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A novel stereoselective synthesis of (−)-β-conhydrine from (*R*)-2,3-*O*-cyclohexylidine glyceraldehyde

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ABSTRACT

A novel stereoselective synthesis of (−)-β-conhydrine is achieved. Stereoselective Grignard reaction of (*R*)-2,3-*O*-cyclohexylidine glyceraldehyde with ethyl magnesium bromide, chelation controlled stereoselective Grignard reaction of allyl imine derivative with allyl magnesium bromide, and ring-closing metathesis (RCM) of the diallyl product provides (−)-β-conhydrine in high yield.

1. Introduction

Biologically active alkaloids containing a 2-(1-hydroxyalkyl)piperidine unit such as **1** and **2** have attracted much attention due to their antiviral and antitumor properties.[1,2] Several routes for the synthesis of these alkaloids along with their epimers and enantiomers (Fig. 1) have been reported.[3–5]

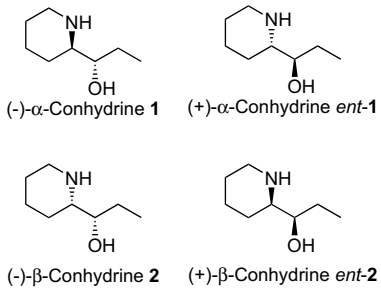
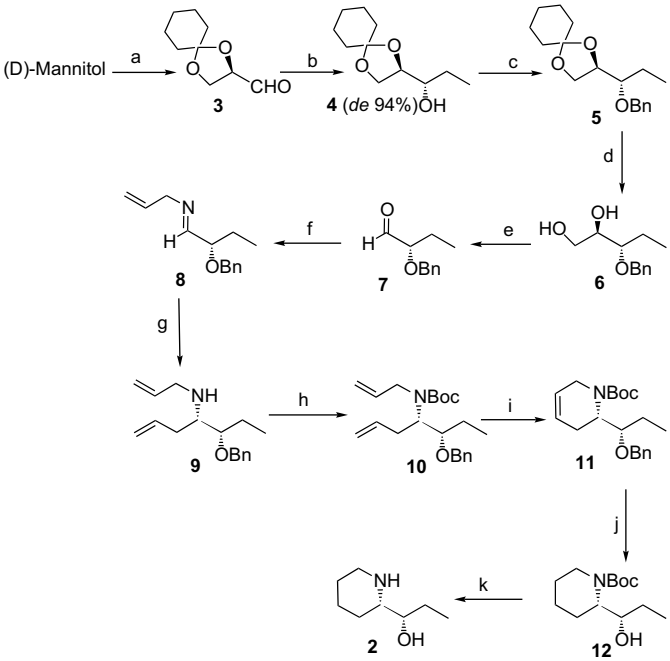


Figure 1.

However, the strategies involving diastereoselective $NaBH_4$-mediated reduction of Weinreb amide derived from (*S*)-phenylglycine[3b,c] or stereoselective addition of diethylzinc to an aldehyde derived from (*S*)-glutamic acid[3a] produce the key chiral intermediates in low diastereoselectivities[3b,c] (de 72%). Herein, we report an efficient stereoselective synthesis of (−)-β-conhydrine **2**, a natural product obtained from seeds and leaves of the poisonous plant *Canium maculatum* L,[6] employing the strategy of chelation controlled, stereoselective Grignard reaction (Scheme 1).



Scheme 1. Reagents and conditions: (a) Ref. 8; (b) EtMgBr, Et_2O, 0 °C, 2 h, 76%; (c) NaH, BnBr, DMF, 0 °C to rt, 1 h, 83%; (d) 90% CF_3COOH in water, 0 °C, 2 h, 80%; (e) $NaIO_4$, 60% CH_3CN in water, 0 °C to rt, 1 h, 90%; (f) allyl amine, anhydrous $MgSO_4$, Et_2O 0 °C to rt, 2 h, 85%; (g) allyl magnesium bromide, Et_2O, 0 °C to rt, 6 h, 78%; (h) Boc_2O, Et_3N, DCM, rt, 1 h, 90%; (i) Grubbs I, DCM, rt, 12 h, 92%; (j) H_2/Pd–C, EtOAc, rt, 4 h, 98%; (k) 85% H_3PO_4, 0 °C, 4 h, 92%.

