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Practical chemoenzymatic synthesis of a 3-pyridylethanolamino β_3 adrenergic receptor agonist

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Abstract

A chemoenzymatic synthesis of β_3 agonist **1** suitable for large scale preparation is described. The key chiral 3-pyridylethanolamine intermediate (*R*)-**7** was prepared via an improved Neber rearrangement and a yeast-mediated asymmetric reduction. The tetrazolone fragment of the molecule was constructed via a dipolar cycloaddition between 1-(cyclopentyl)-3-propylazide and *p*-chlorosulfonyl phenylisocyanate. Sulfonamide coupling of these two intermediates under Shotten–Baumann conditions, followed by a borane reduction of the amide afforded **1** in 20–32% overall yield from 3-acetylpyridine.

Obesity affects approximately 30% of the adult population, and is closely associated with the development of type II diabetes, coronary artery diseases, and hypertension. The morbidities associated with these diseases are sometimes reversed by weight loss.[1] Compound **1** is proposed to act by a novel mechanism elevating metabolic rate through thermogenesis resulting from the stimulation of β_3 adrenergic receptors (AR) in brown adipose tissue.[2] The elevation of metabolic rate, in the absence of increased food intake, will lead to weight loss over time. β_3 AR agonists have also demonstrated a direct improvement on glucose tolerance and therefore may be very important in the treatment of type II diabetes.[1] In order to carry out further studies with this compound, we required a practical chiral synthesis. This paper describes the process used to provide kilogram quantities of compound **1**, a potent, selective β_3 AR agonist.[3]

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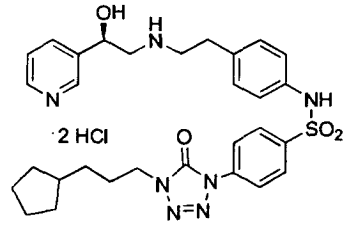
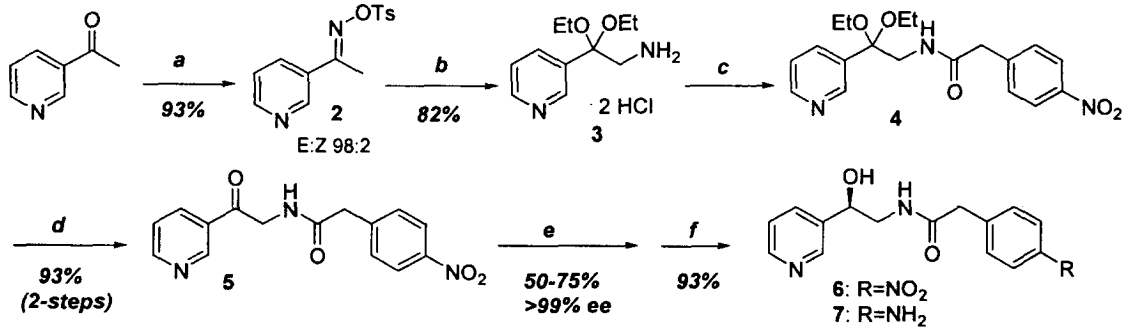


1
di-HCl salt

Compound **1** consists of a chiral *N*-alkylated 3-pyridylethanolamine fragment and a tetrazolone sulfonyl fragment connected through a sulfonamide bond. Previous synthesis of the pyridyl ethanolamine portion involved a (–)-DIP-Cl asymmetric reduction of 3-pyridyl chloromethyl ketone, followed by epoxide formation of the resulting chlorohydrin, and then opening of the epoxide with the appropriate amine.[2] For our synthesis, we took a different approach where the amine moiety was incorporated in the form of amide early in the synthesis prior to introduction of the chiral alcohol. The synthesis of **7** is outlined in Scheme 1.



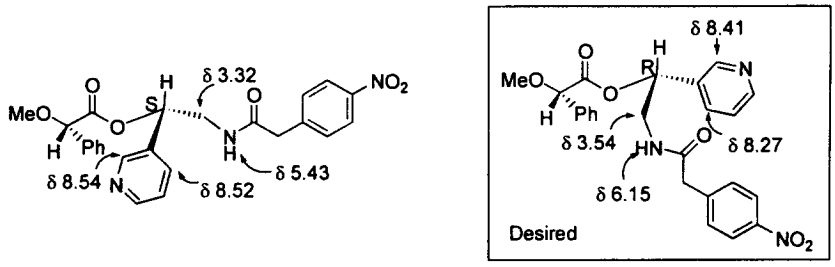
Scheme 1. **a**. 1. $NH_2OH \cdot HCl$; 2. TsCl, pyr; **b**. 1. EtOK, EtOH; 2. HCl, MTBE; **c**. EDC, THF, H_2O, pH 5.5, *p*-nitrophenyl acetic acid; **d**. aq. HCl; **e**. yeast-mediated bioreduction; **f**. H2, Pd/C, MeOH, NH_4OH

