Research Article

Stereoselective Synthesis of (+)- α -Conhydrine from *R*-(+)-Glyceraldehyde

Nageshwar Rao Penumati and Nagaiah Kommu

Fine Chemicals Laboratory, Organic and Biomolecular Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500607, India

Correspondence should be addressed to Nagaiah Kommu; nagaiah@iict.res.in

Received 22 August 2014; Revised 27 September 2014; Accepted 27 September 2014; Published 20 October 2014

Academic Editor: Ashraf Aly Shehata

Copyright © 2014 N. R. Penumati and N. Kommu. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Stereoselective synthesis of (+)- α -Conhydrine was accomplished from protected (*R*)-(+)-glyceraldehyde, a familiar carbohydrate predecessor. Our synthetic strategy featured the following two key reactions. One is Zn-mediated stereoselective aza-Barbier reaction of imine **6** with allyl bromide to afford chiral homoallylic amine **7**, and the other is ring-closing metathesis.

1. Introduction

Exploiting natural products to ascertain a lead has always been important technique in drug discovery. Nature provides a rich source of bioactive compounds with significant biological activity and has therefore received considerable attention from the synthetic organic communities. The major class of biologically active molecules containing substituted piperidines has been widely present in the nature. The efforts to find a short and high yielding synthetic route for this class of natural products were always a contemporary interest. Some of the hydroxylated piperidine alkaloids are reported to be highly toxic and have drawn significant attention through their biological activity [1–3].

Conhydrine is one of the classes of alkaloids which were isolated by Wertheim from the poisonous plant, *Conium maculatum* L [4], in 1856. A highly fatal toxin causing paralysis of the skeletal musculature, 2-(1-hydroxyalkyl)-piperidine is a recurrent unit in many alkaloids such as Homopumiliotoxin 223 G **2**, Slaframine **3**, and Castanospermine **4** (Figure 1). Since the pioneering studies on the synthesis of (+)- α -Conhydrine **1** by Galinovasky and Mulley [5], various methods have been reported normally based on auxiliary supported or chiral pool approach [6–18].

In view of the interesting biological and structural properties, especially the nitrogen containing alkaloids makes (+)- α -Conhydrine **1** as an attractive and challenging synthetic target. As mentioned above (+)- α -Conhydrine **1** was synthesized from various synthetic routes which involve a large number of steps to obtain the target molecule. Thus development of new methods for the synthesis of (+)- α -Conhydrine **1** constitutes an area of current interest. Herein, an efficient synthesis of (+)- α -Conhydrine **1** has been designed starting from 2,3-isopropylidene-*R*-(+)-Glyceraldehyde, by means of Zn-mediated stereoselective Barbier allylation as a key step, which was developed previously for the synthesis of different natural products in our laboratory [19–22]. To the best of our knowledge synthesis of (+)- α -Conhydrine *via* aza-Barbier zinc allylation was not reported so far.

2. Materials and Methods

All reagents were purchased from Aldrich (Sigma-Aldrich, Bangalore, India). All reactions were monitored by TLC, performed on silica gel glass plates containing 60 F-254. Column chromatography was performed with Merck 60–120 mesh silica gel. IR spectra were recorded on a Perkin-Elmer RX-1 FT-IR system. ^1H NMR spectra were recorded on

FIGURE 1: Some important piperidine, quinolizidine and indolizidine alkaloids.

Bruker-300 MHz spectrometer; ^{13}C NMR (75 MHz) spectra were recorded on Bruker-Avance spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) downfield from internal TMS standard. Peaks are labeled as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). ESI spectra recorded on Micro mass, Quattro LC using ESI+ software with a capillary voltage of 3.98 kV and ESI mode positive ion trap detector. Optical rotations were measured on Horiba-SEPA-300 digital polarimeter.

2.1. (S)-N-Allyl-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-amine (7). To a stirred solution of glyceraldehyde **5** (13 g, 100 mmol) in dry ether (150 mL) was added anhydrous magnesium sulfate (20 g). The mixture was cooled in an ice bath and allyl amine (5.75 g, 101 mmol) was added dropwise under nitrogen atmosphere. After stirring for 3 h, the reaction mixture was filtered and concentrated under reduced pressure to obtain imine **6** (14 g, 82%) as colorless oil. The obtained imine **6** was further used in the next step without purification.

