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# Stereoselective Synthesis of (–)-α-Conhydrine and Its Pyrrolidine Analogue

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**Keywords:** Total synthesis / Natural products / Nitrogen heterocycles / Amination

The stereoselective synthesis of (–)-α-conhydrine and its pyrrolidine analogue was achieved from readily available D-erythronolactone. The key step of this synthesis includes a highly regioselective and diastereoselective addition of chlorosulfonyl isocyanate to 1,2-*anti*-dibenzyl ether to afford the 1,2-*anti*-amino alcohol.

## Introduction

Hydroxylated piperidines are among the most interesting discoveries in the field of natural products and have attracted considerable attention by virtue of their interesting biological properties.[1] In particular, 2-(1-hydroxyalkyl)-piperidines are abundant in nature and are of special interest due to their potent antiviral, antitumor, and anti-HIV activities.[2] Representative examples of 2-(1-hydroxyalkyl)-piperidine, (+)-α-conhydrine (**1a**) and (–)-β-conhydrine (**1d**), were first isolated from the seeds and leaves of the poisonous plant *Conium maculatum L.* in 1856 (Figure 1).[3] Since the pioneering effort to synthesize (+)-α-conhydrine by Galinovsky and Mulley,[4] various synthetic methods to produce **1a** and its stereoisomers **1b–d** have been documented. The majority of the synthetic approaches for conhydrines can be divided into three large categories: asymmetric synthesis for the construction of the stereogenic centers,[5] synthetic approaches from chiral starting materials,[6] and catalytic dynamic resolution of *N*-Boc-2-lithiopiperidine.[7] In a representative example of asymmetric synthesis, Chemla described the efficient synthesis of (–)-α-conhydrine (**1b**) and (+)-β-conhydrine (**1c**) via diastereoselective addition of 3-alkoxyallenylzinc onto enantiopure *N*-*tert*-butanesulfinimine.[5d,5h] In a recent example of a synthetic approach using chiral starting materials, Gálvez and de Villegas presented the total synthesis of **1c** through diastereoselective addition of an organometallic reagent to an imine derived from D-mannitol in the presence of a Lewis acid followed by regio- and diastereoselective ring opening of an epoxide with retention of configuration.[6e] Despite several syntheses of stereoisomeric conhydrines, synthetic approaches for pyrrolidine analogues of conhydrines have only been found in a few reports.[5c,8] In an elegant example, Sutherland demonstrated the facile synthesis of the endopeptidase inhibitor[9] (2*R*,1′*S*)-2-(1′-hydroxypropyl)pyrrolidine (**2**) by using Pd-catalyzed and ether-directed aza-Claisen rearrangement as the key step.

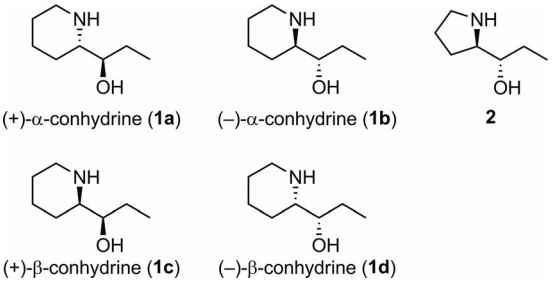


Figure 1. Structures of conhydrine stereoisomers and pyrrolidine analogue.

As part of an ongoing research program aimed at developing asymmetric total syntheses of biologically active compounds,[10] we recently reported a facile strategy for the construction of (–)-lentiginosine and its analogues based on the regioselective and diastereoselective allylic amination of polybenzyl ethers by using chlorosulfonyl isocyanate (CSI).[11] In connection with our previous work on the regioselective and diastereoselective allylic amination of polybenzyl ethers using CSI, we became interested in developing an efficient synthetic route for the preparation of (–)-α-conhydrine (**1b**) and its pyrrolidine analogue **2**. Herein, we describe a facile total synthesis of **1b** and **2** starting from readily available D-erythronolactone via stereoselective amination of *anti*-1,2-dibenzyl ether by using CSI and ring-closing metathesis (RCM) as the key steps.

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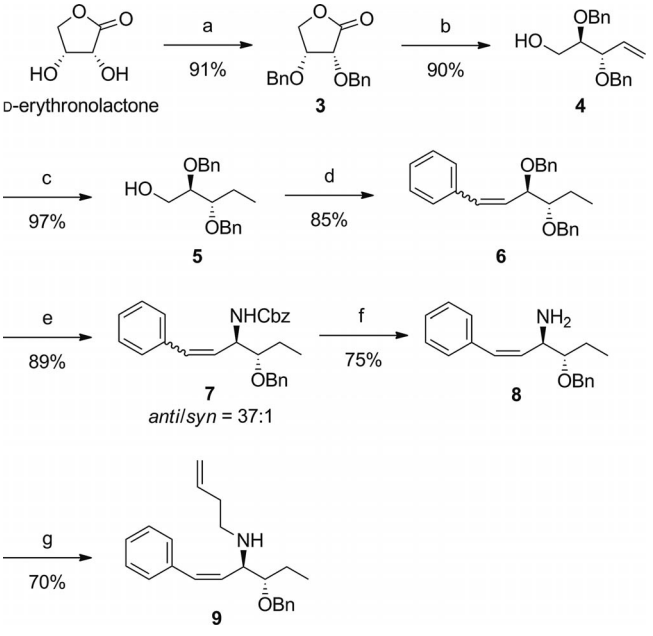
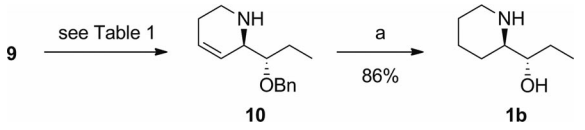
## Results and Discussion

