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An efficient reduction protocol for the synthesis of β-hydroxycarbamates from β-nitro alcohols in one pot: a facile synthesis of (−)-β-conhydrine

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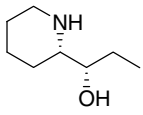
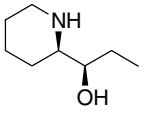
ABSTRACT

An efficient and practical one-pot protocol for the reduction of β-nitro alcohols to their corresponding *N*-(*tert*-butoxycarbonyl) amino alcohols using Zn–NH_4Cl in aqueous methanol is described. Other reducible groups such as ketones and isolated double bonds remained intact. This methodology allows a short synthesis of (−)-β-conhydrine to be achieved.

β-Amino alcohols are useful intermediates in the elaboration of pharmacologically important products and are also widely used in the preparation of chiral auxilaries.[1] They are also found as important partial structures of many bioactive compounds such as α/β-adrenergic agonists or antagonists,[2] HIV protease inhibitors[3] and antifungal or antibacterial peptides.[4] The presence of this moiety and the stereochemistry of the hydroxyl as well as the amino group play a vital role in the biological activity of the parent compound. Moreover, a number of their amide derivatives, isolated from bacterial cultures display significant activity against aminopeptidases.[5] A straightforward method for the synthesis of β-amino alcohols involves reduction of 2-nitroalcohols, which are prepared by condensing aliphatic nitro compounds with a carbonyl compound.[6] Reduction of aromatic nitro compounds to aryl amines can be effected using various reagents.[7] However, procedures for reduction of aliphatic nitro compounds to their corresponding amines are rare.[8] The most commonly used methods for reduction of nitro aliphatics involve catalytic hydrogenation processes and therefore are not applicable to substrates containing double bonds. The use of Zn–NH_4Cl (aq) for reduction of aromatic nitro compounds to their corresponding aryl amines has been reported in the literature, but the scope of this method was not fully explored with aliphatic nitro compounds, especially 2-nitroalcohols, which are known to be susceptible to retro-Henry cleavage.[9] In continuation of our interest in the synthesis of biologically active natural products using aliphatic nitro compounds,[10] and our ongoing efforts to synthesize the alkaloid (−)-β-conhydrine (Fig. 1), we needed a method to reduce 2-nitroalcohol **7a** (Table 1) to its β-hydroxy carbamate without affecting the double bond. Our initial attempts to reduce the nitro group in 4-nitro-6-hepten-3-ol (**7a**) with $NaBH_4$/10% Pd–C,[11] $NaBH_4$–Ni_2B,[12] LAH,[13] LAH–$AlCl_3$[14] and Sn/HCl[15] did not give the desired product and suffered from the drawbacks of complete reduction of both the nitro bond and the double bond and/or decomposition. We argued that Zn–NH_4Cl (aq) might be the system of choice in this case, as catalytic hydrogenation is not a part of the reduction process with this reagent. As expected, when the substrates listed in Table 1 (entries 1–11) were treated with Zn–NH_4Cl (aq) at 0 °C, the reaction proceeded smoothly to give the corresponding 2-amino alcohol in almost quantitative yield (Scheme 1). To our satisfaction, the isolated double bond (entries 3, 7 and 11) remained unaffected under these reaction conditions. We also observed that when Boc_2O was added



(–)-β-conhydrine



(+)-β-conhydrine

Figure 1.