To a stirred suspension of activated zinc (10.8 g, 166 mmol) in 100 mL of dry THF was added solution of imine **6** (14 g, 83 mmol) in 50 mL of dry THF under nitrogen atmosphere at 0°C . After 15 min, allyl bromide (19.9 g, 0.166 mol) was added dropwise over 15 min at 0°C and reaction mixture was stirred for 10 h. After completion of the reaction (monitored by TLC), the reaction was quenched with saturated aqueous ammonium chloride solution (20 mL) at 0°C over 15 min. After being stirred for 1 h, the mixture was filtered through celite pad. The filtrate was concentrated under reduced pressure. The crude product was partitioned between water and ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 2:8) to afford the pure compound amine **7a** (14 g, 80%) as colorless oil. R_f = 0.12 (9:1 EtOAc and hexane) $[\alpha]_D^{27}$ = +18.7 (c 1, CHCl_3); ^1H NMR (300 MHz, CDCl_3): 5.79–5.65 (m, 2H, 2xCH of olefin), 5.17–4.93 (m, 4H, 2xCH₂ of olefin), 4.10 (q, J = 7.5 Hz, 1H,

-OCH), 3.80 (d, J = 6.0 Hz, 1H, H of OCH₂), 3.71 (d, J = 6.8 Hz, 1H, H of OCH₂), 3.61 (d, J = 5.9 Hz, 1H, allylic NCH₂), 3.55 (q, J = 8.1 Hz, 1H, allylic NCH₂), 2.70 (q, J = 5.9 Hz, 1H homoallylic NCH), 2.35 (q, J = 7.3 Hz, 2H, allylic CH₂), 1.43 (s, 6H, 2xCH₃); ^{13}C NMR (75 MHz, CDCl_3): 137.0, 134.9, 117.7, 115.6, 108.6, 77.6, 66.6, 57.9, 50.3, 35.0, 25.3, 25.2; IR (neat): 3404, 3068, 3028, 2926, 2855, 2801, 1640, 1494, 1417, 1368, 1250, 1069, 1029, 994 cm^{-1} ; ESI MS: m/z = 212 (M+H); HRMS (ESI): m/z calculated for $\text{C}_{12}\text{H}_{22}\text{NO}_2$ (M+H) 212.1650, found 212.1652.

2.2. tert-Butyl-allyl((S)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-enyl) Carbamate (8). To a stirred solution of amine **7a** (12.7 g, 60 mmol) in 100 mL dry DCM were added triethylamine (12.12 g, 120 mmol) and catalytic amount of DMAP (1 mol %). The reaction mixture was allowed to stir for 30 min at 0°C . A solution of Boc₂O (14.4 g, 66 mmol) in 50 mL dry DCM was added. The solution was allowed to warm to room temperature, stirred for 5 h. The reaction mixture was partitioned between water and EtOAc. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was purified by column chromatography (hexane/EtOAc, 9.5:0.5) to afford the pure Boc-protected amine **8** (14.7 g, 79%) as pale yellowish oil. R_f = 0.57 (1:9 EtOAc and hexane). $[\alpha]_D^{27}$ = +21.9 (c 1, CHCl_3); ^1H NMR (300 MHz, CDCl_3): 5.90–5.63 (m, 2H, 2xCH of olefin), 5.17–4.99 (m, 4H, 2xCH₂ of olefin), 4.14 (q, J = 7.8 Hz, 1H, -OCH), 3.97–3.92 (m, 1H, homoallylic NCH), 3.83 (d, J = 5.9 Hz, 1H, H of OCH₂), 3.69 (d, J = 6.5 Hz, 1H, H of OCH₂), 3.62 (d, J = 5.9 Hz, 1H, allylic NCH₂), 3.56 (q, J = 8.0 Hz, 1H, allylic NCH₂), 2.49–2.46 (m, 1H, allylic CH₂), 2.40–2.32 (m, 1H, allylic CH₂), 1.47 (s, 3H, -CH₃), 1.43 (s, 6H, 2xCH₃), 1.40 (s, 3H, -CH₃), 1.31 (s, 3H, -CH₃); ^{13}C NMR (75 MHz, CDCl_3): 154.0, 136.4, 135.0, 117.2, 116.8, 109.5, 80.8, 77.4, 66.6, 34.2, 28.2, 26.8; IR (neat): 3078, 2981, 2933, 2693, 1644, 1455, 1399, 1368, 1312, 1251, 1156, 1066, 994 cm^{-1} ; ESI MS (m/z): 334 (M+Na)⁺; HRMS (ESI): m/z calculated for $\text{C}_{17}\text{H}_{29}\text{NO}_4$ (M+Na)⁺ 334.1994, found. 334.2008.

