

Biomass derived furfural-based facile synthesis of protected (2S)-phenyl-3-piperidone, a common intermediate for many drugs†

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An efficient synthetic route towards tosyl-protected (2S)-phenyl-3-piperidone, a common intermediate for many drugs, has been developed in 5 steps in 54% yield from biomass derived furfural. The synthetic utility of the piperidone core structure was demonstrated with the synthesis of a NK₁ receptor antagonist.

The sustained increase in the consumption of finite fossil fuel resources has painted a bleak global energy outlook for the 21st century. This has also attracted considerable research attention to various renewable resources such as biomass, which has the potential to serve as a renewable source of energy and organic carbon.¹ Furfural **1** is a platform chemical which can be derived from biomass^{2a,b} and annually about 300 000 tonnes of agricultural raw materials are dehydrated to form furfural. It is notable that a recent report suggests a possible significant reduction in furfural production costs^{2c} which highlights the potential for lower costs when utilizing furfural as a carbon source. The inclusion of furfural as one of the top “biobased product opportunities”^{3a} emphasizes its usefulness in various domains such as fuels,^{3b} solvents,^{3c} natural product synthesis^{3d-i} and more recently as chiral inducers.^{3j} Annual world production of rice exceeds 500 million tonnes^{4a} and its associated agricultural waste, rice straw, is produced in large quantities in Asian countries such as China (110 Mt per year), India (97 Mt per year), Thailand (22 Mt per year) and the Philippines (11 Mt per year).^{4b,c} Currently rice straw is largely left uncollected in the field or is disposed of through open-field burning which causes air pollution and health hazards.⁴

We envisioned that the xylan content present in rice straw could be used as a feedstock to produce furfural which can then be efficiently transformed into a tosyl-protected (2S)-phenyl-3-piperidone core structure **2** which allows facile access to numerous neurokinin-1 (NK₁) receptor antagonists (Fig. 1). These potent NK₁ receptor antagonists showed promising biological activities which may offer novel cures to disorders such as depression, anxiety and emesis.⁵ Various protected 2-phenyl-3-piperidones have been synthesized by Merck and other research groups with low overall yields (<40%) over a minimum of 6 steps.^{6,7} The advantages of this strategy include the use of a cheap and renewable biomass-derived starting material, being a short synthetic route with only a single silica gel column chromatography step, and obtaining product in a higher yield than existing methods with almost no loss of optical purity.

Modification of a previously reported synthesis of furfural **1** from corn cobs⁸ to rice straw with hourly removal of DCM from

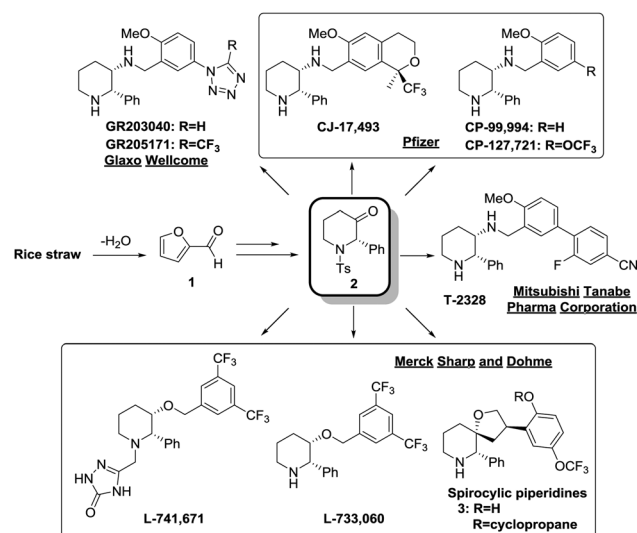


Fig. 1 Construction of the piperidone core structure from furfural to access various potent NK₁ receptor antagonists.

