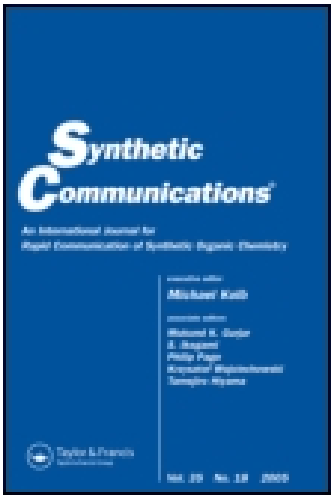

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Formal Synthesis of (+)-α-Conhydrine and Stereoselective Synthesis of Pyrrolidine Analogue via the Diastereoselective Chelation-Controlled Hydride Reduction and Wittig Reaction

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FORMAL SYNTHESIS OF (+)-α-CONHYDRINE AND STEREOSELECTIVE SYNTHESIS OF PYRROLIDINE ANALOGUE VIA THE DIASTEREOSELECTIVE CHELATION-CONTROLLED HYDRIDE REDUCTION AND WITTIG REACTION

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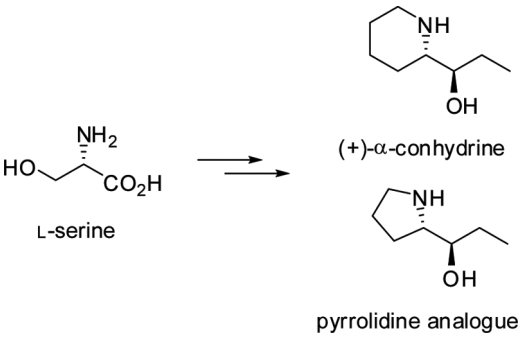
GRAPHICAL ABSTRACT



Abstract *Asymmetric syntheses of (+)-α-conhydrine and its pyrrolidine analogue were achieved from readily available L-serine. The key step involved highly diastereoselective chelation-controlled hydride reduction of the amino ketone to give the* anti-*amino alcohol and Wittig reaction.*

Keywords Asymmetric synthesis; natural products; piperidines; reduction; Wittig reaction

INTRODUCTION

Alkaloids containing 2-(1-hydroxyalkyl)piperidines are abundant in nature and have attracted much attention because of their potent antiviral, antitumor, and

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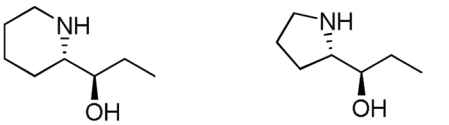


(+)-α-conhydrine **1** pyrrolidine analogue **2**

Figure 1. Structures of (+)-α-conhydrine **1** and its pyrrolidine analogue **2**.

anti-HIV properties.[1] Conhydrine was isolated from the seeds and leaves of the poisonous plant *Coniummaculatum L.* in 1856, whose extracts were used in ancient Greece for the execution of criminals,[2] and its structure was elucidated in 1933 (Fig. 1).[3]

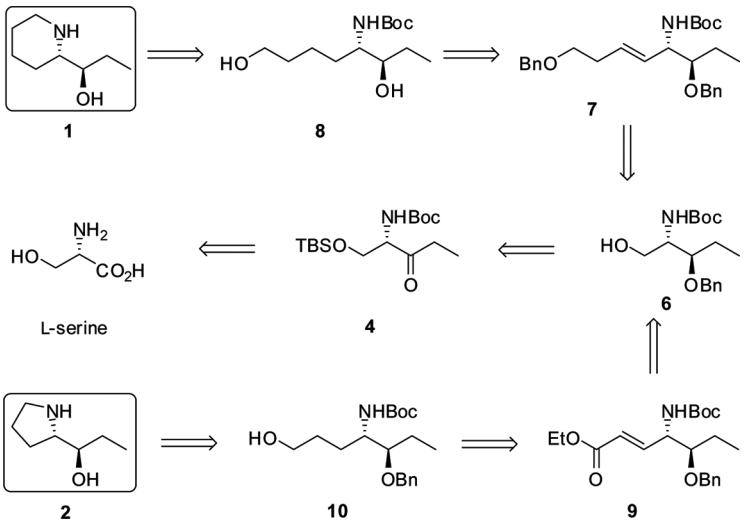
To date, several syntheses of α- and β-conhydrine have been reported employing chiral starting materials,[4] use of chiral auxiliaries,[5] or catalytic asymmetric synthesis.[6] In recent representative publications, Dong et al reported the concise total synthesis of (−)-α-conhydrine, starting from readily available D-erythronolactone, via the regioselective and diastereoseletive allylic amination of *anti*-1,2-dibenzyl ether by using chlorosulfonyl isocyanate and intramolecular olefin metathesis.[4a] Louvel et al. reported synthesis of (+)-β-conhydrine, via stereoselective synthesis of *syn*-β-amino propargylic ethers as a key step.[5a] We have also recently reported a facile strategy for the construction of (+)-α-conhydrine and its pyrrolidine analogue based on the highly diastereoselective chelation-controlled hydride reduction and RCM (ring-closing metathesis).[7a]