2.3. tert-Butyl-allyl-(2S,3S)-1,2-dihydroxyhex-5-en-3-ylcarbamate (9). To a stirred solution of Boc-protected amine **8a** (12.44 g, 40 mmol) in MeOH (75 mL), PTSA (0.688 g, 0.4 mmol) was added at room temperature and stirred for 12 h under nitrogen atmosphere to completion of the reaction. The reaction mixture was quenched with aqueous saturated NaHCO_3 (10 mL) solution, concentrated under reduced pressure. The crude was partitioned between EtOAc and water. The organic layer was washed with brine and dried over anhydrous Na_2SO_4 . The solution was concentrated under reduced pressure and residue was subjected to column chromatography (hexane/EtOAc, 7:3) to afford diol **9** (9.5 g, 88%) as yellowish oil. R_f = 0.45 (1:1 EtOAc and hexane). $[\alpha]_D^{27}$ = +1.9 (c 1, CHCl_3); ^1H NMR (300 MHz, CDCl_3): 5.91–5.71 (m, 2H, 2xCH of olefin), 5.30–5.14 (m, 4H, 2xCH₂ of olefin), 4.16 (q, J = 8.1 Hz, 1H, -OCH), 3.94–3.88 (m, 1H, homoallylic NCH), 3.78 (d, J = 7.9 Hz, 1H, H of OCH₂), 3.68 (d, J = 7.5 Hz, 1H, H of OCH₂), 3.57 (d, J = 5.0 Hz, 1H, allylic NCH₂), 3.47 (q, J = 8.5 Hz, 1H, allylic NCH₂), 2.43 (d, J =

3.0 Hz, 1H, allylic CH₂), 2.34 (dd, *J* = 4.5, 5.3 Hz, 1H, allylic CH₂), 1.47 (s, 3H, -CH₃), 1.40 (s, 3H, -CH₃), 1.31 (s, 3H, -CH₃); ¹³C NMR (75 MHz, CDCl₃): 153.5, 135.4, 134.9, 117.3, 116.5, 80.5, 73.4, 64.0, 58.2, 33.5, 28.2; IR (neat): 3412, 3078, 2976, 2928, 1667, 1456, 1407, 1366, 1330, 1250, 1179, 996 cm⁻¹; ESI MS (*m/z*): 272 (M+H)⁺; HRMS (ESI): *m/z* calculated for C₁₄H₂₆NO₄ (M+H)⁺ 272.1861, found 272.1874.

2.4. (2*S*,3*S*)-3-(Allyl(*tert*-butoxycarbonyl)amino)-2-hydroxyhex-5-enyl 4-Methylbenzenesulfonate (10**).** To a stirred clear solution of Diol **9** (8.13 g, 30 mmol), Bu₂SnO (0.05 mol %), and triethylamine (6.06 g, 60 mmol) in 80 mL dry DCM was added TsCl (5.715 g, 30 mmol) in one portion under nitrogen atmosphere at 0°C and reaction mixture was stirred for 5 h. Upon completion, the reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc, 8:2) to afford monotosylated product **10** (8.16 g, 64%) as pale yellowish oil. *R*_f = 0.55 (1:1 EtOAc and hexane). [α]_D²⁷ = -7.8 (c 1, CHCl₃); ¹H NMR (300 MHz, CDCl₃): 7.75 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.34 (d, *J* = 8.3 Hz, 2H, Ar-H), 5.91–5.60 (m, 2H, 2xCH of olefin), 5.21–5.02 (m, 4H, 2xCH₂ of olefin), 4.21–3.90 (m, 3H, -OCH, OCH₂), 3.88–3.72 (m, 1H, homoallylic NCH), 3.61 (d, *J* = 6.1 Hz, 1H, allylic NCH₂), 3.56 (q, *J* = 7.8 Hz, 1H, allylic NCH₂), 2.48–2.42 (m, 5H, allylic CH₂, Ar-Me), 1.42 (s, 9H, *t*-butyl); ¹³C NMR (75 MHz, CDCl₃): 154.5, 145.1, 140.5, 134.1, 132.9, 131.1, 129.9, 128.9, 128.0, 127.0, 125.9, 120.5, 118.5, 117.6, 70.2, 68.6, 57.2, 48.8, 32.0, 29.6; IR (neat): 3375, 3077, 2978, 2928, 1666, 1599, 1457, 1406, 1363, 1252, 1178, 1098, 978 cm⁻¹; ESI MS (*m/z*): 426 (M+H)⁺; HRMS (ESI): *m/z* calculated for C₂₁H₃₂NO₆S (M+H)⁺ 426.1950, found 426.1962.

2.5. *tert*-Butyl-allyl((4*S*,5*R*)-5-hydroxyhept-1-en-4-yl)carbamate (11**).** To a solution of monotosylated compound **10** (6.375 g, 15 mmol) in 50 mL methanol was added anhydrous K₂CO₃ (2.07 g, 15 mmol) at 0°C, stirred for 1 h. After completion of the reaction, K₂CO₃ was filtered off and the filtrate was concentrated *in vacuo*. The crude was diluted with EtOAc and washed with water and brine, dried over anhydrous Na₂SO₄. The solution was concentrated under reduced pressure to afford desired epoxide (3.415 g, 90%). The formed epoxide was used without purification.

