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Asymmetric synthesis of the optically active piperidine alkaloid (+)-β-conhydrine

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ABSTRACT

A new approach for the stereoselective synthesis of the piperidine alkaloid (+)-β-conhydrine based upon a highly diastereoselective 1,2-nucleophilic addition reaction onto a diastereopure hydrazone and ring-closing metathesis as the key steps has been developed.

1. Introduction

Hydroxylated piperidines represent a structural unit frequently found in many biologically active alkaloids.[1] 2-(1-Hydroxyalkyl)piperidines fall into this category and consequently have attracted considerable attention from the synthetic community because of their potent antiviral and antitumor activities.[1,2] This class of compounds includes α- and β-conhydrine; their stereoisomers (Fig. 1) are representatives of the hemlock alkaloids isolated from the seeds and leaves of the poisonous plant *Conium maculatum* L., whose extracts were used in Ancient Greece to get rid of criminals and undesirable intellectuals, for example, Socrates.[3] Since its isolation in 1856,[4] the elucidation of its structure about eighty years later[5] and following the pioneering work of Galinovsky et al.,[6] various methods for the synthesis of the racemic piperidine alkaloid have been documented in the literature.[7] However, the last decade has witnessed a strong incentive in the development of asymmetric synthetic approaches to α- and β-conhydrine and to the stereoisomers **1**, *ent*-**1**, **2**, and *ent*-**2** (Fig. 1) while interest in their chemistry continues unabated. While a number of auxiliary supported or chiral pool approaches have been reported for natural (−)-α-conhydrine *ent*-**1**[8] and (+)-α-conhydrine **1**[9] much less attention has been paid to the enantioselective syntheses of unnatural (−)-β-conhydrine *ent*-**2**;[9c,10] to the best of our knowledge only two asymmetric syntheses of (+)-β-conhydrine **2**[9e,11] have appeared in print. Most of these elegant approaches have been reported to proceed with moderate yields and varying degrees of success have been claimed with regard to their enantioselectivities.

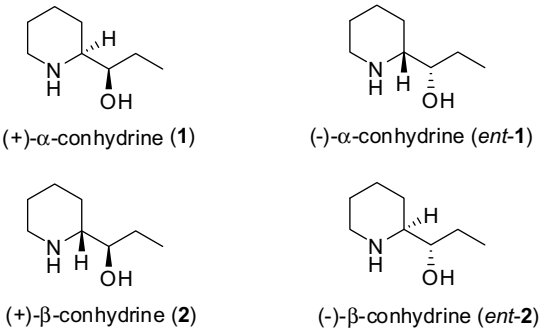

Figure 1. Stereoisomers of α-and β-conhydrine.

As a result, we became interested in developing a feasible, straightforward and highly stereoselective synthetic route to (+)-β-conhydrine **2**; herein, we report on the asymmetric synthesis of this rare unnatural piperidine alkaloid incorporating a 1,2-aminoalcohol moiety.

2. Results and discussion

Initially, we planned to develop the conceptually new synthetic route which is briefly depicted in Scheme 1. We anticipated that the target alkaloid **2** could result from the diastereoselective attack of an appropriate Grignard reagent on the formylated cyclic hydrazide **3** followed by concomitant N–N bond cleavage and reduction of the carbonyl lactam functionality. The highly functionalized piperidine **3** could in turn derive from the polyenic hydrazide **4** through a sequence involving RCM reaction, simultaneous hydrogenation and hydrogenolysis to release the *O*-benzyl protection, and ultimate oxidation to trigger off the creation of the required formyl functionality.

