

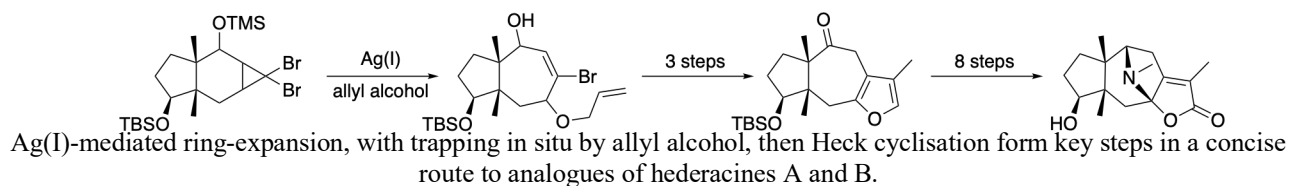
Graphical Abstract

Enantioselective synthesis of C(9) hydroxy analogues of hederacines A and B

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ABSTRACT

A strategy for assembling the 5-7-5 fused ring system of the hederacine alkaloids is reported, based on a sequence of electrocyclic ring expansion, with trapping *in situ*, then Heck cyclisation. Subsequent furan oxidative *N*-cyclisation generates the azabicyclo[3.2.1]octane core, resulting in a synthesis of C(9) hydroxy analogues of hederacines A and B in 19 and 20 steps, respectively, from 2-methylcyclopentane-1,3-dione.

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1. Introduction

In 2003 Sarker and co-workers described the structures of two extended tropane alkaloids, hederacines A (**1**) and B (**2**) from the plant *Glechoma hederaceae* (Figure 1).¹ The same group later reported moderate cytotoxicity against colon cancer cell line CaCo-2, with hederacine A being the more active.²

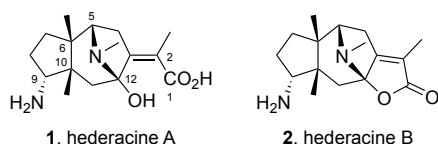
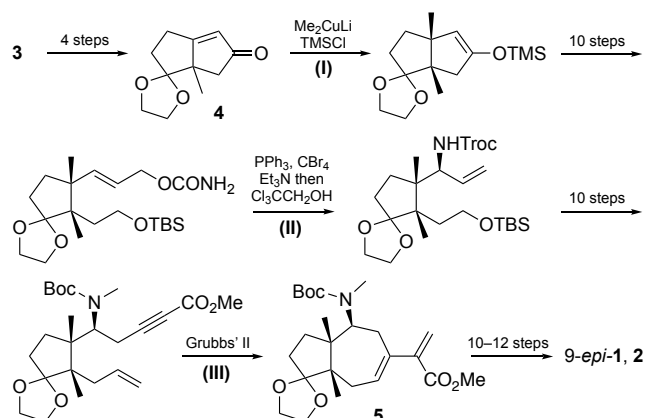


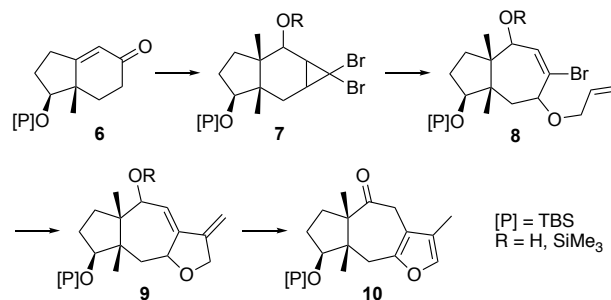
Figure 1 Alkaloids from *Glechoma hederaceae*.