To a solution of epoxide (3.415 g, 13.5 mmol) in 15 mL dry THF was added MeMgI (4.48 g, 27 mmol) in 25 mL dry THF under nitrogen atmosphere at 0°C. The resulting reaction mixture was allowed to stir for 2 h at the same temperature. Then the reaction was quenched with aqueous NH₄Cl (5 mL) at 0°C and extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. The solvent was evaporated *in vacuo* and the residue was subjected to column chromatography (hexane/EtOAc, 8:2) to afford 2° alcohol **11** (2.76 g, 76%) as colorless oil. *R*_f = 0.38 (3:7 EtOAc and hexane). [α]_D²⁷ = -1.5 (c 1, CHCl₃); ¹H NMR (300 MHz, CDCl₃): 5.86–5.67 (m, 2H, 2xCH of olefin), 5.28–5.10 (m, 4H, 2xCH₂ of olefin), 3.96–3.88 (m, 1H, OCH), 3.77 (q, *J* = 8.9 Hz, 1H, homoallylic NCH), 3.64 (d, *J* = 7.9 Hz,

1H, allylic NCH₂), 3.53 (d, *J* = 4.8 Hz, 1H, allylic NCH₂), 2.60–2.51 (m, 1H, allylic CH₂), 2.38–2.30 (m, 1H, allylic CH₂), 1.42 (s, 9H, *t*-butyl), 1.26–1.22 (m, 2H, CH₂), 0.94 (t, *J* = 7.8 Hz, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃): 154.0, 135.8, 135.0, 116.9, 116.5, 79.9, 51.3, 30.7, 28.2, 27.0, 10.4; IR (neat): 3386, 3077, 2966, 2925, 2856, 1668, 1456, 1414, 1368, 1254, 1166, 1095, 919 cm⁻¹; ESI MS (*m/z*): 292 (M+Na)⁺; HRMS (ESI): *m/z* calculated for C₁₅H₂₇NO₃ (M+Na)⁺ 292.1888, found 292.1888.

2.6. (*S*)-*tert*-Butyl-6-((*R*)-1-hydroxypropyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (12**).** To a stirred solution of diene **12** (1.9 g, 7 mmol) in 50 mL dry DCM was added Grubb's 1st generation catalyst (0.3 g, 0.35 mmol) and the resulting purple-colored solution mixture was stirred at room temperature for 8 h. After completion of the reaction, the brown-colored solution was concentrated and subjected to column chromatography (hexane/EtOAc, 8:2) to afford the tetrahydropyridine **12** (1.5 g, 89%) as yellowish oil. *R*_f = 0.30 (3:7 EtOAc and hexane). [α]_D²⁷ = +3.2 (c 1, CHCl₃); ¹H NMR (300 MHz, CDCl₃): 5.88–5.59 (m, 2H, olefinic), 4.33–4.07 (m, 3H, allylic NCH₂, OCH), 3.60–3.55 (m, 1H, homoallylic NCH), 2.40–2.35 (m, 2H, allylic CH₂), 1.42 (s, 9H, *t*-butyl), 1.26 (m, 2H, CH₂), 0.95 (t, *J* = 8.0 Hz, 3H, -CH₃); ¹³C NMR (75 MHz, CDCl₃): 154.2, 123.3, 122.4, 79.8, 72.2, 52.6, 41.3, 28.4, 26.7, 25.6, 10.0; IR (neat): 3445, 2969, 2926, 1685, 1414, 1365, 1307, 1249, 1171, 1113, 1051, 966 cm⁻¹; ESI MS (*m/z*): 264 (M+Na)⁺; HRMS (ESI): *m/z* calculated for C₁₃H₂₃NO₃ (M+Na)⁺ 264.1575, found 264.1584.

