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Asymmetric synthesis and structural assignment of (−)-α-conhydrine

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Abstract—The first asymmetric synthesis of the *conium* alkaloid (−)-α-conhydrine is reported. Starting from a protected glycol aldehyde hydrazone as chiral precusor, a short route based on our α-alkylation/1,2-addition methodology has been developed. After cleavage of the auxiliary and simultaneous deprotection, the concluding ring closure is accomplished under reductive amination conditions. The title compound is obtained in moderate overall yield and in excellent diastereo- and enantiomeric excess (d.e., e.e. >96%). Single-crystal X-ray crystallography as well as ^{1}H NMR NOE experiments confirm the expected relative and absolute (2*R*,7*S*)-configuration of the product.

1. Introduction

Since the isolation of the naturally occuring (+)-α-conhydrine **1** from seeds and leaves of the poisonous plant *Conium maculatum* L.[1] in 1856 and the elucidation of its structure in 1933,[2] many synthetic studies towards this hydroxylated piperidine alkaloid and its diastereomers **2** and *ent*-**2** have been carried out (Fig. 1).

One of the first successful attempts towards the synthesis of (+)-α-conhydrine **1** was carried out by Malinovsky and Mulley.[3] Fodor et al. optimized the procedure by performing the required resolution in a previous step of the synthesis.[4] The stereoselective synthesis of the unnatural (+)-β-conhydrine **2** was achieved by Husson's amino nitrile methodology,[5] followed in recent years by a number of other auxiliary-supported syntheses[6] or ex chiral pool approaches, which were also adapted for its (−)-enantiomer, *ent*-**2**.[7] However, much less attention has been given to the enantioselective synthesis of (−)-α-conhydrine *ent*-**1**.

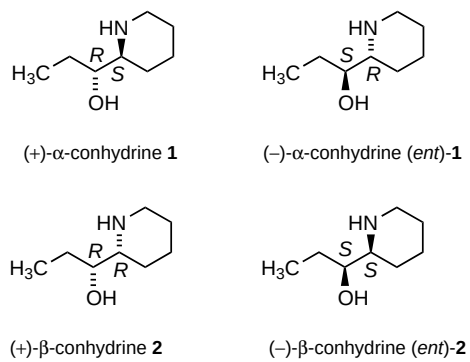

Figure 1. (+)-α-Conhydrine **1** and its stereoisomers.

2. Results and discussion

Herein, we wish to report on the first asymmetric synthesis of (−)-α-conhydrine *ent*-**1** employing our SAMP/RAMP hydrazone methodology in key steps.[8,9]

2.1. Asymmetric synthesis of (−)-α-conhydrine, *ent*-1

Retrosynthetic analysis of the piperidine core unit furnishes an open chain amino aldehyde precursor **3**, which can be employed in a reductive amination-induced ring closure (Scheme 1). The disubstituted 1,2-amino alcohol subunit can be obtained by diastereoselective nucleophilic 1,2-addition of a γ-metallated acetal-protected butanal **4** to the α-substituted glycol aldehyde SAMP hydrazone **5**.[10] The use of this class of hydrazones as versatile chiral synthons for the synthesis of miscellaneous substituted 1,2-amino

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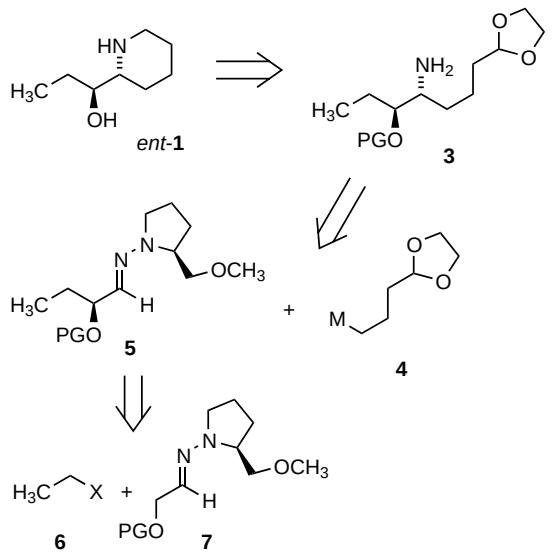