The synthesis of compound **1b** began with lactone **3**, which could be easily prepared from commercially available D-erythronolactone as reported in the literature (Scheme 1).[12] Partial reduction of lactone **3** with DIBAL-H in $CH_2Cl_2$ at –78 °C followed by Wittig reaction of the resulting lactol afforded olefin **4** in 90% yield. Chemoselective hydrogenation of **4** with $PtO_2$ and oxidation with $SO_3$·Pyr gave the aldehyde intermediate, which was converted into cinnamylic dibenzyl ether **6** as a 6:1 mixture of *cis*/*trans* isomers in 85% yield. The regioselective and diastereoselective CSI reaction of compound **6** was carried out in anhydrous toluene at 0 °C for 12 h, followed by desulfonylation with aqueous 25% sodium sulfite solution to give desired *anti*-1,2-amino alcohol **7** in 89% yield with high diastereoselectivity (*anti*/*syn* = 37:1 by NMR analysis). The diastereoselectivity of compound **7** can be explained by the neighboring group effect, whereby the orientation of the NHCbz group retains its original configuration through double inversion of configuration.[11a] To construct the piperidine framework via RCM, we first tried direct introduction of the 3-butenyl moiety into **7** under a range of *N*-alkylation reaction conditions. However, these attempts were unsuccessful and led to recovery of the starting material. Extended reaction times resulted in decomposition of the starting material. In view of these unsuccessful results, we turned our attention to the removal of the Cbz group and the subsequent 3-butenylation of the primary amine. Treatment of **7** with KOH in a 9:1 mixture of DMSO/$H_2O$ afforded primary amine **8**, which was subjected to standard alkylation conditions (4-bromo-1-butene, $K_2CO_3$, DMF) to provide diene **9** in 70% yield.




Scheme 1. Reagents and conditions: (a) $Ag_2O$, BnBr, $CaSO_4$, $CH_3CN$, r.t., 48 h; (b) (i) DIBAL-H, $CH_2Cl_2$, –78 °C, 1 h; (ii) NaHMDS, $MePPh_3Br$, THF, r.t., 12 h; (c) $H_2$, $PtO_2$, MeOH, r.t., 1 h; (d) (i) $SO_3$·Pyr, DMSO, $Et_3N$, $CH_2Cl_2$, 1 h; (ii) NaHMDS, $BnPPh_3Cl$, THF, r.t., 16 h; (e) (i) CSI, $Na_2CO_3$, toluene, 0 °C, 12 h; (ii) 25% $Na_2SO_3$, r.t., 6 h; (f) KOH, DMSO/$H_2O$ (9:1), 80 °C, 48 h; (g) 4-bromo-1-butene, $K_2CO_3$, DMF, 60 °C, 3 h.

To obtain piperidine **10**, several conditions were investigated, as shown in Scheme 2 and Table 1/Figure 2.




Scheme 2. Reagents and conditions: (a) $H_2$, 10% Pd/C, MeOH, 6 N HCl, r.t., 12 h.

Table 1. Selected optimization of RCM of **9**.[a]

| Entry | Catalyst[b] | Additive | Solvent | *T* [°C] | Yield [%][c] |
|---|---|---|---|---|---|
| 1 | **A** | | $CH_2Cl_2$ | 50 | trace |
| 2 | **B** | | toluene | 80 | trace |
| 3 | **B** | $Ti(OiPr)_4$ | $CH_2Cl_2$ | 50 | <5 |
| 4 | **B** | *p*TsOH | $CH_2Cl_2$ | 50 | 72 |

[a] All reactions were performed with the catalyst (8 mol-%) and the additive (100 mol-%) for 18 h. [b] See Figure 2 for the structure of the catalysts. [c] Isolated yield of pure materials.

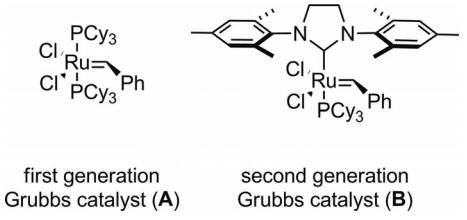


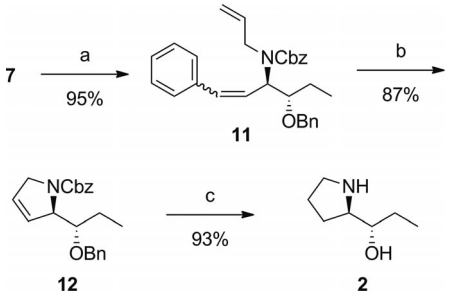

Figure 2. First and second generation Grubbs catalysts for RCM.