All the published synthetic chemistry concerning these alkaloids is contained in Aoyagi's two communications on the synthesis of (±)-9-*epi*-hederacines A and B.³ Aoyagi's route to the complete carbon skeleton is based on three strategic stages (I–III, Scheme 1), requiring 28 steps from 2-methylcyclopentane-1,3-dione (**3**) to advanced intermediate **5**: (I) *exo*-face-selective conjugate methylation of bicyclic enone **4** established the adjacent quaternary stereogenic centres at C(6) and C(10); (II) stereoselective allylcyanoate [3,3]-shift established the C(5) amine stereochemistry; and (III) enyne metathesis closed the cycloheptene ring and installed the butenolide carbons. A further 10–12 steps from intermediate **5** completed the routes to (±)-9-*epi*-hederacines A and B. Access to the natural products, hederacines A and B themselves, was not achieved because an α -configured amino group derailed the acid-mediated *N,O*-acetalisation at C(12), preventing the C(5)-NHMe substituent from participating.

In the original isolation papers, the absolute stereochemistry of these alkaloids was not assigned, specific rotation data were not



Scheme 1 Aoyagi's route to (±)-9-*epi*-hederacines A and B.



Scheme 2 Key steps in an enantioselective route to hederacine precursors (this work).

reported, and this aspect was not addressed in Aoyagi's racemic synthesis; therefore, we set out to apply the furan oxidative spirocyclisation strategy, used in our synthesis of

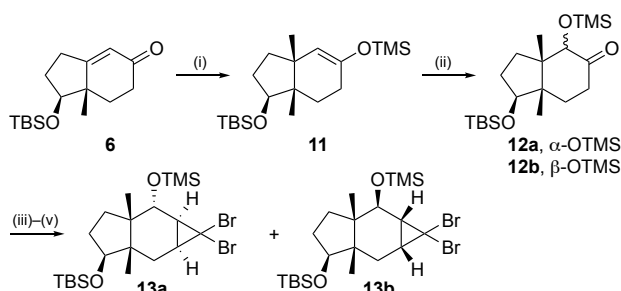
pandamarilactone-1,⁴ in an enantioselective synthesis. As in Aoyagi's route, our route would set the relative stereochemistry at the C(6)/C(10) bridgehead by conjugate addition to a bicyclic enone (**6**, Scheme 2). Apart from that similarity, our projected route to the tricyclic core follows an entirely different strategy. Here, the furanocycloheptane ring was proposed to be accessed by an electrocyclic ring expansion/trapping sequence, followed by Heck cyclisation to close what would become the butenolide ring at C(2) and C(3). Specifically, Ag(I)-mediated ionisation⁵ of dibromocyclopropane **7** in the presence of allyl alcohol was expected to lead to vinyl bromide derivative **8**, from which intramolecular Heck reaction (\rightarrow **9**) and alkene isomerisation would afford the tricyclic furanocycloheptane (**10**). The components of this proposal are precedented; dibromocyclopropane ring-opening and trapping with functionalised alcohols is reported⁶ and there are plenty of examples of transition metal catalysed cross-couplings and similar processes of the ring-expanded vinyl bromide products.⁷ However, the union of these into a single methodology is not directly reported; Banwell's synthesis of a galanthamine isomer offers a related example.⁸

This paper reports an evaluation of this proposal and studies on the elaboration of intermediates with general structure **10** towards enantiomerically enriched hederacines A and B.

2. Results and discussion

2.1. Ring expansion precursors

Addition of lithium dimethyl cuprate to enone (+)-**6**,⁹ and silylation in situ, afforded silyl enol ether **11** (Scheme 3). Various conditions were explored for oxidising this to the corresponding α -hydroxyketone, with dihydroxylation under Upjohn conditions proving to be the cleanest.¹⁰ The separable 5α - (**12a**) and 5β - (**12b**) silyloxy epimers were isolated in ~60:40 ratio, respectively. These ketones were converted separately into the corresponding epimeric cyclohexene derivatives via the enol triflate,¹¹ from which cyclopropanation afforded diastereomers **13a** and **13b**. NOE experiments confirmed the carbenoid to have reacted with *anti*-diastereoselectivity with respect to the silyloxy substituent in each case under the phase transfer catalysis conditions¹² employed.



