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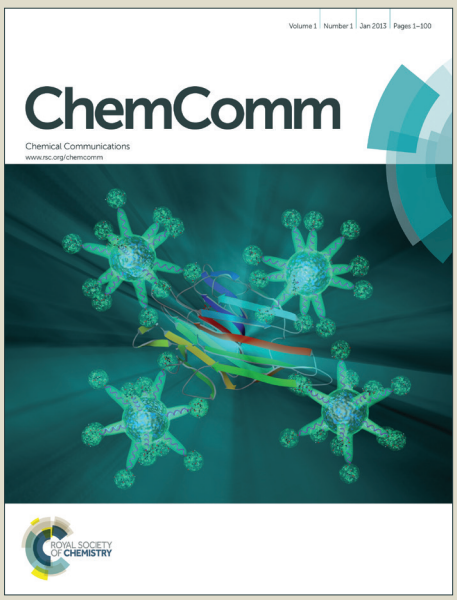

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Biomass Derived Furfural-Based Facile Synthesis of Protected (2*S*)-phenyl-3-piperidone, a Common Intermediate for Many Drugs

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An efficient synthetic route towards tosyl-protected (2*S*)-phenyl-3-piperidone, a common intermediate for many drugs, has been developed in 5 steps with 54% yield from biomass derived furfural. The synthetic utility of the piperidone core structure was demonstrated with the synthesis of a NK_1 receptor antagonist.

Sustained increase in consumption of finite fossil fuel resources has painted a bleak global energy outlook for the 21st century. This has also attracted considerable research attention on 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 cost[2c] which highlights the potential for lower cost price 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/Year), India (97 Mt/Year), Thailand (22 Mt/Year) and the Philippines (11 Mt/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 (2*S*)-phenyl-3-piperidone core structure **2** which allows facile access to numerous neurokinin-1 (NK_1) receptor antagonists (Fig. 1). These potent NK_1 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-piperidone has 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 cheap and renewable biomass-derived starting material, short synthetic route with only a single silica gel column chromatography, almost no loss in optical purity and higher yield than existing methods.

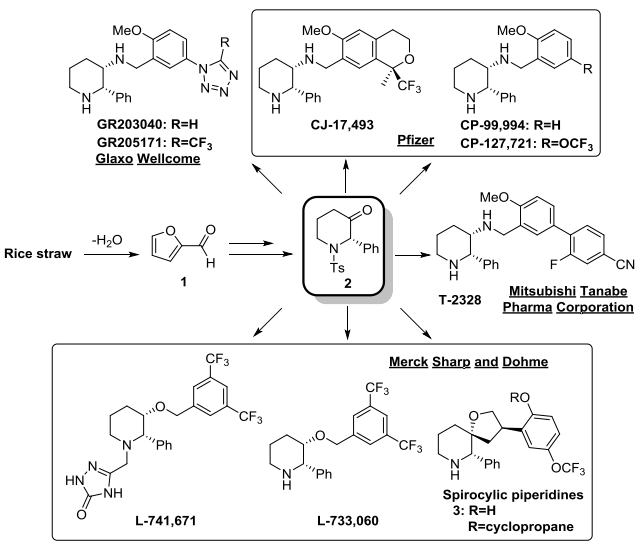
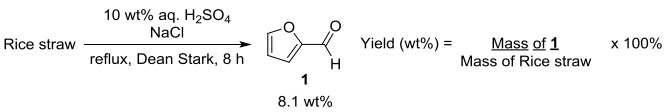


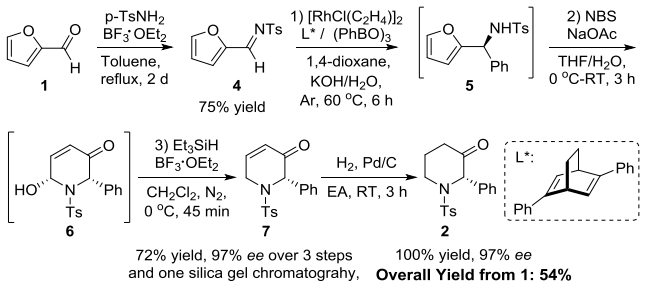
Fig. 1 Construction of piperidone core structure from furfural to access various potent NK_1 receptor antagonists.

