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Short and Efficient Asymmetric Synthesis of (−)-α-Conhydrine†

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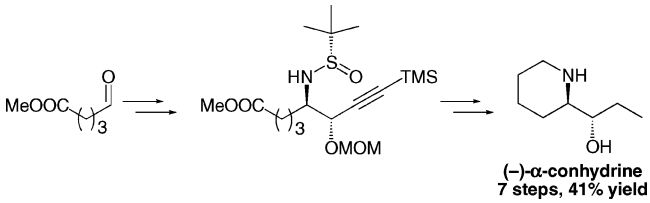

The short and efficient synthesis of (−)-α-conhydrine was accomplished with 41% overall yield in seven steps and high diastereo- and enantioselectivity. The anti-stereochemistry of the two stereogenic centers has been confirmed by the single-crystal X-ray analysis of an intermediate.

Introduction

Hydroxylated piperidines represent a stuctural unit frequently found in many biologically active alkaloids.[1] Conhydrine is one of the alkaloids in hemlock *Conium maculatum* L. isolated from the seeds and leaves of this poisonous plant.[2] Since the pioneering studies on the synthesis of (+)-α-conhydrine by Galinovsky and Mulley,[3] various methods for the synthesis of (−)- or (+)-*β*-conhydrine **2** and *ent*-**2**,[4] of (−)-α-conhydrine[5] **1**, and of (+)-α-conhydrine *ent*-**1**[6,4c,4f] have been reported (Figure 1).

However, these enantioselective syntheses of α-conhydrine are relatively long, with moderate overall yields (steps/overall yield: 12/18%,[4c] 10/14%,[5c] 7/17%,[6a] 14/12%,[6b] 6/22%,[6c] 19/19%,[6d] and 13/4%,[6e] respectively). Despite the various methods used for the synthesis of (−)-α-conhydrine, we believed that it was possible to find a shorter and more efficient way to synthesize this molecule. We reasoned that the use of the methodology involving allenylzinc species recently developed in our laboratory could provide the desired (−)-α-conhydrine **1** quickly and with a good overall yield.

In the past few years, we have reported that racemic 3-chloro allenylzinc species could react efficiently with carbonyl and imine derivatives.[7] We then developed a route to diastereo- and enantiomerically pure acetylenic *trans*- and *cis*-*N*-*tert*-butanesulfinylaziridines[8] using enantiopure Ellman's *N*-*tert*-butanesulfinimines.[9] All these aziridines proved to be good precursors

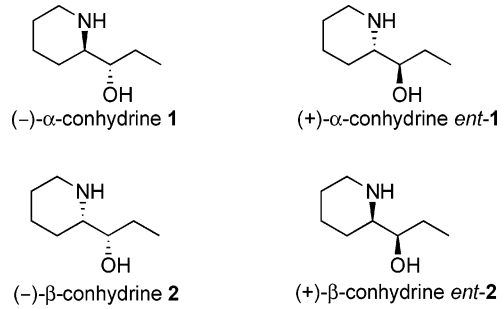

FIGURE 1. α- and *β*-Conhydrines.

† Dedicated to Prof. Miguel Yus on the occasion of his 60th birthday.

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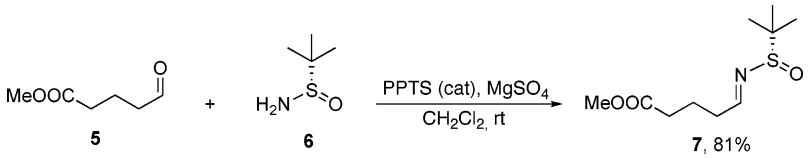
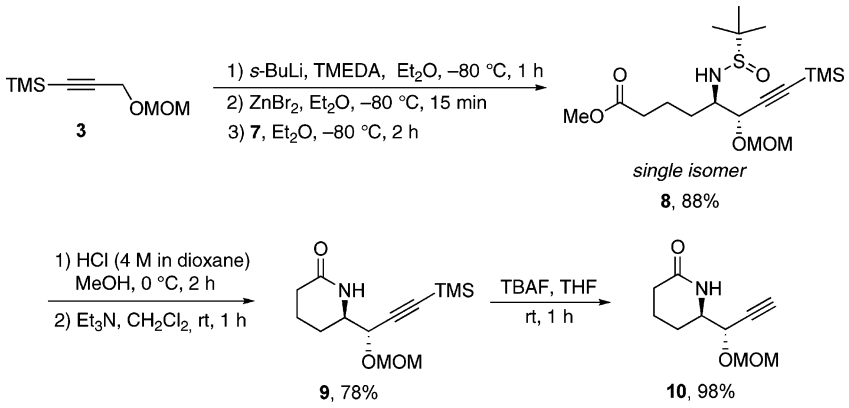
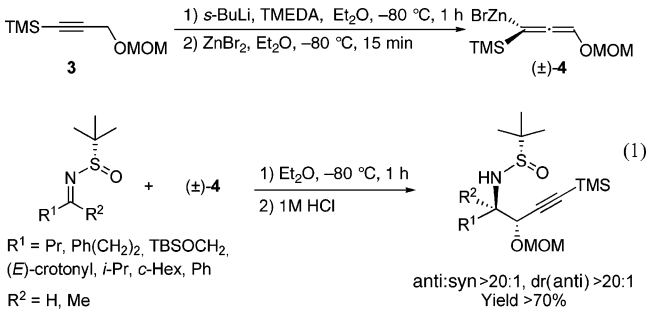
SCHEME 1. Synthesis of Starting (S_s)-sulfinimine 7



