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A concise enantioselective synthesis of L-(−)-733,061 and (2*S*,3*S*)-methyl 3-aminopiperidine-2-carboxylate using catalytic enantioselective aza-Henry reaction as key step

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ABSTRACT

An efficient enantioselective synthesis of L-(−)-733,061 and (2*S*,3*S*)-methyl 3-aminopiperidine-2-carboxylate is accomplished by means of catalytic enantioselective aza-Henry reaction. A key feature of this protocol is organocatalysis as genesis of chirality to ensure high degree of distereo- and enantiocontrol.

1. Introduction

Piperidine motif containing alkaloids are medicinally significant owing to their anaesthetic, analgesic and antibiotic activity.[1] In general, substituted piperidines are becoming progressively more important because of their distinctive biological activities, such as neurokinin-1 (NK-1) receptor antagonist and as a glycosidase inhibitors.[2] Recently, potential therapeutic value was recognized for substituted piperidines, for instance, in (2*R*,3*R*)-3-hydroxypipecolic acid, febrifugine, (+)-*epi*-deoxoprosopinine and (−)-cassine molecules[3] (Fig. 1).

The successful methods that provide enantioselective routes to chiral substituted piperidine derivatives are based on the chiral pool, especially aminoacids; the use of the reagent that utilize chiral catalyst and chiral auxiliaries.[4] It was pragmatic that chiral functional group variation on piperidine ring is expected to generate distinctive properties, that enhance the therapeutic potential of the compounds for the treatment of diseases.

With this initiative, and our continued interest in developing catalytic routes to bioactive small molecules,[5] we have embarked on a program to synthesize L-(−)-733061 **1**, synthetic variants of chiral piperidine derivatives, such as (2*S*,3*S*)-methyl 3-aminopiperidine-2-carboxylate **2**, and their C3 epimers, **1a** and **2a**. Further, we are interested to evaluate their biological activities based on functional modifications (Fig. 2).

2. Results and discussion

Herein, we report a highly practical and organocatalyzed enantioselective synthetic route to L-(−)-733060 **1**, (2*S*,3*S*)-methyl

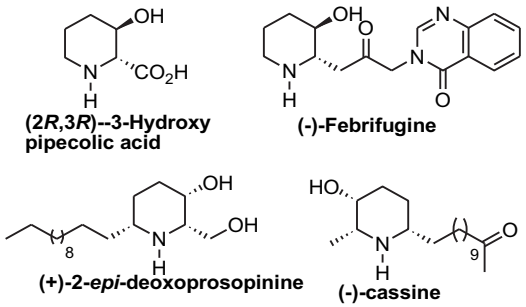

Fig. 1. Substituted piperidine motif molecules.

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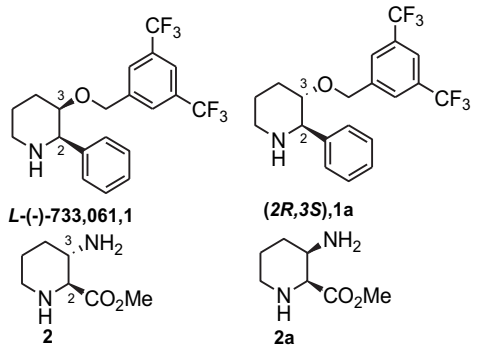
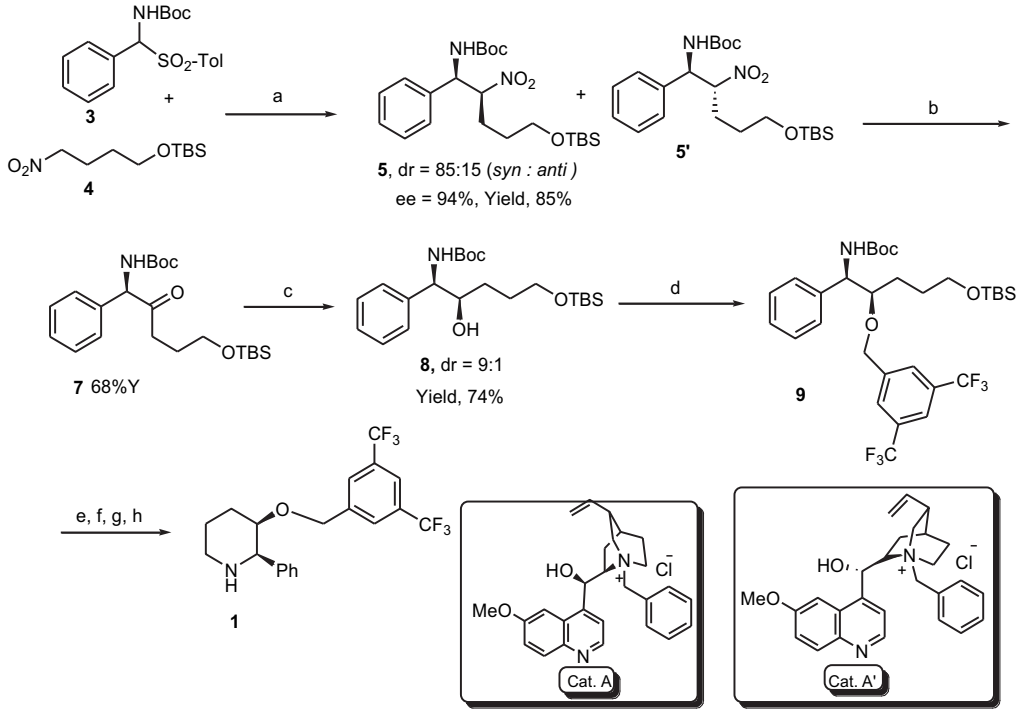


Fig. 2. Synthetic variants of chiral substituted piperidine derivatives.

the presence of 15 mol % of **Cat A′** under identical conditions led to the complete racemic mixture of the expected product.

