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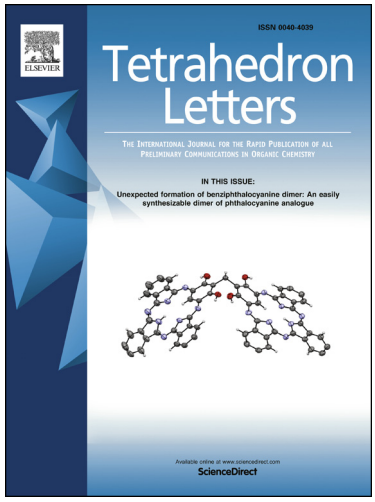

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An enantioselective approach to 3-substituted pyrrolidines: asymmetric synthesis for pyrrolidine core of serotonin norepinephrine reuptake inhibitors (SNRIs)

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ABSTRACT

A novel and efficient synthetic approach to enantiopure 3-substituted pyrrolidine skeleton from readily available (*S*)-PMB glycidyl ether as a starting material and its application to the asymmetric synthesis of pyrrolidine core **1** of serotonin norepinephrine reuptake inhibitors (SNRIs) **2** and **3** are described. The synthesis utilizes the organocatalyzed asymmetric Michael addition reaction as key step.

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Introduction

Pyrrolidines and their substituted derivatives are among the most bioactive *N*-heterocyclic compounds in organic chemistry due to prevalence of these structural motifs either as itself or as a part of a more complex structural moiety in a large number of biologically active molecules and natural products.[1] Among them, enantiomerically pure 3-substituted pyrrolidine **1** and their derivatives are important subclass of compounds possessing interesting pharmacological activities.[2] Serotonin norepinephrine reuptake inhibitors (SNRIs) are advanced novel class of antidepressant drugs which have been suggested for the treatment of several central nervous disorders including chronic painful conditions such as fibromyalgia and diabetic peripheral neuropathic pain.[3] The precise mechanism of action of SNRIs has not yet been fully elucidated, but it is believed to be mainly caused by decreasing the levels of serotonin and norepinephrine in the synaptic cleft, resulting erratic signalling.[4] Currently,

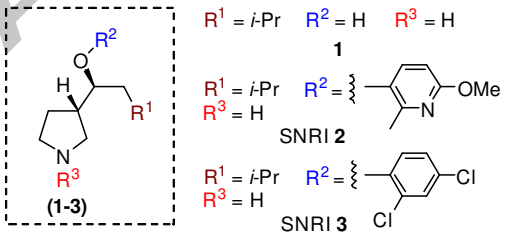

Figure 1: Structures of 3-substituted pyrrolidines **1**-**3**.

several SNRIs marketed worldwide have proven to be effective and safe drugs in chronic painful conditions and mood disorders but the search for new SNRIs has always been of greater significance upon past drugs in regards to efficacy, tolerability and fewer side effects. In 2013, Johansson and co-workers[5] reported the discovery of novel 3-substituted pyrrolidine ether SNRI **2**, which is the first example showing improved norepinephrine transporter activity, acceptable metabolic stability and exhibiting minimal drug to drug interaction. Stangeland and co-workers have also reported previously the discovery of an another novel 3-substituted pyrrolidine ether SNRI **3** which showed inhibition of the serotonin and/or norepinephrine transporter, for the treatment of neuropathic pain with reduced side effects such as nausea (Figure 1).[6]

The SNRIs **2** and **3** have been synthetic targets of considerable interest for pharmaceutical industries due to their utility in treatment of central nervous disorders with an array of functionalities.[5-7] More recently, Magnus and co-workers reported the multistep asymmetric synthesis of the SNRIs **2** and **3** that employed dynamic kinetic resolution (DKR) with enantio- and diastereoselective hydrogenation on β-keto-γ-lactam to afford β-hydroxy-γ-lactam as the key step.[7] As part of our ongoing research programme towards the asymmetric syntheses of bioactive compounds,[8] we became interested in developing a flexible approach to 3-substituted pyrrolidine skeleton offering the diversity for derivatization. Herein, we are reporting a new and highly efficient approach for 3-substituted pyrrolidine and its application to the asymmetric synthesis of pyrrolidine core **1** of

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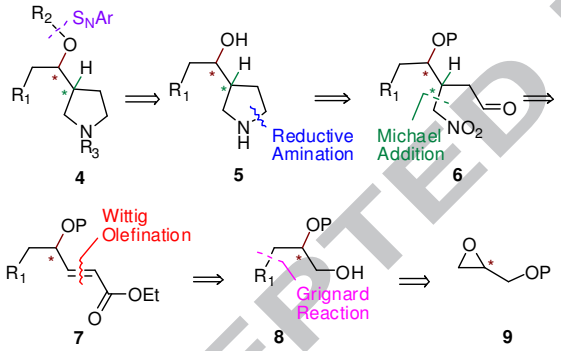
SNRIs **2** and **3** employing organocatalyzed Michael addition reaction as key step.

