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A Concise Synthetic Pathway for *trans*-Metanicotine Analogues

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A convenient pathway for synthesis of *trans*-metanicotine analogues was developed. *trans*-Metanicotine, a subtype($\alpha4\beta2$)-selective ligand for neuronal nicotinic acetylcholine receptor, is under clinical phase for Alzheimer's disease. Zn-mediated allylation of allyl bromide and acetaldehyde followed by Heck reaction with 3-bromopyridine gave 5-pyridin-3-yl-pent-4-en-3-ol **(2)**. Tosylation of 5-pyridin-3-yl-pent-4-en-3-ol followed by substitution reaction with methylamine in sealed tube gave methyl-(1-methyl-4-pyridin-3-yl-but-3-enyl)-amine **(4)** in good yields. Thus, *trans*-metanicotine analogues modified at the α-position of the methylamino group with various functional groups can be obtained in 4 steps.

Key words: Alzheimer' disease, Nicotinic acetylcholine receptor, $\alpha4\beta2$ Subtype, *trans*-Metanicotine, Zn-Mediated allylation, Heck reaction

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive loss of cognitive functions such as memory and judgement, and motor function, which affects aged individuals exclusively and culminates in the death of the patient (Eggert *et al.*, 1996). Although much is known about the neuropathology of AD, the precise etiology of the disease still remains unknown. Multiple genetics, enviromental, infectious and immunological theories about the etiology of AD have been proposed, but there is no general consensus on any of them. There is, however, strong evidence for a central role of the neuronal cholinergic system in cognitive impairment though AD is affected by multiple neurotransmitters. The selective atrophy of cholinergic neurons in the nucleus basalis, the medical septum and other basal forebrain areas, and the pathological changes observed in the hippocampus and cerebral cortex of AD patients are well documented. Decreases in the levels of cholinergic neuronal markers such as acetylcholine, cholin acetyltransferase, and acetylcholineesterase have been documented in AD. Furthermore, the decline in cognitive function in AD patients correlates well with the loss of cholinergic activity in the cortex and hippocampus (Bartus *et al.*, 1982; Coyle *et al.* 1983; Davis and Yamamura, 1978). Based on the cholinergic hypothesis of AD as mentioned above, therapeutic approaches for the treatment of AD have focused on the replacement of lost cholinergic function. This can be accomplished by enhancing endogenous levels of acetylcholine through inhibition of its degradation by acetylcholineesterase or by directly mimicking its actions at receptor levels such as muscarinic or nicotinic receptors.

Much of the recent increase in research on nicotinic ligands has been motivated by a growing body of evidence that nicotinic cholinergic pharmacology plays a role in disorder associated with deficits of cognitive function in humans (Arneric *et al.*, 1995; Karan, 1993; Levin, 1993; Whitehouse, 1993). The importance of developing novel nicotinic ligands as potential therapeutics is emphasized by studies with nicotine itself that have demonstrated many useful CNS and cognitive effects in various disorders such as dementia (Holladay *et al.*, 1997; Williams *et al.*, 1994). However, its side effects at peri-pheral sites such as neuromuscular and cardiovascular limits its usefulness as a therapeutic tool (Corrigal, 1993; Khosla *et al.*, 1994; Oates *et al.*, 1988). Recent advance in molecular biology enables us to understand that nicotinic receptor exists in multiple receptor subtypes (Galzi *et al.* 1995) and among them $\alpha4\beta2$ subtype mediates the cognitive effects. In this regard, we have been interested in synthesis of novel nicotinic ligands that have CNS selectivity, especially to $\alpha4\beta2$ subtype, and may offer the potential beneficial effects of nicotine without the accompanying undesirable peripheral side effects, particularly those at neuromuscular and cardiovascular sites. Toward this end, we select *trans*-metanicotine (Fig. 1) as a lead compound to optimize since it has a great selectivity to the subtype what we are targeted (Bencherif *et al.* 1996; Lippiello *et al.*, 1996) however, it was reported to have a moderate binding

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trans-metanicotine

Fig. 1. Structures of *trans*-Metanicotine and *trans*-Metanicotine Analogues

affinity and be metabolized *in vivo* experiment.