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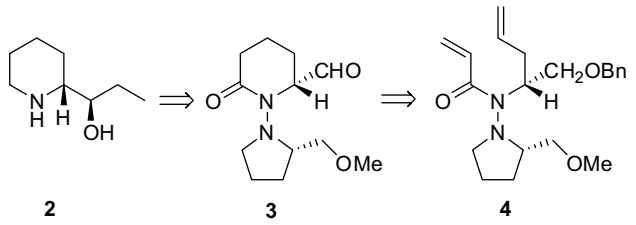
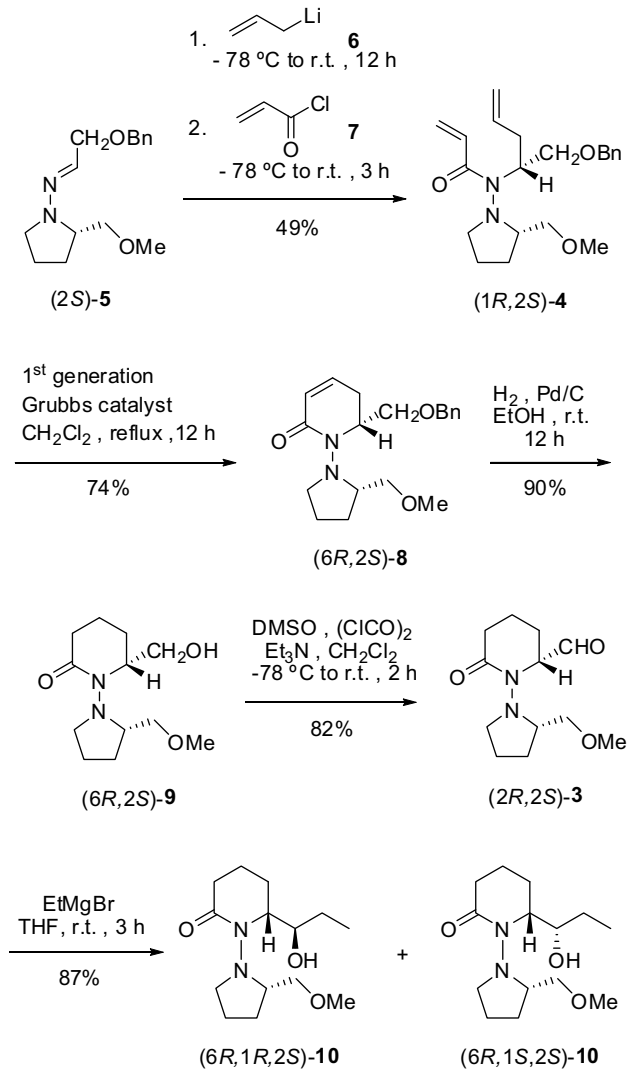


Scheme 1.

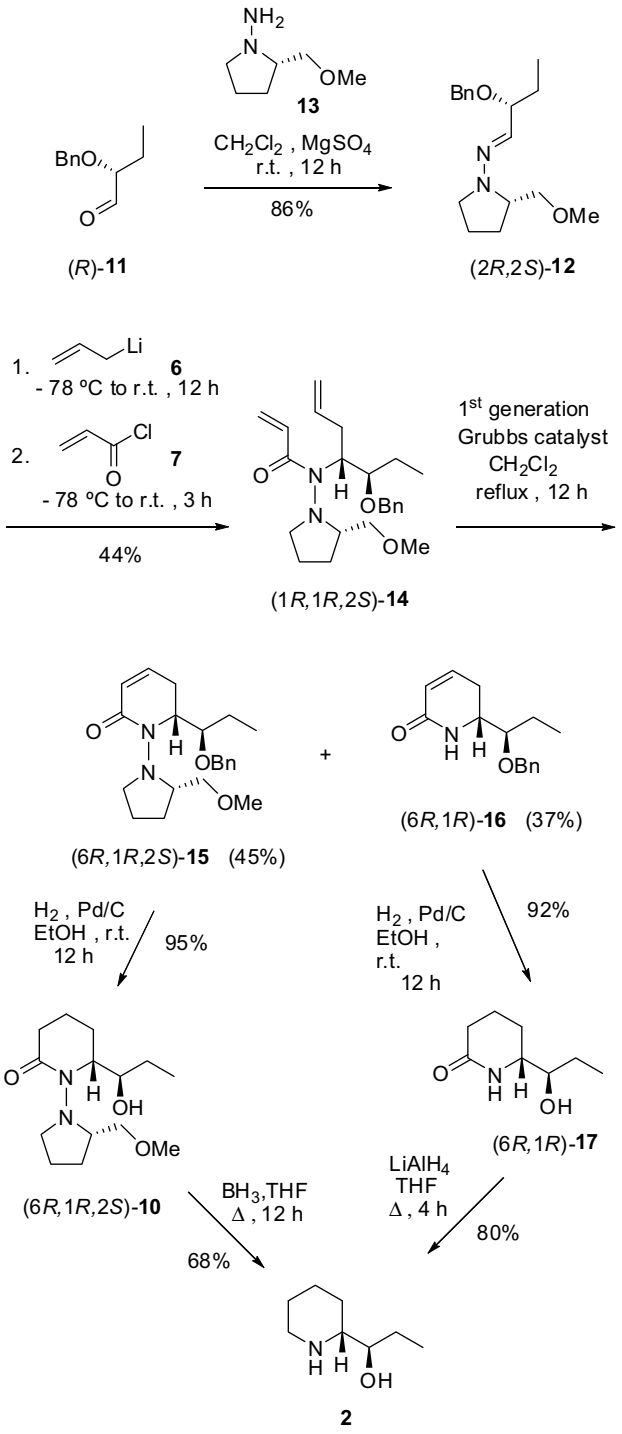
We then embarked on the elaboration of the requisite dienehydrazide **4**. The assembly of this highly conjugated precursor, which is disclosed in Scheme 2, was performed as a single one-pot reaction from the readily available chiral hydrazone **5**. Thus, hydrazone **5** was submitted to an addition reaction with allyllithium **6** and the intermediate lithium hydrazide salt was trapped with acryloyl chloride **7** to give straightforward access to the desired dienehydrazide **4**. This polyenic compound was obtained with satisfactory yield while NMR spectroscopic investigation after chromatographic treatment indicated the presence of a single diastereoisomer thus confirming the high level of diastereoselectivity observed upon the initial 1,2 nucleophilic addition process on the C=N double bond.[12] This procedure allowed the introduction of the absolute configuration at the α-position to the nitrogen atom, that is, at C2 in the final compound **2**, one of the major challenging tasks for the total synthesis of the targeted alkaloid. Ring-closing metathesis of **4** using 1st generation Grubbs catalyst, $Cl_2Ru(=CHPh)(PCy_3)_2$ (5 mol %) in refluxing CH_2Cl_2[13] proceeded smoothly to provide a very satisfactory yield of the virtually diastereochemically pure cyclic enehydrazide (*R*,*S*)-**8**. Catalytic hydrogenation with the concomitant release of the benzyl protection of the hydroxymethyl group proceeded uneventfully to afford the corresponding hydroxymethylated hydrazide (*R*,*S*)-**9** in excellent yield. Subsequent Swern oxidation of **9** delivered the cyclic hydrazide **3** equipped with the mandatory formyl functionality liable to secure installation of the hydroxypropyl appendage with a stereodefined configuration. Compound **3** was then allowed to react with ethylmagnesium bromide and standard work up delivered alcohol **10** in good yield. However, disappointingly the desired compound was obtained as a 2:3 mixture of (*R*,*R*,*S*)-**10** and (*R*,*S*,*S*)-**10** diastereoisomers, the diastereoisomeric ratio being unambiguously evaluated by ^{1}H NMR, namely from integration of the C1 proton of the alkyl chain bearing the hydroxy group. Furthermore all attempts to isolate pure diastereoisomers by chromatographic treatment proved unsuccessful.

