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'Clip-Cycle' approaches to functionalised pyrrolidines, pyrrolizidines and indolizidines

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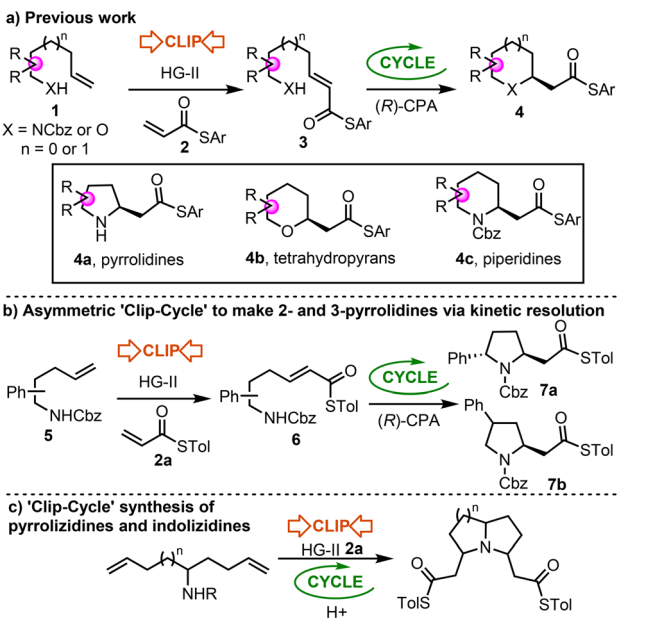
The 'Clip-Cycle' approach is a versatile and modular synthetic method for the synthesis of aza-heterocycles *via* sequential cross metathesis and aza-Michael reactions. In this manuscript, a series of innovations to the 'Clip-Cycle' approach are reported. First, the asymmetric 'Clip-Cycle' syntheses of 2,5- and 3,5-pyrrolidines from chiral starting materials are reported for the first time, using a kinetic resolution method. A two-directional 'Clip-Cycle' approach for the synthesis of pyrrolizidines and indolizidines is then introduced.

Introduction

Aza-heterocycles are highly important in synthetic and medicinal chemistry and modular methods to make them from simple building blocks are valuable.[1,2] The 'Clip-Cycle' approach, developed within the laboratory of Prof Paul A. Clarke§ at the University of York, is one such method (Scheme 1a). 'Clip-Cycle' operates *via* a two-step sequence.[3] The 'Clip' phase of the method uses a cross metathesis reaction catalysed by Hoveyda–Grubbs second generation catalyst (HG-II), to couple an amine- or alcohol-tethered alkene **1** with a thioacrylate **2**. This affords a functionalised Michael acceptor **3**, that can undergo cyclisation *via* an acid-catalysed intramolecular conjugate addition reaction in the 'Cycle' phase, to form the heterocyclic product **4**. The 'Cycle' phase can be done racemically (*e.g.* using *rac*emic camphorsulfonic acid, *rac*-CSA) or enantioselectively using a chiral phosphoric acid (CPA).[4] The thioester moiety is key to the 'Clip-Cycle' approach; the Michael acceptor must be sufficiently reactive to enable the intramolecular conjugate addition in the 'Cycle' step, but not too reactive so that conjugate addition takes place spontaneously following cross metathesis in the 'Clip' phase, as this would preclude asymmetric CPA catalysis.[3a] Prior to this manuscript, the successful application of the 'Clip-Cycle' approach for the enantioselective synthesis of pyrrolidines **4a**,[3a,b] tetrahydropyrans **4b**[3c] and piperidines **4c**[3d] was described.

In this manuscript, a series of innovations to the 'Clip-Cycle' method are reported. Firstly, the synthesis of 2,5- and 3,5-disubstituted pyrrolidines is reported using a kinetic resolution approach.[5] The 'Clip-Cycle' method results in the generation of a new stereogenic centre. However, with the exception of a single scaffold (2 examples, *vide infra*),[2c] all previously published examples have started from achiral starting materials; this simplifies the reaction significantly, as diastereoselectivity and the resolution of a chiral starting material are not considerations. The requirement to use



Scheme 1 Extensions to the 'Clip-Cycle' method to synthesize functionalised pyrrolidine, pyrrolizidines and indolizidines.