2.7. (*S*)-*tert*-Butyl-2-((*R*)-1-hydroxypropyl)piperidine-1-carboxylate (13**).** To a stirred solution of tetrahydropyridine **12** (1.2 g, 5 mmol) in 6 mL methanol was added 10% Pd on activated charcoal (0.5 g). The mixture was stirred for 10 h under hydrogen atmosphere. The reaction mass was filtered on celite pad and washed with MeOH. The filtrate was concentrated under reduced pressure and the crude was purified by column chromatography (hexane/EtOAc, 9:1) to afford pure piperidine **13** (1.1 g, 90%) as colorless oil. *R*_f = 0.45 (2:8 EtOAc and hexane). [α]_D²⁷ = -9.4 (c 1, CHCl₃); ¹H NMR (300 MHz, CDCl₃): 4.31–4.05 (br, 1H, -OH), 3.83–3.78 (m, 1H, OCH), 3.64–3.58 (m, 2H, NCH₂), 3.40–3.34 (m, 1H, NCH), 1.61–1.52 (m, 6H, 3xCH₂, aliphatic), 1.43 (s, 9H, *t*-butyl), 1.25–1.21 (m, 2H, CH₂), 0.95 (t, *J* = 8.0 Hz, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃): 155.2, 79.8, 70.8, 55.3, 40.3, 29.7, 28.4, 26.5, 25.6, 25.2, 24.5, 10.0; IR (neat): 3443, 2963, 2874, 1677, 1462, 1414, 1366, 1250, 1160, 976 cm⁻¹; ESI MS (*m/z*): 266 (M+Na)⁺; HRMS (ESIMS): *m/z* calculated for C₁₃H₂₅NO₃Na (M+Na)⁺ 266.1732, found 266.1742.

2.8. (+)-α-Conhydrine (1**).** To a solution of piperidine **13** (0.243 g, 1 mmol) in 2.5 mL Dry DCM was added dropwise solution of TFA (0.72 g, 5 mmol) in 5 mL dry DCM at 0°C. The resulting reaction mixture was stirred under nitrogen atmosphere for 4 h at 0°C and then treated with saturated NaHCO₃ (20 mL) until it has become alkaline and then extracted with DCM (2 × 5 mL). The combined

SCHEME 1: Retrosynthetic analysis of (+)- α -Conhydrine **1**. SCHEME 2: Reagent and conditions: (a) $\text{CH}_2=\text{CHCH}_2\text{NH}_2$, Et_2O , anhyd. MgSO_4 , 0°C to rt, 3 h, 82%; (b) $\text{CH}_2=\text{CHCH}_2\text{Br}$, Zn, THF, aq. NH_4Cl , 0°C to rt, 10 h, 80%.

organic layers were washed with water and brine, dried, and evaporated under reduced pressure to afford crude product. The crude product was purified by column chromatography (chloroform/methanol, 8 : 2) over silica gel to furnish (+)- α -Conhydrine **1** (90 mg, 64%) as colorless solid. $R_f = 0.12$ (9 : 1 chloroform and methanol). $[\alpha]_D^{27} = +8.8$ (c 1, EtOH); ^1H NMR (300 MHz, CDCl_3): 3.80–3.72 (m, 1H, OCH), 3.04–2.77 (m, 3H, NCH_2 , NCH), 2.1–2.0 (br, 1H, -NH), 1.60–1.20 (m, 8H, $3 \times \text{CH}_2$ -ring, CH_2 -ethyl), 1.0–0.8 (m, 3H, CH_3); ^{13}C NMR (75 MHz, CDCl_3): 71.5, 60.8, 49.9, 29.6, 25.5, 22.3, 21.2, 10.3; IR (neat): 3409, 2923, 2856, 1659, 1458, 1375, 1259, 1093, 797 cm^{-1} ; ESI MS (m/z): 144 ($\text{M}+\text{H}^+$); HRMS (ESI): m/z calculated for $\text{C}_8\text{H}_{18}\text{NO}$ ($\text{M}+\text{H}^+$) 144.1388, found 144.1395.

3. Results and Discussion

A retrosynthetic analysis for (+)- α -Conhydrine **1** based on chiron approach with diastereoselective Barbier allylic addition as the prominent strategy is pictorially presented in Scheme 1. We envisioned that the synthesis of (+)- α -Conhydrine could be achieved by employing stereoselective allylation and ring closing metathesis as key strategy to create this root as more feasible and simple. As illustrated in Scheme 1, we decided to prepare (+)- α -Conhydrine by intercepting olefinic intermediate **12** that we envisaged would be made available from ring closing metathesis of diene **11**, which was successively obtained from the imine **6** by

diastereoselective aza-Barbier zinc allylation. Subsequently this imine **6** could be easily attained from condensation of *R*-(+)-Glyceraldehyde **5** and allyl amine (Scheme 1).

The synthesis of title compound initiates from a well-known carbohydrate precursor (*R*)-2,3-isopropylidene glyceraldehyde **5**, which can be easily prepared from commercially available D-mannitol [23–26]. As depicted in Scheme 2, condensation of allylamine with glyceraldehyde **5** gave imine **6**, which was then further converted to secondary amine **7** by zinc mediated Barbier allylation [13, 27–32] protocol with good diastereoselectivity (*anti/syn* = 9 : 1) in 80% yield.