As a continuation of our previous work on highly diastereoselective chelation-controlled hydride reduction, we became interested in developing a more practical and efficient synthetic route to (+)-α-conhydrine **1** and its pyrrolidine analogue **2**. Herein, we report the asymmetric syntheses of (+)-α-conhydrine **1** and its pyrrolidine analogue **2** via highly diastereoselective chelation-controlled hydride reduction and Wittig reaction as the key steps.

RESULTS AND DISCUSSION

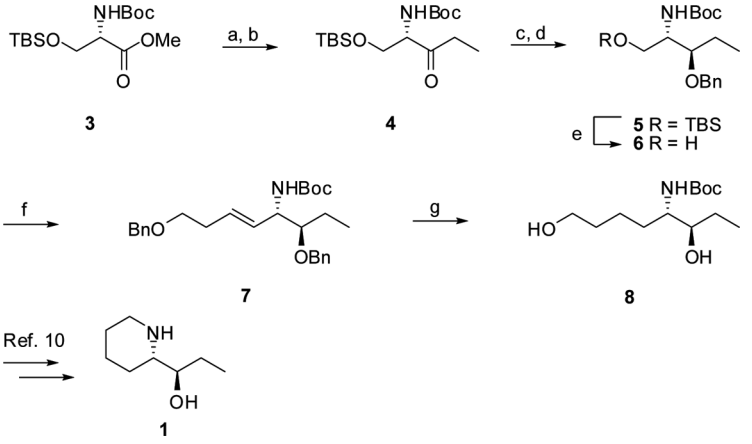
Retrosynthetically, we envisioned that (+)-α-conhydrine **1** could be generated from **8** through an intramolecular cyclization after deprotection of Boc group. The olefin compound **7** could be generated from benzylated 1,2-*anti*-amino alcohol **6** through Wittig olefination. In turn, the common intermediate **6** could be prepared by the diastereoselective reduction of amino ketone **4**. Thus, our synthetic plan for asymmetric synthesis of (+)-α-conhydrine **1** could be traced back to the construction of amino ketone **4**, which we envisaged could be easily achieved from commercially available L-serine (Scheme 1).

We envisioned that pyrrolidine analogue **2** could be prepared from compound **10** by intramolecular cyclization after palladium-catalyzed hydrogenation under acidic conditions. Compound **10** would come from hydrogenation of olefin **9** with platinum(IV) oxide, followed by reduction of ester with lithium aluminium hydride (LAH). It was envisaged that the construction of compound **9** could be afforded from L-serine according to a similar process to that descried for the construction of (+)-α-conhydrine via intermediate **6**.

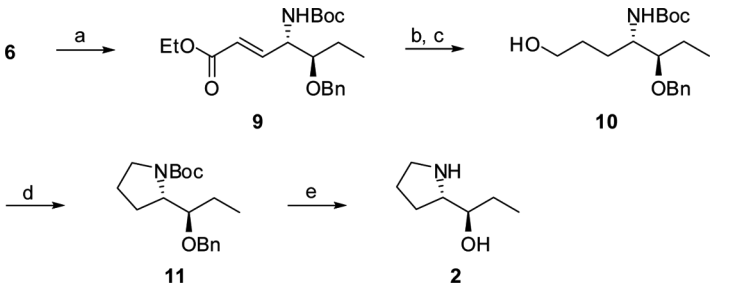


Scheme 1. Retrosynthetic analysis of (+)-α-conhydrine **1** and its pyrrolidine analogue **2**.