SCHEME 2. Synthesis of Lactam 10



of enantiopure *anti*- and *syn*-1,2-amino alcohols through the ring-opening reaction with water under acidic conditions.[10] More recently, we have shown that the use of 3-alkoxy allenylzinc (±)-**4** gives an easy access to *anti*-1,2-*N*-*tert*-butanesulfinamidoalkyl methoxymethyl ethers through kinetic resolution with high diastereo- and enantioselectivity (eq 1).[11] The latter could be further converted efficiently into the corresponding acetylenic *anti*-1,2-amino alcohols in diastereo- and enantioenriched forms.[12]



Results and Discussion

Aiming to synthesize (−)-α-conhydrine **1**, we initially prepared chiral (S_s)-sulfinimine **7** in 81% yield from methyl 5-oxopentanoate **5**[13] and (S_s)-*N*-*tert*-butanesulfinamide **6** according to Ellman's procedure (Scheme 1).[9]

Allenylzinc species (±)-**4** was generated in Et_2O by the lithiation of (3-(methoxymethoxy)prop-1-ynyl)trimethylsilane (**3**)[14] with *sec*-butyllithium in presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and subsequent transmetalation with anhydrous zinc bromide. Addition of the enantiopure (S_s)-sulfinimine **7** to the *in situ* formed racemic allenylzinc (±)-**4** gave, after acidic workup, the desired compound **8** with 88% yield (Scheme 2). As seen by ^{1}H NMR of the crude product, the reaction was highly diastereoselective in favor of the anti-isomer (anti:syn >20:1). This result was in agreement with our previous results.[11] The anti-stereoselectivity and the sense of the stereoinduction observed with 3-alkoxy allenylzinc (±)-**4** was assumed to result from a monocoordinated-transition state **TS1** in which the zinc atom is coordinated only by the nitrogen of the imine (Figure 2). The quantitative deprotection of

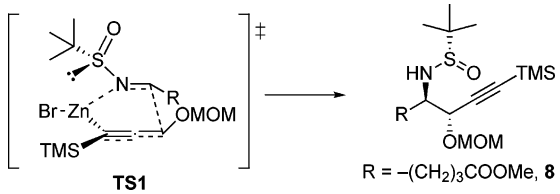


FIGURE 2. Postulated monocoordinated-type transition state **TS1** for the formation of **8**.

N-sulfinimine addition product **8** with methanolic HCl at 0 °C, followed by the addition of triethylamine to the crude product, afforded, after workup and purification, the lactam **9** in 78% overall yield (Scheme 2). It is noteworthy that a related cyclization with chlorine as a nucleofuge has been achieved to synthesize piperidine and pyrrolidine derivatives.[15] Desilylation at the acetylenic position of the alkyne **9**, under classical

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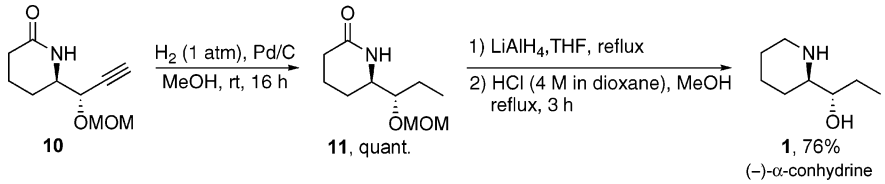
(14) (3-(Methoxymethoxy)prop-1-ynyl)trimethylsilane (**3**) was prepared in a two-step procedure from propargyl alcohol by (i) silylation at the acetylenic position; see Jones, T. K.; Denmark, S. E. *Org. Synth.* **1985**, *64*, 182−185; followed by (ii) treatment of the resulting product with an excess of dimethoxymethane in $CHCl_3$ in the presence of an excess of P_2O_5.