We have improved significantly upon an organic synthesis procedure[4] for the preparation of 3-pyridyl-aminomethyl ketal **3** via a Neber rearrangement reaction, and also noted some safety issues.[5] Compound **3** was prepared in 76% overall yield from 3-acetylpyridine in three steps via tosyl oxime **2**. The oxime formation and the tosylation steps[5] (93% overall yield) were carried out in a one-pot fashion using pyridine as the solvent. Under such conditions, the *E*-isomer of oxime predominates (>97:3). Water was removed by azeotropic distillation prior to the tosylation. Tosyl oxime **2** was crystallized from the reaction mixture by addition of water, and the wet cake was used directly in the Neber rearrangement by adding EtOK to a mixture of **2** in EtOH at 10–30°C. After removal of the TsOK salt,[6] the filtrate was treated with gasesous HCl (final pH 1–2) to precipitate the amino ketal di-HCl salt **3** (82%). A carbodiimide-mediated coupling of **3** with *p*-nitrophenylacetic acid in THF/H_2O followed by a selective hydrolysis of the resulting amide-ketal **4** with concomitant removal of ethanol afforded pyridyl ketone **5** (93% for the two steps).[12]

With ketone **5** in hand, we screened methods for the key asymmetric reduction of the ketone to the chiral alcohol. Unfortunately, preliminary results from most known methods gave poor enantioselectivity and in some cases reduction of pyridine ring was observed (e.g. asymmetric hydrogenation with (*S*)-tol-BiNAP–$RuCl_2$–Et_3N complex afforded the reduced pyridine vinyloguous amide as the major product, with **6** as the minor product in only 6% ee). Alternatively, initial results using Baker's yeast (*Saccharomyces cerevisiae*) were encouraging,[7] which provided product in 70–80% ee. Subsequently, a microbial screen identified the yeast *Candida sorbophila* as a suitable biocatalyst,[8] which furnished the

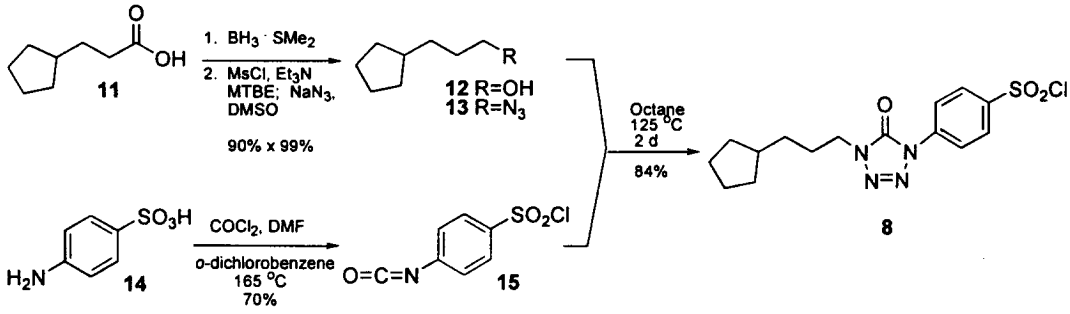
chiral alcohol **6**[12] in ~98% ee and 70–90% conversion after incubation for 2 days at 28°C. The material was routely isolated in ~75% yield and >99.5% ee.[9] The absolute configuration of the secondary alcohol produced in the yeast-mediated reduction of ketone **5** was determined to be the desired *R*-enantiomer by NMR analysis of the (*S*)-methoxyphenylacetate esters based on Trost's method[10] and by comparision with materials derived from Shih's synthesis using (–)-DIP-Cl.[2] As shown below, the chemical shifts of the pyridyl protons of the *R*-isomer was shielded by the mandelate phenyl ring by 0.11–0.25 ppm relative to the *S*-isomer (at +20°C).

The optical purities of the crude **6** in the fermentation broth and the isolated **6** were determined to be >97.5% ee and >99.5% ee, respectively, by chiral HPLC using Chiracel OD-H (20/80 IPA/hexanes, 0.8 mL/min, 254 nm; or SFC, 300 bar CO_2, 16% MeOH (20 mM *i*PrNH$_2$), 1.0 mL/min, 35°C).



