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Extension of hydrogen borrowing alkylation reactions for the total synthesis of (−)-γ-lycorane†

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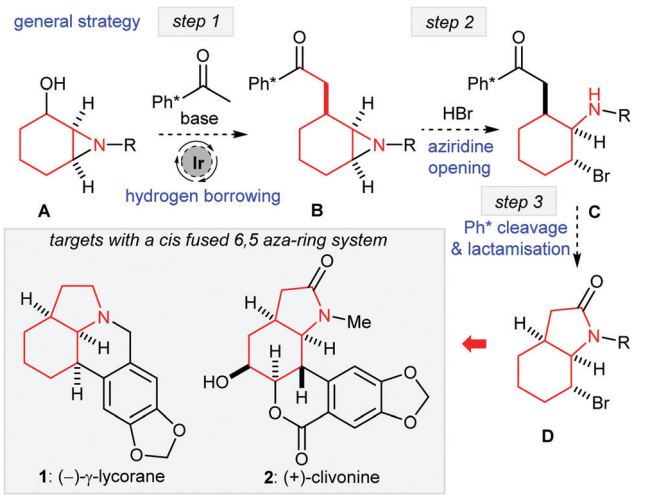
The total synthesis of (−)-γ-lycorane (10 steps) and synthesis of (±)-γ-lycorane (8 steps) was completed from cyclohexenone. A new two step hydrogen borrowing alkylation of an aziridinyl alcohol, coupled with a Ph* (Me_5C_6) deprotection/cyclisation procedure was developed for *de novo* formation of the fused 6,5 heterocyclic ring. This work is one of the first examples of hydrogen borrowing C–C bond formation being used as a key step in a total synthesis project.

The development of hydrogen borrowing catalysis has given rise to several novel C–C bond forming methodologies.[1] The primary strategic advantage of a hydrogen bonding approach for the C-alkylation of enolates is that it allows the direct use of alcohols as alkylating reagents, without the need for a formal activation step (*e.g.* conversion to halide or pseudo-halide).[2] Recently, we developed the use of chiral 1,2-aminoalcohols as novel alkylating agents that can be added as electrophiles in hydrogen borrowing C–C bond forming catalysis.[3] As our next objective, we sought to expand on the utilisation of the 1,2-aminoalcohol motif in the context of a chemical synthesis project. Our attention was drawn to the possible use of 1,2-aziridinyl alcohols (especially cyclic compounds such as **A**, Scheme 1) as alkylating agents. As a general strategy, the successful alkylation of a methyl ketone (here Ph*COMe)[4] with the general alcohol structure as **A** would facilitate some intriguing possibilities for further elaboration. If we could open the product aziridine **B** regio- and stereoselectively to form **C** then deprotection of the Ph* group would allow the possibility of cyclisation to form a *cis*-fused 6,5-lactam system **D** that is found in many natural products either as the lactam or fully reduced form (see **1** and **2**, Scheme 1).

We decided to test our hypotheses regarding aziridinyl alcohol alkylation and ring opening in the context of a synthesis of γ-lycorane (**1**). This is an interesting target for total synthesis for several reasons. Firstly, the pentacyclic structure with three contiguous *cis* stereocentres provides a challenging target for hydrogen borrowing methodology. Moreover, the asymmetric aziridination of cyclohexenone could be recruited to allow the preparation of enantiopure **A** for subsequent hydrogen borrowing alkylation; this should then allow the preparation of enantiopure lycorane.[5] Note that γ-lycorane (**1**) itself is not thought to be a natural product, but a degradation product of several members of the caranine family of alkaloids, first reported by Kotera in 1961,[6] and it has proven to be a popular target for total synthesis.[7]

To test our strategy for the asymmetric synthesis of (−)-**1**, aziridine **5** was prepared from cyclohexanone (**3**) in 98 : 2 er, by



Scheme 1 Hydrogen borrowing alkylation of aziridinyl alcohols and a route to 6,5-fused ring systems: Ph* = Me_5C_6.