Modification of a previously reported synthesis of furfural **1** from corn cobs[8] to rice straw with hourly removal of DCM from the Dean Stark trap gave a yield of 8.1 wt% without optimization (Scheme 1). The crude product obtained was found to sufficiently pure without the need of further purification and could be transformed into imine **4** in the presence of 4-methylbenzenesulfonamide and 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 group[9] 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 rearrangement[10] with *N*-bromosuccinimide (NBS) as oxidant to yield hemiaminal **6** as a *cis* diastereomer, as determined by NMR analysis and single-crystal X-ray crystallography[11] (Fig. 2), probably as a result of anomeric effect. The phenyl substituent at the chiral centre in ***rac*-6** adopts a pseudoaxial orientation due to $A^{1,3}$-strain[12] 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 nucleophile and the latter an alcohol. Crude **6** was able to be immediately reduced[13] without further purification to give **7** with 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 **2** was efficiently synthesized in an overall yield of 54% over 5 steps from rice straw-derived furfural **1**.



Scheme 1 Synthesis of Furfural from rice straw.



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

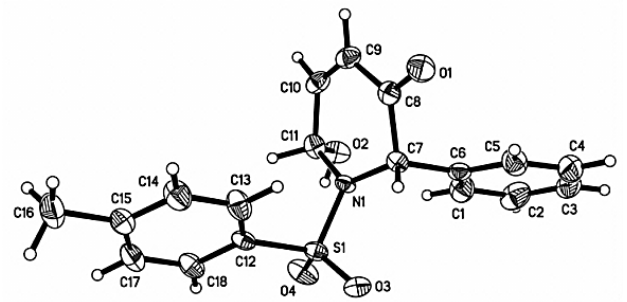


Fig. 2 ORTEP drawing of ***rac*-6**.

The optical rotation obtained for **7** is $[\alpha]^{21}_D$ = +123 (c = 1.32, CH_2Cl_2) for 97% *ee* while that reported in literature[7c] is $[\alpha]^{20}_D$ = -145 (c = 0.3, CH_2Cl_2) and the optical rotation obtained for **2** is $[\alpha]^{23}_D$ = -10.0 (c = 1.01, CH_2Cl_2) for 97% *ee* while that reported in literature[7c] is $[\alpha]^{20}_D$ = +5 (c = 0.2, CH_2Cl_2). The absolute structure of **7** was determined using single-crystal X-ray crystallography[11] (Fig. 3) and further HPLC analysis of the particular single-crystal used in the X-ray crystallography as well as the batch of crystal submitted for analysis showed retention times and elution order that were in agreement with those of experimentally obtained values (see Supporting Information for more details). This rules out the possibility that the structure obtained from 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(2H)-on. This conclusion can be further extended to the absolute configuration of **2** as (*S*)-2-phenyl-1-tosylpiperidin-3-one. The *ee* loss was subsequently determined to be due to the inherent acidity of silica gel chromatography, pre-treatment of silica gel with 1% triethylamine also resulted in *ee* loss 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.