Nitro compound **6** was hydrogenated (20 psi H_2) over 5% Pd/C (4 wt%) in methanol with 1.7 equiv. NH_4OH, conditions which minimized impurities derived from the intermediary nitroso compound. The reaction was run at 40°C for ~3 h until the uptake of H_2 had stopped. Aniline **7** was crystallized in high yield (96–97%) and purity (>99 A%).[12]

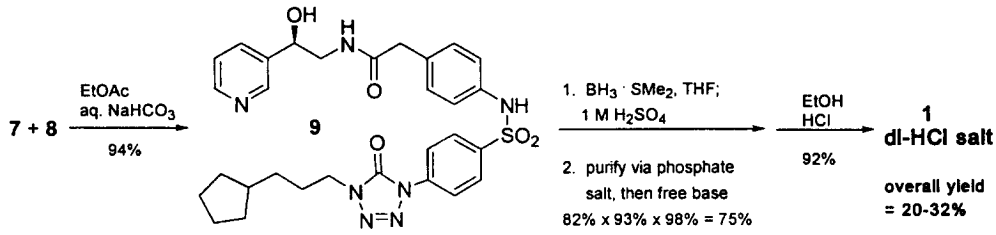
The southern half of the molecule was constructed as shown in Scheme 2. The cycloaddition between azide **13** and isocyanate **15** took place at 125°C to provide the tetrazolone **8** in 84% yield.[11]



Scheme 2.

Subsequent coupling of aniline **7** and sulfonyl chloride **8** under Schotten–Baumann conditions afforded the penultimate amide **9** in 94% yield (Scheme 3). Selective reduction of the amide with $BH_3 \cdot SMe_2$ (7 equiv.) at +20°C followed by 1 M H_2SO_4 work up at +50°C to break up the borane complexes afforded the crude **1** free base in 82% yield after neutralization. This material was purified to >99% pure by crystallization of the corresponding phosphate salt (93%) followed by free basing (98%), since the di-HCl salt gave poor rejection of the impurities. Finally, the di-HCl salt was prepared from ethanolic HCl in 92% yield.[12]

In summary, we have developed a practical synthesis of β_3 AR agonists **1** and have demonstrated it on kilogram scale. The key chiral pyridyl alcohol intermediate (*R*)-**7** was prepared via an improved Neber rearrangement and a yeast-mediated asymmetric reduction. The key dipolar cycloaddition between azide **15** and isocyanate **17** provided an efficient one-step synthesis of the tetrazolone sulfonyl chloride.



Scheme 3.

Coupling of the aniline and the sulfonyl chloride followed by borane reduction of the amide completed the synthesis of **1** in 20–32% overall yield from 3-acetylpyridine.

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5. CAUTION. The tosylation reaction and isolated tosyl oxime **2** both showed exothermic activity beginning at +40°C. The dried tosylate **2** also showed evidence of possible low-level shock sensitivity (discoloration) at 250 kg cm and above. It is recommend that tosyl chloride is added with temperature control, and the batch temperature is kept between +30–35°C, and the product **2** was preferrably handled as a wet cake. Upon tosylation completion, water was added to crystallize the product. The supernatant was removed by a filter stick and the wet cake was washed with cold *i*PrOH until <1.5 wt% water. Ethanol was then added to the wet cake and used directly in the next step. The Neber rearragement step can tolerate up to 30 mol% of water without effecting the yield.
6. Addition of MTBE and solka floc before filtration significantly improved the filtration rate.
7. Baker's yeast reduction of pyridyl ketones and α-amido ketones: Izumi, T.; Fukaya, K. *Bull. Chem. Soc. Jpn.* **1993**, 1216. Takeshita, M.; Terada, K.; Akutsu, N. *Heterocycles* **1987**, 3051.
8. (a) Chartrain, M.; Chung, J. Y. L.; Roberge, C. WO patent 9803672, 1998. (b) Chartrain, M.; Roberge, C; Chung, J.; McNamara, J.; Zhao, D.; Olewinski, R.; Hunt, G.; Salmon, P.; Roush, D.; Yamazaki, S.; Wang, T.; Grabowski, E.; Buckland, B.; Greasham, R. *Enzyme Microb. Technol.* **1999**, in press.
9. The bioconversion assay yield ranged from 70–90% depending on the initial concentrations of ketone **5** (5–50 g/L). The isolation involved removal of cells by centrifugation/ultrafiltration and crystallization of alcohol **6** by neutralization of an acidic aqueous solution. The overall yields from the ketone were 52–76%. The purity of the alcohol ranged from 94–95 wt% and 99.5–99.7% ee.
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12. All the new compounds were well characterized by ^{1}H NMR, ^{13}C NMR and elemental analysis. Data for compounds **3**, **5**, **7**, **8**, and **1** are listed below. For compounds **2**, **4**, **6**, and **9** data are readily available upon request. Amino ketal **3**: ^{1}H NMR (CD_3OD) δ 9.07 (d, J=1.9 Hz, 1H), 8.99 (d, J=6.0 Hz, 1H), 8.83 (dt, J=8.3, 1.6 Hz, 1H), 8.26 (dd, J=8.3, 6.0, 1H), 3.61 (m, 2H), 3.59 (brs, 2H), 3.46 (m, 2H), 1.30 (t, J=7 Hz, 6H); ^{13}C NMR (CD_3OD) δ 147.1, 143.8, 142.5, 139.9, 129.3, 99.9, 59.2, 44.5, 15.0. Anal. calcd for $C_{11}H_{20}Cl_2N_2O_2 \cdot 3/4$ KCl: C, 38.96; H, 5.94; N, 8.26. Found: C, 38.81; H, 5.83; N, 8.00. Keto-amide **5**: ^{1}H NMR ($CDCl_3$) δ 9.17 (d, J=1.7 Hz, 1H), 8.84 (dd, J=4.8, 1.7 Hz, 1H), 8.22 (d, J=8.7 Hz, 2H), 8.23 (m, 1H), 7.52 (d, J=8.7 Hz, 2H), 7.47 (m, 1H), 6.60 (brs, NH), 4.78 (d, J=4.4 Hz, 2H), 3.78 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 193.1, 169.3, 154.7, 149.3, 147.3, 141.8, 135.2, 130.3, 129.7, 124.0, 123.9, 46.7, 43.0. Anal. calcd for $C_{15}H_{13}N_3O_4$: C, 60.20; H, 4.38; N, 14.04. Found: C, 59.82; H, 4.24; N, 13.83. Aniline-alcohol **7**: ^{1}H NMR (CD_3OD) δ 8.49 (d, J=2.0 Hz,