2. Results and discussion

Our strategy for synthesis of **2** is shown in Scheme 1. (*R*)-2,3-*O*-Cyclohexylidine glyceraldehyde **3** readily prepared from D-

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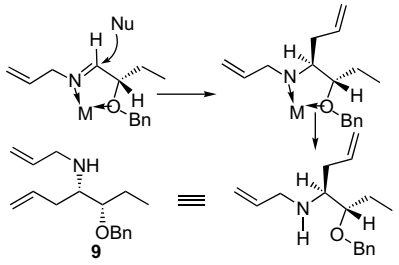
mannitol[7] was treated with ethyl magnesium bromide in diethyl ether at 0 °C to yield *anti*-**4** (76%, de 94%).[8] The preferred formation of *anti*-diastereomer **4** predicted on the basis of Felkin–Anh model is well known.[8,9] The diastereomers were separated by column chromatography and the hydroxy group of **4** was protected as its benzyl ether **5**. The cyclohexylidene protecting group was then removed using 90% trifluoroacetic acid in water and the corresponding diol **6** was cleaved by sodium periodate to give aldehyde **7**. Reaction of allylamine with **7** gave the imine **8** which was subjected to Grignard reaction with allylmagnesium bromide in diethyl ether. The reaction proceeds with excellent stereoselectivity and provides the corresponding diallyl amine **9** in 78% yield as a single diastereomer. The formation of the *syn*-diastereomer **9** during the Grignard reactions can be predicted on the basis of Cram's chelation



Scheme 2. Stereoselectivity control during Grignard reaction of imine **8**.

model[10,11a] wherein the chelation of *O*-benzyl lone pair of imine **8** gives the *syn*-diastereomer **9** (Scheme 2).

Our results are in agreement with those observed by Cativiela et al.[11b,c] who have reported high stereoselectivity during Grignard reaction of *N*-benzylimine derived from 2-*O*-benzyl (D)-glyceraldehyde and phenyl magnesium bromide under similar conditions.

Protection of the amine with $(Boc)_2O$ followed by ring-closing metathesis[12] of **11** using Grubbs first generation catalyst, $Cl_2Ru(=CHPh)(PCy_3)_2$ (5 mol %) in DCM at rt gave **12** in 90% yield. Hydrogenation over Pd–C in EtOAc followed by Boc-deprotection with 85% aqueous phosphoric acid[13] gave **2**. The physical and spectroscopic data of **2** were in agreement with the literature data.[4b]

3. Summary

We have employed the high stereoselectivity in the Grignard reactions involving D-glyceraldehyde template for synthesis of (−)-β-conhydrine. This strategy can be used for making analogues by changing the Grignard reagent. Most of the steps are simple and high yielding and the product is obtained in 22% overall yield.

4. Experimental

4.1. General

All reagents were purchased from Aldrich. IR spectra were recorded on a Perkin–Elmer RX-1 FT-IR system. ^{1}H NMR (200 MHz) spectra were recorded on a Varian Gemini-200 MHz spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Bruker Avance-300 MHz spectrometer. Optical rotations were measured with Horiba-SEPA-300 digital polarimeter. Mass measurement were performed on Q STAR mass spectrometer (Applied Biosystems, USA).

*4.1.1. (1S)-1-[(2R)-1,4-Dioxaspiro[4.5]dec-2-yl]propan-1-ol (**4**)*

The aldehyde **2** (2 g, 11.8 mmol) in dry ether (20 mL) was added dropwise over 30 min to a stirred solution of ethyl magnesium bromide 0.5 M in diethyl ether (59 mL, 29.5 mmol) at 0 °C under nitrogen atmosphere. After being stirred for 2 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with ether (2×100 mL) the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The diastereomers (de 94%) were separated and purified through silica gel column chromatography (EtOAc–PE, 1:9, R_f=0.5 in 20% EtOAc–PE) to afford **3** (1.79 g, 76%) as a yellow oil. $[\alpha]_D^{25}$ +17.4 (*c* 1.5, $CHCl_3$); IR (neat): 3438, 2935, 2860, 1451, 1367, 1279, 1100, 930 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.03 (t, *J*=7.5 Hz, 3H), 1.31–1.63 (m, 12H), 1.86 (d, *J*=3.0 Hz, 1H), 3.69 (m, 1H), 3.83–4.05 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=10.1, 23.7, 23.9, 25.1, 25.6, 34.8, 36.1, 64.1, 72.1, 78, 109.4; EIMS: *m*/*z*=223.7 $[M+Na]^+$. HRMS (EI): *m*/*z* calcd for $C_{11}H_{20}O_3Na$: 223.1310; found: 223.1316.

