Pot-Economical Total Synthesis of (−)-Quinine Using Organocatalyst

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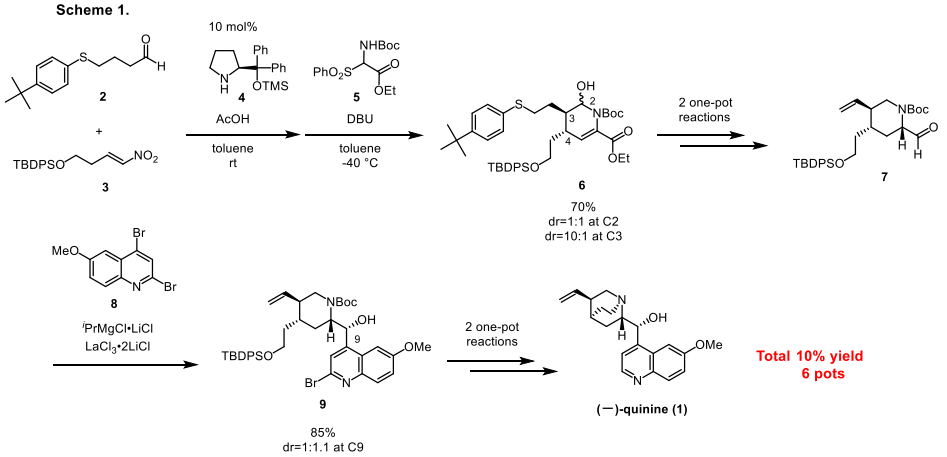
Keywords: *Asymmetric total synthesis; Organocatalyst; One-pot reaction; Michael reaction; Quinine*

Quinine (**1**), with four stereocenters, is a drug for malaria, and syntheses of its derivatives are important to develop new drugs for malaria.[1)] On the other hand, one-pot operations are an effective method for carrying out several transformations and forming several bonds in a single pot while simultaneously eliminating several purification steps, minimizing chemical waste generation, and saving time.[2)] We have accomplished pot-economical enantioselective total syntheses of (-)-quinine (**1**).

The asymmetric Michael/aza-Henry/hemiaminalization/elimination reaction[3)] of aldehyde **2**, nitroolefin **3** and imine precursor **5** in the presence of organocatalyst **4** proceeded with both high yield and stereoselectivity (Scheme 1). Construction of the piperidine ring with the control of C3 and C4 stereocenters was achieved in one pot. Aldehyde **7** was obtained by 2 one-pot reactions from **6**. Dibromoquinoline **8** was used to introduce quinoline moiety. The bromo group at C2-position of **8** plays important roles in controlling the reactivity and introducing the substituents for derivative syntheses. Deprotection, intramolecular S_N2 reaction, and reduction of bromide afforded (−)-quinine (**1**) in 2 one-pot reactions. In summary, the enantioselective synthesis of quinine (**1**) was achieved in total 6 pots, and 10% overall yield from **3**. This method is the smallest number of pots to synthesize (-)-quinine and would be applicable to synthesize quinine derivatives.

Scheme 1.



References

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