Thus, oxidation of nitro functionality **5** by Gissot's protocol ($NaNO_2$ (6 equiv),[7] DMF/H_2O (7:1; 0.4 M), 45 °C, 12 h)[7] led to keto compound **7** in 68% yield. Then, the amino ketone **7** was reduced with $NaBH_4$ under Luche's conditions ($CeCl_3 \cdot 7H_2O$, CH_2Cl_2/EtOH [1:1]) furnished a *syn*-selective (dr=9:1) secondary alcohol **8** (74%). The secondary alcohol **8** was protected with 3,5-bistriflouromethyl benzyl bromide under basic conditions resulted in a separable pure *syn*-isomer **9** (74% yield) and then following deprotection of TBS (TBAF, THF, 0 °C, 3 h) led to a primary alcohol in 80% yield. Mesylation of primary alcohol followed removal of *N*-Boc group with TFA results TFA salt. Then, cyclization under basic condition (Et_3N, MeOH, 2 h, 60 °C) resulted in the desired compound **1** in 65% isolated yield (over three steps).[10] The spectral and analytical data of **1**[4j], **1a**[4f,g] were in full agreement with that reported data, **1** $[\alpha]_D^{25}$ −32.56 (*c* 0.60, $CHCl_3$); {lit.[4] $[\alpha]_D^{25}$ +34.29 (*c* 0.99, $CHCl_3$)} (Scheme 1).



Scheme 1. (a) **Cat A** (15 mol %), CsOH H_2O (1.3 equiv), toluene (0.8 M), −55 °C, 44 h; (b) $NaNO_2$ (6 equiv), DMF/H_2O (7:1), 45 °C, 12 h; (c) $NaBH_4$, $CeCl_3$ $7H_2O$, −78 °C to −40 °C; (d) (i) NaH, TBAI, THF, (ii) 3,5-bis trifluromethyl benzyl bromide, 12 h, rt; (e) TBAF, 0 °C, THF; (f) $MeSO_2Cl$, Et_3N, CH_2Cl_2; (g) TFA, CH_2Cl_2; (h) Et_3N, MeOH, 2 h, 60 °C.

3-aminopiperidine-2-carboxylate **2** and stereoisomer **2a**. In principle, the stereogenic centers at C2 and C3 in L-(−)-733061 **1**, and (2*S*,3*S*)-methyl 3-aminopiperidine-2-carboxylate **2** could be accessed through a catalytic *syn*-selective aza-Henry reaction with high degrees of diastereo- and enantioselectivity using *N*-Boc-sulfone **3**, **10** and nitro compound **4**. To this end, we have appraised the recently reported Palomo-reaction[6] conditions for this transformation. Accordingly, the reaction of *N*-Boc-sulfone **3** with nitro compound **4** employing phase transfer catalyst 15 mol % of **Cat A** in toluene at −55 °C for 44 h resulted in the anticipated product **5** in 85% yield with 85:15 diastereomeric ratio in favour of *syn* isomer. The ee of major *syn* isomer **5** estimated by chiral HPLC analysis in comparison with a racemic mixture and was found to be 94% [corresponding TBS deprotected alcohol **6**, Chiralpak AD-H, 210 nm, flow rate=1 mL/min, *n*-hexane/EtOH (85:15)[6c]]. The absolute stereochemistry of major diastereomer **5** was assigned by analogy.[6] It was anticipated that the use of complementary sense **Cat A′**, i.e., quinidine salt would generate the *anti*-selective diastereomer **5′**. Nevertheless, subjecting *N*-Boc-sulfone **3** and nitro compound **4** in

En route to the synthesis of L-(−)-733,061, we have also considered the synthesis of chiral substituted piperidine derivatives, (2*S*,3*S*)-methyl 3-aminopiperidine-2-carboxylate **2**, and stereoisomer **2a** (Scheme 2). Consequently, the reaction of *N*-Boc-sulfone **10** with nitro compound **4** in the presence of **Cat A** (15 mol %) in toluene at −50 °C for 44 h resulted in the desired product **11** in 81% yield with 80:20 diastereomeric ratio in favour of *syn* isomer with 92% ee. The ee was assessed by chiral HPLC analysis using corresponding racemic mixture [Chiralpak AD-H, 220 nm, flow rate=0.5 mL/min, *n*-hexane/2-propanol (95:5)]. The absolute stereochemistry of major diastereomer **11** was assigned by analogy.[6]

Reduction of **11** with sodium borohydride in the presence of $NiCl_2 \cdot 6H_2O$ (−5 °C, MeOH, 15 min) led to amine, which on protection with CbzCl under basic conditions afforded **12** in 78% yield. Exposure of **12** to TBAF in THF at ambient temperature led to desilylation, and resulting primary alcohol was then converted to mesylate **13** under basic conditions. Deprotection of *N*-Boc under acidic conditions (TFA in CH_2Cl_2) followed by cyclization using Et_3N/MeOH at ambient temperature led to **14** (65%). Subsequent