In this paper, we wish to introduce a concise pathway for synthesis of novel *trans*-metanicotine analogues (Fig. 1). The analogues, which have a substituent at the α-position of the methylamino group in the side chain of *trans*-metanicotine to protect molecules from metabolic fate, are designed since *trans*-metanicotine expect to be biotransformed to several metabolites *in vivo* test (Fig. 2). We expect that the substituents would play a role to prevent the molecules from metabolic reactions by inducing steric hindrance as well as modulate biological profiles by changing electronic environment. It is well established phenomena that metabolic reactions of amines by momoamine oxidase is generally suppressed by introducing a substituent at the α-position of amino groups.

MATERIALS AND METHODS

Materials

All starting materials were obtained from commercial suppliers, and used without further purification. All solvents used for reaction were freshly distilled from proper dehydrating agent under nitrogen gas. All solvents used for chromatography were purchased and directly applied without further purification. ^{1}H-NMR spectra were recorded on a Varian Gemini 2000 instrument (200 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) downfield relative to tetramethylsilane as an internal standard. Peak splitting patterns are abbreviated as m (multiplet), s (singlet), bs (broad singlet), d (doublet), bd (broad doublet), and dd (doublet of doublets). ^{13}C-NMR spectra were recorded on a Varian Gemini 2000 instrument (50 MHz) spectrometer, fully decoupled and chemical shifts are reported in parts per million (ppm) downfield relative to tetramethylsilane as

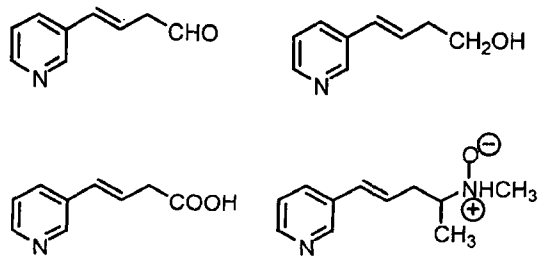
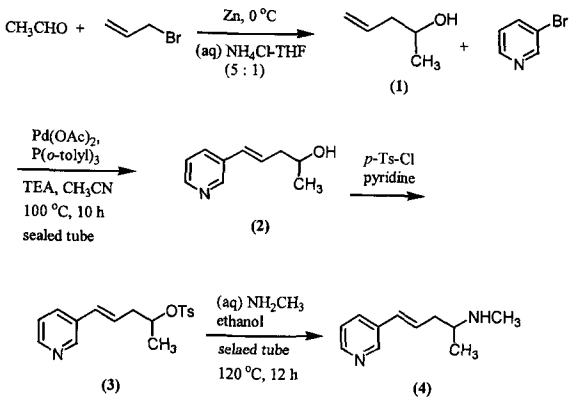


Fig. 2. Structures of *trans*-Metanicotine Metabolites



Scheme 1. Synthetic Pathway for *trans*-Metanicotine Analogues.

an internal standard. Analytical thin-layer chromatography (TLC) was performed using commercial glass plate with silica gel 60F 254 purchased from Merck. Chromatographic purification was carried out by flash chromatography using Kieselgel 60 (230~400 mesh, Merck).

Synthetic procedures

Pent-4-en-2-ol (1)

To a stirred solution of acetaldehyde (1.3 g, 30 mmole) and allyl bromide (10.9 g, 90 mmole) in saturated aqueous ammonium chloride (125 mL) and tetrahydrofuran (25 mL) was added zinc dust (11.9 g, 180 mmole) slowly in ice-bath. After 1 h, the reaction mixture was filtered to remove zinc and the filtrate was extracted with methylene chloride (200 mL). Organic layer was separated and dried over anhydrous magnesium sulfate. After removal of magnesium sulfate, evaporation of the filtrate under reduced pressure gave 2.7 g (91%) of the titled compound as pale yellowish syrup. The product was used to the next reaction without further purification. ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 1.12 (d, J=7.4 Hz, 3H), 1.85-1.87 (bs, 1H), 2.09-2.35 (m, 2H), 3.72-3.93 (m, 1H), 5.18 (dd, J=4 Hz, 0.9 Hz, 2H), 5.73-5.94 (m, 1H).