Treatment of **9** with first or second generation Grubbs catalysts in dichloromethane or toluene provided a trace amount of **10** (Table 1, Entries 1 and 2).[13] In addition, Lewis acid assisted RCM afforded **10** in very low yield (<5%) as well as complex byproducts (Table 1, Entry 3).[14] After several attempts, the best result was realized when diene **9** was exposed to 8 mol-% of second generation Grubbs catalyst in the presence of anhydrous *p*-toluenesulfonic acid (*p*TsOH) as an additive, which furnished cyclic compound **10** in 72% yield (Table 1, Entry 4).[15] Finally, palladium-catalyzed hydrogenation of **10** provided (–)-α-conhydrine (**1b**) as a colorless oil. The spectroscopic data ($^1H$ NMR and $^{13}C$ NMR) and specific rotation of compound **1b** were in full agreement with the reported literature values.[5a,5d]

In parallel to the synthesis of (–)-α-conhydrine, we focused our attention also on the synthesis of pyrrolidine analogue **2** (Scheme 3). Allylation of carbamate **7** under stan-

dard conditions (allyl bromide, NaH, DMF/THF) proceeded cleanly to afford diene **11** required for RCM in 95% yield. Treatment of compound **11** with second generation Grubbs catalyst in refluxing $CH_2Cl_2$ afforded **12** in 87% yield. Finally, catalytic hydrogenation provided (2*R*,1′*S*)-2-(1′-hydroxypropyl)pyrrolidine (**2**) in high yield.[16]




Scheme 3. Reagents and conditions: (a) NaH, allyl bromide, DMF/THF, r.t., 12 h; (b) second generation Grubbs catalyst (8 mol-%), $CH_2Cl_2$, reflux, 6 h; (c) $H_2$, 10% Pd/C, MeOH, 6 N HCl, 12 h.

## Conclusions

In conclusion, we have demonstrated the concise total synthesis of (–)-α-conhydrine (**1b**) and pyrrolidine analogue **2** starting from readily available D-erythronolactone via the regioselective and diastereoselective allylic amination of *anti*-1,2-dibenzyl ether by using chlorosulfonyl isocyanate and intramolecular olefin metathesis. It is believed that this synthetic strategy can be applied to the preparation of a broad range of polyhydroxylated alkaloids or other natural products containing a nitrogen atom in the ring.

## Experimental Section

**General Procedures:** Commercially available reagents were used without additional purification, unless otherwise stated. All anhydrous solvents were distilled from $CaH_2$ or $P_2O_5$ or Na/benzophenone prior to reaction. All reactions were performed under an inert atmosphere of nitrogen or argon. Melting points were measured with a Gallenkamp melting point apparatus or Electrothermal IA9300 melting point apparatus. $^1$H NMR and $^{13}$C NMR spectra were recorded with a Varian Unity Inova 500 MHz spectrometer for $CDCl_3$ solutions and chemical shifts are reported as parts per million (ppm) relative to, respectively, residual $CHCl_3$ $\delta_H$ ($\delta$ =7.26 ppm) and $CDCl_3$ $\delta_C$ ($\delta$ =77.0 ppm) as internal standards. IR spectra were recorded with a Nicolet 205 infrared spectrophotometer or Bruker Vector 22 infrared spectrophotometer. Optical rotations were measured with a Jasco P1020 polarimeter. Thin-layer chromatography was carried out by using plates coated with Kieselgel 60$F_{254}$ (Merck). For flash column chromatography, E. Merck Kieselgel 60 (230–400 mesh) was used. High-resolution mass spectra (HRMS) were recorded with a JEOL, JMS-505, or JMS-600 spectrometer by using the chemical ionization (CI) method.

