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* (Me5C6) 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...
following a modified procedure of Hamada and co-workers using chiral diamine 4 (Scheme 2). Reduction of the ketone 5 gave aziridyl alcohol 6 with modest diastereoselectivity. Next, the Cbz aziridine was smoothly converted into the piperonyl intermediate 7 by 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 (+)-x-aziridyl alcohol 8 afforded 11 in 53% yield as a single (all cis) diastereoisomer. 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) with piperonylamine 13, and reduction of the resultant ketone 14 gave the x-aziridyl alcohol (±)-8 as a single diastereoisomer in excellent yield. Next, racem 18 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 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_N 2 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 alkenyl 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.

In summary we have completed the synthesis of (−)-lycorane in 10 steps and of (±)-lycorane in 8 steps. The hydrogen
borrowing alkylation of an aziridinyl 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.

**Notes and references**

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