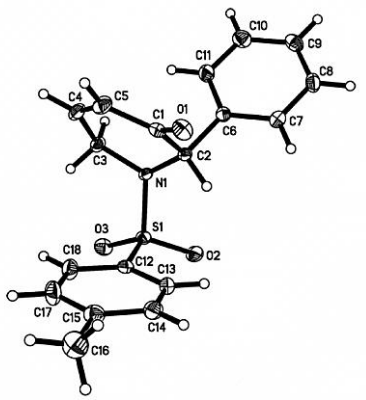
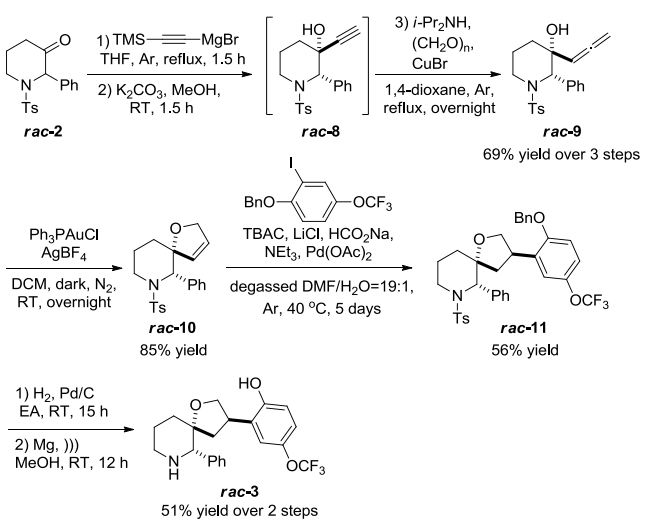


Fig. 3 ORTEP drawing of **7**.

NK_1 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 then subsequent TMS deprotection to form ***rac*-8** which was immediately subjected to Searles-Crabbé Homologation[14] 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 crystallography[11] where the alkyne is *trans* to the phenyl substituent. The preference of the pseudoaxial orientation of the phenyl substituent in ***rac*-2** gives rise to a single diastereomer in the Grignard reaction due to steric hindrance imposed by the phenyl substituent on one face of the carbonyl group.



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

Au-catalyzed cycloisomerisation[15] of ***rac*-9** constructed the spirocycle ***rac*-10** in 85% yield and *rac*-10 was analyzed with single-crystal X-ray crystallography[11]. A regio- and stereoselective 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 analysis[17] 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 in 51% yield over 2 steps to complete the synthesis of ***rac*-3** as a white solid instead of a pale yellow oil reported by Merck[6b] for the reported enantiopure form. The single-crystal X-ray crystallography[11] structure of ***rac*-3** is shown (Fig. 4).

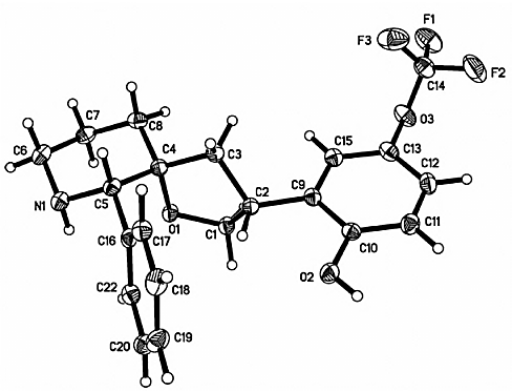


Fig. 4 ORTEP drawing of ***rac*-3.**

Conclusions

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 a shorter route with only a single silica gel chromatography, almost no loss of optical purity, higher yield and originates from a renewable source thus improving its sustainability and alleviates the problems caused by 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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Notes and references

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Electronic Supplementary Information (ESI) available: Additional text with full experimental details, characterization and crystallographic data, chromatograms and NMR spectra. See DOI: 10.1039/b000000x/

1 a) E. E. Hood, P. Nelson and R. Powell, *Plant Biomass Conversion*; Wiley-Blackwell: Chichester, 2011. b) G. Centi and R. A. v. Santen, *Catalysis for renewables: from feedstock to energy production*; Wiley-VCH: Weinheim, 2007. c) D. L. Klass, *Biomass for renewable energy, fuels, and chemicals*; Academic Press: San Diego, 1998.