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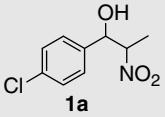
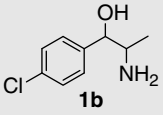
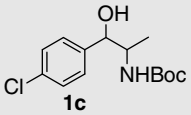
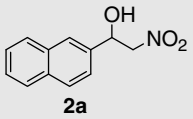
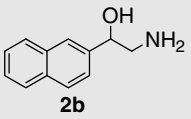
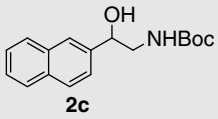
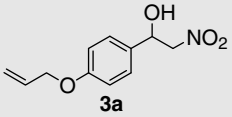
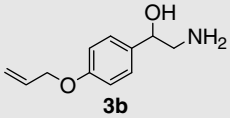
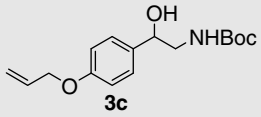
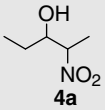
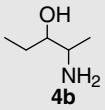
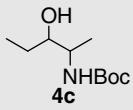
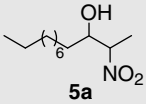
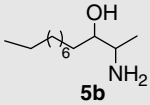
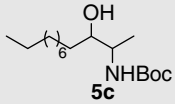
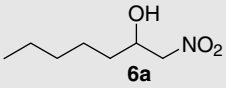
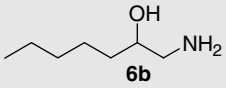
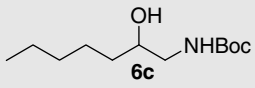
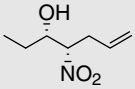
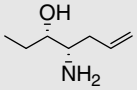
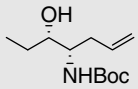
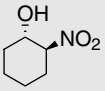
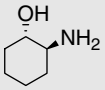
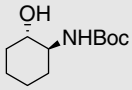
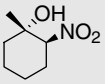
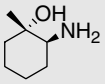
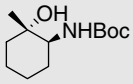
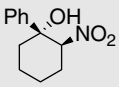
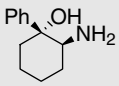
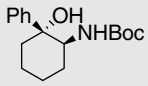
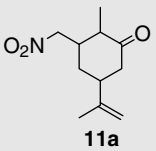
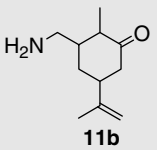
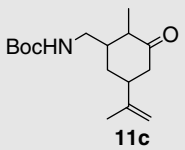
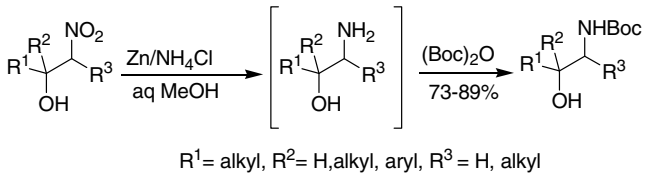
Table 1
Reduction of 2-nitro alcohols to 2-hydroxy carbamates in one-pot using Zn–NH_4Cl(aq)/Boc_2O in methanol

Entry	Substrate[a]	Product		
		2-Amino alcohol	2-Hydroxy carbamate[b]	(Yield)[c]
1	 **1a**	 **1b**	 **1c**	83
2	 **2a**	 **2b**	 **2c**	89
3	 **3a**	 **3b**	 **3c**	78
4	 **4a**	 **4b**	 **4c**	84
5	 **5a**	 **5b**	 **5c**	82
6	 **6a**	 **6b**	 **6c**	83
7	 **7a**	 **7b**	 **7c**	76
8	 **8a**	 **8b**	 **8c**	86
9	 **9a**	 **9b**	 **9c**	79
10	 **10a**	 **10b**	 **10c**	73
11	 **11a**	 **11b**	 **11c**	78

[a] β-Nitroalcohols **1a**–**7a** were prepared by condensing the appropriate nitroalkane with the appropriate aldehyde in the presence of a base. Compounds **8a**–**10a** were prepared from 2-nitrocyclohexane following literature procedures, and compound **11** was prepared by Michael addition of nitromethane to carvone. All the products were characterized by spectroscopic methods before use.
[b] Products were characterized by IR, NMR and MS.
[c] Yield refers to the isolated yield of the carbamate.

to the crude reaction mixtures, the corresponding β-hydroxycarbamates were formed in excellent yields in one-pot.

In a further experiment, carvone was treated with Zn–NH_4Cl (aq) and it was observed that the conjugated double bond of carv-

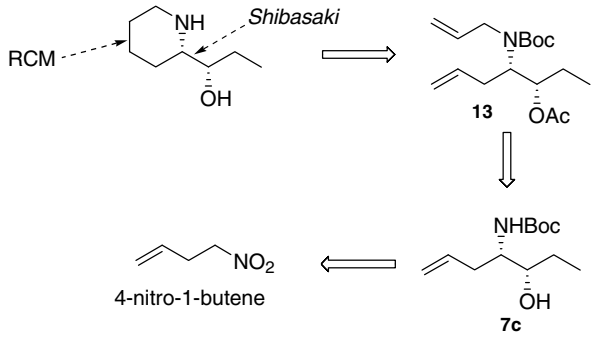


Scheme 1.

one was reduced under these reaction conditions without affecting the isolated double bond which reveals that this reagent works in a single electron transfer (SET) fashion.