5-Pyridin-3-yl-pent-4-en-3-ol (2)

Mixture of pent-4-en-2-ol (2.7 g, 30 mmole), 3-bromopyridine (5 g, 31.5 mmole), palladium acetate (0.1 g, 0.45 mmole), tri-*o*-tolylphosphine (0.55 g, 1.8 mmole), triethylamine (18 mL) and acetonitrile (24 mL) was heated to 100°C in sealed tube for 10 h. The sealed tube was cooled to room temperature and was added methylene chloride (250 mL). The organic layer was washed with brine (150 mL) and dried over anhydrous magnesium sulfate. After removal of solvents, purification of the crude product by flash column chromatography (chloroformmethanol=100 :1) gave 2.7 g (61%) of the titled compound as pale brown color syrup. ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 1.28 (d, J= 6.1 Hz, 3H), 2.10-2.13 (bs, 1H), 2.40-2.45 (m, 2H),

3.90-4.02 (m, 1H), 6.25-6.51 (m, 2H), 7.23 (dd, J=7.9 Hz, 4.9 Hz, 1H), 7.68 (d, J=7.9 Hz, 1H), 8.44 (d, J=4.3 Hz, 1H), 8.56 (s, 1H).

Toluene-4-sulfonic acid 1-methyl-4-pyridin-3-yl-but-3-enyl ester (3)

Mixture of 5-pyridin-3-yl-pent-4-en-3-ol (1.9 g, 11.4 mmole) and *p*-toluenesulfonyl chloride (2.4 g, 12.5 mmole) in anhydrous pyrine (6 mL) was stirred at room temperature for overnight. After removal of pyrine under reduced pressure, purification of the residue by flash column chromatography (chloroform) gave 2.7 g (75%) of the titled compound as white solid. ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 1.36 (d, J=6.4 Hz, 3H), 2.37 (s, 1H), 2.41-2.53 (m, 2H), 4.65-4.73 (m, 1H), 5.90-6.44 (m, 2H), 7.21-7.36 (m, 1H), 7.76 (d, J=8.2 Hz, 1H), 8.45 (bs, 1H), 8.62 (bs, 1H).

Methyl-(1-methyl-4-pyridin-3-yl-but-3-enyl)-amine (4)

Toluene-4-sulfonic acid 1-methyl-4-pyridin-3-yl-but-3-enyl ester (2.7 g, 8.5 mmole) was dissolved in ethanol (5 mL) and aqueous methylamine solution (32%, 5 mL). The mixture was heated to 120°C in sealed tube for 12 hours. The reaction mixture was cooled to room temperature and was added methylene chloride (150 mL). The organic layer was washed with saturated aqueous sodium bicarbonate solution (150 mL), brine (150 mL) and dried over anhydrous magnesium sulfate. After removal of solvents, purification of the crude product by flash column chromatography (chloroform-methanol=20 :1) gave 1.3 g (87%) of the titled compound as pale yellow color syrup. ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 1.39 (d, J=6.4 Hz, 3H), 2.52-2.88 (m, 2H), 2.70 (s, 3H), 3.25-3.35 (m, 1H), 6.16-6.31 (m, 1H), 6.45 (d, J=16.0 Hz, 1H), 7.17 (bd, J=8.2 Hz, 1H), 7.71 (dd, J=8.2 Hz, 10.8 Hz), 8.42 (d, J=4.2 Hz, 1H), 8.53 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.55, 133.05, 131.04, 129.11, 126.01, 128.82, 55.02, 36.66, 30.40, 15.79.

RESULTS AND DISCUSSION

A convenient pathway for synthesis of *trans*-metanicotine analogues was developed as described in Scheme 1. Zinc-mediated allylation (Li, 1993; Petrier *et al.* 1985) of allyl bromide and acetaldehyde in aqueous media gave alcohol **1** in excellent yield (91%). The alcohol and 3-bromopyridine was reacted under "Heck" reaction conditions (Frank *et al.*, 1978) in sealed tube produced coupled product **2**. The product was converted to tosylate **3** under general conditions. Methylamino group was introduced by heating the tosylate with aqueous methylamine solution (32%) in sealed tube. Thus, we could synthesize methyl analogue of *trans*-metanicotine **4** in 4 steps and this pathway is suitable for synthesis of *trans*-metanicotine analogues modified at the α-position of the methylamino group without any protection-deprotection steps.

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