*4.1.2. (2R)-2-[(1S)-1-(Benzyloxy)propyl]-1,4-dioxaspiro[4.5]-decane (**5**)*

A solution of **4** (1.5 g, 7.5 mmol) in dry DMF (10 mL) was added dropwise to a stirred suspension of NaH (0.36 g, 15 mmol) in dry DMF (10 mL) at 0 °C under a nitrogen atmosphere. After stirring at room temperature for 15 min, benzyl bromide (0.87 mL, 7.5 mmol) was added and the reaction mixture was stirred for 1 h, quenched with saturated aq NH_4Cl at 0 °C and extracted with ether (2×50 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (EtOAc–PE, 3:97, R_f=0.4 in 5% EtOAc–PE). The benzyl protected product **5** was obtained as a yellow oil (1.81 g, 83%). $[\alpha]_D^{25}$ +19.5 (*c* 1, $CHCl_3$); IR (neat): 3030, 2935, 2860, 1453, 1365, 1279, 1103, 931, 737, 697 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.97 (t, *J*=7.3 Hz, 3H), 1.32–1.69 (m, 12H), 3.42 (q, *J*=4.39, 5.85 Hz, 1H), 3.76–3.90 (m, 1H), 3.95–4.10 (m, 2H), 4.53–4.58 (m, 2H), 7.20–7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=10.3, 23.2, 24.4, 25.3, 25.7, 34.2, 35.6, 64.2, 71.2, 81.6, 83.2, 106.0, 128.2 (×2), 128.3, 128.6 (×2), 136.6. EIMS: *m*/*z*=313.2 $[M+Na]^+$. HRMS (EI): *m*/*z* calcd for $C_{18}H_{26}O_3Na$: 313.1779; found: 313.1785.

*4.1.3. (2R,3S)-3-(Benzyloxy)pentane-1,2-diol (**6**)*

Compound **5** (1.5 g, 5.17 mmol) was dissolved in 90% aq CF_3COOH (10 mL) at 0 °C and the mixture was stirred at the same temperature for 2 h. The reaction mixture was then extracted with CH_2Cl_2 (3×50 mL). The collected organic layers were combined, washed with 10% $NaHCO_3$ (3×50 mL), water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc–PE, 3:7, R_f=0.4 in 60% EtOAc–PE) to obtain **6** (0.869 g, 80%) as a syrup. $[\alpha]_D^{25}$ +21 (*c* 1, $CHCl_3$); IR (neat): 3410, 2966, 2931, 2877, 1713, 1455, 1274, 1070, 1024, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.00 (t, *J*=7.5 Hz, 3H), 1.50–1.82 (m, 2H), 2.01–2.74 (br, 2H), 3.39–3.54 (m, 1H), 3.55–3.79 (m, 3H), 4.45–4.72 (m, 2H), 7.25–7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=9.6, 23.0, 63.6, 72.2, 72.6, 82.3, 127.7 (×2), 127.9, 128.4 (×2), 138.2; EIMS: *m*/*z*=233.2 $[M+Na]^+$. HRMS (EI): *m*/*z* calcd for $C_{12}H_{18}O_3Na$: 233.1153; found: 233.1158.

*4.1.4. N-Allyl-N-{(1S)-1-[(1S)-1-(benzyloxy)propyl]-3-butenyl}amine (**9**)*

To a solution of **6** (0.8 g, 3.81 mmol) in 60% aq CH_3CN (20 mL) was added $NaIO_4$ (1.63 g, 7.6 mmol) in one portion. The mixture was stirred at room temperature for 1 h and filtered. The reaction mixture was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give aldehyde **7** (0.61 g, 90%) as a colourless oil. The crude aldehyde **7** (0.61 g, 3.42 mmol) was dissolved in cold dry diethyl ether (15 mL). $MgSO_4$ (1.5 g) and allyl amine (0.266 mL, 3.42 mmol) were added in cold, the reaction mixture was slowly allowed to reach room temperature (0.5 h) and stirring was continued at room

