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A new approach to functionalised spiropiperidines through tandem RCM and nitrogen-directed reactions†

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The synthesis of a functionalised spiropiperidine *via* a tandem ring closing metathesis strategy is described, furthermore, the regio- and stereoselective functionalisation of this compound has been achieved through a novel nitrogen-directed epoxidation reaction.

Olefin metathesis has emerged as one of the most popular carbon–carbon bond forming methods in modern synthetic organic chemistry.[1] Our own research efforts in this area have focused on a series of polyolefin containing systems that undergo selective tandem ring closing metathesis (RCM) reactions and provide spirocyclic[2] and angularly fused tricyclic[3] compounds in good to excellent yield. More recently, we have been examining the application of this methodology towards the synthesis of histrionicotoxin analogues.[4] As depicted in Fig. 1, our synthetic strategy centred around a tandem RCM reaction of azatetraene **1** to provide the functionalised spiropiperidine **2**. However, in order to further elaborate **2** to the desired histrionicotoxin analogues **3** we required a regio- and stereoselective alkene functionalisation method. We report herein that this goal has been achieved through a novel nitrogen-directed epoxidation reaction.

We embarked on the synthesis of the nitrogen containing tetraene **1** from commercially available Boc-protected aminomalonate **4** as outlined in Scheme 1. Alkylation of **4** with 5-bromopent-1-ene proceeded smoothly and the diester was subsequently reduced to the corresponding diol **5** on treatment with LAH. We next attempted to convert the diol moiety in **5** to the requisite 1,4-pentadiene using an oxidation/Wittig olefination protocol. Unfortunately, this strategy did not provide the expected diene due to decomposition of the aldehyde intermediate. We therefore opted to protect one of the alcohol units in **5** and carry out the oxidation/methylenation sequence in a stepwise fashion. In an effort to minimise the introduction of external protecting groups, we decided to exploit the available Boc-group to temporarily mask one of the hydroxyls. Accordingly, treatment of diol **5** with NaH resulted in an efficient cyclisation to oxazolidinone **6**. We were pleased to find that the oxidation/Wittig process now took place efficiently to give **7** in 85% overall yield. We next took advantage of the ready alkylation of oxazolidinones to introduce the homoallylic amine moiety at this stage. Therefore, alkylation of **7** with 4-bromobut-1-ene in the presence of NaH proceeded in high yield, notably however, only after portionwise addition of excess alkylating agent and base. Finally, hydrolysis of the carbamate **8** followed by formation of the trifluoroacetate amine salt allowed the remaining alcohol to be cleanly oxidised to the aldehyde which was converted to desired tetraene **1** after a Wittig reaction. We subsequently found that the alkylation/hydrolysis sequence (**7** → **9**) can be carried out in a single step with NaOH and K_2CO_3 in the presence of a phase transfer catalyst. Importantly, as well as reducing the number of steps, this protocol requires fewer equivalents of alkylating agent.

With the tetraene **1** in hand, we next investigated the tandem RCM reaction for the formation of the spiropiperidine nucleus. The Ru-catalyst systems are incompatible with unprotected amine functional groups and therefore *N*-protection is generally carried out by conversion to an amide or ammonium salt.[5] In the event, we chose to examine trifluoroacetamide **10** and ammonium triflate **11** which were prepared in high yield as outlined in Scheme 2. We were pleased to find that the key tandem RCM processes took place efficiently with both tetraene substrates, however, conversion of **10** required considerably less catalyst and a shorter reaction time in comparison to **11** and therefore this route was utilised when preparing larger quantities of spirocycle **2**.