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§ The development of the 'Clip-Cycle' approach will not continue at the University of York as Prof Paul A. Clarke passed away in November 2023.

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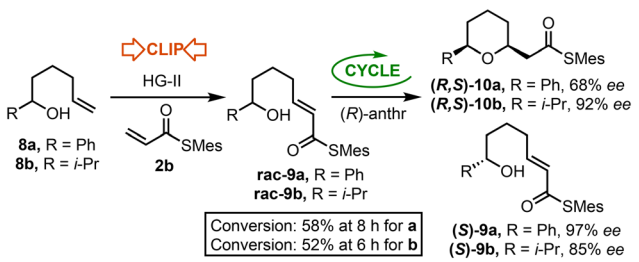
achiral starting materials places a significant limitation on the scope of the method however. To address this, the synthesis of 2,5- and 3,5-disubstituted pyrrolidines from chiral amine derivatives is described herein for the first time (Scheme 1b). Furthermore, a novel two-directional 'Clip-Cycle' approach is introduced and used in the synthesis of pyrrolizidines and indolizidines from amino diene precursors (Scheme 1c).

'Clip-Cycle' synthesis of 2,5- and 3,5-pyrrolidines *via* kinetic resolution

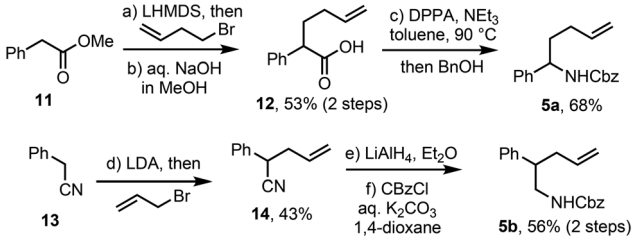
Previously reported 'Clip-Cycle' reactions made use of achiral starting materials, with the exception of the synthesis of tetrahydropyrans (***R*,*S*)-10a** and (***R*,*S*)-10b** (Scheme 2).[3c] In this series, cross metathesis of alcohols **8a** and **8b** with thioacrylate **2b**, mediated by HG-II, afforded racemic Michael acceptors ***rac*-9a** and ***rac*-9b** respectively. Cyclisation with a chiral CPA catalyst was then performed aiming for ≈50% conversion (58% and 52% respectively), which resulted in effective kinetic resolution of both racemic starting materials, with enantio-enriched tetrahydropyran products (***R*,*S*)-10a** (68% ee) and (***R*,*S*)-10b** (92% ee) isolated, along with recovered starting materials (***S*)-9a** (97% ee) and (***S*)-9b** (85% ee), concomitantly enriched as the *R*-enantiomer.

To extend the kinetic resolution hypothesis to 2,5- and 3,5-pyrrolidines, the syntheses of racemic amines **5a** and **5b** were performed. To synthesise the 2-phenyl amine **5a**, methyl phenylacetate **11** was first alkylated with 4-bromo-1-butene, mediated by LHMDS, and the resultant ester hydrolysed to afford carboxylic acid **12**. Subsequent Curtius rearrangement, followed by trapping with benzyl alcohol, afforded amine **5a** in good overall yield. Synthesis of the 3-substituted amine **5b** proceeded *via* alkylation of nitrile **13** with allyl bromide to give alkene **14**, reduction using $LiAlH_4$ and Cbz-protection to afford **5b** (Scheme 3).