temperature for 2 h more. After completion of the reaction, the reaction mixture was filtered and the filtrate was concentrated in vacuo to give imine **8** (0.632 g, 85%) as a yellow syrup. The crude imine **8** (0.632 g, 2.91 mmol) in dry ether (10 mL) was added drop wise over 30 min to a stirred solution of allyl magnesium bromide in diethyl ether (0.5 M, 14.56 mL, 7.2 mmol) at 0 °C under nitrogen atmosphere. After stirring for 6 h at room temperature, the reaction mixture was poured in to saturated aqueous NH_4Cl (20 mL), the organic layer was dried over Na_2SO_4, concentrated in vacuo and the residue was purified by silica gel column chromatography (EtOAc–PE, 1:9, R_f=0.5 in 25% EtOAc–PE) to give **9** (0.588 g, 78%) as yellow oil. $[\alpha]_D^{25}$ +22 (*c* 0.25, $CHCl_3$); IR (neat): 3369, 2980, 2943, 2832, 2246, 1635, 1450, 1376, 1248, 1101, 1033, 918, 787 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=0.96 (t, *J*=7.5 Hz, 3H), 1.47–1.64 (m, 1H), 1.66–1.84 (m, 1H), 2.08–2.12 (m, 1H), 2.31–2.48 (m, 2H), 2.75 (q, *J*=11.3 Hz, 1H), 3.16–3.39 (m, 3H), 4.54 (m, 2H), 5.01–5.21 (m, 4H), 5.72–5.93 (m, 2H), 7.23–7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=10.1, 22.4, 34.7, 50.5, 57.8, 72.1, 81.9, 115.6, 116.8, 127.4, 127.7 (×2), 128.3 (×2), 136.2, 137.3, 139.0; EIMS: *m*/*z*=260.2 $[M+H]^+$. HRMS (EI): *m*/*z* calcd for $C_{17}H_{26}NO$: 260.2014; found: 260.2010.

4.1.5. tert-Butyl N-allyl-N-{(1S)-1-[(1S)-1-(benzyloxy)propyl]-3-butenyl}carbamate (**10**)

Triethylamine (0.09 mL, 0.675 mmol) followed by Boc_2O (0.39 mL, 1.69 mmol) were added to a solution of **9** (0.175 g, 0.675 mmol) in dry DCM (10 mL) at 0 °C. The reactants were then stirred at room temperature for 1 h. After completion of the reaction, the reaction mixture was washed with saturated NH_4Cl (5 mL) and extracted with CH_2Cl_2 (2×10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc–PE, 2:98, R_f=0.4 in 5% EtOAc–PE) to obtain **10** as a syrup (0.218 g, 90%). $[\alpha]_D^{25}$ +25.5 (*c* 1, $CHCl_3$); IR (neat): 3050, 2990, 2836, 1626, 1435, 1240, 1053, 925, 725 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=0.97 (t, *J*=7.3 Hz, 3H), 1.46 (s, 9H), 1.55–1.80 (m, 2H), 2.27–2.58 (m, 2H), 3.43–3.58 (m, 1H), 3.74–4.01 (m, 2H), 4.09–4.27 (m, 1H), 4.4–4.65 (m, 2H), 4.95–5.16 (m, 4H), 5.63–5.93 (m, 2H), 7.21–7.44 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=9.8, 23.9, 28.4 (×3), 34.3, 48.4, 57.7, 72.3, 79.2, 82.3, 115.3, 116.7, 127.4 (×2), 127.9, 128.2 (×2), 135.7, 136.2, 136.6, 153; EIMS: *m*/*z*=382.2 $[M+Na]^+$. HRMS (EI): *m*/*z* calcd for $C_{22}H_{33}NO_3Na$: 382.2358; found: 382.2355.

