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Synthesis of (1-(Aminomethyl)-2,3-dihydro-1*H*-inden-3-yl)methanol: Structural Confirmation of the Main Band Impurity Found in Varenicline® Starting Material

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Abstract: Described here is the synthesis of (1-(aminomethyl)-2,3-dihydro-1*H*-inden-3-yl)methanol **1**, the previously unidentified impurity found in the synthesis of **2**,[1] providing a confirmation of the structure. Fabbrica Italiano Sintetici (FIS), working in conjunction with Pfizer Groton, reported an unidentified impurity, referred to as the "main band impurity", in **2** at levels of 0.4 to 0.8%. The structure was postulated to be **1**, the open-ring product of the lithium aluminum hydride (LAH) reduction of **3** to **2.** Although the cis isomer of **1** was previously reported in the literature,[2] a much shorter racemic synthesis was developed using intermediates employed for the production of Varenicline®. Several reducing agents were screened for the synthesis of **1**, with $LiAlH_4$ followed by basic workup conditions giving optimal results. High performance liquid chromatography (HPLC) analysis ultimately confirmed the structure of **1** as the main band impurity generated during the synthesis of **2**.

Keywords: Varenicline, amino alcohol, reduction

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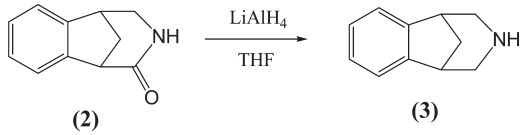
INTRODUCTION

Varenicline® is being developed by Pfizer for the treatment of nicotine addiction. It was selected because of its partial agonist effect upon the $\alpha 4\beta 2$-nicotinic receptor.[3] The development goal was to suppress the biochemical reward of smoking while helping to alleviate the cravings of withdrawal.[4] Smoking tobacco contributes to an estimated 440,000 premature deaths in the United States each year; including an estimated 90% of the 157,200 lung cancer deaths annually in the United States.[5] Additionally, smoking contributes to mortality through chronic obstructive pulmonary disease (COPD), stroke, heart disease, and other cancers. The surgeon general of the United States has concluded that "smoking harms nearly every organ in your body".[6] To advance this candidate, large-scale production of the intermediates was required. During the scale-up of this chemistry, analysts reported an unidentified impurity at 0.4 to 0.8% in **3**, a key intermediate in the Varenicline® process. In the Varenicline® synthesis,[7,8] **2** is reduced with $LiAlH_4$ to give **3**[9–11] as shown in Scheme 1. The identification and synthesis of this impurity is described in this article. Understanding of the structure and its formation allowed process improvements to minimize formation of **1**.

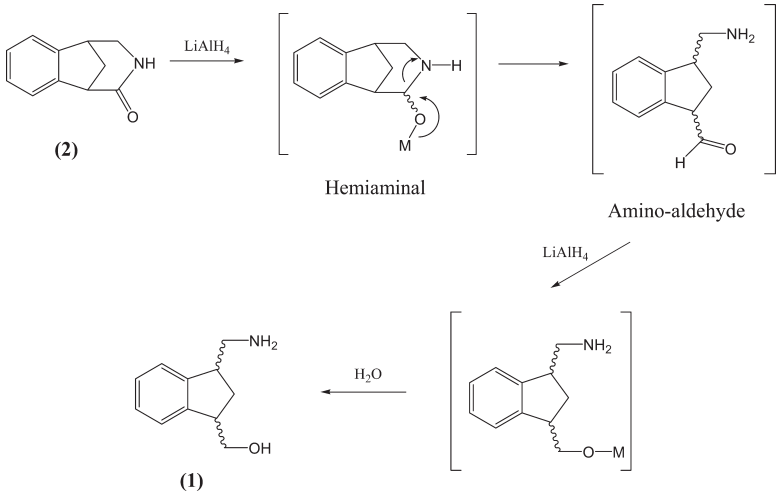
The impurity was initially found to co-elute with the main peak in the initial HPLC method. This resulted in modification of the HPLC method to show the impurity hidden by the main band of **3**; hence it became referred to as the "main band impurity." In a subsequent modified HPLC method, it was possible to resolve the impurity from the main band. The main band impurity was then analyzed by liquid chromatography/mass spectrum (LC/MS), resulting in a monoisotopic mass of 177 amu, which corresponded to the molecular weight of **1**. The structure was hypothesized as the open-ring amino-alcohol. The open structure is in agreement with the standard mechanism of $LiAlH_4$ reductions[12,13] where the hemiaminal intermediate of **2** can undergo ring opening followed by hydrolysis to the amino-aldehyde, which is subsequently reduced to the corresponding amino-alcohol, **1**. The proposed mechanism of formation is shown in Scheme 2.

