Synthesis of (–)-(*R*)-angustureine by formal alkynylation of a chiral ß-amino ester

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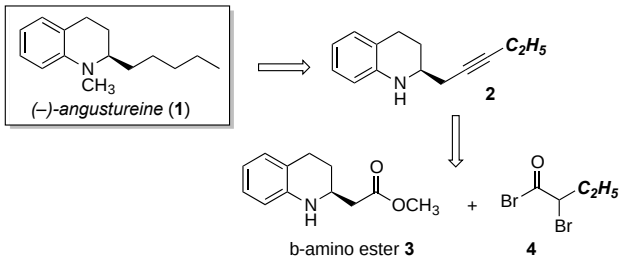
INTRODUCTION

The South American angostura tree, *Galipea officinalis* Hancock, is one of the twenty species of the genus *Galipea* Aublet.[1] In 1999, Jacquemond described the isolation of tetrahydroisoquinoline alkaloids including angustureine (**1**, Scheme 1) from the angostura tree bark;[2] antimalarial and cytotoxic properties of this and congeneric alkaloids were later found.[3] The promising biological activity of its alkaloid extracts, and a general interest in tetrahydroisoquinoline synthesis has led to considerable attention on angustureine from the synthetic community.

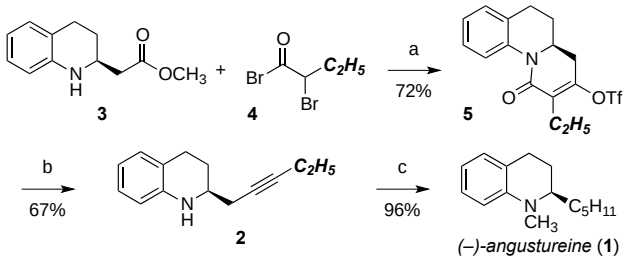
RESULTS AND DISCUSSION

The synthesis of angustureine presented the opportunity to explore a formal ester alkynylation strategy for converting readily available β-amino esters into functionalized homopropargyl amines using an annulation and fragmentation sequence. Thus, our retrosynthetic analysis (Scheme 1) focuses on propargyl-tetrahydroisoquinoline **2** as the key intermediate, which is expected to be available by a formal alkynylation of β-amino ester **3**.



Scheme 1. Retrosynthetic analysis of angustureine.

The synthesis of (*R*)-angustureine (**1**) begins with the preparation of (*S*)-β-amino ester **3** by enzymatic kinetic resolution of racemic **3**.[4] The material thus obtained was subjected to a three-step annulation sequence to dihydropyridone (DHPD) triflate **5**: acylation of secondary amine **3**, Reformatsky-type cyclocondensation, and enol triflation (**3**+**4**→**5**) (Scheme 2). This annulation sequence is conveniently conducted without purification of intermediates to afford **5** in 72% overall yield.



Scheme 2. Synthesis of angustureine. (a) i. 4, DMAP, CH_2Cl_2, 60°C ii. *t*-BuMgCl, THF, 60°C iii. Tf_2O, Et_3N, CH_2Cl_2, −78°C ; (b) MeLi, $PhCH_3$, −78°C to rt; (c) i. H_2, 5% Pd/C, CH_2Cl_2 ii. CH_3I, K_2CO_3, acetone.

Next, the main aim was to execute a domino sequence in which addition, fragmentation, and deacylation (**5**→**2**) are all accomplished under a unified set of conditions. In the event (Scheme 2), subjecting DHPD triflate **5** to 3.0 equiv of methyllithium yielded amine **2** in 67% yield: Addition/fragmentation of **5** generates amide **6**, which in the presence of excess methyllithium undergoes subsequent addition/elimination to amine **2**. Alkyne hydrogenation was catalyzed using 5% palladium on carbon; after filtration and solvent exchange, *N*-methylation provided angustureine **1**.

CONCLUSION

In summary, an annulation and domino fragmentation sequence, which formally results in β-amino ester alkynylation, has been applied to the synthesis of (–)-(*R*)-angustureine (**1**). The six-step sequence from β-amino ester **3** to the natural product was achieved in 46% yield, with no protecting groups and only three purifications.

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