4.1.6. tert-Butyl (2S)-2-[(1S)-1-(benzyloxy)propyl]-1,2,3,6-tetrahydro-1-pyridinecarboxylate (**11**)

The diene **10** (0.18 g, 0.5 mmol) was dissolved in dry CH_2Cl_2 (50 mL). Grubbs' first generation catalyst (41 mg, 0.05 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. The dark brown solution was concentrated in vacuo and the residue was purified by column chromatography (EtOAc–PE, 5:95, R_f=0.5 in 10% EtOAc–PE). The compound **11** was obtained as colorless oil (0.152 g, 92%). $[\alpha]_D^{25}$ −35 (*c* 1.5, $CHCl_3$); IR (neat): 2965, 2927, 2855, 1693, 1457, 1411, 1365, 1219, 1173, 1109, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=0.98 (t, *J*=7.5 Hz, 3H), 1.42 (s, 9H), 1.43–1.50 (m, 2H), 1.50–1.79 (m, 1H), 1.99–2.18 (m, 1H), 2.35–2.51 (m, 1H), 3.39–3.53 (m, 2H), 4.04–4.27 (m, 1H), 4.27–4.65 (m, 3H), 5.54–5.79 (m, 2H), 7.19–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=11.3, 28.3 (×3), 30.3, 34.6, 42.2, 59.3, 72.2, 78.6, 82.1, 124.0, 127.1 (×2), 127.5 (×2), 128.2, 129.9, 136.7, 153.5; EIMS: *m*/*z*=354.2 $[M+Na]^+$. HRMS (EI): *m*/*z* calcd for $C_{20}H_{30}NO_3$: 332.2225; found: 332.2229.

4.1.7. tert-Butyl (2S)-2-[(1S)-1-hydroxypropyl]hexahydro-1-pyridine carboxylate (**12**)

A solution of **11** (0.12 g, 0.362 mmol) in ethyl acetate (10 mL) was stirred with 20 mg of 10% Pd/C under hydrogen atmosphere for 4 h. The reaction mixture was filtered and the filtrate was concentrated. The crude product was purified on silica gel column chromatography (EtOAc–PE, 4:6, R_f=0.5 in 30% EtOAc–PE) to obtain **12** as a viscous liquid (0.086 g, 98%). $[\alpha]_D^{25}$ −26.8 (*c* 1, $CHCl_3$); IR (neat): 3460, 2932, 2870, 2357, 1671, 1421, 1269, 1167 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=1.01 (t, *J*=7.5 Hz, 3H), 1.2–1.45 (m, 2H), 1.46 (s, 9H), 1.46–1.75 (m, 6H), 2.9–3.02 (br s, 1H), 3.68–3.76 (m, 1H), 3.77–4.15 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=9.3, 19.5, 25.1, 25.6, 27.2, 28.4 (×3), 40.2, 55.6, 70.2, 79.8, 152.0; EIMS: *m*/*z*=266.2 $[M+Na]^+$. HRMS (EI): *m*/*z* calcd for $C_{13}H_{25}NO_3Na$: 266.1732; found: 266.1738.

4.1.8. (1S,2S)-Piperidine-2-yl-propan-1-ol (**2**)

To a solution **12** (50 mg, 0.21 mmol) in DCM (1 mL) at room temperature, aqueous phosphoric acid (85 wt %, 2.8 mL) was added drop wise. The mixture was stirred for 4 h and cooled in ice after addition of water (5 mL). The reaction mixture was then slowly neutralized with 10 N NaOH. The mixture was then extracted with DCM (2×20 mL). The combined DCM extracts were dried over Na_2SO_4 and concentrated in vacuo to give the desired product **2** as a white solid (27 mg, 92%). Mp: 67–68 °C (lit.[4b] mp. 67 °C); $[\alpha]_D^{25}$ −34.5 (*c* 1, $CHCl_3$), lit.[4b] $[\alpha]_D^{20}$ −31.1 (*c* 1, $CHCl_3$); IR (neat): 3285, 2928, 2855, 1726, 1635, 1455, 1269, 1114, 976 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=0.93 (t, *J*=7.5 Hz, 3H), 1.04–1.55 (m, 8H), 2.3 (ddd, *J*=2.5, 7.5, 10.2 Hz, 1H), 2.52 (td, *J*=2.7, 11.5 Hz, 1H), 3.0–3.08 (m, 1H), 3.18 (td, *J*=3.5, 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=10.4, 25, 26.9, 29.7, 47, 61.3, 76; EIMS: *m*/*z*=144.1 $[M+H]^+$. HRMS (EI): *m*/*z* calcd for $C_8H_{18}NO_3$: 144.1025; found: 144.1022.

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