Combining two-directional synthesis and tandem reactions, part II:
second generation syntheses of (±)-hippodamine and (±)-epi-hippodamine
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Abstract

Background: Hippodamine is a volatile defence alkaloid isolated from ladybird beetles which holds potential as an agrochemical agent and was the subject of a synthesis by our group in 2005.

Results: Two enhancements to our previous syntheses of (±)-hippodamine and (±)-epi-hippodamine are presented which are able to shorten the syntheses by up to two steps.

Conclusion: Key advances include a two-directional homologation by cross metathesis and a new tandem reductive amination/double intramolecular Michael addition which generates 6 new bonds, 2 stereogenic centres and two rings, giving a single diastereomer in 74% yield.

Background

Ladybird beetles (Coleoptera: Coccinellidae) are important predators contributing to the natural control of pest aphid populations and are therefore of considerable commercial interest. However, ladybirds themselves are attacked by a range of natural enemies. General predation on ladybirds by vertebrates such as birds is largely prevented by highly toxic defence alkaloids contained in a reflex bleed released when the ladybird is attacked. To date, eight alkaloids of this type have been isolated from coccinellid beetles,[1] all of them being formally derivatives of perhydro-9b-azaphenalene (Figure 1). Another group of natural enemies, parasitic insects, can cause substantial reductions in populations of ladybird species. Recent research [2] has shown that the parasites locate the ladybirds through perception of certain defence alkaloids that they emit. If ladybirds are to be used effectively in insect pest control then their parasites must be controlled as well. The significant attraction of parasitic insects to the ladybird alkaloids suggests that there is potential for development of control strategies for this particular natural enemy. To further test this theory significant amounts of the defensive alkaloids will be needed. Coccinelid beetles seem to be the sole source of the defence alkaloids. Consequently much attention has been paid to developing syntheses of these compounds.

Hippodamine (1) is a naturally occurring alkaloid isolated from a ladybird beetle Hippodamia convergens by Tursch and co-workers in 1972. [3] The structure of hippodamine (1) was established two years later by the same group[4] on the basis of a single-crystal X-ray diffrac-
Results and Discussion

When we decided to take a second look at the syntheses of hippodamine and epi-hippodamine, we decided to focus on the synthesis of the key common intermediate 7 and try to realise an improvement over our earlier work. This paper discloses two such improvements. The first of these is the conversion of dialkene 4 into the diacrylate derivative 6. Originally this was achieved by oxidative cleavage of the two alkene moieties of 4 to form the rather sensitive dialdehyde 5. Whilst we were able to purify compound 5, this resulted in a significant loss of material through deg-
tandem reductive amination/double intramolecular Michael addition. Our results are shown in scheme 3 below.

Thus ketone 8 was formed by reaction of the commercially available hex-5-enyl nitrile with 4-pentenylnitriylmagnesium bromide in 70% yield. [13] Double cross-metathesis was found to proceed smoothly in 89% yield using the Hoveyda-Grubbs second generation catalyst in dichloromethane at room temperature for 3 days, giving keto diester 9. [14] We tried a range of reductive amination conditions for the formation of quinolizidine 7. The ammonia equivalents tried were ammonium acetate, ammonium chloride and ammonium formate, along with sodium borohydride, sodium cyanoborohydride and Hantzsch ester in either ethanol or ethanol/acetic acid solvent systems. A summary of conditions tried is shown in Table 1 below. The ketodiester 9 was dissolved in ethanol and the ammonia source and desiccant were added and allowed to stir overnight to form the iminium species, before the hydride source was added and the reaction allowed to proceed for a further 24 h. The hydride source was quenched with acetone before excess glacial acetic acid was added and the reaction mixture was heated for 48 hours giving a 74% yield as monitored by TLC to quinolizidine 7, giving a 74% yield after purification by column chromatography over Brockmann Grade (III) neutral alumina. See Additional File 1 for full experimental data. The tandem reductive amination/double intramolecular Michael addition generates 6 new bonds, 2 stereogenic centres and two rings, giving a single diastereomer.

In conclusion, we have increased the yield of our original hippodamine synthesis and reduced the number of steps required using a two-directional cross-metathesis of dialkene 4 with ethyl acrylate. We have also reported a new tandem reductive amination/double intramolecular Michael addition, which forms directly the quinolizidine core of hippodamine in a single step from a symmetrical keto-diester linear precursor. This new tandem reaction also reduces the number of steps for the synthesis of hippodamine to seven, and also removes any protecting group chemistry from the synthetic sequence and reduces waste whilst equalling the yield of the previous approach.

Additional material

Additional file 1

Experimental. Experimental procedures for compounds 4, 6, 7, 9.
Click here for file
[http://www.biomedcentral.com/content/supplementary/1860-5397-4-4-S1.doc]

Acknowledgements

The authors wish to thank Leverhulme Trust (MR), AstraZeneca (AFN, CASE award) and EPSRC (RAS, Advanced Research Fellowship) for funding and EPSRC Mass spectrometry service, Swansea for carrying out some of the high resolution mass-spectra.
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