We next focused our attention on the synthesis of (−)-β-conhydrine, which is a natural alkaloid having a 2-(1-hydroxyalkyl) piperidine unit and was isolated from the seeds and leaves of the poisonous plant *Conium maculatum* L.[16] Various methods documented in the literature[17] for the synthesis of (−)-β-conhydrine are based mainly on either auxiliary-supported or chiral pool approaches. In formulating a synthetic route to (−)-β-conhydrine, we envisaged that the piperidine ring unit could be obtained from ring-closing metathesis of the dialkene **13** followed by catalytic hydrogenation. The key intermediate amino alcohol **7c** can be traced back to 4-nitro-1-butene. We contemplated that the stereochemistry at the C-3 and C-4 positions of β-conhydrine could be secured via Shibasaki's asymmetric Henry reaction[18] (Scheme 2).

The synthesis was initiated employing Shibasaki's asymmetric Henry reaction of 4-nitro-1-butene[19] with propionaldehyde in the presence of La-(*R*)-BINOL catalyst at −50 °C in THF to afford the key intermediate **7a** in 74% yield and 91% ee[20] (Scheme 3). Treatment of 2-nitroalcohol **7a** with Zn–NH_4Cl (aq)/Boc_2O gave the corresponding β-hydroxy carbamate **7c** in 76% yield, which was then protected as the acetate **12** with acetic anhydride and



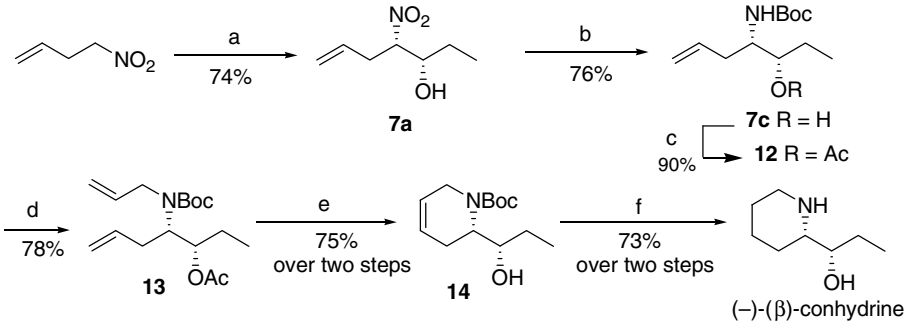
Scheme 2. Retrosynthetic analysis of (−)-β-conhydrine.

pyridine in 90% yield. In order to install the piperidine ring system present in the target molecule, compound **12** was subjected to allylation with allyl bromide and NaH in DMF at room temperature to give the diallyl compound **13** in 78% yield. Compound **13** was then treated with 10 mol % of Grubbs' second generation catalyst following a reported method[21] to give the expected cyclic enamine which was further hydrolysed using K_2CO_3 in methanol to furnish the corresponding alcohol **14** in 75% yield over two steps. Finally, the cyclic enamine **14** was subjected to Pd-C catalyzed hydrogenation followed by Boc deprotection to afford (−)-β-conhydrine. The physical and spectral properties of our synthetic material closely matched with the literature data. Similarly, the synthesis of the other isomer, (+)-β-conhydrine can be achieved simply by changing the ligand in the asymmetric Henry reaction step.

In conclusion, an efficient synthesis of (−)-β-conhydrine has been achieved in 21% overall yield using an asymmetric Henry reaction and our new method for reduction of β-nitro alcohols to their β-hydroxy carbamates as the key steps. To the best of our knowledge, this is the first asymmetric synthesis of (−)-β-conhydrine using Shibasaki's asymmetric Henry reaction as the source of chirality. The synthetic strategy described has significant potential for further extension to the synthesis of (+)-β-conhydrine.