Results and Discussion

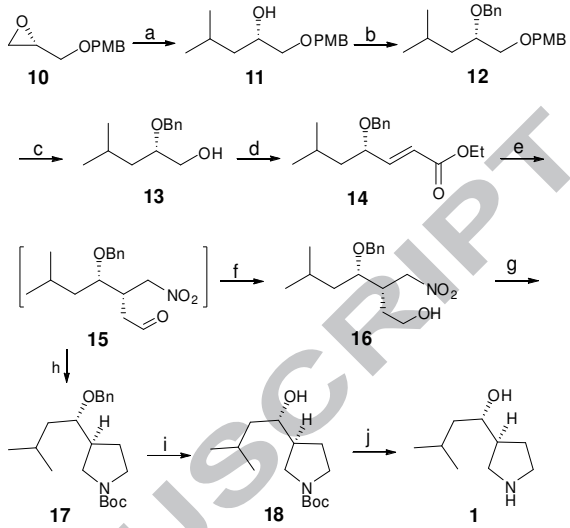
Our synthetic approach for the stereoselective synthesis of 3-substituted pyrrolidine skeleton **4** was envisioned *via* the retrosynthetic route as shown in Scheme 1. The pyrrolidine core unit **5** could be used as a synthetic intermediate from which 3-substituted pyrrolidine ethers **4**, SNRIs **2** and **3** could be synthesized *via* base catalyzed nucleophilic aromatic substitution reaction (S_NAr) with corresponding commercially available aromatic halides. The pyrrolidinol derivative **5** in turn could be obtained from nitroaldehyde derivative **6** *via* intramolecular reductive amination. We envisaged that the nitroaldehyde **6** would serve as a key intermediate in this approach and could be prepared by means of (*S*)- or (*R*)-diphenylprolinol silyl ether catalyzed asymmetric Michael addition of nitromethane to *α,β*–unsaturated aldehyde derived from the reduction of olefinic ester derivative **7**. The ester derivative **7** could be assembled from mono-protected terminal alcohol derivative **8** by oxidation followed by Wittig olefination. Enantiomerically pure alcohol derivative **8** could be easily accessed from the chiral glycidyl ether **9** *via* suitable Grignard reagents followed by standard organic transformations. The desired configuration of 3-substituted pyrrolidine skeleton **4** could be obtained by simply changing the (*S*)- and (*R*)- configuration of the readily available glycidyl ether and/or by using L- and D-diphenylprolinol silyl ether catalyst during Michael addition step. Thus, in principle, all the four isomers of SNRIs **2** and **3** along with different substitutions at three different sites R_1, R_2 and R_3 could be accessed by this approach.



Scheme 1: Retrosynthesis of 3-substituted pyrrolidines **4**.

As displayed in Scheme 2, the synthesis of pyrrolidine core **1** of SNRIs **2** and **3** commenced with Cu(I)-catalyzed regioselective ring-opening of (*S*)-PMB (*p*-methoxybenzyl) glycidyl ether **10**[9] with *iso*-propylmagnesium bromide at -20 °C which furnished the PMB protected alcohol (*S*)-**11** in 86% yield. Treatment of alcohol (*S*)-**11** with BnBr under the basic conditions successfully delivered the protected diol (*S*)-**12** in 89% yield. The selective deprotection of *O*-PMB ether group of (*S*)-**12** with DDQ furnished the terminal alcohol derivative (*S*)-**13** in 93% yield. Oxidation of alcohol (*S*)-**13** under Swern conditions[10] and subsequent treatment of aldehyde with (ethoxycarbonyl-methylene)triphenylphosphorane in THF afforded the *trans*-olefinic ester (*S*)-**14** in 90% yield.

Our next aim was to carry out the synthesis of 3-substituted pyrrolidine moiety. Towards this end, DIBAL-H reduction of ester (*S*)-**14** at -78 °C to *α,β*–unsaturated aldehyde and subsequent conjugate addition[11] of nitromethane in the presence of (*R*)-diphenylprolinol silyl ether (10 mol%) furnished the nitroaldehyde adduct **15** which on spontaneous intramolecular reductive amination with Zn/CH_3COOH[12] followed by *N*-Boc protection under basic conditions furnished *N*-Boc-pyrrolidine skeleton **17** in 81% yield.