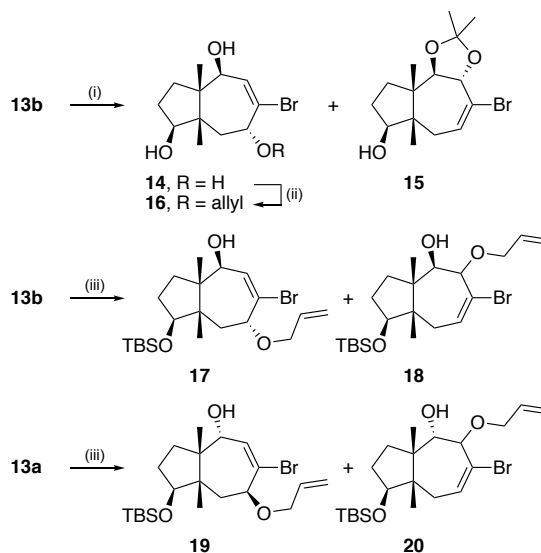
Scheme 3 Reagents and conditions: (i) Me_2CuLi , Et_2O then TMSCl , Et_3N , $-15^\circ\text{C} \rightarrow \text{RT}$ (92%); (ii) OsO_4 , NMO , aq. acetone then TMSCl , Et_3N , DMAP , CH_2Cl_2 , RT (**12a**, 44%; **12b**, 28%); (iii) KHMDS , PhNTf_2 , THF , -78°C (92%, 94%); (iv) Bu_3SnH , LiCl , $\text{Pd}(\text{PPh}_3)_4$, THF , 55°C (70%, 76%); (v) CHBr_3 , NaOH , BnEt_3NCl , aq. benzene, 70°C (**13a**, 50%; **13b**, 58%).

2.2. Ring expansion/trapping reaction

In a preliminary study, heating the diastereomer **13b** with AgClO_4 in aq. acetone^{5,13} formed two ring-expanded products in which, in both cases, the TMS and TBS groups had been cleaved (Scheme 4). The stereochemistry in triol **14** was supported by NOE experiments; that in acetonide **15** was assigned on the basis of a 9.5 Hz vicinal coupling constant for the acetonide methine protons.¹⁴ Some selectivity was observed in the allylation of triol **14** to provide allyloxy diol **16** in low yield. In a modification of

the conditions reported by Wulff for ring-expansion and trapping with simple alcohols (ROH : $\text{R} = \text{Me}$, Et , $i\text{-Pr}$, $t\text{-Bu}$),¹⁵ diastereomer **13b** was converted directly into a mixture of the allyloxy-incorporated products **17** and **18**. Under these non-aqueous conditions the TMS group was cleaved but the TBS group was retained, allowing the two neopentyl hydroxyls to be distinguished subsequently. Again, the stereochemistry in the desired product (**17**) was supported by NOE studies; that in the 1,2-adduct was not assigned (but see below). An analogous outcome (\rightarrow **19** and **20**) resulted when diastereomer **13a** was subjected to the same conditions.

In the three cases studied, the ring-expansion/trapping reactions are stereospecific, with the newly-introduced oxy-substituent attaching to the seven-membered ring from the cyclopropane-bearing face in the substrate; i.e., the α -face from substrate **13b** and the β -face from substrate **13a**. This outcome is expected when the abstraction of bromide (by Ag^+ ion) is coupled to nucleophilic addition to the forming allylic cation. Torquoselective *disrotatory* ionisation engages the cyclopropane σ -bonding electrons with the $(\text{C}-\text{Br})\sigma^*$ orbital; addition of water or allyl alcohol (shown, **Figure 2**) into the developing p-orbital before the system has flattened to a fully-formed π -system must then occur with inversion at the site of addition, leading to products **17** and **19**, respectively.¹⁶ The proposed *trans*-stereochemistry in acetonide **15** is consistent with this $\text{S}_{\text{N}}2'$ mechanism, and a 1,2-*trans*-stereochemistry is predicted in the isomers **18** and **20**.