The stage was now set to examine the key epoxidation reaction which would differentiate the alkene units in **2** and set the required C–O stereochemistry for elaboration to histrionicotoxin analogues. We envisaged that the amine group in the piperidine ring could be used to deliver an appropriate reagent to functionalise the cyclohexene ring in a regio- and stereoselective fashion. Indeed, a number of examples have

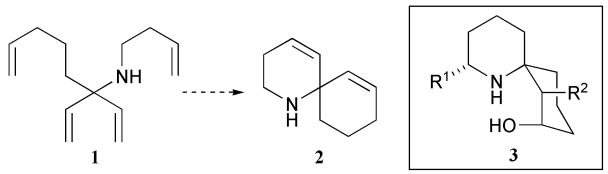
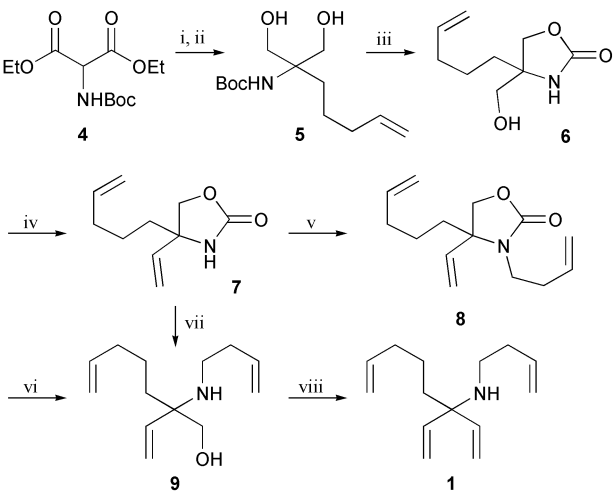


Fig. 1



Scheme 1 *Reagents and conditions*: i, CH_2=$CH(CH_2)_3Br$, NaOEt, EtOH, 100%; ii, LAH, THF 78%; iii, NaH, THF, 71%; iv, (a) Swern; (b) Ph_3P=CH_2, 85% over two steps; v, 6 Equiv. CH_2=$CH(CH_2)_2Br$, NaH, EtOH, 79%; vi, NaOH, MeOH, 88%; vii, 3 Equiv. CH_2=$CH(CH_2)_2Br$, NaOH, K_2CO_3, 10 mol% *n*-Bu_4NHSO_4, toluene, 73%; viii, (a) TFA; (b) Swern; (c) Ph_3P=CH_2, 84% over three steps.

† Electronic supplementary information available: experimental procedures and data for all new compounds. See http://www.rsc.org/suppdata/cc/b2/b203851j/

