Combining two-directional synthesis and tandem reactions: desymmetrisation by intramolecular cycloaddition/triazoline fragmentation†‡

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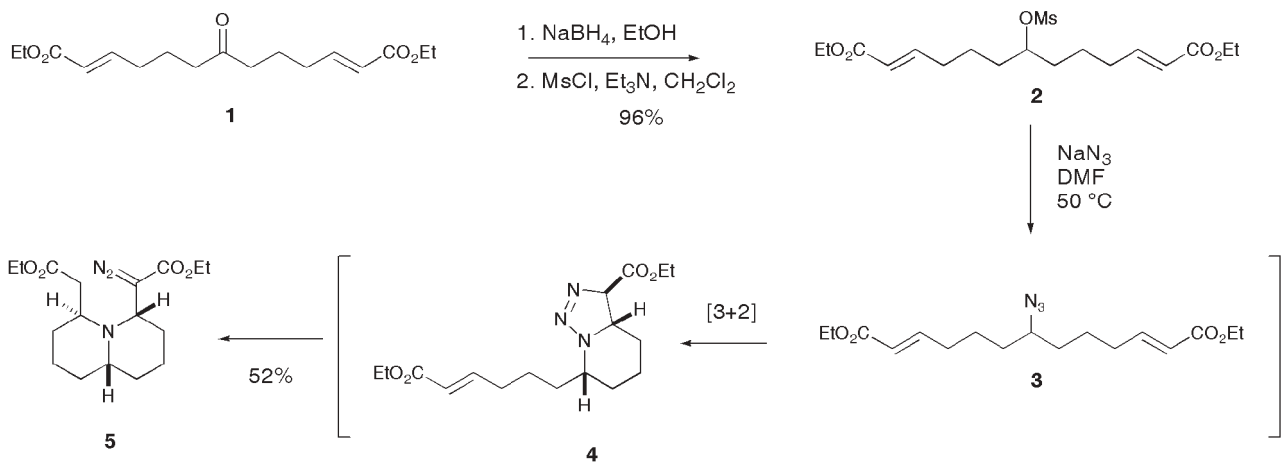
A tandem azide formation/intramolecular cycloaddition/ triazoline fragmentation/Michael addition, which results in a non-symmetrical quinolizidine from an acyclic symmetrical precursor, is presented.

The strategies of two-directional synthesis[1] and tandem reactions[2] both offer the potential to substantially reduce the number of operations required to synthesise complex molecules. As part of an on-going programme studying the potential of combining two-directional synthesis and tandem reactions,[3] we herein disclose a remarkable self-desymmetrising cascade reaction.

Two-directional synthesis intrinsically generates symmetrical products. By using two-directional synthesis as a means of forming simple symmetrical functionalised chains, then using a tandem reaction to "fold" these chains, creating rings and stereocentres, we have the potential to form complex polycyclic compounds in just a few steps. Our recent syntheses of perhydrohistrionicotoxin[4] and hippodamine[5] exemplify this approach to the synthesis of complex alkaloids.

During an investigation related to our work on hippodamine, we wished to synthesise symmetrical azide **3**, such that we could investigate a Staudinger-type azide reduction/tandem Michael cyclisation. In order to access azide **3**, we started with the symmetrical ketone **1** (Scheme 1), which is available in 4 steps from 1,3-dithiane, or in 5 steps from ethyl formate.[6] Reduction of the ketone with sodium borohydride followed by conversion of the resulting pseudo-C2 symmetric alcohol to mesylate **2** proceeded uneventfully in 96% yield over two steps. Reaction of mesylate **2** with sodium azide in DMF at 50 °C was expected to result in the formation of azide **3**. TLC showed one clear product, with a further amount of baseline material, which we considered was possibly due to azide overaddition/decomposition. However, upon inspection of the crude ^{1}H NMR, it was quickly obvious that something far more complicated than azide **3** had been formed in the reaction pot. Indeed, after purification by column chromatography, it was found that the sole isolable product of the reaction was quinolizidine derivative **5** (52%). Key observations which led us to assign the structure of bicyclic diazo compound **5** were the obvious asymmetry present in the ^{1}H and ^{13}C spectra (including two ester carbonyl peaks in the ^{13}C NMR spectrum), and the characteristic diazo stretch in the IR at 2150 cm^{-1}. High resolution mass-spectral data confirmed the molecular mass of 338.2075 (M + H). However, in order to further confirm the stereochemistry of our product, we decided it would be best to make a crystalline derivative suitable for X-ray structure



Scheme 1 Two-directional synthesis and tandem reaction of azide **3**.

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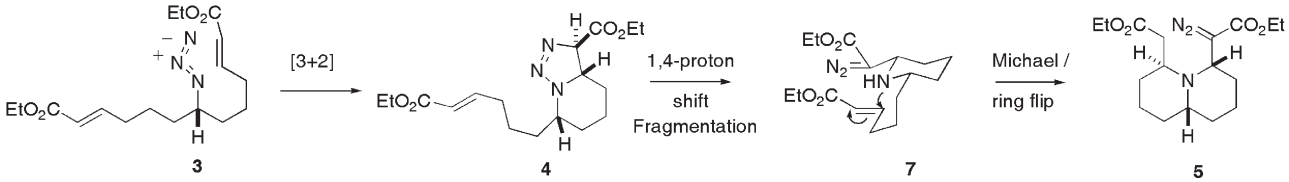
† Part 7 in our series concerning two-directional synthesis and tandem reactions.
‡ This paper is dedicated to the memory of Mark Jones.