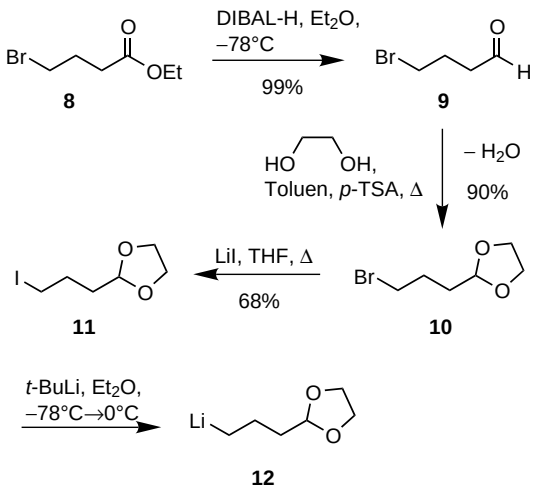
Scheme 1. Retrosynthetic analysis of (−)-α-conhydrine *ent*-**1**.

alcohol units has already been reported by our group.[11] Introduction of the short alkyl chain can be achieved by α-alkylation with **6** of a protected glycol aldehyde SAMP hydrazone **7** which already has the two heteroatoms of the target molecule installed in the skeleton.

The required acetal-containing organolithium reagent **12** was prepared by halogen–metal exchange reaction from the corresponding iodoacetal **11**, following the procedure of Negishi and Bailey[12] (Scheme 2).

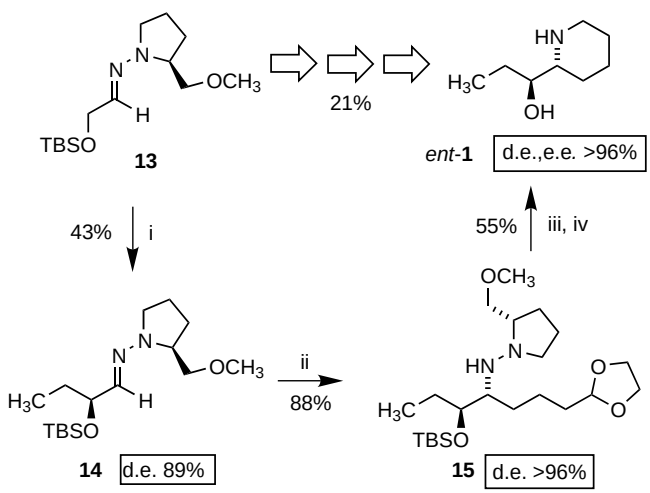
In turn, iodoacetal **11** is easily available from 4-bromobutyric acid ester **8** by DIBAL-H reduction to the aldehyde **9** followed by acetalization to **10**.[13] The subsequent Finkelstein reaction in THF with lithium iodide led to the desired iodide **11**.[14]

The enantiopure TBS-protected glycol aldehyde SAMP hydrazone **13** is readily available in high yield by a three-step sequence in a multigram scale from commercially available (*Z*)-butenediol, which is first protected before ozonolytic cleavage to the aldehyde and concluding condensation with the SAMP hydrazine to **13**.[11c]



Scheme 2. Synthesis of nucleophile **12**.

As depicted in Scheme 3, treatment of hydrazone **13** with LDA at low temperature gave the intermediate lithium azaenolate, which was trapped at the same temperature with ethyl iodide to form the α-substituted species **14** in moderate yield and good diastereomeric excess. After isolation by flash column chromatography the product was employed in the highly diastereoselective 1,2-addition to the carbon–nitrogen double bond[11] (d.e. >96%). Due to its light- and air-sensitivity the hydrazine **15** had to be isolated immediately by flash chromatography and could thus be obtained in high yield. Because of the incomplete asymmetric induction in the alkylation leading to **14** a minor diastereomer was expected, but NMR spectroscopic investigations showed no significant signals. We assume that the undesired isomer was separated during the purification procedure. Removal of the remaining part of the auxiliary was facilitated by a reductive nitrogen–nitrogen bond cleavage with BH_3THF complex in refluxing THF.[15] After completion the reaction mixture was treated with hydrochloric acid to destroy the excess borane. In addition, complete deprotection of the intermediate amine took place. Besides the acid-catalyzed silyl ether cleavage, acetal hydrolysis occurred and the resulting amino aldehyde underwent spontaneous cyclization to the corresponding imine. The solvents were evaporated and the remaining residue was dissolved in EtOH without further purification. Finally, $NaBH_4$ reduction completed the reductive amination to (−)-α-conhydrine (*ent*-**1**) in moderate yield over three steps; an overall yield of 21% starting from glycol aldehyde hydrazone **13** was achieved with both diastereomeric and enantiomeric excess greater than 96%, as determined by ^{1}H and ^{13}C NMR.