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† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data and copies of NMR spectra are available. CCDC 2151105. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d2cc01248k

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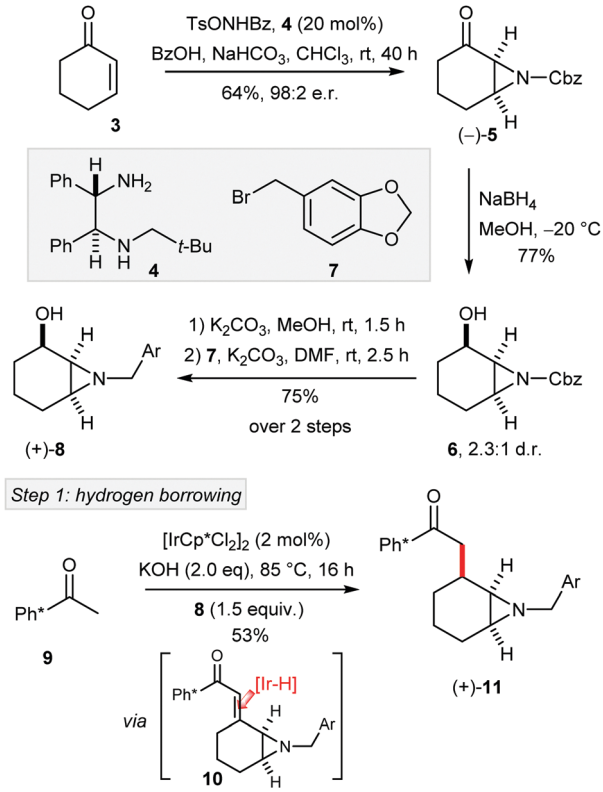
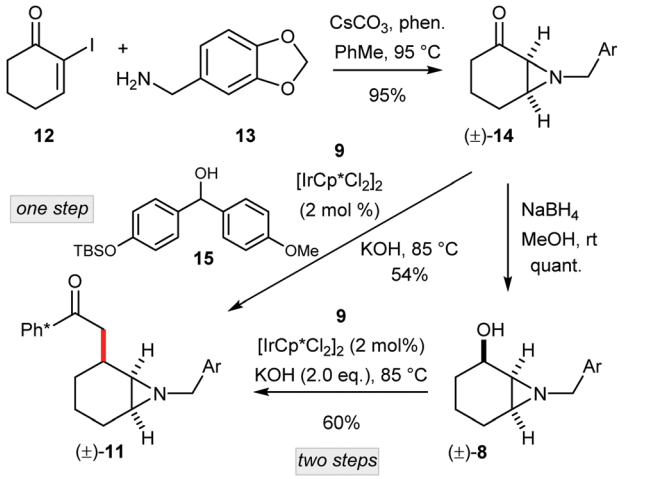


Scheme 2 Asymmetric synthesis of fragment **11**. Er of **5** measured by HPLC against a racemic standard.



Scheme 3 Synthesis of racemic fragment **11**.

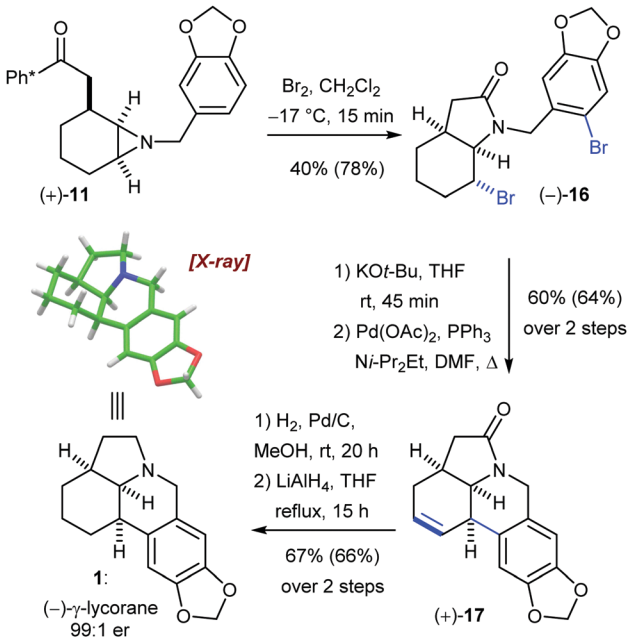
following a modified procedure of Hamada and co-workers using chiral diamine **4** (Scheme 2).[8] Reduction of the ketone **5** gave aziridyl alcohol **6** with modest diastereoselectivity. Next, the Cbz aziridine was smoothly converted into the piperonyl amine (**8**) in two steps comprising of Cbz removal and N-alkylation. Then we were ready to test the first key step, namely hydrogen borrowing catalysed alkylation of Ph*COMe with aziridinyl alcohol **8** (note that this class of alcohol has not been previously employed in hydrogen borrowing alkylation). Pleasingly, the iridium catalysed alkylation of **9** with (+)-α-aziridyl alchohol **8** afforded **11** in 53% yield as a single (all *cis*) diastereoisomer.[9] We presume that the desired *cis* stereochemistry of **11** derives from selective [Ir–H] reduction of enone intermediate **10** from the less hindered convex face.

