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...
anti-HIV properties.[1] Conhydrine was isolated from the seeds and leaves of the poisonous plant *Conium maculatum* 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 diastereoselective 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 described for the construction of (−)-α-conhydrine via intermediate 6.
The asymmetric synthesis of (+)-α-conhydrine is described in Scheme 2. Reaction of 3 with NH(OMe)Me·HCl in the presence of AlMe3 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(OtBu)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, AlMe3, CH2Cl2, 0 °C, 95%; (b) EtMgBr, THF, 0 °C, 92%; (c) LiAlH(OtBu)3, EtOH, −78 °C, 89%; (d) BnBr, NaH, TBAI, THF, rt, 85%; (e) TBAF, THF, rt, 92%; (f) (i) Dess–Martin periodinane, CH2Cl2, rt; (ii) (3-benzyloxypropyl)triphenylphosphonium bromide, n-BuLi, THF, 0 °C to rt, 72% (2 steps); (g) Pd/C, H2, MeOH, rt, 87%. 
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 (+)-$\alpha$-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 (+)-$\alpha$-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 $S_N^2$-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 (+)-$\alpha$-conhydrine 1 in two steps, and to pyrrolidine analogue 2 in

![Scheme 3](image-url)
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. $^1$H 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$_2$Cl$_2$ was distilled from calcium hydride.

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

A solution of the primary alcohol (152 mg, 0.49 mmol) in CH$_2$Cl$_2$ (5 mL) was added to a solution of Dess–Martin periodinane (250 mg, 0.59 mmol) in anhydrous CH$_2$Cl$_2$ (3 mL) at rt. The reaction mixture was stirred at rt. for 2 h. The mixture was diluted with Et$_2$O (20 mL); then saturated aqueous NaHCO$_3$ (5 mL) and Na$_2$S$_2$O$_3$ (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$_2$O and H$_2$O. 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$_3$); $R_T$ = 0.73 (hexanes–EtOAc, 2:1); FT-IR (neat) 3383, 2948, 2834, 1661, 1452, 1114, 1032, 698 cm$^{-1}$; $^1$H 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.
(4S,5R,E)-Ethyl 5-(Benzyloxy)-4-(tert-butoxycarbonylamino)hept-2-enoate (9)

A solution of the primary alcohol (84 mg, 0.27 mmol) in CH₂Cl₂ (3 mL) was added to a solution of Dess–Martin periodinane (138 mg, 0.33 mmol) in anhydrous CH₂Cl₂ (3 mL) at rt. The reaction mixture was stirred at rt for 2 h. The mixture was diluted with Et₂O (10 mL × 2); then saturated aqueous NaHCO₃ (5 mL) and Na₂S₂O₃ (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 MgSO₄, 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 H₂O (1 mL). The aqueous layer was extracted with EtOAc (5 mL × 2). The organic layer was washed with H₂O and brine, dried over MgSO₄, 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.

δ [α]D²⁵ = +11.29 (c 1.9, CHCl₃); Rf = 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, CDCl₃) 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), 4.52 (s, 1 H), 4.63 (s, 1 H), 4.88 (br, 1 H), 5.06 (d, J = 1.5 Hz, 1 H), 6.00 (d, J = 1.0 Hz, 1 H), 7.28–7.37 (m, 5 H); ¹³C NMR (125 MHz, CDCl₃) δ 10.24, 14.45, 23.68, 28.56, 53.45, 60.64, 70.47; HRMS-FAB m/z [M + H]+ calcd. for C₂₁H₃₁NO₅: 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 (CHCl₃-MeOH, 1:1) to give the HCl salt of 2 (19.8 mg, 92%) as a white solid.

δ [α]D²⁵ = −38.2 (c 0.9, CHCl₃); Rf = 0.10 (CHCl₃-MeOH, 1:1); FT-IR (neat) 3375, 2943, 2830, 1663, 1459, 1110, 1031, 690 cm⁻¹; ¹H NMR (300 MHz, D₂O) 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); ¹³C NMR (125 MHz, D₂O) δ 9.59, 23.34, 23.59, 26.88, 45.98, 63.62, 70.47; HRMS-FAB m/z [M + H]+-HCl calcd. for C₇H₁₆ClNO: 130.1232; found 130.1230.

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher’s website.

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