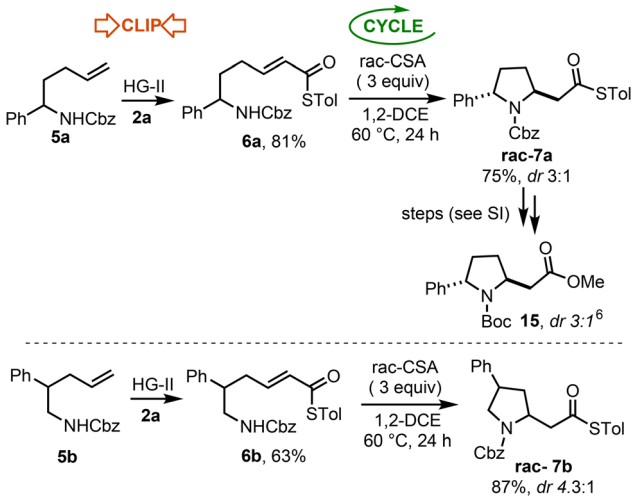
The 'Clip-Cycle' of secondary amines **5a** and **5b** was then examined, initially to generate racemic pyrrolidine products. In both cases, the cross metathesis with thioacrylate **2a** proceeded smoothly, to afford Michael acceptors **6a** and **6b** in good yields, both as single *E*-isomers. Cyclisation was then promoted by excess rac-CSA, as a Brønsted acid catalyst, to afford the expected 2,5- and 3,5-pyrrolidine products ***rac*-7a** and ***rac*-7b** respectively (Scheme 4). These experiments confirm the approach is synthetically viable for these substrate classes,



Scheme 2 'Clip-Cycle' synthesis of 2,6-disubstituted tetrahydropyrans *via* kinetic resolution.



Scheme 3 Synthesis of amines **5a** and **5b**.

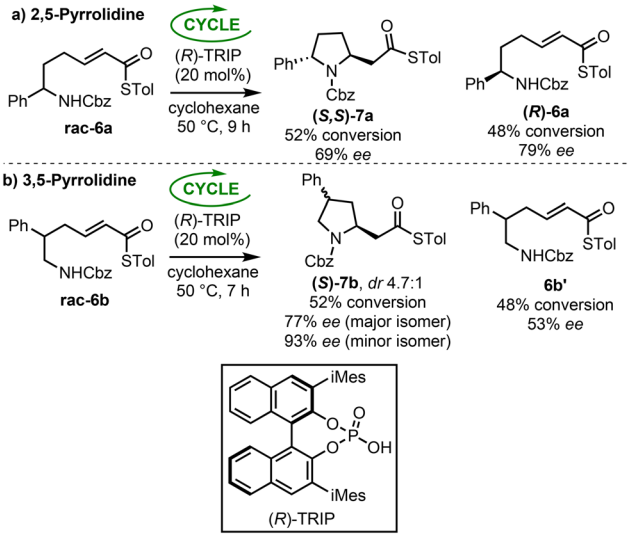


Scheme 4 Racemic 'Clip-Cycle' synthesis of 2,5- and 3,5-pyrrolidines.

and also provided racemic product standards, which were needed for the asymmetric studies to follow. In the case of 2,5-pyrrolidine ***rac*-7a**, the product was obtained as *a* ≈ 3 : 1 mixture of diastereoisomers, with the *trans* isomer shown assigned as the major diastereoisomer. To make this assignment, ***rac*-7a** was converted into its *N*-Boc protected amino ester derivative and its NMR spectroscopic data compared to those of the known *trans* diastereoisomer **15**.[6] 3,5-Pyrrolidine ***rac*-7b** was isolated as a 4.3 : 1 mixture of diastereoisomers; the relative stereochemistry of the major and minor diastereoisomers could not be unequivocally determined in this case.

Attention was then placed on assessing the feasibility of achieving the kinetic resolution of both racemic substrates ***rac*-6a** and ***rac*-6b**. Based on our previous pyrrolidine 'Clip-Cycle' work,[3a,b] the CPA catalyst (*R*)-TRIP (20 mol%, see Scheme 5 box) was selected as the cyclisation catalyst, with cyclohexane as the solvent at 50 °C. In both cases, the reactions were analysed at regular intervals by chiral HPLC and stopped when around 50% of the starting material was converted. Details of the reaction conversion and ee at all measured time points is included in the SI; a summary of the end point of the reactions is summarised in Scheme 5 and described below.