**2,3-Di-*O*-benzyl-D-erythronolactone (3):** To a solution of D-erythronolactone (5.0 g, 42.3 mmol, 100 mol-%) in anhydrous acetonitrile (250 mL) at room temperature was added benzyl bromide (38 mL, 317 mmol, 750 mol-%) and calcium sulfate (29 g, 212 mmol, 500 mol-%). The resulting mixture was stirred for 10 min, at which time silver(I) oxide (20 g, 84.6 mmol, 200 mol-%) was added in three portions over 10 min. The resulting reaction flask was covered in aluminum foil and allowed to stir vigorously at room temperature for 12 h, at which point a second portion of silver(I) oxide (20 g, 84.6 mmol, 200 mol-%) was added, and the resulting mixture allowed to stir for 48 h. The reaction mixture was then filtered through a Celite pad to remove the solids, and the resulting filter cake was washed with acetonitrile (3 × 120 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc, 2:1) to afford **3** (11.5 g, 91%) as a white solid. $R_f$ = 0.3 (*n*-hexane/EtOAc, 2:1). $[\alpha]_D^{22}$ = +2.2 (*c* = 3, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3032, 2871, 1788, 1497, 1456, 1344, 1215, 1158, 1108, 1027, 960, 773, 743, 699, 604 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 4.13–4.21 (m, 3 H), 4.32–4.35 (m, 1 H), 4.62 (d, *J* = 12.0 Hz, 1 H), 4.72 (d, *J* = 12.0 Hz, 1 H), 4.81 (d, *J* = 12.5 Hz, 1 H), 4.94 (d, *J* = 12.5 Hz, 1 H), 7.29–7.40 (m, 10 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 69.8, 72.3, 72.7, 74.2, 74.3, 128.1, 128.3, 128.4, 128.5, 128.8, 128.8, 137.0, 137.4, 173.4 ppm. HRMS (CI): calcd. for $C_{18}H_{17}O_4$ [M – H]$^+$ 297.1129; found 297.1127.

**(2*R*,3*S*)-2,3-Bis(benzyloxy)pent-4-en-1-ol (4):** To a solution of **3** (9.0 g, 30 mmol, 100 mol-%) in $CH_2Cl_2$ (300 mL) cooled to –78 °C was added DIBAL-H (1.0 M in toluene, 39 mL, 39 mmol, 130 mol-%). The resulting solution was stirred at –78 °C for 1 h, at which time it was quenched with a mixture of $Na_2SO_4$·10$H_2O$/Celite (2:1). At this time, the cooling bath was removed and enough $CH_2Cl_2$ was added to afford a vigorously stirring solution. Stirring was then continued for 10 h, at which time the solution was filtered and the filter cake was washed with EtOAc (2 × 500 mL). Concentration of the organic layers afforded the crude lactol as an oil (8.8 g), which was used without further purification. To a stirred solution of $MePPh_3Br$ (31.4 g, 87.9 mmol, 300 mol-%) in THF (150 mL) was added a solution of NaHMDS (1.0 M in THF, 88 mL, 88 mmol, 300 mol-%) at 0 °C. The resulting solution was stirred for 1 h at room temperature. A solution of the crude lactol (8.8 g, 29 mmol, 100 mol-%) in THF (50 mL) was then added dropwise to the reaction flask, the ice bath was removed, and the reaction mixture was stirred for 12 h at room temperature. The resulting mixture was quenched with a solution of aqueous saturated $NH_4Cl$ (50 mL) and extracted with EtOAc. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc, 4:1) to afford **4** (8.0 g, 90%) as a colorless syrup. $R_f$ = 0.27 (*n*-hexane /EtOAc, 4:1). $[\alpha]_D^{22}$ = +28.1 (*c* = 4.3, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3421, 3064, 3031, 2873, 1602, 1496, 1455, 1394, 1352, 1210, 1068, 994, 931, 739, 699, 607 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 2.20 (br., 1 H), 3.54 (dd, *J* = 10.0, 5.5 Hz, 1 H), 3.71–3.76 (m, 2 H), 3.97 (dt, *J* = 6.5, 5.5 Hz, 1 H), 4.40 (d, *J* = 12.0 Hz, 1 H), 4.58–4.69 (m, 3 H), 5.34–5.38 (m, 2 H), 5.83–5.90 (m, 1 H), 7.27–7.36 (m, 10 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 62.2, 70.9, 73.0, 81.1, 81.5, 119.5, 127.9, 128.0, 128.2, 128.7, 135.9, 138.3, 138.4 ppm. HRMS (CI): calcd. for $C_{19}H_{23}O_3$ [M + H]$^+$ 299.1650; found 299.1647.

**(2*R*,3*S*)-2,3-Bis(benzyloxy)pentan-1-ol (5):** To a solution of **4** (5.0 g, 16.75 mmol, 100 mol-%) in MeOH (16 mL) was added a solution of platinum(IV) oxide (0.19 mg, 0.84 mmol, 5 mol-%). The reaction mixture was shaken on a Parr apparatus under an atmosphere of hydrogen (60 psi) for 1 h. The resulting mixture was filtered through a Celite pad and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc, 4:1) to afford **5** (4.88 g, 97%) as a colorless syrup. $R_f$ = 0.25 (*n*-hexane/EtOAc, 4:1). $[\alpha]_D^{22}$ = +3.2 (*c* = 2, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3421, 3064,

3031, 2965, 2932, 2876, 1496, 1456, 1366, 1216, 1103, 1029, 772, 739, 698, 609 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 0.94 (t, $J$ = 8.0 Hz, 1 H), 1.64–1.70 (m, 2 H), 2.27 (t, $J$ = 6.5 Hz, 1 H), 3.51 (d, $J$ = 5.0 Hz, 1 H), 3.60 (d, $J$ = 5.5 Hz, 1 H), 4.59–4.70 (m, 4 H), 7.25–7.38 (m, 10 H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 9.8, 24.0, 61.8, 72.4, 73.0, 80.6, 80.8, 127.2, 127.9, 128.0, 128.1, 128.2, 128.6, 128.7, 128.8, 138.4, 138.6 ppm. HRMS (CI): calcd. for $C_{19}H_{25}O_3$ $[M + H]^+$ 301.1800; found 301.1804.