2 a) K. J. Zeitsch, *The Chemistry and Technology of Furfural and its Many By-Products*; Sugar Series, Vol. 13; Elsevier: Amsterdam, 2000. b) A. Corma, S. Iborra and A. Velty, *Chem. Rev.*, 2007, **107**, 2411-2502. c) R. Xing, W. Qi and G. W. Huber, *Energy Environ. Sci.*, 2011, **4**, 2193-2205.

3 a) J. J. Bozell and G. R. Petersen, *Green Chem.*, 2010, **12**, 539-554. b) J.-P. Lange, E. van der Heide, J. van Buijtenen and R. Price, *ChemSusChem*, 2012, **5**, 150-166. c) F. W. Lichtenthaler and S. Peters, *C. R. Chim.*, 2004, **7**, 65-90. d) P. Srihari and Y. Sridhar, *Eur. J. Org. Chem.*, 2011, **2011**, 6690-6697. e) C. A. Leverett, M. P. Cassidy and A. Padwa, *J. Org. Chem.*, 2006, **71**, 8591-8601. f) M. P. Cassidy and A. Padwa, *Org. Lett.*, 2004, **6**, 4029-4031. g) J. M. Harris and A. Padwa, *J. Org. Chem.*, 2003, **68**, 4371-4381. h) J. M. Harris and A. Padwa, *Org. Lett.*, 2002, **4**, 2029-2031. i) M. H. Haukaas and G. A. O'Doherty, *Org. Lett.*, 2001, **3**, 401-404. j) A. Kabro, E. C. Escudero-Adán, V. V. Grushin and P. W. N. M. van Leeuwen, *Org. Lett.*, 2012, **14**, 4014-4017.

4 a) K. L. Kadam, L. H. Forrest and W. A. Jacobson, *Biomass Bioenergy*, 2000, **18**, 369-389. b) Q. Li, S. Hu, D. Chen and B. Zhu, *Biomass Bioenergy*, 2012, **47**, 277-288. c) B. Gadde, C. Menke and R. Wassmann, *Biomass Bioenergy*, 2009, **33**, 1532-1546.

5 See Supporting Information for complete list of references for NK_1 receptor antagonists.

6 a) P. E. Maligres, M. M. Waters, J. Lee, R. A. Reamer, D. Askin, M. S. Ashwood and M. Cameron, *J. Org. Chem.*, 2002, **67**, 1093-1101. b) D. J. Wallace, J. M. Goodman, D. J. Kennedy, A. J. Davies, C. J. Cowden, M. S. Ashwood, I. F. Cottrell, U.-H. Dolling and P. J. Reider, *Org. Lett.*, 2001, **3**, 671-674. c) J. J. Kulagowski, N. R. Curtis, C. J. Swain and B. J. Williams, *Org. Lett.*, 2001, **3**, 667-670.

7 a) J. Lee, T. Hoang, S. Lewis, S. A. Weissman, D. Askin, R. P. Volante and P. J. Reider, *Tetrahedron Lett.*, 2001, **42**, 6223-6225. b) C. G. Kokotos and V. K. Aggarwal, *Chem. Commun.*, 2006, 2156-2158. c) X. Gaucher, M. Jida and J. Ollivier, *Synlett*, 2009, 3320-3322. d) N. M. Garrido, M. García, M. R. Sánchez, D. Díez and J. G. Urones, *Synlett*, 2010, 387-390. e) M. Atobe, N. Yamazaki and C. Kibayashi, *J. Org. Chem.*, 2004, **69**, 5595-5607. f) O. Calvez and N. Langlois, *Tetrahedron Lett.*, 1999, **40**, 7099-7100. g) K. Takahashi, H. Nakano and R. Fujita, *Tetrahedron Lett.*, 2005, **46**, 8927-8930. h)

P.-Q. Huang, L.-X. Liu, B.-G. Wei and Y.-P. Ruan, *Org. Lett.*, 2003, **5**, 1927-1929. i) L.-X. Liu, Y.-P. Ruan, Z.-Q. Guo and P.-Q. Huang, *J. Org. Chem.*, 2004, **69**, 6001-6009. j) S. V. Pansare and E. K. Paul, *Org. Biomol. Chem.*, 2012, **10**, 2119-2125.