After reacting ***rac*-6a** for 9 hours, 52% conversion into 2,5-pyrrolidine (***S*,*S*)-7a** was observed by chiral HPLC analysis, hence the reaction was stopped at this time point. The ee of (***S*,**



Scheme 5 'Clip-Cycle' synthesis of 2,5- and 3,5-pyrrolidines *via* kinetic resolution.

***S*)-7a** was measured to be 69% ee, while the remaining 48% of the reaction mixture was accounted for by unreacted starting material, enriched to 79% ee as the (*R*)-enantiomer **(*R*)-6a**. The assignment of the absolute stereochemistry of **(*S*,*S*)-7a** and **(*R*)-6a** was made assuming the same sense of selectivity as that observed during our previous work on the asymmetric 'Clip-Cycle' synthesis of 2,5-pyrrolidines.[3a,b] The diastereomeric ratio of **(*S*,*S*)-7a** was not measured in this case, as the *trans*- and *cis*-diastereoisomers of **7a** were not resolved by the HPLC analytical method used.

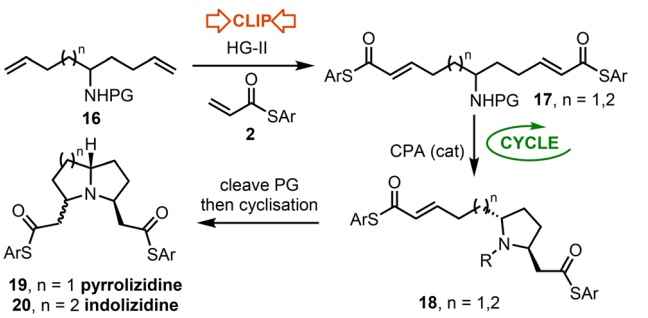
For the resolution of ***rac*-6b**, 52% conversion into 3,5-pyrrolidine **(*S*)-7b** was observed by chiral HPLC after 7 hours at 50 °C and the reaction halted at this time point. In this case, the chiral HPLC method used was able to resolve both the *cis*- and *trans*-diastereoisomers of **7b** and each of their enantiomeric pairs, meaning that both the dr, and the ee for both isomers could be monitored simultaneously. A high ee was observed for both diastereoisomers (77% and 93% for the major and minor isomers respectively), with enantioenriched unreacted starting material **6b′** (48% of the reaction mixture). The newly formed stereogenic centre at the 5-position is again likely to be the (*S*)-enantiomer shown based on our previous work.[3a,b] For ***rac*-7b**, the relative stereochemistry of the major diastereomer of **(*S*)-7b** was not determined, and hence the absolute configuration of the major enantiomer of **6b′** could not be deduced also.

3,5-Disubstituted pyrrolizidines and Indolizidines

The second half of this study focuses on the synthesis of 3,5-disubstituted pyrrolizidines and indolizidines using the 'Clip-Cycle' approach. Pyrrolizidines and indolizidines are common motifs in biologically active alkaloids, isolated from a variety of natural sources, ranging from poison dart frogs and ants to plants and trees.[7] In view of their importance, various synthetic approaches to make them have been established,[8] with two-directional approaches based on the elaboration of symmetrical (or pseudo-symmetrical) precursors amongst the most effective.[9] We recognised an opportunity to utilise the 'Clip-Cycle' approach, summarised in Scheme 6. Thus, a double cross metathesis reaction (**16** → **17**, 'Clip') followed by an aza-Michael reaction[10] (**17** → **18**, 'Cycle') would deliver a desymmetrised pyrrolidine intermediate **18** asymmetrically using a suitable CPA catalyst. Cleavage of the N-protecting group (PG below) would then be expected to facilitate a second aza-Michael reaction spontaneously, to afford either a pyrrolizidine **19** or indolizidine **20** depending on the chain length (*n* = 1 or 2).