The ratio of diastereomers was determined by gas chromatography. The diastereoselectivity [32–34] of this reaction can be explained by Felkin-Anh model (Figure 2), the carbon nucleophile preferentially approach from the less hindered side (i.e., from the side of H), thus resulting in the formation anti-diastereomer predominantly. However, the *syn*- and *anti*-relative configuration of stereogenic centre was unambiguously established based on ^1H NMR, in which proton at newly formed stereocentre of *anti*-isomer **7a** appeared at δ 2.70 (q, J = 5.9 Hz, 1H) whereas *syn*-isomer **7b** is at δ 2.62 (q, J = 6.5 Hz, 1H). These values were in good agreement with earlier reports [34].

The major diastereomer **7a** upon treatment with Boc-anhydride and TEA in DCM using catalytic amount of DMAP at 0°C to rt produced carbamate **8** with 79% yield. The acetonide deprotection of carbamate **8** was achieved

FIGURE 2: Felkin-Anh model for antistereoselectivity.

SCHEME 3: Reagent and conditions: (a) Boc_2O , Et_3N , DMAP, DCM, 0°C to rt, 5 h, 79%; (b) PTSA, MeOH, rt, 12 h, 88%; (c) TsCl, Bu_2SnO , Et_3N , DCM, 0°C to rt, 5 h, 64%; (d) (i) K_2CO_3 , MeOH, 0°C , 1 h, 90%; (ii) MeMgI, THF, 0°C , 2 h, 76%; (e) Grubbs' catalyst I gen., DCM, rt, 8 h, 89%; (f) 10% Pd/C, H_2 , MeOH, rt, 10 h, 90%; (g) TFA, DCM, 0°C to rt, 4 h, 64%.

successfully by using catalytic amount of PTSA in methanol at room temperature for 12 h which gave desired diol **9** in 88% yield. The primary hydroxyl group of glycol **9** was regioselectively monotosylated [35–37] by using TsCl and Et_3N in the presence of dibutyltin oxide at 0°C to rt in DCM to afford sulfonate **10** in 64% yield. Sulfonate **10** was treated with K_2CO_3 followed by methyl magnesium iodide in dry THF at 0°C which affords dienol **11** via the formation of epoxide and regioselective ring opening; formation of epoxide was confirmed by its FT-IR spectrum which showed disappearance of absorption band at 3375 cm^{-1} ($-\text{OH}$ stretching). Upon ring-closing metathesis [38–40] of dienol **11** in the presence of Grubbs' 1st generation catalyst (5 mol%) in CH_2Cl_2 at room temperature delivered tetrahydropyridine **12** in 89% yield. Catalytic hydrogenation of tetrahydropyridine **12** in presence of 10% Pd/C in MeOH at room temperature afforded piperidine **13** with 90% yield. Boc-deprotection of piperidine **13** with TFA in DCM accomplished desired compound **1** (Scheme 3). The physical and spectroscopic data of title compound **1** were in excellent agreement with the earlier report.

4. Conclusions

In conclusion, we achieved a stereoselective total synthesis of (+)- α -Conhydrine from a common carbohydrate precursor,

(*R*)-2,3-isopropylidene glyceraldehyde. The prominent steps involved are zinc mediated Aza-Barbier allylation and construction of piperidine ring by RCM. Further investigations towards other 2-(α -hydroxyl alkyl) piperidine analogues and indolizidines by introduction of various alkenyl substituents in the Barbier allylation are in progress.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgment

Nageshwar Rao Penumati thanks UGC-New Delhi, for the award of fellowship.

References

- [1] G. Casiraghi, F. Zanardi, G. Rassu, and P. Spanu, "Stereoselective approaches to bioactive carbohydrates and alkaloids-with a focus on recent syntheses drawing from the chiral pool," *Chemical Reviews*, vol. 95, no. 6, pp. 1677–1716, 1995.
- [2] J. P. Michael, "Indolizidine and quinolizidine alkaloids," *Natural Product Reports*, vol. 14, no. 6, pp. 619–636, 1997.
- [3] M. G. P. Buffat, "Synthesis of piperidines," *Tetrahedron*, vol. 60, no. 8, pp. 1701–1729, 2004.