Consequently, we decided to switch our plans and we thus set out to achieve an alternative strategy to secure the stereochemistry of the hydroxyalkyl appendage on the piperidine template at an early stage of the synthesis. The synthesis, which is depicted in Scheme 3, started from the enantiopure benzyl protected 2-hydroxypropionaldehyde **11** which was quantitatively converted into the SAMP hydrazone **12** by simply mixing with enantiomerically pure hydrazine (*S*)-(−)-1-amino-2-(methoxymethyl)pyrrolidine **13**. Sequential treatment with allyllithium **6** and interception with acryloyl chloride **7** as already described for **4** delivered the diolefin hydrazide **14** as a single diastereoisomer detectable by NMR (de >95%) after chromatographic treatment. It is noteworthy that the presence of the SAMP auxiliary in hydrazone **12** was rewarded here: modest selectivities have been indeed observed upon addition of allyl Grignard reagents onto the *N*-benzylaldimine derived from *O*-benzylglyceraldehyde which is structurally related to **11**.[14] This bis-olefin was then subjected to ring-closing metathesis; this operation delivered a 55:45 mixture of diastereomerically pure **15** along with the NH free piperidine **16** released from the chiral appendage. N–N bond cleavage of hydrazides has been very well documented in its synthetic and mechanistic aspects[15] but to the best of our knowledge this phenomenon is unprecedented.

Catalytic hydrogenation of the olefinic double bond was accomplished with the concomitant retrieval of the hydroxy functionality and this operation afforded the diastereochemically pure cyclic hydrazide (*R*,*R*,*S*)-**10** almost quantitatively. Interestingly, the exclusive formation of (*R*,*R*,*S*)-**10** allowed the assignment of the predominant stereoisomer in the diastereoisomeric mixture obtained in the synthetic route portrayed in Scheme 2. Finally, the reductive N–N bond cleavage with the BH_3·THF complex was accomplished via the simultaneous reduction of the lactam carbonyl functionality to complete the synthesis of the target alkaloid (+)-β-conhydrine **2**. The absolute configuration of the stereogenic centers was confirmed to be (1*R*,2*R*) and the enantiopurity of our synthetic (+)-β-conhydrine was clearly established from the sign and value of the specific rotation and from spectroscopic data that matched those reported for the unnatural product.[9e,11] The same stereoisomer was also obtained by sequential catalytic hydrogenation of (*R*,*R*)-**16** followed by standard reduction of the carbonyl group of the resulting lactam (*R*,*R*)-**17**. The latter procedure markedly improved the yield for the formation of the title compound **2** (29% vs 56% from **14**).



Scheme 2.



Scheme 3.

3. Conclusion

In conclusion, we have developed a simple and direct route for the synthesis of (+)-β-conhydrine. The key steps are a highly diastereoselective 1,2-nucleophilic addition process applied to a diastereopure hydrazone equipped with a stereodefined chiral appendage, followed by RCM to form the piperidine ring system. We believe that this conceptually new approach could be extended to a range of analogues with varying sizes and that the formation of unsaturated hydrazide intermediates could be exploited for further synthetic planning; for example, including functionalization, but not limited to epoxidation and dihydroxylation. Finally, the synthetic strategy has significant potential for further extension to the synthesis of the (1*R*,2*S*)-isomer, that is, (+)-α-conhydrine **1**, owing to the availability of the RAMP chiral auxiliary.