At the same time as our development of a route to enantioenriched (–)-γ-lycorane, a route to (±)-**1** was also completed (Scheme 3). In this case the lack of requirement for an asymmetric aziridination allowed access to **11** *via* a shorter sequence. Thus, aziridination of **12** (prepared from cyclohexanone in one step)[10] with piperonylamine (**13**), and reduction of the resultant ketone **14** gave the α-aziridyl alchohol (±)-**8** as a single diastereoisomer in excellent yield. Next, racemic **8** was used to alkylate Ph* methyl ketone (**9**) affording (±)-**11** in 60% yield. However, in this route we questioned the need to reduce ketone **14** to alcohol **8**, only to have it re-oxidised in the hydrogen borrowing step. To this end, we envisioned the direct alkylation of ketone **9** with another ketone (here **14**). Note that this particular reaction necessitates the addition of a stoichiometric hydrogen donor to provide hydride for reduction of the enone precursor to **11** (*i.e.* (±)-**10**). After experimentation, we selected alcohol **15**[11] which we reasoned would be readily oxidised *in situ*, and thus provide hydride for the catalyst controlled enone reduction. Note that in this case the ketone by-product from this oxidation would not readily compete in the aldol reactions that occur in hydrogen borrowing alkylation. Pleasingly, the use of the benzhydrol derivative **15** gave (±)-**11** directly from ketone (±)-**14** with only a slightly diminished yield compared to the two-step procedure.

With both enantiopure and racemic **11** in hand we now turned to elaboration of the aziridine and completion of the synthesis (Scheme 4). Pleasingly, preliminary experiments had shown that cleavage of the Ph* group from **11** using molecular bromine had the beneficial added effect of activating the acyl carbonyl as either an acylium ion or acid bromide. We found that the aziridine nitrogen was able to intercept this reactive intermediate to form an aziridinium ion *in situ*; this was subsequently opened regio- and stereoselectively by a strain-release S_N2 displacement by bromide ion. Thus, this protocol allowed the combination of steps 2 and 3 from the general plan (Scheme 1).

Treatment of **11** with Br_2 provided smooth conversion to the dibrominated lactam **16** in 44% yield (78% for racemic **11**). Note that this reaction also delivered, as desired, a monobromination of the aromatic ring. From here, regioselective elimination of the alkyl bromide followed by a regio- and stereoselective intramolecular Heck reaction forged the final C–C bond to give **17** in 67% yield (60% racemic). Finally, catalytic hydrogenation of the alkene with Pd/C, followed by amide reduction with $LiAlH_4$ afforded (–)-γ-lycorane (**1**) in 68% yield (66% racemic). The spectroscopic data for the synthetic material matched that reported in the literature, and we were also able to obtain a single crystal X-ray diffraction structure of racemic lycorane which confirmed the relative stereochemistry of this product.[12]

In summary we have completed the synthesis of (–)-lycorane in 10 steps and of (±)-lycorane in 8 steps. The hydrogen



Scheme 4 Endgame for the synthesis of γ-lycorane **1**. Yields in parentheses are for racemic material. Er of **1** was measured by HPLC against a racemic standard.

borrowing alkylation of an azridinyl alcohol was crucial in our synthetic strategy, and this general methodology should allow the synthesis of a broad range of complex polycyclic nitrogen containing natural products. Furthermore, to the best of our knowledge, this is the first case where C–C bond forming hydrogen borrowing catalysis has been employed as a key step in a total synthesis. Future work will concentrate on expanding the applicability of hydrogen borrowing strategies in chemical synthesis projects.

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Conflicts of interest

There are no conflicts to declare.

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