Scheme 4 Reagents and conditions: (i) AgClO_4 , aq. acetone, reflux (**14**, 53%; **15**, 16%); (ii) NaH , allyl bromide, THF , RT (31%); (iii) AgBF_4 , CaCO_3 , allyl alcohol, 90°C (**17**, 32%; **18**, 27%; **19**, 30%; **20**, 20%).

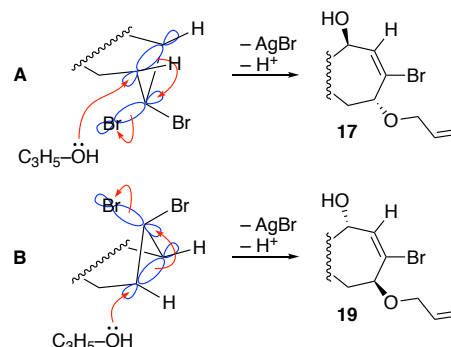
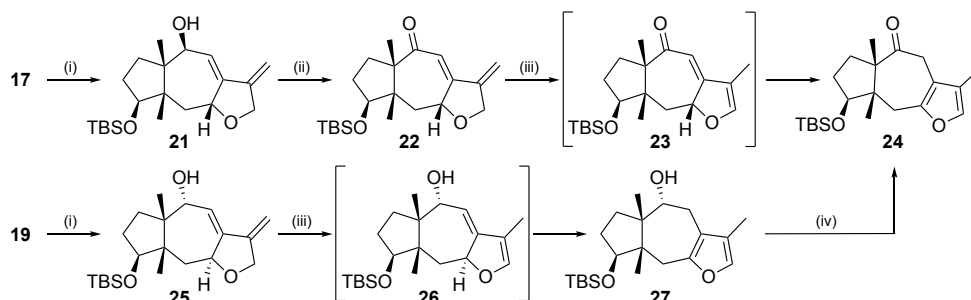


Figure 2 Stereocontrol in the ring expansion/trapping reactions of substrates **13b** \rightarrow **17** (A) and **13a** \rightarrow **19** (B).



Scheme 5 Reagents and conditions: (i) $\text{Pd}(\text{PPh}_3)_4$ (10 mol%), Ag_2CO_3 , K_2CO_3 , toluene, 85–110 °C, 1.5–2 h (**21**, 82%; **25**, 72%); (ii) DMP, NaHCO_3 , CH_2Cl_2 , 0 °C, 2 h (83%); (iii) $\text{Ru}(\text{PPh}_3)_2\text{Cl}_2$ (20 mol%), *i*-Pr₂NEt, toluene, 85 °C, 15 h then *p*-TsOH·H₂O, benzene, RT, 1 h (**24**, 62%; **27**, 45% + **S3**, 27%); (iv) $\text{Ru}(\text{PPh}_3)_2\text{Cl}_2$ (50 mol%), NMO, acetone, RT, 24 h (36%).

2.3. Heck cyclisation and aromatisation to the furan

Small-scale trials showed that variations of Overman's conditions¹⁷ for Heck cyclisation were effective. Reactions conducted in DMF, acetonitrile, or toluene all proceeded in similar yield, and toluene was selected for ease of product separation in reactions on 1–2 mmol scale. Both diastereomers cyclised efficiently (Scheme 5), with the reactions of the α -allyloxy- β -hydroxy isomer **17** being slightly more efficient [mean isolated yield 80% (*n* = 4) vs. 71% (*n* = 6) for the reactions of **19**]. Elaboration of the β -hydroxy Heck cyclisation isomer **21** into ketone **24** was achieved by alcohol oxidation then alkene isomerisation. Efficient DMP oxidation led to dienone **22** [ave. 77% (*n* = 5)]. In a small-scale test reaction, this dienone was converted directly into ketofuran **24** under basic conditions (*t*-BuOK, DMSO, 80 °C; 53%). A more reliable two-step process was employed for larger scale reactions that comprised Ru(II)-mediated isomerisation of the exocyclic double bond,¹⁸ leading to doubly vinylogous ester **23**, then mild acid-catalysed aromatisation to complete the process; overall yields for the conversion **21** → **24** averaged 55%. An unexpected tendency of dienone **22** to undergo Diels–Alder dimerisation was responsible for lowering the yields in this route.