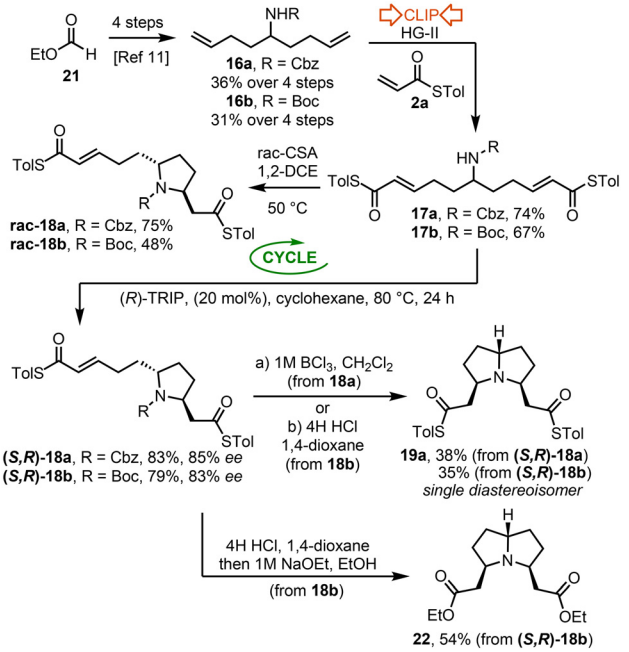
The 'Clip-Cycle' pyrrolizidine synthesis started with the 4-step conversion of ethyl formate **21** into dienes **16a** and **16b**, using a modified literature procedure, based on a report by Nicolai and Waser.[11] Both dienes **16a** and **16b** were then reacted with thioacrylate **2a** and the Hoveyda–Grubbs second generation catalyst, which promoted a double cross metathesis reaction to form dienes **17a** and **17b** in the 'Clip' phase of the process. Each was formed as a single *E*,*E*-geometrical isomer. Next, the 'Cycle' step was performed, first using *rac*-CSA to form pyrrolidines ***rac*-18a** and ***rac*-18b**, with both pyrrolidines isolated as a single *trans*-diastereoisomer.[12] The 'Cycle' step was then repeated using our standard conditions for asymmetric pyrrolidine formation,[3a,b] using CPA catalyst (*R*)-TRIP (20 mol%) in cyclohexane as the solvent. For both diene substrates the cyclisation worked well; pyrrolidines **(*S*,*R*)-18a** and **(*S*,*R*)-18b** were isolated in 83% and 79% yields, and in 85% ee and 83% ee respectively. As for the racemic reaction, both products were isolated as a single *trans*-diastereoisomer.[12]

Attention then turned to N-protecting group cleavage and the second aza-Michael reaction. In the case of *N*-Cbz derivative **18a**, the alkene groups precluded a standard hydrogenolysis approach, therefore a Lewis acidic method was chosen, using BCl_3;[13] these conditions promoted Cbz-cleavage and spontaneous aza-Michael reaction to afford pyrrolizidine **19a** in 38% yield. The same pyrrolizidine **19a** was also obtained from **18b**, following reaction with 4 M HCl in 1,4-dioxane. Both methods furnished **19a** as a single diastereoisomer. The optical rotation of **19a** was measured to be zero; as an enantioenriched starting material was used, this indicated that *meso*-