- [4] T. Wertheim, "Ueber ein neues Alkaloid in *Conium maculatum*," *Justus Liebigs Annalen der Chemie*, vol. 100, no. 3, pp. 328–339, 1856.
- [5] F. Galinovsky and H. Mulley, "Synthese des natürlichen Conhydrins," *Monatshefte für Chemie*, vol. 79, no. 5, pp. 426–429, 1948.
- [6] P. Guerreiro, V. Ratovelomanana-Vidal, and J.-P. Genêt, "Asymmetric synthesis of hydroxylated pyrrolizidine, indolizidine, and (+)- α -conhydrine via ruthenium-catalyzed hydrogenation," *Chirality*, vol. 12, no. 5-6, pp. 408–410, 2000.
- [7] D. L. Comins and A. L. Williams, "Asymmetric synthesis of erythro- and threo-2-(1-hydroxyalkyl)piperidines via iodocyclocarbamation of 1-acyl-2-alkenyl-1,2,3,6-tetrahydropyridines," *Tetrahedron Letters*, vol. 41, no. 16, pp. 2839–2842, 2000.
- [8] S. K. Pandey and P. Kumar, "Stereoselective syntheses of (+)- α - and (–)- β -conhydrine from L-aspartic acid," *Tetrahedron Letters*, vol. 46, no. 23, pp. 4091–4093, 2005.
- [9] K. Nagata, Y. Toriizuka, and T. Itoh, "A concise enantioselective synthesis of (+)- α -conhydrine," *Heterocycles*, vol. 66, no. 1, pp. 107–109, 2005.
- [10] M.-Y. Chang, Y.-H. Kung, and S.-T. Chen, "Synthesis of α -conhydrine," *Tetrahedron*, vol. 62, no. 47, pp. 10843–10848, 2006.
- [11] A. G. Jamieson and A. Sutherland, "Ether-directed, stereoselective aza-claisen rearrangements: synthesis of the piperidine alkaloid, α -conhydrine," *Organic Letters*, vol. 9, no. 8, pp. 1609–1611, 2007.
- [12] D. Rodríguez, A. Picó, and A. Moyano, "A highly stereocontrolled route to 2-(2 α -oxiranyl)piperidines and pyrrolidines: enantioselective synthesis of (+)- α -conhydrine," *Tetrahedron Letters*, vol. 49, no. 48, pp. 6866–6869, 2008.
- [13] S. Roy, A. Sharma, S. Mula, and S. Chattopadhyay, "Metal-dependent reaction tuning with cyclopentylmetal reagents: application to the asymmetric synthesis of (+)- α -conhydrine and (S)-2-cyclopentyl-2-phenylglycolic acid," *Chemistry—A European Journal*, vol. 15, no. 7, pp. 1713–1722, 2009.
- [14] A. K. Srivastava, S. K. Das, and G. Panda, "An approach towards the total synthesis of (+)-epiquinamide and (+)- α -conhydrine from Garner aldehyde," *Tetrahedron*, vol. 65, no. 27, pp. 5322–5327, 2009.
- [15] S. Liu, J.-H. Xie, W. Li, W.-L. Kong, L.-X. Wang, and Q.-L. Zhou, "Highly enantioselective synthesis of chiral cyclic amino alcohols and conhydrine by ruthenium-catalyzed asymmetric hydrogenation," *Organic Letters*, vol. 11, no. 21, pp. 4994–4997, 2009.
- [16] T. M. Shaikh and A. Sudalai, "Enantioselective synthesis of (+)- α -conhydrine and (–)-sedamine by L-proline catalysed α -aminooxylation," *European Journal of Organic Chemistry*, vol. 2010, no. 18, pp. 3437–3444, 2010.
- [17] E. Reyes, N. Ruiz, J. L. Vicario, D. Badía, and L. Carrillo, "Stereoselective total synthesis of (–)- β -conhydrine and (+)- α -conhydrine," *Synthesis*, no. 3, Article ID T19910SS, pp. 443–450, 2011.
- [18] T. Jin, Y. Mu, G. W. Kim et al., "Stereoselective synthesis of piperidine alkaloid (+)- α -Conhydrine and its pyrrolidine analogue," *Asian Journal of Organic Chemistry*, vol. 1, no. 3, pp. 232–237, 2012.
- [19] S. P. Kumar, K. Nagaiah, and M. S. Chorghade, "The first total synthesis of (S)-clavulazine from d-mannitol," *Tetrahedron Letters*, vol. 47, no. 40, pp. 7149–7151, 2006.
- [20] K. Nagaiah, D. Sreenu, R. Srinivasa Rao, and J. S. Yadav, "Stereoselective synthesis of the phytotoxic nonenolide herbarumin-I from l-ascorbic acid," *Tetrahedron Letters*, vol. 48, no. 40, pp. 7173–7176, 2007.
- [21] K. Nagaiah, K. Srinivasu, S. P. Kumar, J. Basha, and J. S. Yadav, "Stereoselective synthesis of (S,S)-palythazine from D-mannitol," *Tetrahedron: Asymmetry*, vol. 21, no. 7, pp. 885–889, 2010.