For the α -hydroxy Heck cyclisation isomer **25**, low yields (~35%) in the initial oxidation step meant that alkene isomerisation was effected first. Isomerisation to dienol **26** was achieved with Ru(II) catalysis, as with dienone **22**, in reasonable yield, with subsequent completion of the isomerisation under acidic conditions suffering competing dehydration, leading to alkenyl furan **S3** (see Supporting Information). Overall yields for furan (**27**) formation from Heck product **25** were slightly lower than those for the sequence from **21** (to **24**). Even following alkene isomerisation, the oxidation of this alcohol epimer remained problematic, with preparative reactions using DMP (0.2 mmole scale) or Sharpless's Ru(II)/NMO method¹⁹ (0.08 mmol scale)

affording yields of 25% and 36%, respectively, along with decomposition products.

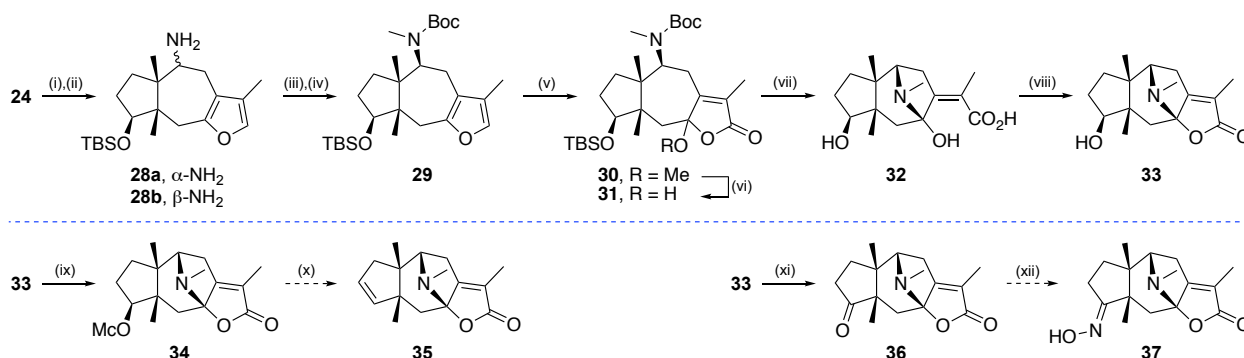
2.4. C(5)-Functionalisation and N,O-acetalisation

Having assembled the complete carbon skeleton of the hederacines in nine steps from enone (+)-**6**, attention turned to effecting overall reductive amination of the C(5) carbonyl group, formation of the C(5)–C(12) aza-bridge, and conversion of the C(9) silyloxy substituent into the free amino group found in the natural products.

Model studies established that introducing a nitrogen substituent at C(5) stereospecifically by S_N2 chemistry was not viable, and direct reductive amination at this hindered centre also failed (as noted by Aoyagi in the context of the C(9) centre). Oxime formation and reduction afforded a 50:50 ratio of amine diastereomers **28a** and **28b** (Scheme 6). After Boc-protection, the carbamate diastereomers were methylated and the desired β -isomer **29** was separated to complete the C(5) functional group chemistry.

Based on our previous work,⁴ intermediate **29** was treated with singlet oxygen in methanol to provide methoxybutenolide **30** in excellent yield. Direct acid-mediated condensation of the amine into C(12) in this intermediate was partially successful (→ **32**, 50%); however, higher yields were obtained from the *hydroxy*-butenolide **31**, with subsequent acidification leading efficiently to the 9-hydroxy hederacine A analogue **32**. Lactonisation to the 9-hydroxy hederacine B analogue **33** was effected in high yield, although a small amount (~10 mol%) of contaminating diethyl carbonate was not removed by chromatography.