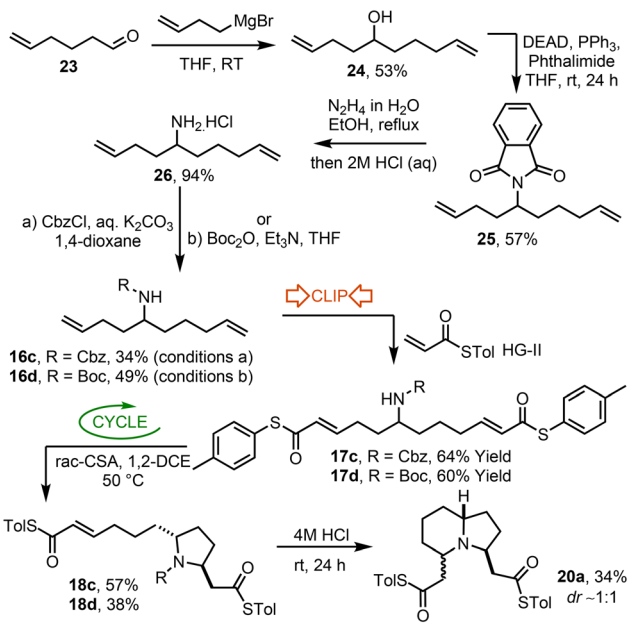


Scheme 6 'Clip-Cycle' approach to pyrrolizidines and indolizidines.

isomer has likely be formed. This assignment was corroborated by the formation of pyrrolizidine **22**, the diethyl ester analogue of **19a**. Three of the possible diastereoisomers of pyrrolizidine **22** have been reported previously by two groups, Stockman and coworkers[9c] and Spring and coworkers.[9e] Comparison of our NMR spectroscopic data with those published, confirmed the assignment of **19a** as the *meso*-isomer shown (Scheme 7).



Scheme 7 'Clip-Cycle' approach to pyrrolizidine **19a**.



Scheme 8 'Clip-Cycle' approach to indolizidine **20a**.

The 'Clip-Cycle' indolizidine synthesis started with the conversion of aldehyde **23** [14] into secondary alcohol **24** using a Grignard reagent (Scheme 8). Subsequent Mitsunobu reaction, hydrazinolysis and carbamate formation then delivered unsymmetrical amino dienes **16c** and **16d**. The 'Clip' step worked as expected, with HG-II catalyst promoting a double cross metathesis reaction to form dienes **17c** and **17d**, both as single *E*,*E*-geometrical isomers. The 'Cycle' step was then performed using *rac*-CSA, which furnished pyrrolidines **18c** and **18d** as the *trans* diastereoisomers shown; notably this diastereoselectivity matches that observed during the synthesis of 2,5-pyrrolidine **7a** described in the first half of this manuscript. Finally, the conversion of one of these 2,5-pyrrolidines (Boc-protected derivative **18d**) into indolizidine **20a** was completed by reaction with 4 M HCl at RT, which promoted concomitant Boc-cleavage and aza-Michael reaction to form indolizidine **20a** with a 1 : 1 mixture of separable diastereomers, in 34% unoptimised yield.

Conclusion

In conclusion the synthetic potential of the 'Clip-Cycle' approach for the synthesis of aza-heterocycles is expanded significantly by the innovations reported in this study. First, the asymmetric 'Clip-Cycle' synthesis of 2,5- and 3,5-pyrrolidines from chiral starting materials is reported for the first time, using an effective kinetic resolution method. Furthermore, a two-directional 'Clip-Cycle' approach for the synthesis of pyrrolizidines and indolizidines has also been disclosed, from appropriate amino diene precursors.

Future work on the 2,5- and 3,5-pyrrolidine series should focus on expanding the preliminary kinetic resolution results described, further optimising for improved ee, and unequivocally establishing the relative and absolute stereoselectivity for the 3,5-pyrrolidine system. Expanding the substrate scope of the asymmetric kinetic resolution method and demonstrating its efficacy in preparative reactions is also important. Here, automated methods (HTE) and data science tools, including machine learning approaches, may be particularly useful.[14,15]