Scheme 3. Asymmetric synthesis of (−)-α-conhydrine (*ent*-**1**). *Reagents and conditions*: (i) LDA, THF, −78°C, then EtI, −78°C; (ii) **12**, THF, −78°C, then $NaHCO_3$ (aq.); (iii) BH_3·THF, THF, Δ, then 3 M HCl (aq.), CH_2Cl_2, rt; (iv) $NaBH_4$, EtOH, rt.

2.2. Structural assignment

Unfortunately, the spectroscopic data obtained from *ent*-**1** were not in accord with those published in the literature for the enantiomer **1**. Especially most of the described ^{1}H and ^{13}C NMR data did not show enough similarity. Only two ^{1}H NMR data sets of (+)-α-conhydrine **1** has been reported.[4,6] But, only Fodor described similar chemical shifts.

As shown in Table 1, a comparison of the reported ^{13}C chemical shifts gave a significant matching with data of the β-isomers (Table 1). Therefore, in combination with a negative optical rotation value of *ent*-**1** the formation of the (2*S*,7*S*)-configured (−)-β-conhydrine *ent*-**2** was assumed (see Fig. 1, Table 2).

However, the proposed configuration generated by the SAMP auxiliary according to the mechanism is (2*R*,7*S*).

Table 1. Reported ^{13}C NMR data of (+)-α-conhydrine **1**, (+)-β-conhydrine **2** and (−)-β-conhydrine *ent*-**2** in comparison to *ent*-**1**

	^{13}C NMR data in ppm[a]
ent-**1**	10.6, 24.4, 25.1, 25.5, 26.5, 47.0, 60.3, 75.7
	(+)-α-Conhydrine **1**
Comins[6]	10.5, 24.3, 25.8, 26.9, 44.0, 54.5, 70.5[b]
	β-Conhydrines
Comins[6]	10.2, 24.5, 26.4, 29.1, 46.6, 61.1, 75.4 **2**[b]
Couty[7b]	10.5, 24.8, 26.8, 26.9, 29.5, 46.9, 61.3, 75.9 *ent*-**2**
Husson[5]	10.2, 24.5, 26.3, 26.4, 29.1, 46.6, 61.1, 75.4 **2**

[a] Measured in $CDCl_3$.
[b] One signal is missing.

Table 2. Reported melting points and optical rotation values of (+)-α-conhydrine **1**, (+)-β-conhydrine **2** and (−)-β-conhydrine *ent*-**2** in comparison to *ent*-**1**

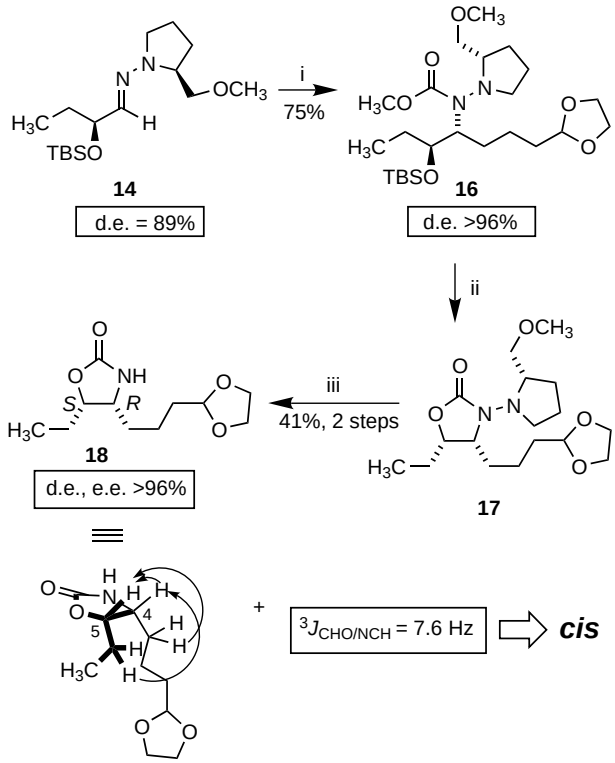
	Mp [°C][a]	$[\alpha]^{b}$
ent-**1**	118	−8.6
	(+)-α-Conhydrine **1**	
Galinovsky[3]	121	+9.6
Comins[6]	–	+9.0
Fodor[4]	120	+8.6
Masaki[7c]	119–121	+8.9
	β-Conhydrines	
Comins[6] **2**	–	+8.0
Beak[17] (±)-**2**	68–70	–
Couty[7b] *ent*-**2**	67	−34.1[c]
Husson[5] **2**	72	+8.6

[a] Partly recrystallized from different solvents and uncorrected.
[b] Measured in EtOH.
[c] Measured in $CHCl_3$.