SCHEME 3. Access to (−)-α-Conhydrine 1



conditions, gave a crystalline compound **10** nearly quantitatively (Scheme 2). The *anti*-relationship between the two stereogenic carbons created in the key-step reaction (i.e., the condensation of allenylzinc (±)-**4** onto imine **7)** was confirmed by the single-crystal X-ray analysis of the compound **10**.[16] The complete hydrogenation (1 atm) of the alkyne **10** over palladium on charcoal afforded **11** in quantitative yield. Reduction of the lactam with $LiAlH_4$ and subsequent deprotection of the alcohol with HCl (4 M in dioxane) furnished (−)-α-conhydrine **1** with 76% yield over the last two steps and 41% overall yield from **5** (Scheme 3).

(−)-α-Conhydrine {$[\alpha]^{20}_D = -8.7$ (*c* 0.78, EtOH), Mp 118 °C} so obtained was physically and spectroscopically identical to the literature data {$[\alpha]^{27}_D = -8.6$ (*c* 0.68, EtOH), Mp 118 °C}.[6a] The negative sign of the optical rotation is the ultimate confirmation of the expected relative and absolute (6*R*,7*S*)-configuration of the product.

Conclusion

In summary, the condensation of a racemic 3-alkoxy allenylzinc onto the enantiopure (S_s)-*N*-*tert*-butanesulfinimine derived from 5-oxopentanoate allowed us to develop an efficient stereoselective synthesis of (−)-α-conhydrine. Indeed, the total synthesis of (−)-α-conhydrine has been achieved in seven steps with 41% overall yield. To the best of our knowledge, this is the most efficient synthesis in the conhydrine family in terms of yield. Further syntheses of compounds presenting biological interest is now under investigation and will be reported in due course.

Experimental Section

General. See the Supporting Information.

(+)-(S_S)-Ethyl 5-(*tert*-Butylsulfinylimino)pentanoate (7). The synthesis was performed according to the previously described procedure.[9a] Under a nitrogen atmosphere, a suspension of ethyl 5-oxopentanoate[13] **5** (520 mg, 4.00 mmol), (S_S)-(+)-*tert*-butanesulfinamide **6** (>99% ee by chiral GC analysis on a Lipodex E capillary column, 404 mg, 3.33 mmol), PPTS (42 mg, 0.17 mmol), and anhydrous $MgSO_4$ (2.00 g) in CH_2Cl_2 (6 mL) was stirred for 14 h at room temperature. The mixture was filtered through a pad of Celite and concentrated in vacuo. The residual oil was purified by flash chromatography on silica gel (80% Et_2O/cyclohexane) to produce the desired compound **7** as an oil (626 mg, 81%): R_f 0.69 (pure Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (t, J = 4.3 Hz, 1H), 3.59 (s, 3H), 2.51 (dt, J = 7.3, 4.3 Hz, 2H), 2.33 (t, J = 7.3 Hz, 2H), 1.90 (quint, J = 7.3 Hz, 2H), 1.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 168.3, 56.5, 51.6, 35.1, 33.1, 22.3, 20.4; IR: ν_{max} = 2955, 1734, 1623, 1437, 1250, 1164, 1081 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{20}NO_3S$ $[M + H]^+$: 234.1158, found: 234.1158; $[\alpha]_D^{20} = +230.0$ (*c* 1.70, $CHCl_3$).

