (3 mol%) was added and the solution stirred at 38 °C for a further 24 h. Grubbs first-generation catalyst (10 mol%) was added and after degassing of the solvent, the reaction mixture was stirred for 1 h at room temperature. 4 Å Molecular sieves (1.00 g) were then added, the reaction sealed under argon and stirred at 155 °C for 3 h. Flash column chromatography (petroleum ether/ethyl acetate 7 : 3) afforded the desired compound (0.20 g, 70%) as a white solid. Chiral HPLC (Chiralcel IB column) analysis using 4% isopropanol in hexane as the elution solvent indicated 89% ee. $[\alpha]_D^{24}$ +59.2 (*c* 1.2, $CHCl_3$). All other spectroscopic data matched that previously reported for (1*S**,5*S**,6*S**)-5,7,7-trichloro-8-oxo-9-azabicyclo[4.3.0]nonane (**4**).

(1*R*,5*R*,6*R*)-5,7,7-Trichloro-8-oxo-9-azabicyclo[4.3.0]nonane (15)

(1*R*,5*R*,6*R*)-5,7,7-Trichloro-8-oxo-9-azabicyclo[4.3.0]nonane (**15**) was synthesised according to general procedure 3 using (2*E*)-octa-2,7-dien-1-ol (**1**) (0.1 g, 0.8 mmol). The reaction was stirred with (*R*)-COP–Cl (3 mol%) for 36 h at 38 °C. A second quantity of (*R*)-COP–Cl (3 mol%) was added and the solution stirred at 38 °C for 72 h. A final quantity of (*R*)-COP–Cl (3 mol%) was added and the solution stirred at 38 °C for a further 24 h. Grubbs first-generation catalyst (10 mol%) and 4 Å molecular sieves (1.00 g) were added and after degassing of the solvent, the reaction mixture was stirred at room temperature for 1 h followed by 3 h at 155 °C. Flash column chromatography (petroleum ether/ethyl acetate 7 : 3) afforded the desired compound (0.10 g, 53%) as a white solid. Chiral HPLC (Chiralcel IB column) analysis using 4% isopropanol in hexane as the elution solvent indicated 89% ee. $[\alpha]_D^{24}$ −63.5 (*c* 1.3, $CHCl_3$). All other spectroscopic data matched that previously reported for (1*S**,5*S**,6*S**)-5,7,7-trichloro-8-oxo-9-azabicyclo[4.3.0]nonane (**4**).

(1*S*,4*S*,5*S*)-4,6,6-Trichloro-7-oxo-8-azabicyclo[3.3.0]octane (16)

(1*S*,4*S*,5*S*)-4,6,6-Trichloro-7-oxo-8-azabicyclo[3.3.0]octane (**16**) was synthesised according to general procedure 3 using (2*E*)-hepta-2,6-dien-1-ol (0.10 g, 0.9 mmol). The reaction was stirred with (*S*)-COP–Cl (3 mol%) for 36 h at 38 °C. A second quantity of (*S*)-COP–Cl (3 mol%) was added and the solution stirred at 38 °C for 72 h. A final quantity of (*S*)-COP–Cl (3 mol%) was added and the solution stirred at 38 °C for a further 24 h. Grubbs first-generation catalyst (10 mol%) was added and after degassing of the solvent, the reaction mixture was stirred at room temperature for 1 h. 4 Å Molecular sieves (1.00 g) were then added, the reaction sealed under argon and stirred at 155 °C for 4 h. Flash column chromatography (petroleum ether/ethyl

acetate 7 : 3) afforded the desired compound (0.10 g, 51%) as a white solid. Chiral HPLC (Chiralcel IB column) analysis using 4% isopropanol in hexane as the elution solvent indicated 94% ee. $[\alpha]_D^{24}$ +45.5 (*c* 0.5, $CHCl_3$). All other spectroscopic data matched that previously reported for (1*S**,4*S**,5*S**)-4,6,6-trichloro-7-oxo-8-azabicyclo[3.3.0]octane (**6**).

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