1H), 8.40 (dd, J=4.9, 1.6 Hz, 1H), 7.72 (dt, J=8.0, 1.6 Hz, 1H), 7.34 (dd, J=7.8, 5.0 Hz, 1H), 6.94 (d, J=8.4 Hz, 2H), 6.66 (d, J=8.4 Hz, 2H), 4.78 (t, J=6.1 Hz, 1H), 3.42 (d, J=6.1 Hz, 2H), 3.31 (s, 2H); ^{13}C NMR (CD_3OD) δ 175.2, 149.1, 148.3, 147.7, 140.2, 136.3, 130.8, 125.9, 125.1, 116.8, 71.1, 47.5, 43.1. Anal. calcd for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.07; H, 6.35; N, 15.29. Tetrazole sulfonyl chloride **8**: ^{1}H NMR ($CDCl_3$) δ 8.35 (d, J=9.1 Hz, 2H), 8.16 (d, J=9.1 Hz, 2H), 4.03 (t, J=7.2 Hz, 2H), 1.90 (m, 2H), 1.85–1.70 (m, 3H), 1.65–1.45 (m, 4H), 1.40 (m, 2H), 1.08 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 148.7, 142.2, 139.9, 128.7, 118.8, 45.6, 39.5, 32.7, 32.6, 27.6, 25.1. Anal. calcd for $C_{15}H_{19}ClN_4O_3S$: C, 48.58; H, 5.16; Cl, 9.56; N, 15.11. Found: C, 48.87; H, 5.21; Cl, 9.29; N, 14.90. 1·2HCl: ^{1}H NMR (CD_3OD) δ 9.01 (d, J=1.2 Hz, 1H), 8.86 (d, J=5.6 Hz, 1H), 8.76 (dt, J=8.1, 1.5 Hz, 1H), 8.14 (dd, J=8.1, 5.6 Hz, 1H), 8.06 (d, J=8.9 Hz, 2H), 7.88 (d, J=8.9 Hz, 2H), 7.19 (d, J=8.6 Hz, 2H), 7.10 (d, J=8.6 Hz, 2H), 5.37 (dd, J=9.8, 3.1 Hz, 1H), 4.00 (t, J=7.1 Hz, 2H), 3.49 (dd, J=12.8, 3.3 Hz, 1H), 3.35–3.20 (m, 3H), 3.00 (m, 2H), 1.92–1.70 (m, 5H), 1.70–1.45 (m, 4H), 1.45–1.30 (m, 2H), 1.10 (m, 2H); ^{13}C NMR (CD_3OD) δ 150.1, 145.9, 143.3, 142.5, 141.1, 139.7, 139.4, 137.8, 134.4, 130.7, 129.7, 128.7, 122.8, 120.0, 66.9, 53.7, 50.0, 46.4, 40.9, 33.9, 33.6, 32.4, 28.6, 26.1. Anal. calcd for $C_{30}H_{39}C_{12}N_7O_4S$: C, 54.21; H, 5.91; Cl, 10.67; N, 14.75; S, 4.82. Found: C, 54.35; H, 5.90; Cl, 10.78; N, 14.64; S, 4.87.