The asymmetric synthesis of (+)-α-conhydrine is described in Scheme 2. Reaction of **3** with NH(OMe)Me · HCl in the presence of $AlMe_3$ gave Weinreb amide in quantitative yield. Treatment of the Weinreb amide with EtMgBr in tetrahydrofuran (THF) at 0 °C provided **4** in 92% yield. Reduction of **4** with $LiAlH(O^tBu)_3$ in EtOH at −78 °C gave the desired *anti*-amino alcohol as the major compound with excellent yield and stereoselectivity (*anti*/*syn* > 10:1 by ^1H NMR spectroscopy). The diastereoselectivity of this reduction resulted from a chelation-controlled process.[7,8] The secondary alcohol was protected as benzyl ether and the TBS group was deprotected



Scheme 2. Reagents and conditions: (a) NH(OMe)Me · HCl, $AlMe_3$, CH_2Cl_2, 0 °C, 95%; (b) EtMgBr, THF, 0 °C, 92%; (c) $LiAlH(O^tBu)_3$, EtOH, −78 °C, 89%; (d) BnBr, NaH, TBAI, THF, rt, 85%; (e) TBAF, THF, rt, 92%; (f) (i) Dess–Martin periodinane, CH_2Cl_2, rt; (ii) (3-benzyloxypropyl)triphenylphosphonium bromide, *n*-BuLi, THF, 0 °C to rt, 72% (2 steps); (g) Pd/C, H_2, MeOH, rt, 87%.



Scheme 3. Reagents and conditions: (a) (i) Dess–Martin periodinane, CH_2Cl_2, rt; (ii) (carbethoxymethylene)triphenylphosphorane, THF, 0 °C to rt, 79% (2 steps); (b) PtO_2, H_2, MeOH, rt, 90%; (c) LAH, THF, 0 °C to rt, 85%; (d) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C; (ii) NaH, THF, 0 °C to rt, 92% (2 steps); (e) Pd/C, H_2, MeOH, 6 N HCl, rt, 92%.

with tetra-*n*-butylammonium fluoride (TBAF), leading to the corresponding primary alcohol in good yield. Dess–Martin oxidation of primary alcohol afforded corresponding aldehyde, which was treated with (3-benzyloxypropyl)triphenylphosphonium bromide and *n*-BuLi in tetrahydrofuran (THF) at 0 °C to afford olefin **7** in moderate yield.[9a,9b]

Catalytic hydrogenation of **7** with Pd/C furnished **8** by simultaneous deprotection of the benzyl group and reduction of the double bond. Compound **8** had previously been transformed into (+)-α-conhydrine **1**, thus completing the formal total synthesis.[10]

Oxidation of primary alcohol **6** with the Dess–Martin periodinane afforded the corresponding aldehyde, which was treated with (carbethoxymethylene)triphenylphosphorane in THF at 0 °C to room temperature provided the olefinic ester **9**.[9c,9d]

Hydrogenation of the olefin **9** with platinum(IV) oxide gave ester in good yield.[11] Reduction of ester with LAH to afford alcohol **10**. Treatment of **10** with methanesulfonyl chloride and triethylamine afforded the corresponding mesylate, which was subjected to cyclization using NaH furnished compound **11** (Scheme 3). Further, catalytic hydrogenation of **11** with Pd/C under acidic conditions furnished **2** by simultaneous deprotection of the benzyl and Boc groups. The spectroscopic data for synthetic **2** agreed with those reported.[5d,7a]