For the pyrrolizidine synthesis, it is unfortunate that the second aza-Michael reaction delivers a *meso*-product **19a**, as this means that the enantioselectivity imparted in the preceding cyclisation step is lost. Future work can therefore focus on developing strategies to maintain chirality in the indolizidine product following cyclisation. This could be done by using an unsymmetrical diene precursor; for example, a diene analogous to **17a**/**b** with one of the thioesters replaced by a simple ethyl ester would likely react similarly to afford a chiral indolizidine product *via* the same route. In the indolizidine series, future work can focus on combining the indolizidine synthesis described with the 2,5-pyrrolidine kinetic resolution method, to enable asymmetric indolizidine synthesis. For both the pyrrolizidine and indolizidine series, future applications in target synthesis are of interest.[7,9] We encourage other researchers interested in continuing to study 'Clip-Cycle' reactivity based on the results described herein and elsewhere[3] to do so.§

Author contributions

Synthetic studies on 2,5- and 3,5-pyrrolidines were done by S. Y. and A. A. Synthetic studies on pyrrolizidines and indolizidines were done by L. C. D. and C. J. M. Both projects were conceived, designed and led by P. A. C. The paper was written by W. P. U. and I. J. S. F., with contributions from L. C. D. and S. Y.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data that support the findings of this study are available in the published article and its supplementary information (SI). Supplementary information is available. See DOI: https://doi.org/10.1039/d5ob01746g.

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References

1 (*a*) C.-V. T. Vo, G. Mikutis and J. W. Bode, *Angew. Chem., Int. Ed.*, 2013, **52**, 1705–1708; (*b*) W.-Y. Siau and J. W. Bode, *J. Am. Chem. Soc.*, 2014, **136**, 17726–17729; (*c*) J. A. Rossi-Ashton, A. K. Clarke, R. J. K. Taylor and W. P. Unsworth, *Org. Lett.*, 2020, **22**, 1175–1181; (*d*) I. Zalessky, J. M. Wootton, J. K. F. Tam, D. E. Spurling, W. C. Glover-Humphreys, J. R. Donald, W. E. Orukotan, L. C. Duff, B. J. Knapper, A. C. Whitwood, T. F. N. Tanner, A. H. Miah, J. M. Lynam and W. P. Unsworth, *J. Am. Chem. Soc.*, 2024, **146**, 5702–5711.

2 (*a*) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274; (*b*) N. M. Nasir, K. Ermanis and P. A. Clarke, *Org. Biomol. Chem.*, 2014, **12**, 3323–3335; (*c*) R. D. Taylor, M. MacCross and A. D. G. Lawson, *J. Med. Chem.*, 2014, **57**, 5845–5859.

3 (*a*) C. J. Maddocks, K. Ermanis and P. A. Clarke, *Org. Lett.*, 2020, **22**, 8116–8121; (*b*) C. J. Maddocks and P. A. Clarke, *Tetrahedron*, 2021, **78**, 131789; (*c*) K. Alomari, N. S. P. Chakravarthy, B. Duchadeau, K. Ermanis and P. A. Clarke, *Org. Biomol. Chem.*, 2022, **20**, 1181–1185; (*d*) S. Ravi, C. Maddocks, I. J. S. Fairlamb, W. P. Unsworth and P. A. Clarke, *Org. Biomol. Chem.*, 2025, **23**, 649–653.

4 Z. Sun, G. A. Winschel, P. M. Zimmerman and P. Nagorny, *Angew. Chem., Int. Ed.*, 2014, **53**, 11194–11198.

5 For selected asymmetric methods for the synthesis of pyrrolidines, see: (*a*) X. Fang and C.-J. Wang, *Org. Biomol. Chem.*, 2018, **16**, 2591–2601; (*b*) X. Ma, I. R. Hazelden, T. Langer, R. H. Munday and J. F. Bower, *J. Am. Chem. Soc.*, 2019, **141**, 3356–3360.