**(3*R*,4*S*)-1-Phenylhex-1-ene-3,4-diyl-bis(oxy)bis(methylene)dibenzene (6):** To a stirred solution of alcohol **5** (4.5 g, 15 mmol, 100 mol-%) in $CH_2Cl_2$ (150 mL) was added DMSO (34 mL), triethylamine (12.5 mL, 90 mmol, 600 mol-%), and $SO_3$·Pyr (7.2 g, 45 mmol, 300 mol-%). The reaction mixture was then stirred at room temperature for 3 h. At this point, $CH_2Cl_2$ was concentrated in vacuo, and the resulting syrup was taken up in $Et_2O$ (600 mL). The organic layer was then washed with a saturated $CuSO_4$ solution (3 × 150 mL) followed by $H_2O$ (150 mL). The organic layers were then dried with $MgSO_4$ and concentrated in vacuo. The residue was used without further purification in the next step. To a stirred solution of $BnPPh_3Cl$ (11.7 g, 30 mmol, 200 mol-%) in THF (125 mL) was added a solution of NaHMDS (1.0 M in THF, 30 mL, 30 mmol, 200 mol-%) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The crude lactol (4.38 g) suspended in THF (25 mL) was added dropwise to the reaction mixture at 0 °C. The resulting mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with $H_2O$ and extracted with EtOAc (100 mL). The organic layer was washed with $H_2O$ and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc, 10:1) to afford **6** (4.75 g, 85%) as a colorless syrup. $R_f$ = 0.37 (*n*-hexane/EtOAc, 10:1). $[\alpha]_D^{22}$ = –86.8 ($c$ = 3, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3259, 3061, 3029, 2925, 2857, 1738, 1495, 1455, 1366, 1217, 1072, 773, 738, 699, 611 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 0.94 (t, $J$ = 7.5 Hz, 2.6 H), 0.98 (t, $J$ = 7.5 Hz, 0.4 H), 1.60–1.77 (m, 2 H), 3.53–3.59 (m, 0.86 H), 4.02–4.04 (m, 0.14 H), 4.25 (d, $J$ = 12.0 Hz, 1 H), 4.44–4.49 (m, 1 H), 4.55–4.74 (m, 3 H), 4.76 (d, $J$ = 12.0 Hz, 1 H), 5.81 (dd, $J$ = 12.0, 9.5 Hz, 0.86 H), 6.31 (dd, $J$ = 16.0, 8.0 Hz, 0.14 H), 6.64 (d, $J$ = 16.0 Hz, 0.14 H), 6.91 (d, $J$ = 12.0 Hz, 0.86 H), 7.15–7.47 (m, 15 H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 10.0, 10.3, 24.3, 24.4, 70.3, 70.6, 73.1, 73.2, 75.6, 82.4, 82.7, 83.2, 126.9, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5 (2 C), 128.6 (2 C), 128.8, 129.1, 130.9, 134.2, 134.3, 137.1, 138.7, 139.2 ppm. HRMS (CI): calcd. for $C_{26}H_{27}O_2$ $[M - H]^+$ 371.2012; found 371.2011.

**Benzyl (3*R*,4*S*)-4-(Benzyloxy)-1-phenylhex-1-en-3-ylcarbamate (7):** To a stirred solution of **6** (2.87 g, 7.71 mmol, 100 mol-%) in anhydrous toluene (26 mL) was added $Na_2CO_3$ (3.7 g, 34.71 mmol, 450 mol-%) and CSI (2.0 mL, 23.14 mmol, 300 mol-%) at 0 °C under an atmosphere of $N_2$. The reaction mixture was stirred for 16 h at 0 °C and quenched with $H_2O$ (13 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL). The organic layer was added to a solution of aqueous 25% $Na_2SO_3$ (10 mL), and the reaction mixture was stirred for 6 h at room temperature. The organic layer was washed with $H_2O$ and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc, 8:1) to afford **7** (2.85 g, 89%, *anti*/*syn* = 37:1) as a white solid. $R_f$ = 0.28 (*n*-hexane/EtOAc, 8:1). $[\alpha]_D^{22}$ = +88.2 ($c$ = 2, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3327, 3029, 2965, 2875, 1718, 1498, 1454, 1344, 1215, 1070, 776, 699, 610 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 0.67 (t, $J$ = 7.5 Hz, 2.3 H), 0.97 (t, $J$ = 7.5 Hz, 0.7 H), 1.33–1.71 (m, 2 H), 3.43 (br., 0.8 H), 3.50–3.51 (br., 0.2 H), 4.47–4.67 (m, 3 H), 4.84–4.87 (br., 1 H), 5.05–5.14 (br., 3 H), 5.67 (dd, $J$ = 11.5, 10.0 Hz, 0.8 H), 6.16–6.21 (m, 0.2 H), 6.65 (d, $J$ = 11.5 Hz, 1 H), 7.21–7.40 (m, 15 H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 10.1, 10.2, 23.9, 51.1, 66.7, 72.3, 72.5, 82.9, 83.0, 126.8, 127.4, 127.9, 128.0, 128.1, 128.2, 128.3, 128.6, 128.7, 132.9, 133.0, 136.8, 138.7, 155.8 ppm. HRMS (CI): calcd. for $C_{27}H_{30}NO_3$ $[M + H]^+$ 416.2221; found 416.2226.