4. Experimental

4.1. General

Melting points were determined on a Reichert-Thermopan apparatus and are uncorrected. NMR spectra were recorded on a Bruker AM 300 spectrometer. These were referenced against internal tetramethylsilane; Coupling constants (*J*) are rounded to the nearest 0.1 Hz. Optical rotations were measured on a Perkin Elmer P 241 polarimeter. Elemental analyses were obtained using a Carlo-Erba CHNS-11110 equipment. The silica gel used for flash column chromatography was Merck Kieselgel of 0.040–0.063 mm particle size. Petroleum ether (PE, boiling range 40–60 °C), ethyl acetate (AcOEt), CH_2Cl_2, and methanol (MeOH) were used as eluents. Dry glassware was obtained by oven-drying and assembled under Ar atmosphere. Ar was used as the inert atmosphere and was passed through a drying tube to remove moisture. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl immediately before use. Methanol (MeOH) and ethanol (EtOH) were distilled from magnesium turnings and dichloromethane (CH_2Cl_2) from CaH_2, before storage on 4 Å molecular sieves.

The hydrazone **5**[16] and the aldehyde **11**[17] were prepared according to reported procedures.

4.2. (2*R*,2*S*)-(−)-(*E*)-*N*-(2-Benzyloxybutylidene)-*N*-(2-methoxymethylpyrrolidin-1-yl)amine 12

(*S*)-1-Amino-2-methoxymethylpyrrolidine **13** (SAMP, 2.34 g, 0.018 mol, 1.2 equiv) and $MgSO_4$ (0.5 g) were added to a solution of the aldehyde (*R*)-**11** (2.67 g, 0.015 mol) in CH_2Cl_2 (20 mL). The mixture was stirred at rt for 12 h, filtered and after evaporation of the solvent, the crude product was purified by flash column chromatography on silica gel using AcOEt–PE (20:80) as eluent to afford the hydrazone (2*R*,2*S*)-**12** (4.48 g, 86%) as a colorless oil. $[\alpha]_D^{20} = -31.4$ (*c* 2.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.96 (t, J = 7.4 Hz, 3H, CH_3), 1.63–1.99 (m, 6H, $4H_{SMP} + CH_2$), 2.78–2.86 (m, 1H), 3.31–3.39 (m, 1H), 3.41 (s, 3H, OCH_3), 3.47–3.61 (m, 3H), 3.78–3.83 (m, 1H), 4.46 (d, J = 11.9 Hz, 1H, OCH_2Ph), 4.62 (d, J = 11.9 Hz, 1H, OCH_2Ph), 6.41 (d, J = 7.3 Hz, 1H, CH=N), 7.22–7.36 (5H, m, H_{arom}). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 9.9, 22.2, 26.6, 27.5, 49.6, 59.3, 63.0, 70.2, 74.6, 80.8, 127.3, 127.9, 128.3, 136.6, 139.0. Anal. Calcd for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.02; N, 9.65. Found: C, 70.15; H, 9.16; N, 9.60.

4.3. General procedure for the synthesis of dienehydrazides 4 and 14

Phenyllithium (1.8 M in dibutylether, 1.11 mL, 2 mmol) was added dropwise to a solution of allyltriphenyltin (780 mg, 2 mmol) in Et_2O (10 mL). After stirring at room temperature for 30 min, the suspension was cooled at −78 °C and a solution of hydrazones **5** and **12** (2 mmol) in diethyl ether (3 mL) was added dropwise by syringe. The reaction mixture was stirred at −78 °C for 40 min then allowed to warm to rt and stirred for an additional 12 h. The reaction mixture was then recooled to −78 °C and acryloyl chloride (6 mmol, 545 mg) was added dropwise. After stirring at this temperature for 30 min, the reaction mixture was allowed to warm to rt over 3 h. Water (10 mL) was added and the mixture was filtered and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, the solvent was removed under vacuum,

and the product was purified by flash column chromatography on silica gel using AcOEt–PE (20:80) as eluent to afford dienehydrazides **4** (352 mg, 49%) and **14** (340 mg, 44%) as a yellow oil.