In the interest of controlling and identifying process-related impurities, an effort was made to synthesize the proposed amino-alcohol, **1**. A literature search found that a chiral synthesis of the target amino-alcohol compound **1** had previously been described.[2] The synthesis, however, consisted of a lengthy seven-step sequence. For this study, it was unnecessary to isolate



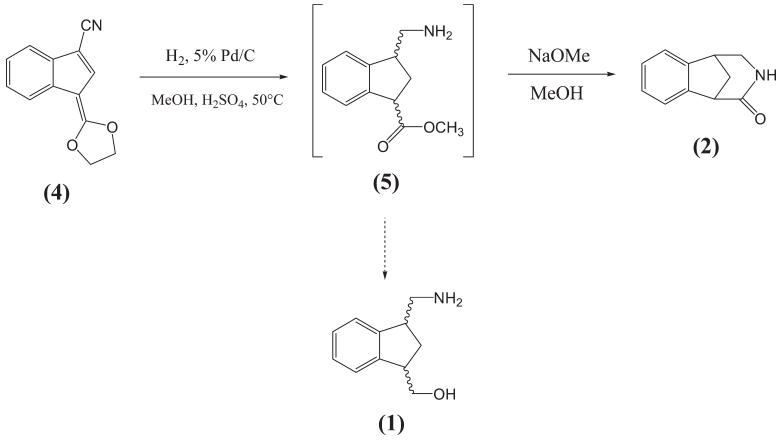
(2) (3)

Scheme 1. Synthesis of **3**.



Scheme 2. Mechanistic pathway to **1**.

the chirally pure, amino-alcohol so it was decided that modifying the chemistry from known Varenicline process intermediates would be much more efficient. As part of the existing Varenicline process, the synthesis of **2** was already well established. Compound **5**, a nonisolated intermediate in the synthesis, has been observed to be a mixture of diastereomers. Compound **5** can be cyclized to **2** in good yield as the isomeric center adjacent to the ester is epimerized under the basic cyclization conditions.[11] Then the precursor to **2**, possessing an ester functionality, would potentially allow reduction to the corresponding alcohol, **1**, as shown in Scheme 3.



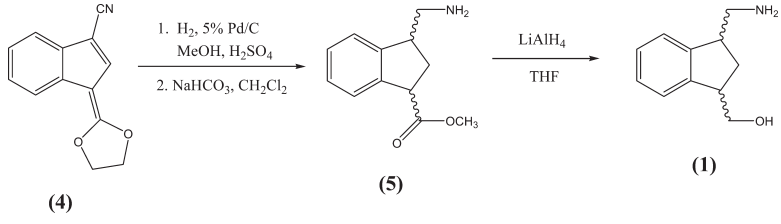
Scheme 3. Going through **5**, the common intermediate.

The reduction of esters to their corresponding alcohols are well known in the literature, with reagents such as $LiAlH_4$,[14] $LiBH_4$,[14] and $NaBH_4$.[15] Hydrogenation of **4**[1] under acidic conditions gives **5**. In the Varenicline process, the **5**/MeOH solution is used without further workup and telescoped directly into the subsequent step to give the cyclized product, **2** (Scheme 3). During the synthesis of **1**, however, **5** is generated similarly, but given a basic workup and isolated as a crude oil prior to being carried forward to the reduction step. As shown in Scheme 4, synthesis of **1** was achieved using $LiAlH_4$ as the reducing agent. Experiments using $LiBH_4$ and $NaBH_4$ were less efficient in the formation of **1**. This observation is consistent with the low-level formation of **1** observed in the conversion of **2** to **3**, as shown in Scheme 1.

The $LiAlH_4$ reduction of **5** successfully produced **1** but also formed higher-molecular-weight molecules, which were shown to be dimeric structures. Under basic reaction conditions, the formation of dimers is not unexpected. Once **5** is produced, it can react with itself to form an amide dimer, followed by partial or complete reduction of the remaining ester functionality. In an effort to maximize the formation of **1** and suppress dimer side products, reverse addition of the **5**/THF mixture to the $LiAlH_4$/tetrahydrofuran (THF) solution was carried out. This decreased the amount of dimer formation but did not eliminate it altogether. Additional reaction parameters were introduced ($-30^{\circ}C$ temperature and slow addition rate of the **5**/THF mixture to the $LiAlH_4$/THF solution), which further maximized the amount of **1** produced. Compound **1** was ultimately isolated via flash chromatography.