**(3*R*,4*S*,*Z*)-4-(Benzyloxy)-1-phenylhex-1-en-3-amine (8):** To a stirred solution of carbamate **7** (2 g, 4.8 mmol, 100 mol-%) in DMSO (22.5 mL) was added a solution of KOH (2.2 g, 38.4 mmol, 800 mol-%) in $H_2O$ (2.5 mL) at 0 °C. The reaction mixture was stirred at 80 °C for 48 h and then cooled to room temperature. The resulting solution was extracted with $CH_2Cl_2$ (2 × 20 mL). The organic layer was washed with $H_2O$ and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc, 1:2) to afford **8** (1 g, 75%) as a bright yellow syrup. $R_f$ = 0.23 (*n*-hexane/EtOAc, 1:2). $[\alpha]_D^{22}$ = +6.8 ($c$ = 1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3259, 3026, 2963, 2928, 2873, 1601, 1494, 1454, 1372, 1071, 805, 773, 739, 700, 611 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 0.86 (t, $J$ = 7.5 Hz, 3 H), 1.48–1.69 (m, 2 H), 3.34–3.38 (br., 1 H), 4.03–4.05 (br., 1 H), 4.55–4.60 (m, 2 H), 5.72 (dd, $J$ = 11.5, 10.0 Hz, 1 H), 6.56 (d, $J$ = 11.5 Hz, 1 H), 7.22–7.34 (m, 10 H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 10.4, 23.6, 50.7, 72.4, 84.4, 127.2, 127.8, 127.9, 128.5, 128.6, 128.8, 129.2, 130.7, 133.4, 137.4, 139.1 ppm. HRMS (CI): calcd. for $C_{19}H_{24}NO$ $[M + H]^+$ 282.1860; found 282.1858.

**(3*R*,4*S*)-4-(Benzyloxy)-*N*-(but-3-enyl)-1-phenylhex-1-en-3-amine (9):** To a stirred solution of amine **8** (0.2 g, 0.71 mmol, 100 mol-%) in anhydrous DMF (4.0 mL) was added 4-bromo-1-butene (0.1 mL, 0.92 mmol, 130 mol-%) and $K_2CO_3$ (0.4 g, 2.84 mmol, 400 mol-%) at room temperature. The reaction mixture was stirred at 60 °C for 3 h. DMF was removed under reduced pressure, and the residue was diluted with EtOAc. The resulting solution was washed with $H_2O$ and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc, 8:1) to afford **9** (167 mg, 70%) as a colorless oil. $R_f$ = 0.23 (*n*-hexane/EtOAc, 8:1). $[\alpha]_D^{22}$ = –6.6 ($c$ = 3, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3062, 3026, 2966, 2931, 2873, 1723, 1640, 1601, 1494, 1453, 1363, 1208, 1070, 1029, 994, 915 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 0.86 (t, $J$ = 7.5 Hz, 3 H), 1.53–1.76 (m, 2 H), 1.81 (s, 1 H), 2.13 (dd, $J$ = 13.5, 7.0 Hz, 2 H), 2.39–2.44 (m, 1 H), 2.66–2.71 (m, 1 H), 3.41–3.44 (m, 1 H), 3.84–3.87 (m, 1 H), 4.55 (s, 2 H), 5.00 (dd, $J$ = 11.0, 3.5 Hz, 2 H), 5.58 (dd, $J$ = 12.0, 10.0 Hz, 1 H), 5.67–5.75 (m, 1 H), 6.68 (d, $J$ = 12.0 Hz, 1 H), 7.22–7.36 (m, 10 H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 10.8, 23.9, 34.6, 46.7, 57.0, 72.4, 83.8, 116.4, 127.1, 127.8, 128.0, 128.4, 128.5, 128.7, 129.6, 132.4, 132.8, 136.8, 137.7, 139.1 ppm. HRMS (CI): calcd. for $C_{23}H_{30}NO$ $[M + H]^+$ 336.2327; found 336.2327.