(+)-(5*R*,6*S*,S_S)-Ethyl 5-(*tert*-Butylsulfinamido)-6-(methoxymethoxy)-8-(trimethylsilyl)oct-7-ynoate (8). To a stirred solution of (3-(methoxymethoxy)prop-1-ynyl)trimethylsilane (760 μL, 4.00 mmol) and TMEDA (60 μL, 0.40 mmol) in anhydrous Et_2O (35 mL) under a nitrogen atmosphere, at −78 °C, was added dropwise *sec*-butyllithium (1.3 M in 92% cyclohexane/hexane, 3.08 mL, 4.00 mmol). The resulting clear yellow mixture was stirred for 1 h at −78 °C, and then a 1 M ethereal solution of $ZnBr_2$ (4.0 mL, 4.00 mmol) was added. The resulting white slurry of allenylzinc was stirred at −78 °C for an additionnal 20 min before enantiopure (S_S)-ethyl 5-(*tert*-butylsulfinylimino)pentanoate **7** (234 mg, 1.00 mmol) in anhydrous Et_2O (2.0 mL) was added over a period of 2 min. After 1 h of stirring at −78 °C, aq 1 M HCl (35 mL) was added and the mixture was warmed to room temperature. The layers were separated, and the aqueous one was extracted twice with Et_2O. The combined organic layers were washed with saturated $NaHCO_3$ solution, water, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (75% Et_2O/cyclohexane) to produce the desired compound **8** as an oil (356 mg, 88%): R_f 0.36 (pure Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (d, J = 6.5 Hz, 1H), 4.51 (d, J = 6.5 Hz, 1H), 4.23 (d, J = 3.8 Hz, 1H), 3.59 (s, 3H), 3.46 (d, J = 8.3 Hz, 1H), 3.36−3.31 (m, 1H), 3.30 (s, 3H), 2.30 (dt, J = 7.3, 2.0 Hz, 2H), 1.93−1.81 (m, 1H), 1.81−1.61 (m, 2H), 1.58−1.46 (m, 1H), 1.16 (s, 9H), 0.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 101.3, 94.3, 92.9, 70.2, 60.1, 56.4, 55.9, 51.5, 33.5, 31.6, 22.7, 21.2, −0.2; IR: ν_{max} = 3236, 2900, 2361, 2342, 1737, 1438, 1363, 1250, 1151, 1024, 842, 760 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{36}NO_5SSi$ $[M + H]^+$: 406.2078, found 406.2077; $[\alpha]_D^{20} = +90.4$ (*c* 1.65, $CHCl_3$).

(+)-(6*R*)-[(1*S*)-1-(Methoxymethoxy)-3-(trimethylsilyl)prop-2-ynyl]piperidin-2-one (9). To a stirred solution of **8** (150 mg, 0.37 mmol) in MeOH (3 mL) was added a 4 M HCl solution in dioxane (925 μL, 3.70 mmol), under a nitrogen atmosphere at 0 °C. After 2 h of stirring at 0 °C, saturated $NaHCO_3$ solution was added and the MeOH was evaporated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was taken up in CH_2Cl_2 (4 mL), and TEA (205 μL, 1.48 mmol) was added. The solution was stirred 2 h, and water was added. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (60% EtOAc/cyclohexane) to produce the desired compound **9** as an oil (78 mg, 78%): R_f 0.30 (60% EtOAc/cyclohexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (bs, 1H), 4.92 (d, J = 6.8 Hz, 1H), 4.56 (d, J = 6.8 Hz, 1H), 4.21 (d, J = 5.3 Hz, 1H), 3.56 (m, 1H), 3.36 (s, 3H), 2.45−2.35 (m, 1H), 2.34−2.20 (m, 1H), 1.98−1.90 (m, 2H), 1.70−1.58 (m, 2H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 100.0, 94.1, 93.9, 69.3, 56.0, 55.6, 31.6, 24.7, 19.3, −0.2; IR: ν_{max} = 2955, 2360, 1667, 1408, 1250, 1150, 1101, 1026, 841, 760 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{24}NO_3Si$ $[M + H]^+$: 270.1520, found: 270.1517; $[\alpha]_D^{20} = +135.8$ (*c* 1.20, $CHCl_3$).