- [22] A. Venkatesham and K. Nagaiah, "Stereoselective total synthesis of stagonolide-C," *Tetrahedron Asymmetry*, vol. 23, no. 15-16, pp. 1186–1197, 2012.
- [23] D. Marton, D. Stivanello, and G. Tagliavini, "Stereochemical study of the allylation of aldehydes with allyl halides in cosolvent/water(salt)/Zn and in cosolvent/water(salt)/Zn/halo-organotin media," *Journal of Organic Chemistry*, vol. 61, no. 8, pp. 2731–2737, 1996.
- [24] C. Pétrier and J.-L. Luche, "Allylzinc reagent additions in aqueous media," *Journal of Organic Chemistry*, vol. 50, no. 6, pp. 910–912, 1985.
- [25] C. Petrier, J. Einhorn, and J. L. Luche, "Selective tin and zinc mediated allylations of carbonyl compounds in aqueous media," *Tetrahedron Letters*, vol. 26, no. 11, pp. 1449–1452, 1985.
- [26] C. Einhorn and J.-L. Luche, "Selective allylation of carbonyl compounds in aqueous media," *Journal of Organometallic Chemistry*, vol. 322, no. 2, pp. 177–183, 1987.
- [27] J. Mulzer, M. Kappert, G. Huttner, and I. Jibril, "Optional diastereo- and enantioselective synthesis of vicinal threo- or erythro-dihydroxy derivatives," *Angewandte Chemie International Edition*, vol. 23, no. 9, pp. 704–705, 1984.
- [28] D. Enders and U. Reinhold, "Asymmetric synthesis of amines by nucleophilic 1,2-addition of organometallic reagents to the CN-double bond," *Tetrahedron Asymmetry*, vol. 8, no. 12, pp. 1895–1946, 1997.
- [29] E. J. Thomas, "Control and applications of remote asymmetric induction using allylmetal reagents," *Chemical Communications*, no. 5, pp. 411–418, 1997.
- [30] R. Bloch, "Additions of organometallic reagents to CN bonds: reactivity and selectivity," *Chemical Reviews*, vol. 98, no. 4, pp. 1407–1438, 1998.
- [31] S. Kobayashi and H. Ishitani, "Catalytic enantioselective addition to imines," *Chemical Reviews*, vol. 99, no. 5, pp. 1069–1094, 1999.
- [32] J. P. Adams, "Imines, enamines and oximes," *Journal of the Chemical Society, Perkin Transactions 1*, no. 2, pp. 125–139, 2000.
- [33] A. Mengel and O. Reiser, "Around and beyond Cram's Rule," *Chemical Reviews*, vol. 99, no. 5, pp. 1191–1224, 1999.
- [34] T. Biswas, J. P. Mukherjee, and S. K. Chattopadhyay, "Enantio-divergent synthesis of N-protected azetidine-2-carboxylic acid," *Tetrahedron Asymmetry*, vol. 23, no. 18-19, pp. 1416–1422, 2012.
- [35] M. J. Martinelli, N. K. Nayyar, E. D. Moher, U. P. Dhokte, J. M. Pawlak, and R. Vaidyanathan, "Dibutyltin oxide catalyzed selective sulfonylation of α -chelatable primary alcohols," *Organic Letters*, vol. 1, no. 3, pp. 447–450, 1999.
- [36] M. J. Martinelli, R. Vaidyanathan, J. M. Pawlak et al., "Catalytic regioselective sulfonylation of α -chelatable alcohols: Scope and mechanistic insight," *Journal of the American Chemical Society*, vol. 124, no. 14, pp. 3578–3585, 2002.
- [37] M. J. Martinelli, R. Vaidyanathan, and V. van Khau, "Selective monosulfonylation of internal 1,2-diols catalyzed by di-n-butyltin oxide," *Tetrahedron Letters*, vol. 41, no. 20, pp. 3773–3776, 2000.
- [38] R. H. Grubbs, S. J. Miller, and G. C. Fu, "Ring-closing metathesis and related processes in organic synthesis," *Accounts of Chemical Research*, vol. 28, no. 11, pp. 446–452, 1995.

- [39] T. M. Trnka and R. H. Grubbs, "The development of $L_2X_2RU=CHR$ olefin metathesis catalysts: an organometallic success story," *Accounts of Chemical Research*, vol. 34, no. 1, pp. 18–29, 2001.
- [40] S. Lebrun, A. Couture, E. Deniau, and P. Grandclaoudon, "Asymmetric synthesis of 6-alkyl- and 6-arylpiperidin-2-ones. Enantioselective synthesis of (S)-(+)-coniine," *Organic Letters*, vol. 9, no. 13, pp. 2473–2476, 2007.