8 R. Adams and V. Voorhees, *Org. Synth.* 1941**, 1**, 280.

9 a) N. Tokunaga, Y. Otomaru, K. Okamoto, K. Ueyama, R. Shintani and T. Hayashi, *J. Am. Chem. Soc.*, 2004, **126**, 13584-13585. b) G. Berthon and T. Hayashi, Rhodium- and Palladium-Catalyzed Asymmetric Conjugate Additions. In *Catalytic asymmetric conjugate reactions*; ed. A. Córdova, Wiley-VCH: Weinheim, Germany, 2010; p 1-44.

10 a) O. Achmatowicz Jr, P. Bukowski, B. Szechner, Z. Zwierzchowska and A. Zamojski, *Tetrahedron*, 1971, **27**, 1973-1996. b) E. A. Couladouros and M. P. Georgiadis, *J. Org. Chem.*, 1986, **51**, 2725-2727. c) Review: M. A. Ciufolini, C. Y. W. Hermann, Q. Dong, T. Shimizu, S. Swaminathan and N. Xi, *Synlett*, 1998, 105,114. d) Y. Lefebvre, *Tetrahedron Lett.*, 1972, **13**, 133-136. e) Z.-H. Lu and W.-S. Zhou, *J. Chem. Soc., Perkin Trans. 1*, 1993, 593-596. f) Z. Wei-Shan, X. Wen-Ge, L. Zhi-Hui and P. Xin-Fu, *Tetrahedron Lett.*, 1995, **36**, 1291-1294. g) W.-S. Zhou, W.-G. Xie, Z.-H. Lu and X.-F. Pan, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2599-2604. h) L.-X. Liao, Z.-M. Wang, H.-X. Zhang and W.-S. Zhou, *Tetrahedron: Asymmetry*, 1999, **10**, 3649-3657. i) W.-S. Zhou, Z.-H. Lu, Y.-M. Xu, L.-X. Liao and Z.-M. Wang, *Tetrahedron*, 1999, **55**, 11959-11983. j) H.-J. Altenbach and R. Wischnat, *Tetrahedron Lett.*, 1995, **36**, 4983-4984. k) J. C. P. Hopman, E. van den Berg, L. O. Ollero, H. Hiemstra and W. Nico Speckamp, *Tetrahedron Lett.*, 1995, **36**, 4315-4318. l) The mechanism for aza-Achmatowicz rearrangement is illustrated in the Supporting Information.

11 The CIF files, ORTEP drawings and CCDC Deposition Numbers of the crystalline compounds are provided in the Supporting Information.

12 a) J. D. Brown, M. A. Foley and D. L. Comins, *J. Am. Chem. Soc.*, 1988, **110**, 7445-7447. b) S.-e. Yoo and S. H. Lee, *J. Org. Chem.*, 1994, **59**, 6968-6972.

13 M. D. Lewis, J. K. Cha and Y. Kishi, *J. Am. Chem. Soc.*, 1982, **104**, 4976-4978.

14 S. Searles, Y. Li, B. Nassim, M.-T. R. Lopes, P. T. Tran and P. Crabbé, *J. Chem. Soc., Perkin Trans. 1*, 1984, 747-751.

15 B. Gockel and N. Krause, *Org. Lett.*, 2006, **8**, 4485-4488.

16 R. F. Heck, Palladium-Catalyzed Vinylation of Organic Halides. In *Organic Reactions*; ed. W. G. Dauben, John Wiley & Sons Inc: New York, 1982; Vol. 27, p 345.

17 COSY, HMQC and Nuclear Overhauser Effect analysis are available in Supporting Information.