CONCLUSION

We have developed asymmetric syntheses of (+)-α-conhydrine **1** and its pyrrolidine analogue **2** and demonstrated the usefulness of the highly diastereoselective chelation-controlled hydride reduction of the amino ketone to give the *anti*-amino alcohol. This article described practical and efficient S_N2-type cyclization procedure, which employed a reaction using mesylates instead of that used for the RCM procedure in our previous work. In addition, the substrate for the cyclization reaction was easily obtained from the intermediate **6** via the Wittig reaction. The net results was the syntheses from linear sequence of eight steps from *N*-Boc-L-serine-methyl ester **3** in 38.1% overall yield for compound **8**, which has previously been transformed to (+)-α-conhydrine **1** in two steps, and to pyrrolidine analogue **2** in

31.1% overall yield in 12 steps. Further extension of this work to the syntheses of other structurally related natural products are in progress.

Therefore, we have performed efficient, stereoselective syntheses of (+)-α-conhydrine **1** and its pyrrolidine analogue **2.** These results are better than those reported in the previous syntheses of either **1** or its pyrrolidine analogue **2**.

EXPERIMENTAL

Optical rotations were measured with a polarimeter in the solvent specified. ^1H and ^{13}C NMR spectroscopic data were recorded on Varian or Bruker FT-NMR 125, 175, 300, 500, and 700 MHz spectrometers at the Cooperative Center for Research Facilities in Sungkyunkwan University. Chemical shift values are reported in parts per million relative to TMS or $CDCl_3$ as the internal standard, and coupling constants are reported in hertz. Infrared (IR) spectra were measured with a Bruker FT-IR spectrometer. High-resolution fast atom bombardment (FAB) mass spectra were recorded using a Jeol JMS-700 mass spectrometer at the Daegu Center of KBSI, Korea. Chromatography was performed using mixtures of EtOAc and hexanes as eluent. Unless otherwise noted, all nonaqueous reactions were carried out in an argon atmosphere with commercial-grade reagents and solvents. THF was distilled from sodium and benzophenone (indicator). CH_2Cl_2 was distilled from calcium hydride.

tert-Butyl (3*R*,4*S*,*E*)-3,8-Bis(benzyloxy)oct-5-en-4-ylcarbamate (7)

A solution of the primary alcohol (152 mg, 0.49 mmol) in CH_2Cl_2 (5 mL) was added to a solution of Dess–Martin periodinane (250 mg, 0.59 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt. The reaction mixture was stirred at rt. for 2 h. The mixture was diluted with Et_2O (20 mL); then saturated aqueous $NaHCO_3$ (5 mL) and $Na_2S_2O_3$ (0.94 g) were added and the heterogeneous mixture was stirred at rt for 20 min. The ether layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give the crude aldehyde. *n*-BuLi (1.6 M in hexanes, 0.31 mL, 0.50 mmol) was added dropwise to a mixture of (3-benzyloxypropyl)triphenylphosphonium bromide (251 mg, 0.50 mmol) in anhydrous THF (5 mL) at 0 °C. After 10 min stirring at 0 °C, the crude aldehyde (139 mg, 0.45 mmol) dissolved in anhydrous THF (1 mL) was added dropwise. After 6 h, the reaction was partitioned between Et_2O and H_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography on a silica-gel column (hexanes–EtOAc, 6:1) to afford **7** (142 mg, 72%, 2 steps) as a colorless oil.

$[\alpha]_D^{25} = -14.09$ (*c* 1.3, $CHCl_3$); $R_f = 0.73$ (hexanes–EtOAc, 2:1); FT-IR (neat) 3383, 2948, 2834, 1661, 1452, 1114, 1032, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, $J = 7.5$ Hz, 3 H), 1.37–1.46 (m, 10 H), 1.53–1.60 (m, 1 H), 2.39–2.56 (m, 2 H), 3.45–3.54 (m, 4 H), 4.48–4.62 (m, 4 H), 4.85 (br, 1 H), 5.48–5.65 (m, 2 H), 7.21–7.33 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.57, 24.01, 28.70, 28.79, 50.02, 69.98, 72.59, 73.04, 79.33, 83.03, 127.74, 127.86, 127.88, 127.97, 128.58, 128.66, 130.25, 138.76, 138.99, 155.42. HRMS-FAB *m/z* $[M + H]^+$ calcd. for $C_{27}H_{37}NO_4$: 440.2801; found 440.2804.