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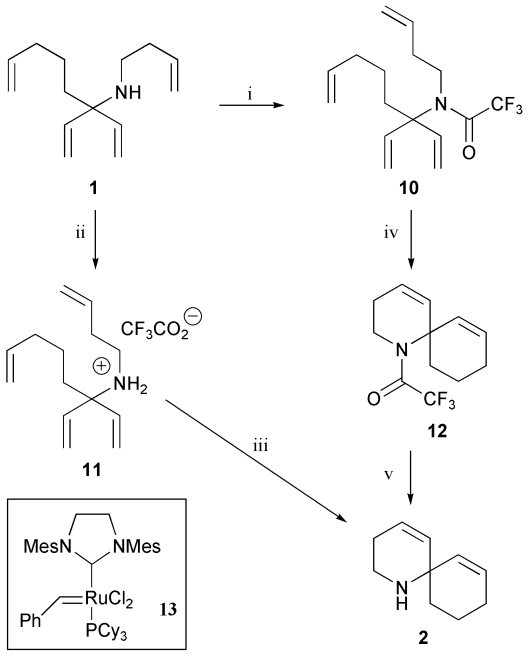
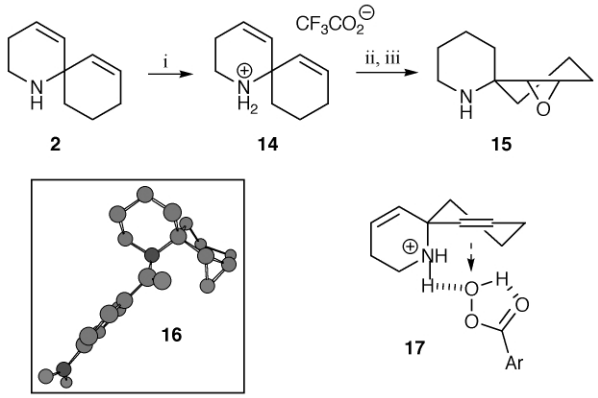
been reported whereby sulfonamide,[6] amide[7] and carbamate[8] N–H groups direct peracid addition in a manner similar to that for hydroxyl-directed reactions.[9] We were clearly unable to use an analogous strategy for **2** given that we had a secondary amine, however, the apparent importance of an acidic N–H in the reported literature led us to attempt the epoxidation on the ammonium salt of the spiropiperidine.[10] Accordingly, treatment of **2** with TFA followed by exposure of ammonium salt **14** to 1.2 equiv. of peracid provided a clean epoxide product in good yield. 2D COSY ^{1}H NMR spectroscopy confirmed that epoxidation had taken place at the desired cyclohexene moiety, however, identification of the product stereochemistry could not be achieved at this stage. Finally, Rh-catalysed hydrogenation of the remaining alkene proceeded without reduction of the epoxide to provide **15** in high yield. Elucidation of the epoxide stereochemistry was ultimately attained by preparation of the corresponding *p*-nitrobenzamide **16** (represented as a Chem-draw 3D™ picture, H-atoms omitted for clarity) and X-ray crystallographic analysis‡ which confirmed that the desired epoxide diastereomer had indeed been formed.[11] Whilst the exact mechanism of this remarkably selective reaction must await further experimental data, it is tempting to draw an analogy with the well known hydroxyl-directed reaction such that an intramolecular hydrogen bonding process leads to a highly organised transition structure **17** as illustrated in Scheme 3.

In conclusion, we report a novel and efficient method for the synthesis of spirocyclic piperidines through a tandem RCM reaction and that these intermediates undergo a highly regio- and stereoselective epoxidation reaction. The investigation of this unusual ammonium-directed reaction and the application of this strategy to the synthesis of histrionicotoxin analogues is underway and will be reported in due course.



Scheme 2 *Reagents and conditions*: i, TFAA, Et_3N, 82%; ii, TFA; iii, 5 mol% **13**, toluene, 80 °C, 16 h, 71% (two steps, one-pot); iv, 1 mol% **13**, toluene, 80 °C, 1 h, 100%; v, K_2CO_3, MeOH, 95%.



Scheme 3 *Reagents and conditions*: i, TFA; ii, mcpba, DCM, 64% (two steps, one-pot); iii, H_2, 5 mol% Rh.alumina, 82%.

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Notes and references

‡ *Crystal data* for $C_{17}H_{20}N_2O_4$, M = 316.35, crystallises from hexane/ethanol as colourless blocks, a = 11.882(3), b = 9.5188(19), c = 13.700(3) Å, β = 97.160(4)°, U = 1537.4(6) Å^3, Temp. = 150(2) K, space group $P2_1/c$ (C'_h, No. 14), Z = 4, Mo-Kα radiation (= 0.71073 Å), μ(MoKα) = 0.098 mm^{-1}, crystal dimensions 0.32 × 0.29 × 0.18 mm^3. Total number of observed [$|F|/\sigma(|F|) > 4.0$] and independent reflections 6647, 1562 [R(int) = 0.0765]. Full matrix least squares methods on F^2 give final R = 0.0737 (wR_2 = 0.2270, for all 6647 data, 208 parameters, mean and maximum δ/σ 0.000, 0.000). CCDC 184035. See http://www.rsc.org/suppdata/cc/b2/b203851j/ for crystallographic data in .cif or other electronic format.

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11 Experimental procedures and data for all new compounds are provided in the supplementary material.