4.3.1. (1*R*,2*S*)-(−)-*N*-[1-(Benzyloxymethyl)but-3-enyl]-*N*-(2-methoxymethylpyrrolidin-1-yl)acrylamide 4

$[\alpha]_D^{20} = -32.5$ (*c* 0.92, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): 1.65–1.89 (m, 4H, H_{SMP}), 2.63–2.93 (m, 5H), 3.15–3.41 (m, 6H, H_{SMP}), 3.79 (dd, *J* = 5.4, 9.5 Hz, 1H, CH_2O), 4.11 (dd, *J* = 6.9, 9.5 Hz, 1H, CH_2O), 4.52 (s, 2H, OCH_2Ph), 5.04–5.18 (m, 2H, H_{vinyl}), 5.59 (dd, *J* = 2.3, 10.4 Hz, 1H, H_{vinyl}), 5.73–5.86 (m, 1H, H_{vinyl}), 6.30 (dd, *J* = 2.3, 17.2 Hz, 1H, H_{vinyl}), 7.14 (dd, *J* = 10.5, 17.2 Hz, 1H, H_{vinyl}), 7.23–7.38 (m, 5H, H_{arom}). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.2, 25.7, 35.4, 51.9, 56.3, 58.6, 58.8, 70.9, 73.2, 73.3, 117.4, 126.3, 127.5, 127.8, 128.3, 129.2, 135.4, 138.1, 169.3. Anal. Calcd for $C_{21}H_{30}N_2O_3$: C, 70.36; H, 8.44; N, 7.81. Found: C, 70.29; H, 8.51; N, 8.02.

4.3.2. (1*R*,1*R*,2*S*)-(−)-*N*-[1-(1-Benzyloxypropyl)but-3-enyl]-*N*-(2-methoxymethylpyrrolidin-1-yl)acrylamide 14

$[\alpha]_D^{20} = -9.3$ (*c* 1.54, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): 1.02 (t, *J* = 7.3 Hz, 3H, CH_3), 1.41–1.93 (m, 6H), 2.47–2.53 (m, 1H), 2.75–3.18 (m, 5H), 3.20–3.35 (m, 5H), 4.16–4.24 (m, 1H), 4.48 (d, *J* = 11.0 Hz, 1H, OCH_2Ph), 4.52 (d, *J* = 11.0 Hz, 1H, OCH_2Ph), 5.03–5.18 (m, 2H, H_{vinyl}), 5.61 (dd, *J* = 2.4, 10.5 Hz, 1H, H_{vinyl}), 5.72–5.85 (m, 1H, H_{vinyl}), 6.33 (dd, *J* = 2.4, 17.1 Hz, 1H, H_{vinyl}), 7.13 (dd, *J* = 10.5, 17.1 Hz, 1H, H_{vinyl}), 7.24–7.39 (m, 5H, H_{arom}). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 9.2, 21.5, 25.4, 26.7, 36.2, 51.8, 58.9, 59.0, 60.2, 73.7, 74.1, 79.2, 117.0, 126.3, 127.3, 128.0, 128.1, 136.1, 136.3, 137.2, 169.6. Anal. Calcd for $C_{23}H_{34}N_2O_3$: C, 71.47; H, 8.87; N, 7.25. Found: C, 71.61; H, 8.59; N, 7.03.

4.4. General procedure for the ring-closing metathesis of dienehydrazides 4, 14

A solution of the dienehydrazides **4** and **14** (1 mmol) and the first generation Grubbs catalyst (0.05 mmol, 5 mol %) in anhydrous CH_2Cl_2 (10 mL) was refluxed for 12 h under Ar (reaction monitored by TLC). The reaction mixture was concentrated under vacuum and the residue was purified by column chromatography on silica gel using AcOEt–PE (40:60) as eluent.

Ring-closing metathesis of **4** afforded enehydrazide **8** (244 mg, 74%) as a yellow oil.

For the ring-closing metathesis of **14**, chromatographic treatment furnished two fractions containing enehydrazide **15** (242 mg, 45%) as a yellow oil and enamide **16** (136 mg, 37%) as a colorless oil.

4.4.1. (6*R*,2*S*)-(−)-6-Benzyloxymethyl-1-(2-methoxymethylpyrrolidin-1-yl)-5,6-dihydro-1*H*-pyridin-2-one 8

$[\alpha]_D^{20} = -7.0$ (*c* 0.30, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): 1.48–1.53 (m, 1H, H_{SMP}), 1.64–1.77 (m, 1H, H_{SMP}), 1.93–2.11 (m, 2H, H_{SMP}), 2.52–2.71 (m, 2H, CH_2), 3.04–3.13 (m, 1H), 3.31–3.36 (m, 6H, H_{SMP}), 3.52–3.65 (m, 2H, H_{SMP}), 3.74–3.96 (m, 2H, CH_2O), 4.50 (d, *J* = 11.8 Hz, 1H, OCH_2Ph), 4.56 (d, *J* = 11.8 Hz, 1H, OCH_2Ph), 5.79 (m, 1H, H_{vinyl}), 6.31–6.38 (m, 1H, H_{vinyl}), 7.24-7.37 (m, 5H, H_{arom}). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.1, 26.6, 27.2, 52.8, 58.9, 60.4, 60.7, 68.9, 73.3, 76.5, 125.8, 127.6, 127.7, 128.4, 137.2, 138.0, 162.9. Anal. Calcd for $C_{19}H_{26}N_2O_3$: C, 69.06; H, 7.93; N, 8.48. Found: C, 69.17; H, 8.09; N, 8.62.