**(*R*)-6-[(*S*)-1-(Benzyloxy)propyl]-1,2,3,6-tetrahydropyridine (10):** To a solution of **9** (118 mg, 0.35 mmol, 100 mol-%) in anhydrous $CH_2Cl_2$ (2 mL) was added second generation Grubbs catalyst (24 mg, 0.028 mmol, 8 mol-%) and anhydrous *p*TsOH (66 mg, 0.35 mmol, 100 mol-%) under an atmosphere of $N_2$. The reaction mixture was heated at reflux for 6 h. The resulting mixture was filtered through a Celite pad and concentrated in vacuo. The residue was purified by column chromatography ($CHCl_3$/MeOH = 15:1) to afford **10** (60 mg, 72%) as a brownish oil. $R_f$ = 0.30 (*n*-hexane/EtOAc, 5:1). $[\alpha]_D^{22}$ = +1.3 ($c$ = 0.2, MeOH). IR (neat): $\tilde{\nu}$ = 3259, 1219, 1077, 772 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 0.94 (t, $J$ = 7.2 Hz, 3 H), 1.53–1.81 (m, 2 H), 2.14–2.20 (br., 1 H), 3.02–3.10 (m, 1 H), 3.50–3.53 (br., 1 H), 3.61–3.67 (m, 1 H), 3.97 (br. s, 1 H), 4.58 (d, $J$ = 11.4 Hz, 2 H), 5.66–5.70 (br., 1 H), 5.98–6.01 (br., 1 H), 7.22–7.36 (m, 5 H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 10.0, 22.0, 23.1, 40.8, 54.6, 72.5, 80.2, 121.1, 127.7, 128.1, 128.2,

128.7, 137.8 ppm. HRMS (CI): calcd. for $C_{15}H_{22}NO$ $[M + H]^+$ 232.1701; found 232.1701.

**(*S*)-1-[(*R*)-Piperidin-2-yl]propan-1-ol [(–)-α-Conhydrine] (1b):** To a stirred solution of **10** (60 mg, 0.26 mmol, 100 mol-%) in EtOH (10 mL) was added a solution of 6 N HCl (2 mL) and 10% Pd/C (50 mg). The reaction mixture was shaken on a Parr apparatus under an atmosphere of hydrogen (60 psi) for 24 h. The resulting mixture was filtered through a Celite pad and concentrated in vacuo. The residue was dissolved in EtOAc, and 30% aqueous solution of $NH_4OH$ was added to the resulting mixture at 0 °C. The reaction mixture concentrated in vacuo. The residue was purified by column chromatography (EtOAc/MeOH/$NH_4OH$, 10:1:0.1) to afford **1b** (32 mg, 86%) as colorless oil. $R_f$ = 0.32 (EtOAc/MeOH, 10:1). $[\alpha]_D^{19}$ = –7.82 (*c* = 2, EtOH). IR (neat): $\tilde{\nu}$ = 3305, 2129, 1644, 1106, 710 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 0.96 (t, *J* = 7.5 Hz, 3 H), 1.24–1.47 (m, 6 H), 1.55–1.58 (br., 2 H), 1.81–1.83 (br., 1 H), 2.43 (br. s, 2 H), 2.52–2.56 (m, 1 H), 2.62–2.70 (m,1 H), 3.08 (d, *J* = 10 Hz, 1 H), 3.36–3.40 (m, 1 H) ppm. $^{13}C$ NMR (125 MHz, $D_2O$): $\delta$ = 9.8, 21.6, 21.7, 22.2, 25.1, 45.2, 60.5, 72.5 ppm. HRMS (FAB): calcd. for $C_8H_{18}NO$ $[M - H]^+$ 144.1388; found 144.1386.

**Benzyl Allyl [(3*R*,4*S*)-4-(Benzyloxy)-1-phenylhex-1-en-3-yl]carbamate (11):** To a stirred solution of **7** (0.3 g, 0.72 mmol, 100 mol-%) in anhydrous THF (3 mL) and DMF (3 mL) was added NaH (45 mg, 1.1 mmol, 150 mol-%, 60% in mineral oil) and allyl bromide (0.2 mL, 2.16 mmol, 300 mol-%) at 0 °C under an atmosphere of $N_2$. The reaction mixture was stirred for 12 h at room temperature and quenched with $H_2O$ (10 mL). The aqueous layer was extracted with EtOAc (80 mL), and the organic layer was washed with $H_2O$ and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc, 8:1) to afford **11** (0.31 g, 95%) as a yellowish syrup. $R_f$ = 0.37 (*n*-hexane/EtOAc, 8:1). $[\alpha]_D^{23}$ = +44.1 (*c* = 3, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3030, 2966, 1697, 1496, 1455, 1408, 1358, 1247, 1070, 921, 742, 699, 605 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 0.66–0.97 (br., 3 H), 1.45–1.59 (br., 2 H), 3.57–4.05 (br., 4 H), 4.48–4.54 (br., 2 H), 4.81–5.16 (m, 6 H), 5.69–5.76 (br., 1 H), 5.96–6.05 (br., 1 H), 6.72 (d, *J* = 12.0 Hz, 1 H), 7.21–7.35 (m, 15 H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 9.8, 24.6, 25.8, 49.0, 55.9, 56.7, 67.2, 67.5, 73.1, 75.1, 82.2, 82.8, 83.3, 111.8, 116.7, 122.3, 126.1, 126.3, 126.7, 127.5, 127.7, 127.9, 128.0, 128.2, 128.5, 128.6, 128.8, 128.9, 133.0, 134.6, 135.3, 136.7, 139.0, 155.8 ppm. HRMS (CI): calcd. for $C_{30}H_{34}NO_3$ $[M + H]^+$ 456.2540; found 456.2539.