6 A. Farwick and G. Helmchen, *Adv. Synth. Catal.*, 2010, **352**, 1023–1032.

7 (*a*) J. Robertson and K. Stevens, *Nat. Prod. Rep.*, 2014, **31**, 1721–1788; (*b*) J. P. Michael, *Nat. Prod. Rep.*, 2001, **18**, 520–542; (*c*) J. Robertson and K. Stevens, *Nat. Prod. Rep.*, 2017, **34**, 62–89; (*d*) J. Zhang, S. L. Morris-Natschke, D. Ma, X.-F. Shang, C.-J.- Yang, Y.-Q. Liu and K.-H. Lee, *Med. Res. Rev.*, 2021, **41**, 928–960; (*e*) W. T. Bradner, *Cancer Treat. Rev.*, 2001, **27**, 35–50; (*f*) M. Tomasz, *Chem. Biol.*, 1995, **2**, 575–579; (*g*) K. Whitby, T. C. Pierson, B. Geiss, K. Lane, M. Engle, Y. Zhou, R. W. Doms and M. S. Diamond, *J. Virol.*, 2005, **79**, 8698–8706.

8 (*a*) N. K. Ratmanova, I. A. Andreev, A. V. Leontiev, D. Momotova, A. M. Novoselov, O. A. Ivanova and I. V. Trushkov, *Tetrahedron*, 2020, **76**, 131031; (*b*) C. Bhat and S. G. Tilve, *RSC Adv.*, 2014, **4**, 5405–5452.

9 For relevant 2-directional approaches to related bicyclic scaffolds, see: (*a*) S. R. Magnuson, *Tetrahedron*, 1995, **51**, 2167–2213; (*b*) A. F. Newton, S. J. Roe, J. C. Legeay, P. Aggarwal, C. Gignoux, N. J. Birch, R. Nixon, M.-L. Alcarazc and R. A. Stockman, *Org. Biomol. Chem.*, 2009, **7**, 2274–2277; (*c*) J. C. Legeay, W. Lewis and R. A. Stockman, *Chem. Commun.*, 2009, **45**, 2207–2209; (*d*) A. Barthelme, D. Richards, I. R. Mellorb and R. A. Stockman, *Chem. Commun.*, 2013, **49**, 10507–10509; (*e*) M. D. Galvilan, W. R. J. D. Galloway, K. M. G. O'Connell, J. T. Hodkingson and D. R. Spring, *Chem. Commun.*, 2010, **46**, 776–778; (*f*) M. Guerola, M. Sánchez-Roselló, C. Mulet, C. del Pozo and S. Fustero, *Org. Lett.*, 2015, **17**, 960–963.

10 For aza-Michael reactions leading to azacycles, see: (*a*) G. J. Noordzij and C. H. R. M. Wilsens, *Front. Chem.*, 2019, 729; (*b*) P. Sharma, R. Gupta and R. K. Bansal, *Beil. J. Org. Chem.*, 2021, **17**, 2585–2610; (*c*) K. Y. Palate, Z. Yang, A. C. Whitwood and W. P. Unsworth, *RSC Chem. Biol.*, 2022, **3**, 334–340; (*d*) A. Y. Rulev, *Eur. J. Org. Chem.*, 2023, e202300451; (*e*) Z. Yang, I. Zalessky, R. G. Epton, A. C. Whitwood, J. M. Lynam and W. P. Unsworth, *Angew. Chem., Int. Ed.*, 2023, **62**, e202217178.

11 S. Nicolai and J. Waser, *Org. Lett.*, 2011, **13**, 6324–6327.

12 The assigned *trans*-relative stereochemistry agrees with the diastereoselectivity observed in the 2,5-pyrrolidine syntheses described earlier in this manuscript and was confirmed retrospectively based on the assignment pyrrolizidine **22**. It is likely that a smaller amount of the *cis*-pyrrolidine was also formed during the cyclisation step but was removed during chromatographic purification.

13 D. R. Williams, D. L. Brown and J. W. Benbow, *J. Am. Chem. Soc.*, 1989, **111**, 1923–1925.

14 D. Yepes, F. Neese, B. List and G. Bistoni, *J. Am. Chem. Soc.*, 2020, **142**, 3613–3625.

15 A. F. Zahrt, J. J. Henle, B. T. Rose, Y. Wang, W. T. Darrow and S. E. Denmark, *Science*, 2019, **363**, 6424.