Either the 1,2-addition of the oxo-functionalized nucleophile **12** established an unexpected (2*S*)-configuration or during the reaction sequence starting from (*S*,*R*)-hydrazine **15** to the title compound an undesired epimerization to the (2*S*,7*S*)-configured product occurs. Both explanations are quite unsatisfying, because numerous examples proved the proposed mechanism for the 1,2-addition supported by the SAMP auxiliary[11,16] and the improbable complete epimerization of one of the stereogenic centers. Moreover, a comparison of the reported melting points and optical rotations values gave a striking indication for the existence of the proposed product *ent*-**1** (Table 2). The ease of a clear distinction between the higher melting α-isomer and the lower melting β-isomer is evident. In fact, the similar optical rotation values prevent an exact assigment of the respective enantiomers. A few groups reported IR spectroscopic data of conhydrine species,[17] but a striking similarity was only shown again by those of (+)-α-conhydrine **1** described by Fodor.[4]

Thereupon we started further investigations to confirm the expected configuration of *ent*-**1**. At first, we focused our efforts on the determination of the relative configuration of the key intermediate, hydrazine **15**. Applying our methodology for the synthesis of disubstituted oxazolidin-2-ones, we trapped the resulting lithium hydrazide of the 1,2-addition of nucleophile **12** to hydrazone **14** with methyl chloroformate (MocCl) (Scheme 4).[11c] The resulting methyl carbamate **16** was transformed to the desired 4,5-disubstituted oxazolidin-2-one **18** by fluoride-induced cyclization and reductive nitrogen–nitrogen single bond cleavage effected by reaction with lithium in liquid ammonia. Our goal was to provide a more rigid system which would allow NOE experiments for structural determination of the 1,2-amino alcohol subunit. As is summarized in Scheme 4, irradiation of the C(4) proton of **18** gave a significant enhancement of the resonance at the C(5) proton. Other observed interactions between these nuclei and the methylene protons of substituents attached at the 4 and 5 ring positions are less strong. Both observations indicate the proposed *cis* configuration of **18**. In addition, the determination of the coupling constant of the annular protons $^{3}J_{CHO/NCH}$ with 7.6 Hz provides another strong evidence for the *cis* stereochemistry. In the oxazolidin-2-one ring $^{3}J_{CHO/NCH}$ of the *cis* isomer is in general higher (6–9 Hz) than the *trans* isomer (4–6 Hz).[18] The determined *cis* configuration of **18** confirms the (*S*,*R*)-absolute configuration of the two vicinal stereogenic centers generated by the α-alkylation/1,2-addition sequence starting from the glycol aldehyde SAMP hydrazone **13**.

On the other hand, one major intention of our investigations towards the absolute configuration of (−)-α-conhydrine *ent*-**1** was to prove the racemization-free reaction pathway starting from hydrazine **15**. We obtained suitable crystals of the title compound by recrystallization from ether at room temperature. The X-ray crystallographic analysis confirmed unambiguously the relative *anti* configuration (Fig. 2). In combination with the negative optical rotation the proposed absolute configuration (2*R*,7*S*) is confirmed.



Scheme 4. Confirmation of the proposed relative configuration by NOE experiments and determination of the coupling constant $^3J_{CHO/NCH}$ of oxazolidin-2-one **18**. *Reagents and conditions:* (i) **12**, THF, −78°C, then MocCl, −78°C; (ii) TBAF, THF, rt; (iii) Li/NH_3, −33°C.

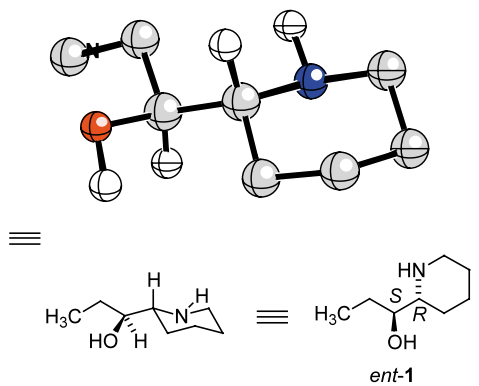


Figure 2. Crystal structure and confirmed absolute configuration of *ent*-**1**.

3. Conclusion

In summary, we succeeded in accomplishing the asymmetric synthesis of (−)-α-conhydrine *ent*-**1**. The target molecule was obtained in moderate overall yield and excellent diastereo- and enantiomeric excess. We were able to confirm the proposed (2*R*,7*S*) absolute configuration of the isolated product by NMR spectroscopic methods and by X-ray crystallography in two independent ways. Further investigations towards other 2-(α-hydroxyalkyl)piperidine analogs of (−)-α-conhydrine by introduction of various alkyl substituents in the α-alkylation of hydrazone **13** are now in progress.