Scheme 2: *Reagents and conditions*: (a) $(CH_3)_2CHMgBr$, anhydrous THF, CuI, -20 °C, 6 h, 86%; (b) $PhCH_2Br$, NaH, DMF, 0 °C to rt, 3 h, 89%; (c) DDQ, CH_2Cl_2, rt, 8 h, 93%; (d) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to -60 °C, 2 h, (ii) PPh_3=CHCOOEt, THF, rt, 24 h, 90% (over two steps); (e) (i) DIBAL-H, CH_2Cl_2, -78 °C, 1 h, (ii) (*R*)-diphenylprolinol silyl ether (10 mol%), CH_3NO_2, benzoic acid, MeOH, rt, 24 h; (f) $NaBH_4$, MeOH, 0 °C, 30 min, 85%; (g) (i) MsCl, NEt_3, CH_2Cl_2, 0 °C to rt, 1 h, (ii) Zn, CH_3COOH, H_2O, 0 °C to rt, 3 h, (iii) $(Boc)_2O$, NaH, DMAP, DMF, 0 °C to rt, 10 h, 76% (over three steps); (h) (i) Zn, CH_3COOH, H_2O, 0 °C to rt, 3 h, (ii) $(Boc)_2O$, NaH, DMAP, DMF, 0 °C to rt, 10 h, 81%; (i) H_2, Pd/C, MeOH, rt, 24 h, 87%; (j) TFA, CH_2Cl_2, rt, 5 h, 92%.

To further elucidate the stereochemistry during the Michael addition, the conjugate addition of nitromethane to *α,β*–unsaturated aldehyde was carried out with racemic catalyst (±)-diphenylprolinol silyl ether followed by reduction with $NaBH_4$ furnished the *syn*-/*anti*-nitroalcohol diastereomers (dr, 1:1) with 87% combined yield.[13] On the other side, the conjugate addition in the presence of catalytic amount of (*R*)-diphenylprolinol silyl ether furnished the *syn*-nitroalcohol derivative **16** as a single diastereomer in 85% yield, which is in accordance with the previously proven model in organocatalytic Michael addition reaction.[11,13-14] The *syn*-nitroalcohol derivative **16** was converted to pyrrolidine **17** *via* *O*-Ms followed by reduction with Zn/AcOH and subsequent *N*-Boc protection in 76% yield. With enantiomerically pure pyrrolidine derivative **17** in hand, it was then subjected to debenzylation under 1 atm H_2 pressure in the presence of a catalytic amount of Pd/C which afforded the alcohol **18** in 87% yield. The alcohol **18** upon S_NAr reaction with commercially available 6-chloro-2-methylpyridine and subsequent *N*-Boc deprotection with TFA followed by methoxide moiety addition using the literature report[5] would furnish the SNRI **2**. Finally, the *N*-Boc deprotection of derivative **18** with TFA furnished the pyrrolidine core unit **1** in 92% yield $[\alpha]_D^{25}$ -25.6 (*c* 0.5, CH_3OH). On the other hand, pyrrolidine core unit **1** on S_NAr reaction with commercially available 1,3-dichloro-4-fluorobenzene under basic conditions would furnish the pyrrolidine ether SNRI **3** using the known procedure.[7]

In conclusion, we have described a novel and efficient enantioselective approach for the synthesis of 3-substituted

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pyrrolidine skeleton **4** and its application to the asymmetric synthesis of pyrrolidine core unit **1** of SNRIs **2** and **3** from readily available chiral epoxide as starting material employing diphenylprolinol silyl ether mediated asymmetric Michael addition reaction as key step. The overall yield for the pyrrolidine core unit **1** was 42% after seven column chromatographic purification steps. The merits of described synthesis are excellent enantio- and diastereoselectivity with high yielding reaction steps. The synthetic approach described has also significant potential for variation of substituents at the 3-alkyl site, *O*-aryl and *N*-alkyl sites to synthesize various 3-substituted pyrrolidines with expected increase in antidepressant activities.

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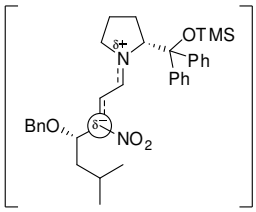
13. The diastereomeric ratio (dr) was determined from ^{1}H-NMR spectral data.
14. The transition state model of asymmetric Michael addition reaction for the synthesis of compound **17** is proposed below.



Supplementary Material

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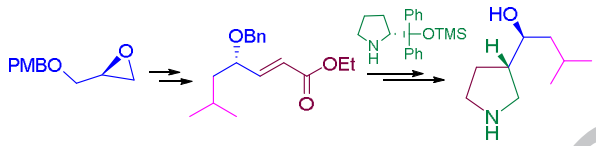

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3. Asymmetric synthesis of pyrrolidine core of SNRIs
4. Organocatalytic asymmetric Michael addition reaction key step

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