With the intention of completing the functional group chemistry at C(9), and thus the total synthesis, this alcohol (**33**) was activated as the chloromesylate (**34**) and treated with LiN₃ in warm DMF. We had found these conditions to be optimal for the conversion of model compound **38** (Figure 3) into azide **39**.²⁰ In this case, however, no azide-containing products were found;



Scheme 6 Reagents and conditions: (i) $\text{NH}_2\text{OH}\cdot\text{HCl}$, pyridine, EtOH, reflux, 2 h (88%); (ii) H_2 , Raney Ni, EtOH, RT, 48 h (97%); (iii) Boc₂O, Et₃N, CH_2Cl_2 , RT, 4 h (66%); (iv) NaH, MeI, DMF, RT, 16 h (50% + 41% C(5) epimer); (v) O_2 , rose bengal, MeOH, hv, 0 °C, 15 min then Ac₂O, pyridine, RT, 15 min (91%); (vi) LiOH, aq. THF, RT, 36 h (82%); (vii) aq. HCl, EtOH, 100 °C, 7 h (99%); (viii) EtOCOCl, Et₃N, THF, RT, 16 h (94%); (ix) $\text{ClCH}_2\text{SO}_2\text{Cl}$ (MeCl), pyridine, 0 °C, 1 h (79%); (x) LiN₃, DMF, 50–70 °C, 48 h (see text); (xi) DMP, NaHCO_3 , CH_2Cl_2 , 0 °C, 2 h (92%); (xii) $\text{NH}_2\text{OH}\cdot\text{HCl}$, pyridine, EtOH, reflux, 3 h (see text).

^1H NMR analysis suggested elimination product **35** to be present [δ_{H} 5.43 (1H, dt, J 5.5, 1.5 Hz) and 5.54 (1H, dt, J 5.5, 2.5 Hz, HC=CH)] but a pure sample of this compound could not be obtained. When the ketone (**36**) derived from alcohol **33** was subjected to oxime formation, a single major compound was formed but HRMS data indicated the incorporation of two molecules of hydroxylamine [m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{24}\text{O}_3\text{N}_3$, 306.1812; found, 306.1813]. Furthermore, the IR spectrum showed just a single strong absorption in the carbonyl region (ν_{max} 1715s), supporting disruption of both the lactone and the cyclopentanone (ν_{max} typically ~ 1760 and 1740 cm^{-1} , respectively). Clearly the desired oxime (**37**) was not formed but the identity of the product could not be established definitively. Repeating the reaction with a sub-stoichiometric quantity of hydroxylamine and raising the reaction temperature slowly from RT to 70°C led only to apparent reaction at the butenolide, leaving the ketone intact. Ultimately, and bearing in mind the model studies conducted with alcohol **38**, efforts to convert the C(9) hydroxyl in intermediate **33** into the inverted amine had to be terminated. Although intermediate **29** was amenable to manipulation at C(9), leading to 9-*epi*-hederacine A, this work led to no further advance beyond Aoyagi's and the results are not reported here.²⁰

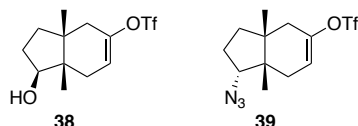


Figure 3 Structures in a model study of the OH \rightarrow N_3 transformation at C(9) in compound **33**.

3. Conclusion

This study mapped out a relatively short route from known enone **6** to hederacine A and B analogues **32** and **33** (16 and 17 steps, respectively) which differ from the natural products by the presence of a β -configured hydroxy group at C(9) in place of the required α -configured amino group. Attempts to complete the C(9) functional group conversion have so far been unsuccessful; a solution may be found in an enzymatic transformation, potentially sufficiently mild to leave the bridged aza-bicyclic butenolide structure intact.²¹

This investigation has validated a strategy for the assembly of furanocycloheptanes by a dibromocyclopropane ring-opening/trapping/Heck cyclisation sequence, and added new examples that highlight stereospecificity in the Ag(I)-mediated dibromocyclopropane solvolysis step.

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Supplementary material

Supporting information containing the experimental procedures and copies of ^1H and ^{13}C NMR data for novel compounds.