(4*S*,5*R*,*E*)-Ethyl 5-(Benzyloxy)-4-(*tert*-butoxycarbonylamino)hept-2-enoate (9)

A solution of the primary alcohol (84 mg, 0.27 mmol) in CH_2Cl_2 (3 mL) was added to a solution of Dess–Martin periodinane (138 mg, 0.33 mmol) in anhydrous CH_2Cl_2 (3 mL) at rt. The reaction mixture was stirred at rt for 2 h. The mixture was diluted with Et_2O (10 mL × 2); then saturated aqueous $NaHCO_3$ (5 mL) and $Na_2S_2O_3$ (0.52 g) were added and the heterogeneous mixture was stirred at rt for 20 min. The ether layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give the crude aldehyde, which was used in a further reaction. The crude aldehyde was dissolved in THF (3 mL) and (carbethoxymethylene)triphenylphosphorane (119 mg, 0.33 mmol) was added. The reaction mixture was stirred for 12 h at rt and quenched with H_2O (1 mL). The aqueous layer was extracted with EtOAc (5 mL × 2). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (hexanes–EtOAc, 6:1) to afford α,β-unsaturated ester **9** (81 mg, 79%, two steps) as a colorless oil.

$[\alpha]_D^{25} = +11.29$ (*c* 1.9, $CHCl_3$); $R_f = 0.61$ (hexanes–EtOAc, 3:1); FT-IR (neat) 3671, 2974, 2868, 1714, 1520, 1367, 1167, 1066, 1011, 611 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, $J = 7.5$ Hz, 3 H), 1.29 (t, $J = 7.0$ Hz, 3 H), 1.42 (s, 9 H), 1.44–1.49 (m, 1 H), 1.63–1.69 (m, 1 H), 3.44–3.47 (m, 1 H), 4.19 (dd, $J = 7.0$, 14.5 Hz, 2 H), 4.49 (s, 1 H), 4.52 (s, 1 H), 4.61 (s, 1 H), 4.63 (s, 1 H), 4.88 (br, 1 H), 5.96 (d, $J = 1.5$ Hz, 1 H), 6.00 (d, $J = 1.0$ Hz, 1 H), 6.91 (dd, $J = 6.0$, 6.5 Hz, 1 H), 7.28–7.37 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.24, 14.45, 23.68, 28.56, 53.45, 60.64, 72.19, 79.94, 82.24, 123.02, 128.04, 128.71, 138.35, 144.55, 155.38, 166.30. HRMS-FAB *m/z* $[M + H]^+$ calcd. for $C_{21}H_{31}NO_5$: 378.2280; found 378.2279.

(*R*)-1-((*S*)-Pyrrolidin-2-yl)propan-1-ol (2)

A solution of the substrate **11** (42 mg, 0.13 mmol) in a mixture of 6 N HCl (0.2 mL) and MeOH (2 mL) was refluxed for 12 h and concentrated in vacuo. The residue was purified by chromatography on a silica-gel column ($CHCl_3$-MeOH, 1:1) to give the HCl salt of **2** (19.8 mg, 92%) as a white solid.

Mp 111–113 °C; $[\alpha]_D^{25} = -38.2$ (*c* 0.9, $CHCl_3$); $R_f = 0.10$ ($CHCl_3$-MeOH, 1:1); FT-IR (neat) 3375, 2943, 2830, 1663, 1459, 1110, 1031, 690 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 0.99 (t, $J = 7.5$ Hz, 3 H), 1.46–1.62 (m, 2 H), 1.84–2.17 (m, 4 H), 3.35 (t, $J = 7.2$ Hz, 2 H), 3.67–3.73 (m, 1 H), 3.86–3.92 (m, 1 H); ^{13}C NMR (125 MHz, D_2O) δ 9.59, 23.34, 23.59, 26.88, 45.98, 63.62, 70.47; HRMS-FAB *m/z* $[M + H]^+$-HCl calcd. for $C_7H_{16}ClNO$: 130.1232; found 130.1230.

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SUPPORTING INFORMATION

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