General procedure for the one-pot reduction of 2-nitro alcohols to 2-hydroxy carbamates: To a stirred solution of the 2-nitro alcohol (1 mmol) in methanol and saturated ammonium chloride solution (4 mL, 1:1) was added zinc dust (10 mmol) portionwise over 15 min while maintaining the temperature at 0 °C. After 10 min, $(Boc)_2O$ (1.2 mmol) was added and the reaction mixture was allowed to warm to room temperature. After completion of the reaction (TLC), the reaction mixture was filtered through Celite, the methanol was distilled off under vacuo and the aqueous residue was extracted with diethyl ether (3 × 15 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography over silica gel.

Spectral data of selected compounds: *Compound* **3c:** ^{1}H (300 MHz, $CDCl_3$): 7.43–7.26 (m, 2H), 6.92–6.89 (m, 2H), 6.11–5.98 (m, 1H), 5.38 (dd, 2H, *J* = 18.0, 9.0 Hz), 5.02–5.00 (m, 1H), 4.52 (d, 2H, *J* = 6.0 Hz), 3.71–3.66 (m, 1H), 3.62–3.61 (m, 1H), 1.45 (s, 9H); ^{13}C (75 MHz, $CDCl_3$): δ 153.5, 132.8, 126.9, 125.5, 114.4, 78.2, 74.6, 68.5, 37.4, 27.9; IR ($CHCl_3$): *ν* 3392, 1698, 1632 cm^{-1}; MS (ESI) *m/z*: 293.1 (M^+); *Compound* **4c**: ^{1}H (300 MHz, $CDCl_3$): 4.82–4.79 (m, 1H), 3.49–3.47 (m, 1H), 3.3 (br s, 1H), 2.7 (br s, 1H), 1.44 (m, 2H), 1.37 (s, 9H), 1.01 (d, 3H, *J* = 9.0 Hz), 0.89 (t, 3H, *J* = 4.5 Hz); ^{13}C (75 MHz, $CDCl_3$): δ 155.9, 79.0, 75.5, 49.5, 28.0, 26.06, 18.03, 9.1; IR ($CHCl_3$): *ν* 3440, 2977, 1690 cm^{-1}; MS (ESI) *m/z*: 203.1 (M^+); *Compound* **5c**: ^{1}H (300 MHz, $CDCl_3$): 4.90–4.85 (m, 1H), 3.6–3.5 (m, 1H), 1.42 (s, 9H), 1.26–1.18 (m, 16H), 1.06 (d, 3H, *J* = 6.0 Hz), 0.85 (t, 3H, *J* = 6.0 Hz); ^{13}C (75 MHz, $CDCl_3$): δ 155.9, 79.0, 74.4, 50.1, 33.8, 33.1, 31.5, 29.2, 28.0, 27.4, 25.7, 22.3, 13.7;



Scheme 3. Reagents and conditions: (a) propionaldehyde, La-(*R*)-BINOL, THF, −50 °C, 60 h; (b) Zn–NH_4Cl/MeOH, $(Boc)_2O$, 0 °C–rt, 2 h; (c) Ac_2O, pyridine, rt, 2 h; (d) NaH, allyl bromide, DMF, 0 °C–rt; (e) (i) Grubbs' catalyst, CH_2Cl_2, rt, 10 h; (ii) K_2CO_3, MeOH; (f) (i) H_2, 10% Pd–C, MeOH, 1 atm (ii) TFA, rt.