CONFIRMATION OF 1 AS THE MAIN BAND IMPURITY

Compound **1** was subjected to the HPLC assay to confirm whether this did indeed match the main band impurity found when analyzing **3**. HPLC analysis of the authentic sample confirmed that **1** was in fact the main band impurity. HPLC analysis also showed compound **1** to be a mixture of diastereomers, as expected. The synthesis of **1** was maximized to permit formation of



Scheme 4. Synthesis of **1**.

a multigram sample by reverse addition of **5** to the LAH solution at low temperature, thus decreasing dimer formation.

The isolation of **3** as a hydrochloride salt, rather than telescoping a solution of the free base forward, greatly reduced the level of **1** in subsequent batches of **3**, thereby minimizing the risk for this impurity to carry over into later steps.

EXPERIMENTAL SECTION

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400-MHz spectrometer. HPLC analysis was performed on an Agilent 1100 using a UV detector at 210 nm. Mass spectral data were collected on a Micromass LCZ instrument using APCI (atmospheric pressure chemical ionization). LC/mass spectral data were collected on a Micromass LCZ (ESI Electrospray).

The palladium on carbon catalyst was manufactured by Johnson Matthey. Flash chromatography was performed on silica gel (Baker 40 μm) and analytical thin-layer chromatography (TLC) on precoated silica-gel glass plates (Analtech Uniplate, 250 μm).

(1-(Aminomethyl)-2,3-dihydro-1*H*-inden-3-yl)methanol (1)

A solution of (**4**) (10 g, 473.4 mmol) in methanol (200 mL) was transferred to a 500-mL stainless steel Parr reactor. Then 50% wet 5% palladium on carbon (1.2 g) was added, followed by sulfuric acid (4.6 g, 473.4 mmol). The system was purged with nitrogen (3 × 20 psi), followed by purging with hydrogen (3 × 20 psi). The system was pressurized to 50 psi hydrogen, warmed to 50°C, and allowed to stir overnight. Mass spectral analysis confirmed the product. The product mixture was filtered through a pad of Celite® to remove spent catalyst. The filtrate was collected, the solvent was evaporated under reduced pressure, and the resulting oil was taken up in methylene chloride (200 mL). This was washed with a saturated aqueous solution of sodium bicarbonate (75 mL). The methylene chloride layer was collected, treated with sodium sulfate and activated carbon, filtered, and the solvent was evaporated under reduced pressure affording (**5**) as a brown oil. The oil, (**5**), was dissolved in THF (110 mL) and added dropwise over 60 min to a 1.0 M solution of $LiAlH_4$ in THF (64.3 mL, 643.2 mmol), which had been cooled to −30°C under a nitrogen atmosphere. Once addition was complete, the pot temperature was kept at −20°C to −30°C for 1 h. In a separate flask, a 95:5 CH_3CN–H_2O mixture (200 ml) was cooled to 0°C. The product mixture was added portionwise to the CH_3CN/H_2O system to quench the reaction. The resulting slurry was allowed to stir 30 min. The inorganic salts were filtered off; the filtrate was collected and vacuum stripped to a brown oil. The brown oil was taken up in EtOAc (100 mL)

and washed with H_2O (50 mL) and brine (50 mL), dried with Na_2SO_4, filtered, and vacuum stripped to an oil. The oil was flash chromatographed (9:1 CH_2Cl_2–MeOH with 1% triethylamine). The clean fractions containing (**1**) were collected and combined, and the solvent was evaporated under reduced pressure to afford (**1**) (2.0 g, 23.8%) as a light brown oil.

Data

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28–7.19 (m, 4H); 3.91 (m, 2H); 3.35 (m, 2H); 3.03 (d, 2H); 2.52 (m, 1H); 2.48 (s, 2H); 2.48 (s, 1H); 1.82 (m, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz) d 145.20 (C); 145.10 (C); 127.38 (CH); 127.32 (CH); 124.41 (CH); 124.01 (CH); 66.38 (CH_2); 46.62 (CH_2); 46.42 (CH_2); 45.58 (CH); 32.35 (CH_2). MS (AP) 178 (M + 1). Anal. calcd. for $C_{11}H_{15}NO$: C, 74.54; H, 8.53. Found: C, 74.36; H, 8.41.

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