(+)-(6*R*)-[(1*S*)-1-(Methoxymethoxy)prop-2-ynyl]piperidin-2-one (10). To a solution of **9** (60 mg, 0.22 mmol) in dry THF (3 mL) at room temperature was added a 1 M solution of TBAF in THF (270 μL, 0.27 mmol). The solution was stirred 2 h, and water

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(16) CCDC 641262 contains the supplementary crystallographic data for compound **10**. These data can be obtained free of charge via www.ccdc.ac.uk/conts/retrieving.html [or from Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, U.K. Fax: +44(1223)-366033. E-mail: deposit@ccdc.cam.ac.uk].

was added. After extraction with EtOAc, the organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (EtOAc) to produce the desired compound **10** (43 mg, 98%). Suitable crystals of **10** were obtained from Et_2O at room temperature by slow evaporation of the solvent: R_f 0.37 (5% MeOH/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (bs, 1H), 4.93 (d, J = 6.8 Hz, 1H), 4.58 (d, J = 6.8 Hz, 1H), 4.27 (dd, J = 4.8, 1.8 Hz, 1H), 3.65−3.57 (m, 1H), 3.36 (s, 3H), 2.49 (d, J = 2.0 Hz, 1H), 2.44−2.35 (m, 1H), 2.34−2.23 (m, 1H), 1.98−1.90 (m, 2H), 1.75−1.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 94.2, 78.5, 76.7, 68.6, 56.0, 55.6, 31.6, 24.5, 19.4; IR: ν_{max} = 3194, 2954, 2891, 2105, 1657, 1493, 1408, 1301, 1174, 1150, 1105, 1086, 1045, 1008, 916, 752, 729, 665 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{16}NO_3$ [M + H]$^+$: 198.1125, found: 198.1126; $[\alpha]_D^{20}$ = +144.4 (*c* 1.27, $CHCl_3$).

(+)-(6*R*)-[(1*S*)-1-(Methoxymethoxy)propyl]piperidin-2-one (11). To **10** (62.4 mg, 0.32 mmol) in MeOH (8 mL) was added Pd/C (10 wt. %, 35 mg), and the flask was flushed with H_2. The reaction mixture was stirred for 16 h under 1 atm of H_2. The reaction mixture was filtered through a pad of celite. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (pure EtOAc to 5% MeOH/EtOAc) to afford the desired compound **11** as an oil (63.6 mg, 100%): R_f 0.27 (5% MeOH/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (bs, 1H), 4.63 (d, J = 6.8 Hz, 1H), 4.59 (d, J = 6.8 Hz, 1H), 3.62−3.54 (m, 1H), 3.44−3.36 (m, 1H), 3.34 (s, 3H), 2.41−2.31 (m, 1H), 2.28−2.15 (m, 1H), 1.96−1.85 (m, 1H), 1.81−1.72 (m, 1H), 1.71−1.58 (m, 1H), 1.56−1.36 (m, 3H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 96.4, 80.7, 55.9, 55.4, 31.5, 23.7, 22.5, 20.1, 10.2; IR: ν_{max} = 2941, 2874, 2361, 2341, 1662, 1466, 1409, 1149, 1105, 1033, 917, 669 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{19}NNaO_3$ [M + Na]$^+$: 224.1257, found: 224.1255; $[\alpha]_D^{20}$ = +8.4 (*c* 1.05, $CHCl_3$).

(−)-(1*S*)-[(2*R*)-Piperidin-2-yl]propan-1-ol; (−)-α-conhydrine (1). Lactam **11** (60 mg, 0.30 mmol) in THF (4.5 mL) was added to a suspension of $LiAlH_4$ (34 mg, 0.90 mmol) in dry THF (2 mL). The mixture was refluxed for 2 h, and then H_2O was added dropwise. EtOAc was then added, the white suspension was filtered over Celite, and the filtrate was concentrated under vacuum. The crude product was taken up in MeOH (4.0 mL), and a 4 M HCl solution in dioxane was added (300 μL, 1.19 mmol). After 2 h of stirring at reflux, a saturated $NaHCO_3$ solution was added, and the mixture was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (50% MeOH/CH_2Cl_2) to produce **1** (32.1 mg, 76%) as a white solid. Mp 118 °C. {lit.[3] Mp 118 °C}. $[\alpha]_D^{20}$ = −8.7 (*c* 0.78, EtOH). {lit.[5a] $[\alpha]_D^{20}$ = −8.6 (*c* 0.68, EtOH)}. The physical and spectroscopic data of **1** were in total agreement with those reported in the literature.[5a]

Acknowledgment. The authors thank Dr. A. Perez-Luna for helpful discussions and Mr. P. Herson for the determination of the single-crystal X-ray analysis of compound **10**. A.V. thanks CNRS for financial support.

Supporting Information Available: General methods, ^{1}H and ^{13}C spectra for (−)-α-conhydrine **1** and compounds **7**−**11**, ORTEP diagram and CIF of compound **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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