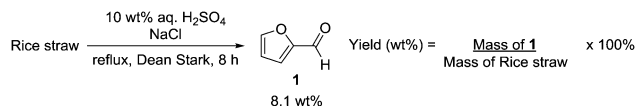
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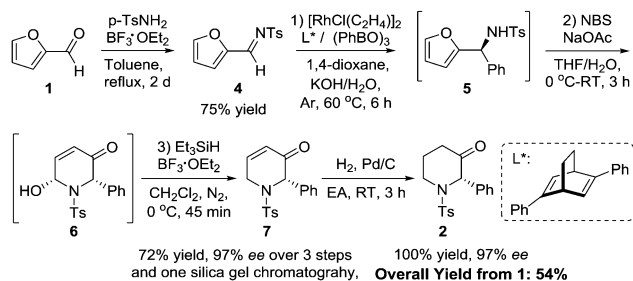
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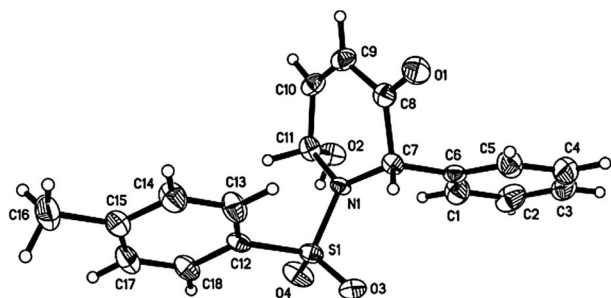
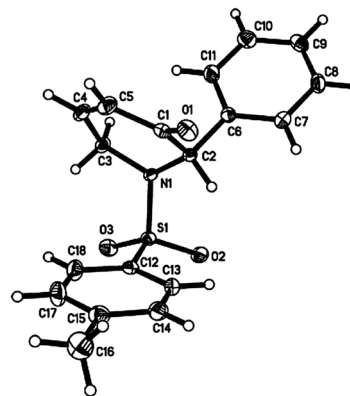




Scheme 1 Synthesis of furfural from rice straw.

Scheme 2 Facile synthesis of piperidone **2** from biomass-derived furfural.

the Dean Stark trap gave a yield of 8.1 wt% without optimization (Scheme 1). The crude product obtained was found to be sufficiently pure without the need for further purification and could be transformed into imine **4** in the presence of 4-methylbenzenesulfonamide and a Lewis acid catalyst with a recrystallization yield of 75% (Scheme 2). Imine **4** was then subjected to a rhodium-catalyzed asymmetric arylation methodology developed by Hayashi's group⁹ to afford furylamine **5** with 97% yield and 99% enantiomeric excess (ee) after column chromatography. In view of the efficiency of this step, subsequent reactions were not subjected to chromatographic purification and crude **5** was able to undergo the aza-Achmatowicz rearrangement¹⁰ with *N*-bromosuccinimide (NBS) as the oxidant to yield hemiaminal **6** as a *cis* diastereomer, as determined by NMR analysis and single-crystal X-ray crystallography¹¹ (Fig. 2), probably as a result of an anomeric effect. The phenyl substituent at the chiral centre in *rac*-**6** adopts a pseudoaxial orientation due to A^{1,3}-strain¹² with the tosyl protecting group. The aza-Achmatowicz rearrangement is a variation of the Achmatowicz rearrangement where the former involves an amine functional group as a nucleophile and the latter an alcohol. Crude **6** was able to be immediately reduced¹³ without further purification to give **7** in 72% yield and 97% ee over 3 steps from **4**. **7** was hydrogenated using Pd/C in a quantitative conversion to yield tosyl-protected (2*S*)-phenyl-3-piperidone **2**. Thus, key intermediate

Fig. 2 ORTEP drawing of *rac*-**6**.Fig. 3 ORTEP drawing of **7**.

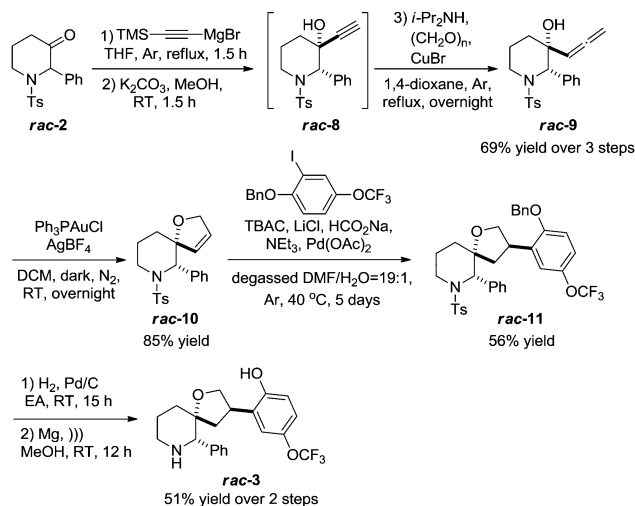
2 was efficiently synthesized in an overall yield of 54% over 5 steps from rice straw-derived furfural **1**.