4.4.2. (6*R*,1*R*,2*S*)-(+)-6-(1-Benzyloxypropyl)-1-(2-methoxymethylpyrrolidin-1-yl)-5,6-dihydro-1*H*-pyridin-2-one 15

$[\alpha]_D^{20} = +24.7$ (c 0.72, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): 0.98 (t, *J* = 7.2 Hz, 3H, CH_3), 1.23–1.37 (m, 2H, CH_2), 1.52–1.91 (m, 4H, H_{SMP}), 2.14–2.25 (m, 1H), 2.51–2.68 (m, 2H, CH_2), 3.16–3.35 (m, 6H, H_{SMP}), 3.65–3.71 (m, 1H), 3.78–4.03 (m, 2H), 4.52 (d, *J* = 11.6 Hz, 1H, OCH_2Ph), 4.63 (d, *J* = 11.6 Hz, 1H, OCH_2Ph), 5.71 (dd, *J* = 1.9, 9.8 Hz, 1H, CH=), 6.28–6.34 (m, 1H, CH=), 7.21–7.35 (m, 5H, H_{arom}). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 10.9, 22.8, 23.5, 24.1, 27.4, 51.9, 58.7, 58.8, 60.0, 72.5, 75.4, 80.6, 125.4, 127.7, 128.0, 129.0, 136.2, 138.4, 163.8. Anal. Calcd for $C_{21}H_{30}N_2O_3$: C, 70.36; H, 8.44; N, 7.81. Found: C, 70.58; H, 8.49; N, 7.69.

4.4.3. (6*R*,1*R*)-(+)-6-(1-Benzyloxypropyl)-5,6-dihydro-1*H*-pyridin-2-one 16

$[\alpha]_D^{20} = +15.1$ (*c* 0.99, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): 0.98 (t, *J* = 7.5 Hz, 3H, CH_3), 1.43–1.61 (m, 2H, CH_2), 2.11–2.24 (m, 1H, CH_2), 2.28–2.41 (m, 1H, CH_2), 3.34–3.42 (m, 1H), 3.65–3.71 (m, 1H), 4.44 (d, *J* = 11.2 Hz, 1H, OCH_2Ph), 4.66 (d, *J* = 11.2 Hz, 1H, OCH_2Ph), 5.91–5.98 (m, 2H, NH + CH=), 6.56–6.63 (m, 1H, CH=), 7.30–7.39 (m, 5H, H_{arom}). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 7.8, 21.7, 26.5, 52.4, 71.5, 81.4, 124.8, 127.8, 127.9, 128.6, 137.6, 139.7, 166.2. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.33; H, 7.61; N, 5.66.

4.5. General procedure for the synthesis of piperidin-2-ones 9, 10 and 17

A solution of enehydrazides **8**, **15**, **16** (1.0 mmol) in EtOH (15 mL) was stirred with activated Pd/C (10%, 15 mg) under H_2 (1 atm) at rt for 12 h at which time TLC indicated complete consumption of the starting material. The mixture was filtered on a pad of Celite that was further eluted with EtOH (30 mL) and CH_2Cl_2 (30 mL). The filtrate was concentrated under vacuum and purification of the residue by column chromatography on silica gel using AcOEt–PE (80:20) as eluent gave piperidin-2-ones **9** (218 mg, 90%), **10** (256 mg, 95%) and **17** (144 mg, 92%) as a yellow oil.

4.5.1. (6*R*,2*S*)-(−)-6-Hydroxymethyl-1-(2-methoxymethylpyrrolidin-1-yl)piperidin-2-one 9

$[\alpha]_D^{20} = -23.4$ (*c* 0.80, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): 1.33–1.81 (m, 6H), 1.94–2.38 (m, 4H), 3.07–3.15 (m, 1H), 3.24–3.31 (m, 5H, H_{SMP}), 3.35 (dd, *J* = 3.6, 9.7 Hz, 1H), 3.48–3.56 (m, 2H), 3.64–3.74 (m, 2H), 3.80–3.85 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.2, 23.4, 27.1, 27.3, 33.7, 53.5, 58.8, 60.3, 64.1, 67.3, 75.1, 168.9. Anal. Calcd for $C_{12}H_{22}N_2O_3$: C, 59.48; H, 9.15; N, 11.56. Found: C, 59.66; H, 8.96; N, 11.44.