IR ($CHCl_3$): ν 3440, 2976, 1687 cm^{-1}; MS (ESI) *m/z*: 301.2 (M^+); *Compound* **9c**: ^1H (300 MHz, $CDCl_3$): 4.5 (br s, 1H), 3.49–3.36 (m, 1H), 1.77–1.70 (m, 2H), 1.66–1.62 (m, 2H), 1.45 (s, 9H), 1.18–1.17 (m, 4H), 1.11 (s, 3H); ^{13}C (75 MHz, $CDCl_3$): δ 156.1, 79.7, 75.1, 54.1, 30.0, 28.0, 24.4, 22.7, 22.5, 19.3; IR ($CHCl_3$): ν 3343, 2932, 1686 cm^{-1}; MS (ESI) *m/z*: 229.1 (M^+); *Compound* **7a**: $[\alpha]_D^{20}$ −6.6 (*c* 0.6, $CHCl_3$); ^1H (300 MHz, $CDCl_3$): 5.75–5.71 (m, 1H), 5.21 (dd, 2H, *J* = 9.0, 3.0 Hz), 4.53–4.50 (m, 1H), 3.85–3.81 (m, 1H), 2.62–2.57 (m, 2H), 1.60–1.49 (m, 2H), 0.97 (t, 3H, *J* = 7.5 Hz); ^{13}C (75 MHz, $CDCl_3$): δ 136.7, 124.2, 96.6, 78.2, 39.5, 31.3, 10.8; IR ($CHCl_3$): ν 3420, 2924, 1637, 1551 cm^{-1}; MS (ESI) *m/z*: 159.0 (M^+); *Compound* **7c**: $[\alpha]_D^{20}$ −24.1 (*c* 0.8, $CHCl_3$); ^1H (300 MHz, $CDCl_3$): 5.72–5.70 (m, 1H), 5.19–5.16 (m, 2H), 3.17–3.14 (m, 1H), 3.02–2.99 (m, 1H), 2.57–2.51 (m, 2H), 1.58–1.46 (m, 2H), 1.38 (s, 9H), 0.94 (t, 3H, *J* = 4.8 Hz); ^{13}C (75 MHz, $CDCl_3$): δ 134.1, 122.8, 85.5, 77.5, 36.5, 30.5, 27.3, 10.9; IR ($CHCl_3$): ν 3396, 2929, 1743, 1641 cm^{-1}; MS (ESI) *m/z*: 229.2 (M^+); *Compound* **12**: $[\alpha]_D^{20}$ −7.6 (*c* 0.7, $CHCl_3$); ^1H (300 MHz, $CDCl_3$): 5.71–5.69 (m, 1H), 5.20 (dd, 2H, *J* = 8.5, 3.0 Hz), 4.68 (m, 1H), 3.24–3.23 (m, 1H), 2.56–2.53 (m, 2H), 1.82 (s, 3H), 1.66–1.61 (m, 2H), 1.36 (s, 9H), 0.97 (t, 3H, *J* = 7.5 Hz); ^{13}C (75 MHz, $CDCl_3$): δ 169.6, 159.2, 130.2, 119.8, 88.6, 72.9, 46.3, 33.7, 29.9, 21.0, 20.4, 11.6; IR ($CHCl_3$): ν 3428, 1689, 1642, 1219 cm^{-1}; MS (ESI) *m/z*: 294.1 (M^++ Na); *Compound* **13**: $[\alpha]_D^{20}$ −6.5 (*c* 0.4, $CHCl_3$); ^1H (300 MHz, $CDCl_3$): 5.63–5.47 (m, 2H), 5.10–5.05 (m, 4H), 4.30–4.21 (m, 1H), 3.11–3.09 (m, 1H), 2.55–2.43 (m, 4H), 1.85 (s, 3H), 1.64–1.62 (m, 2H), 1.43 (s, 9H), 1.05 (t, 3H, *J* = 9.0 Hz); ^{13}C (75 MHz, $CDCl_3$): δ 168.5, 158.7, 131.7, 125.5, 118.6, 87.9, 71.8, 45.9, 38.3, 29.0, 20.9, 19.4, 12.2, 7.5; IR ($CHCl_3$): ν 3403, 1702, 1638, 772 cm^{-1}; MS (ESI) *m/z*: 311.1 (M^+); *Compound* **14**: $[\alpha]_D^{20}$ −28.5 (*c* 0.4, $CHCl_3$); ^1H (300 MHz, $CDCl_3$): 5.22–5.17 (m, 1H), 4.98–4.91 (m, 1H), 3.83–3.80 (m, 2H), 3.64–3.61 (m, 1H), 3.53–3.49 (m, 1H), 2.45–2.43 (m, 2H), 1.54–1.51 (m, 2H), 1.37 (s, 9H), 0.87 (t, 3H, *J* = 7.5 Hz); ^{13}C (75 MHz, $CDCl_3$): δ 155.5, 129.7, 121.2, 75.2, 69.1, 52.3, 42.5, 28.8, 21.5, 18.7, 7.2; IR ($CHCl_3$): ν 3403, 1687, 1634 cm^{-1}; MS (ESI) *m/z*: 264.1 (M^++Na).

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