The optical rotation obtained for **7** is $[\alpha]_D^{21} = +123$ ($c = 1.32$, CH₂Cl₂) for 97% ee while that reported in the literature^{7c} is $[\alpha]_D^{20} = -145$ ($c = 0.3$, CH₂Cl₂), and the optical rotation obtained for **2** is $[\alpha]_D^{23} = -10.0$ ($c = 1.01$, CH₂Cl₂) for 97% ee while that reported in the literature^{7c} is $[\alpha]_D^{20} = +5$ ($c = 0.2$, CH₂Cl₂). The absolute structure of **7** was determined using single-crystal X-ray crystallography¹¹ (Fig. 3), and further HPLC analysis of the particular single-crystal used in the X-ray crystallography as well as the batch of crystals submitted for analysis showed retention times and an elution order that were in agreement with those of experimentally obtained values (see ESI† for more details). This rules out the possibility that the structure obtained from the single-crystal X-ray crystallography is the minor enantiomer and hence it can be concluded that the experimentally obtained **7** is indeed the desired (*S*)-2-phenyl-1-tosyl-1,6-dihydropyridin-3(2*H*)-one. This conclusion can be further extended to assign the absolute configuration of **2** as (*S*)-2-phenyl-1-tosylpiperidin-3-one. The loss of ee was subsequently determined to be due to the inherent acidity of the silica gel chromatography; pre-treatment of silica gel with 1% triethylamine also resulted in a loss of ee while recrystallization attempts proved to be futile. The acid and base sensitivity of **2** and **7** may be attributed to the lability of the α-hydrogen at the chiral centre.

NK₁ receptor antagonist **3** was synthesized to illustrate the synthetic utility of piperidone **2** (Scheme 3). *Rac*-**2** was able to undergo a Grignard reaction and subsequent TMS deprotection step to form *rac*-**8**, which was immediately subjected to Searles-Crabbé homologation¹⁴ conditions without further purification to transform the alkyne moiety to an allene *rac*-**9** in 69% yield over 3 steps. The relative stereochemistry in *rac*-**8** was established using single-crystal X-ray crystallography¹¹ where the alkyne is *trans* to the phenyl substituent. The preference for the pseudoaxial orientation of the phenyl substituent in *rac*-**2** gives rise to a single diastereomer in the Grignard reaction due to the steric hindrance imposed by the phenyl substituent on one face of the carbonyl group.

Au-catalyzed cycloisomerisation¹⁵ of *rac*-**9** constructed the spirocycle *rac*-**10** in 85% yield and *rac*-**10** was analyzed with





Scheme 3 Synthesis of **rac-3** using a Searles–Crabbé homologation, Au-catalyzed cycloisomerisation and reductive Heck reaction.

single-crystal X-ray crystallography.¹¹ A regio- and stereo-selective reductive Heck reaction developed by Merck^{6b,c} transformed **rac-10** to **rac-11** in 56% yield. The stereoselectivity of the reductive Heck reaction can be rationalized by the preferential approach of the arylpalladium species from the less hindered face of the dihydrofuran moiety in **rac-10**, while the regioselectivity arises due to steric considerations.¹⁶

The relative stereochemistry of **rac-11** was also confirmed using NOE analysis¹⁷ where the two benzylic protons in **rac-11** were shown to have NOE correlations, in agreement with the results reported by Merck. **Rac-11** was finally subjected to Pd-catalyzed hydrogenation and Mg-promoted tosyl deprotection with the help of sonication to complete the synthesis of **rac-3** in 51% yield over 2 steps as a white solid instead of a pale yellow oil reported by Merck^{6b} for the reported enantiopure form. The single-crystal X-ray crystal¹¹ structure of **rac-3** is shown (Fig. 4).

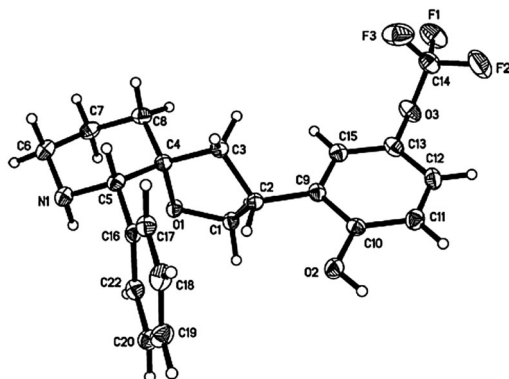
We have demonstrated the efficiency of synthesizing tosyl-protected (2*S*)-phenyl-3-piperidone **2**, a common intermediate for many drugs, from rice straw-derived furfural **1** by employing Hayashi's highly enantioselective rhodium-catalyzed arylation methodology as well as the aza-Achmatowicz rearrangement

reaction. This synthetic strategy has the advantage of being a shorter route with only a single silica gel chromatography step, generating product in higher yield with almost no loss of optical purity, and originating from a renewable source, thus improving its sustainability and alleviating the problems caused by the open-field burning of rice straw. Most importantly, **2** allows facile access to numerous biologically active compounds and its synthetic usefulness has been demonstrated with the synthesis of **rac-3**.

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