4.5.2. (6*R*,1*R*,2*S*)-(+)-6-(1-Hydroxypropyl)-1-(2-methoxymethylpyrrolidin-1-yl)piperidin-2-one 10

$[\alpha]_D^{20} = +24.1$ (*c* 0.54, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): 1.00 (t, *J* = 7.3 Hz, 3H, CH_3), 1.43–1.91 (m, 9H), 2.15–2.22 (m, 1H), 2.31 (t, *J* = 6.5 Hz, 2H, $CH_2C{=}O$), 3.12–3.21 (m, 2H, H_{SMP}), 3.26–3.44 (m, 6H, H_{SMP}), 3.61–3.68 (m, 1H), 4.05–4.12 (m, 1H), 6.24 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 9.4, 19.5, 23.4, 26.1, 27.1, 27.4, 34.3, 50.3, 58.7, 60.3, 65.2, 75.4, 75.9, 170.6. Anal. Calcd for $C_{14}H_{26}N_2O_3$: C, 62.19; H, 9.69; N, 10.36. Found: C, 61.94; H, 9.87; N, 10.21.

4.5.3. (6*R*,1*R*)-(+)-6-(1-Hydroxypropyl)piperidin-2-one 17

$[\alpha]_D^{20} = +15.3$ (*c* 0.84, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): 1.02 (t, *J* = 7.3 Hz, 3H, CH_3), 1.31–1.44 (m, 2H, CH_2), 1.53–1.70 (m, 2H, CH_2), 1.88–2.01 (m, 2H, CH_2), 2.17–2.29 (m, 1H, CH_2), 2.35–2.48 (m, 1H, CH_2), 3.19–3.31 (m, 2H), 4.04 (br s, 1H, OH), 6.99 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 9.4, 19.9, 25.0, 26.3, 31.1, 57.4, 76.0, 172.8. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.26; H, 9.83; N, 8.74.

4.6. (2*S*,2*R*)-(−)-1-(2-Methoxymethylpyrrolidin-1-yl)-6-oxopiperidin-2-carbaldehyde 3

A solution of DMSO (320 mg, 4.1 mmol) in CH_2Cl_2 (2 mL) was added dropwise at −78 °C to a solution of oxalyl chloride

(470 mg, 3.72 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at −78 °C for 30 min, and a solution of alcohol **9** (450 mg, 1.86 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After 30 min, Et_3N (10 mg, 10 mmol, 5 equiv) was added and the mixture was allowed to warm to rt and stirred for 2 h. Water (5 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel using AcOEt as eluent to give aldehyde **3** (366 mg, 82%) as a yellow oil. $[\alpha]_D^{20} = -41.1$ (*c* 2.30, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): 1.35–1.41 (m, 1H), 1.52–1.64 (m, 3H), 1.78–2.02 (m, 4H), 2.31 (t, *J* = 6.6 Hz, 2H, $CH_2C{=}O$), 3.03–3.24 (m, 6H, H_{SMP}), 3.58–3.66 (m, 1H, H_{SMP}), 3.73–3.84 (m, 1H, H_{SMP}), 4.29 (td, *J* = 2.5, 6.6 Hz, 1H, CHN), 9.54 (d, *J* = 2.5 Hz, 1H, CHO). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.7, 22.9, 24.5, 27.1, 33.6, 53.3, 58.6, 60.2, 71.2, 77.1, 168.9, 199.9. Anal. Calcd for $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 59.82; H, 8.22; N, 11.55.

4.7. Reaction of aldehyde 3 with ethylmagnesium bromide

A solution of ethylmagnesium bromide (1.0 M in THF, 1.25 mL, 1.5 equiv) was slowly added to a solution of **3** (300 mg, 1.25 mmol) in dry THF (10 mL) at −78 °C. After stirring for 3 h at this temperature, the reaction mixture was allowed to warm to rt and quenched with a satd aq $NaHCO_3$ solution (15 mL). The separated aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4. Concentration under vacuum and purification by column chromatography on silica gel using AcOEt as eluent afforded alcohol **10** as an inseparable 40:60 mixture of (*R*,*R*,*S*)-**10** and (*R*,*S*,*S*)-**10** (295 mg, 87%).

4.8. Synthesis of β-(+)-conhydrine 2

4.8.1. Starting from piperidin-2-one 17

A solution of piperidin-2-one **17** (100 mg, 0.64 mmol) in THF (2 mL) was added slowly to a suspension of $LiAlH_4$ (36 mg, 0.95 mmol) in anhydrous THF (5 mL) at 0 °C under Ar. The resulting mixture was stirred at reflux for 4 h. After cooling satd aq NH_4Cl (5 mL) was carefully added followed by CH_2Cl_2 (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude residue was purified by column chromatography using CH_2Cl_2-MeOH (50:50) as eluent to give (+)-β-conhydrine **2** (66 mg, 80%) as a colorless oil. $[\alpha]_D^{20} = +8.3$ (*c* 0.9, EtOH).