Scheme 2 Proposed mechanism for the formation of **5**.

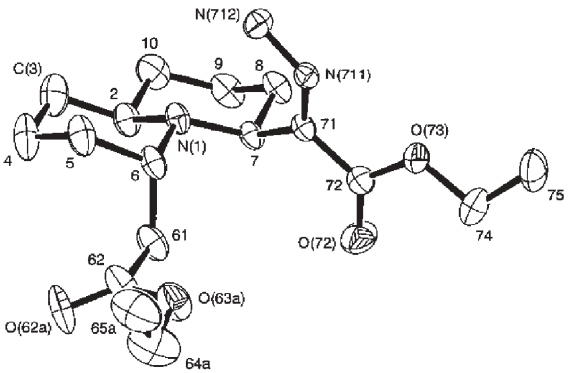


Fig. 1 X-ray structure of hydrazone **6**, formed by hydrogenation of **5**.

determination. Thus upon exposure to standard hydrogenation conditions (10% Pd/C, 1 atm hydrogen), diazo compound **5** was quantitatively converted to the crystalline hydrazone **6**, whose X-ray structure[7] is shown in Fig. 1.

Study of the X-ray structure of **6**, combined with the isolation of a small amount of triazoline **4** from the reaction mixture when stopped early, has allowed us to postulate a mechanism for this tandem reaction sequence, which is presented in Scheme 2. Thus, [3 + 2] cycloaddition of azide **3** with one of the enoate functionalities results in the thermodynamically most favoured cycloadduct **4**. 1,4-Prototopic shift within the triazoline of **4**, followed by fragmentation to yield diazo 2,6-disubstituted piperidine **7** and subsequent Michael-type ring closure is the most satisfactory mechanism. Although the triazoline fragmentation[8] to a piperidine is precedented under basic conditions,[9] lending weight to this mechanistic proposal, we were unable to detect quantities of the intermediate piperidine **7**. However, we were able to detect these types of piperidine intermediate in our hippodamine synthesis,[5] which used a similar Michael-type ring closure to a 4,6-disubstituted quinolizidine. It could also be envisaged that the formation of **5** from **4** could be achieved through a concerted ene-type mechanism, with the tertiary nitrogen and the proton α to the ester on the triazoline being delivered to either end of the electron deficient alkene, with concomitant triazoline fragmentation.

In conclusion, the power of combining two-directional synthesis and tandem reactions has provided a short and efficient entry into a non-symmetrical 4,6-disubstituted quinolizidine skeleton. Further studies into the use of the tandem azide formation/[3 + 2]/fragmentation reaction are on-going and our results will be reported in due course.

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Notes and references

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7 Crystal data for **6**: $C_{17}H_{29}N_3O_4$, M = 339.4. Triclinic, space group P-1, a = 8.048(2), b = 15.296(3), c = 7.872(3) Å, α = 104.54(2), β = 93.23(3), γ = 80.36(2)°, V = 924.7(4) Å^3. Z = 2, D_c = 1.219 g cm^{-3}, F(000) = 368, T = 293(1) K, μ(Mo-Kα) = 0.9 cm^{-1}, λ(Mo-Kα) = 0.71069 Å. Crystals are clear, colourless plates. Intensity data were measured on a Rigaku/MSC AFC7R diffractometer (Mo-Kα radiation, graphite monochromator); 3533 reflections (θ_{max} = 25°), 3277 unique (R_{int} = 0.034), 2006 'observed' with $I > 2\sigma_I$. Structure determined by direct methods (SHELXS-97 program[10a]); refinement by full-matrix least-squares methods, on F^2's, in SHELXL-97.[10b] One ester group is disordered equally in two alternative orientations. Two hydrogen atoms were located on the β-nitrogen atom of the NNH_2 group and refined freely; all other hydrogen atoms were included in idealised positions with U_{iso} values 'riding'. At convergence, wR_2 = 0.166 and R_1 = 0.108 for all 3277 reflections weighted $w = [\sigma^2(F_o^2) + (0.0790P)^2]^{-1}$ with $P = (F_o^2 + 2F_c^2)/3$; for 'observed' data only, R_1 = 0.060. CCDC 277408. See http://dx.doi.org/10.1039/b508969g for crystallographic data in CIF or other electronic format.
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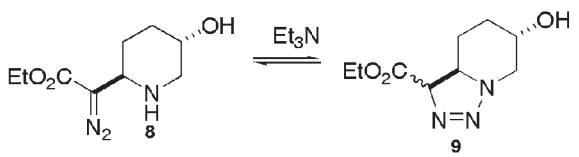

Base induced equilibration of triazolidine and diazoester was found to be facile by Herdeis.

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