**(*R*)-Benzyl 2-[(*S*)-1-(Benzyloxy)propyl]-2,5-dihydro-1*H*-pyrrole-1-carboxylate (12):** To a stirred solution of **11** (0.16 g, 0.35 mmol, 100 mol-%) in anhydrous $CH_2Cl_2$ (5 mL) was added second generation Grubbs catalyst (24 mg, 0.028 mmol, 8 mol-%) under an atmosphere of $N_2$. The reaction mixture was heated at reflux for 12 h. The resulting mixture was filtered through a Celite pad and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc, 4:1) to afford **12** (107 mg, 87%) as a brownish oil. $R_f$ = 0.26 (*n*-hexane/EtOAc, 4:1). $[\alpha]_D^{23}$ = +8.4 (*c* = 1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3282, 3032, 2965, 1707, 1624, 1495, 1454, 1417, 1323, 1212, 1106, 1070 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 0.93 (t, *J* = 7.5 Hz, 3 H), 1.43–1.62 (m, 2 H), 3.71–4.60 (m, 6 H), 5.08–5.17 (m, 2 H), 5.78–5.93 (m, 2 H), 7.19–7.63 (m, 10 H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 10.9, 11.0, 25.7, 25.9, 54.0, 54.5, 66.9, 67.2, 68.0, 68.9, 73.6, 74.2, 76.7, 80.0, 80.8, 126.0, 126.2, 127.1, 127.3, 127.6, 127.7, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 136.9, 137.2, 138.9, 139.2, 154.7 ppm. HRMS (CI): calcd. for $C_{22}H_{26}NO_3$ $[M + H]^+$ 352.1918; found 352.1913.

**(*S*)-1-[(*R*)-Pyrrolidin-2-yl]propan-1-ol (2):** To a stirred solution of **12** (80 mg, 0.23 mmol, 100 mol-%) in EtOH (10 mL) was added a solution of aqueous 6 N HCl (2 mL) and 10% Pd/C (50 mg). The reaction mixture was shaken on a Parr apparatus under an atmosphere of hydrogen (60 psi) for 24 h. The resulting mixture was filtered through a Celite pad and concentrated in vacuo. The residue was dissolved in EtOAc and $H_2O$ and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/MeOH = 12:1) to afford **2** (40 mg, 93%) as a hydrochloride salt. $R_f$ = 0.28 (EtOAc/MeOH = 12:1). $[\alpha]_D^{22}$ = +40.6 (*c* = 2.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3359, 2945, 2833, 1662, 1453, 1030, 657 $cm^{-1}$. $^1H$ NMR (500 MHz, $D_2O$): $\delta$ = 0.94 (t, *J* = 7.5 Hz, 3 H), 1.34–1.52 (m, 2 H), 1.72–2.03 (m, 4 H), 3.20–3.28 (br., 2 H), 3.59 (br., 1 H), 3.77–3.79 (m, 1 H) ppm. $^{13}C$ NMR (125 MHz, $D_2O$): $\delta$ = 9.6, 23.3, 23.6, 26.8, 45.9, 63.6, 70.4 ppm. HRMS (CI): calcd. for $C_7H_{16}NO$ $[M + H]^+$ 130.1234; found 130.1232.

**Supporting Information** (see footnote on the first page of this article): $^1H$ NMR and $^{13}C$ NMR spectra for compounds **1b** and **2**–**12**.

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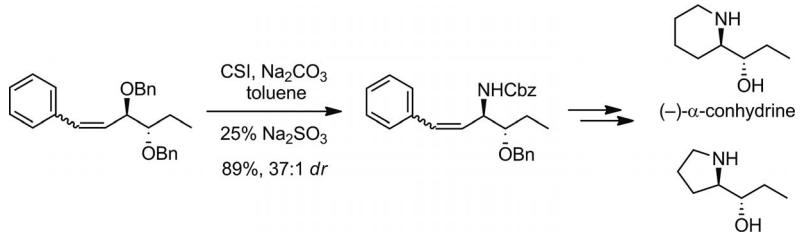


501 The total synthesis of (–)-α-conhydrine and its pyrrolidine analogue starting from readily available D-erythronolactone was achieved via the regioselective and diastereoselective allylic amination of *anti*-1,2-dibenzyl ether by using chlorosulfonyl isocyanate.



**Keywords:** Total synthesis / Natural products / Nitrogen heterocycles / Amination

  