4.8.2. Starting from piperidin-2-one 10

BH_3·THF (1 M in THF, 15 equiv, 8,5 mL) was slowly added to a solution of **10** (150 mg, 0.55 mmol) in dry THF (3 mL) at 0 °C. After refluxing for 12 h, the reaction mixture was cooled to rt and carefully quenched with HCl (3 M, 10 mL). Then CH_2Cl_2 (20 mL) was added and the mixture was stirred for 4 h. After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography using CH_2Cl_2-MeOH (50:50) as eluent to give (+)-β-conhydrine **2** (48 mg, 68%) as a colorless oil. $[\alpha]_D^{20} = +7.9$ (*c* 0.6, EtOH).

References

1. Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P. *Chem. Rev.* **1995**, *95*, 1677–1716.
2. Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 619–636.
3. (a) Vetter, J. *Food Chem. Toxicol.* **2004**, *42*, 1373–1382; (b) Reynolds, T. R. *Phytochemistry* **2005**, *66*, 1399–1406.
4. Wertheim, T. *Liebigs Ann. Chem.* **1856**, *100*, 328–339.
5. Späth, E.; Adler, E. *Monatsh. Chem.* **1933**, *63*, 127–140.
6. Galinovsky, F.; Mulley, H. *Monatsh. Chem.* **1948**, *79*, 426–429.
7. (a) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109–1117; (b) Stock, G.; Jacobson, R. M.; Levitz, R. *Tetrahedron Lett.* **1979**, *20*, 771–774; (c) Shono, T.; Matsumura, Y.; Kanazawa, T. *Tetrahedron Lett.* **1983**, *24*, 4577–4580; (d) Pilard, S.; Vaultier, M. *Tetrahedron Lett.* **1984**, *25*, 1555–1556.
8. (a) Voituriez, A.; Ferreira, F.; Chemla, F. *J. Org. Chem.* **2007**, *72*, 5358–5361; (b) Kandula, S. V.; Kumar, P. *Tetrahedron: Asymmetry* **2005**, *16*, 3268–3274; (c) Kandula, S. V.; Kumar, P. *Tetrahedron Lett.* **2003**, *44*, 1957–1958; (d) Enders, D.; Nolte, B.; Raabe, G.; Runsink, J. *Tetrahedron: Asymmetry* **2002**, *13*, 285–291.
9. (a) Jamieson, A. G.; Sutherland, A. *Org. Lett.* **2007**, *8*, 1609–1611; (b) Chang, M.-Y.; Kung, Y.-H.; Chen, S.-T. *Tetrahedron* **2006**, *62*, 10843–10848; (c) Pandey, S. K.; Kumar, P. *Tetrahedron Lett.* **2005**, *46*, 4091–4093; (d) Nagata, K.; Toriizuka, Y.; Itoh, T. *Heterocycles* **2005**, *66*, 107–109; (e) Comins, D. L.; Williams, A. L. *Tetrahedron Lett.* **2000**, *41*, 2839–2842; (f) Guerreiro, P.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Chirality* **2000**, *12*, 408–410; (g) Masaki, Y.; Imaeda, T.; Nagata, K.; Oda, H.; Ito, A. *Tetrahedron Lett.* **1989**, *30*, 6393–6395; (h) Fodor, G.; Bauerschmidt, E. *J. Heterocycl. Chem.* **1968**, *5*, 205–209.
10. (a) Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron Lett.* **2000**, *41*, 4113–4116; (b) Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron* **2001**, *57*, 5393–5401; (c) Pandey, S. K.; Kumar, P. *Tetrahedron Lett.* **2005**, *46*, 4091–4093.
11. Ratovelomanana-Vidal, V.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1985**, *26*, 3803–3806.
12. Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253–2329.
13. (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446–452; (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29; (c) Lebrun, S.; Couture, A.; Deniau, E.; Grandclaudon, P. *Org. Lett.* **2007**, *9*, 2473–2476.
14. Franz, T.; Hein, M.; Veith, U.; Jäger, V.; Peters, E. M.; Peters, K.; von Schnering, H. G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1298–1301.
15. (a) Fernández, R.; Ferrete, A.; Lassaletta, J. M.; Llera, J. M.; Monge, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2893–2897; (b) Fernández, R.; Ferrete, A.; Lassaletta, J. M.; Llera, J. M.; Martín-Zamora, E. *Angew. Chem., Int. Ed.* **2002**, *41*, 831–833; (c) Fernández, R.; Ferrete, A.; Llera, J. M.; Magriz, A.; Martín-Zamora, E.; Díez, E.; Lassaletta, J. M. *Chem. Eur. J.* **2004**, *10*, 737–745; (d) Enders, D.; Braig, V.; Raabe, G. *Can. J. Chem.* **2001**, *79*, 1528–1535; (e) Enders, D.; Teschner, P.; Raabe, G. *Heterocycles* **2000**, *52*, 733–749; (f) Enders, D.; Teschner, P.; Raabe, G. *Synlett* **2000**, 637–640.
16. Enders, D.; Reinhold, U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1219–1222.
17. Aoyagi, S.; Hirashima, S.; Saito, H.; Kibayashi, C. *J. Org. Chem.* **2002**, *67*, 5517–5526.