4. Experimental

4.1. General

Melting points were determined on a Tottoli melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 1750 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 300 or 500 MHz and 75 or 125 MHz, respectively, on Varian VXR 300, Varian Gemini 300 or Varian Unity spectrometers. $^3J_{H,H}$ coupling constants were expressed in Hz. All measurements were performed in $CDCl_3$ and chemical shifts are expressed in ppm (δ) with tetramethylsilane as an internal standard. Mass spectra (MS) were obtained on a Varian MAT 212 or Finnigan SSQ 7000. Optical rotations were measured on a Perkin–Elmer P 241 polarimeter. Microanalyses were performed on Heraeus CHN-O-Rapid, Elementar Vario EL. In case of sensitive compounds high resolution mass spectra (HR-MS) were obtained on a Finnigan MAT 95.

4.2. Synthesis of (−)-α-conhydrine (*ent*-1)

4.2.1. (2*S*,2*S*)-(−)-(*E*)-*N*-[2-(*tert*-Butyldimethylsilyloxy)-but-1-ylidene]-*N*-(2-methoxymethylpyrrolidin-1-yl)-amine, 14. A solution of **13** (2.87 g, 10 mmol) in dry THF (5 mL) was slowly added to a solution of 2.0 equiv. LDA (freshly prepared from a solution of *n*-butyllithium (1.6 m) in hexane (12.5 mL, 20 mmol) and diisopropylamine (2.9 mL, 20.5 mmol) in dry THF (20 mL) at −78°C. After stirring at −78°C for 15 h, ethyl iodide (2.40 mL, 30 mmol) was added at −100°C. The solution was stirred for 1 h at −100°C and then allowed to warm to room temperature within 20 h. The reaction mixture was quenched with saturated NH_4Cl solution (15 mL). The aqueous phase was extracted with Et_2O (3×10 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. After the isomer ratio was determined, flash column chromatography of the residue on silica gel eluting with pentane–Et_2O (4:1, 1 vol% of Et_3N) gave **14** (940 mg, 43%, 70% conversion). R_f (silica, pentane–Et_2O 4:1): 0.9. d.e. = 89% (^{1}H, ^{13}C NMR). $[\alpha]_D^{24}$ −78.0 (*c* 1.03, $CHCl_3$). ^{1}H NMR (300 MHz): δ 0.04 (s, 3H, SiCH_3), 0.08 (s, 3H, SiCH_3), 0.89 (s, 9H, C(CH_3)$_3$), 0.92 (d, J=7.4, 3H, CH_3CH$_2$), 1.52–1.64 (m, 2H, CH$_3$CH_2), 1.77–2.00 (m, 4 H, CH_2CH_2), 2.79 (q, J=8.2, 1H, NCHH), 3.26–3.57 (m, 4H, CH_2OCH$_3$, NCHCH$_2$, NCHH), 3.36 (s, 3H, OCH_3), 4.10 (q, J=6.5, 1H, CHOSi), 6.40 (d, J=6.5, 1H, CHN). ^{13}C NMR (75 MHz): δ −4.72 (SiCH$_3$), −4.17 (SiCH$_3$), 9.80 (CH$_2$$CH_3$), 18.27 ($C$(CH$_3$)$_3$), 22.17 (NCH$_2$$CH_2$), 25.94 (C($CH_3$)$_3$), 26.60 (NCH$CH_2$), 29.98 ($CH_2CH_3$), 49.65 (N$CH_2$), 59.21 (O$CH_3$), 63.20 (N$C$H), 74.58 ($CH_2OCH_3$), 74.97 ($C$HOSi), 139.18

(N=*C*H). MS (EI): *m*/*z* (%) 314 (7, $M^{+\bullet}$), 285 (12, $M^{+\bullet}$–CH_3CH_2), 270 (18), 269 (100, $M^{+\bullet}$–CH_2OCH_3), 257 (16, $M^{+\bullet}$–*t*Bu), 173 (7), 115 (8), 75 (6), 73 (21), 70 (5). IR ($CHCl_3$): *v* 2957, 2930, 2882, 2857, 2827, 1599, 1463, 1387, 1361, 1341, 1253, 1198, 1092, 1043, 1004, 939, 909, 837, 794, 777, 673. Anal. calcd for $C_{16}H_{34}N_2O_2Si$: C, 61.10; H, 10.90; N, 8.91. Found: C, 61.34, H, 11.07; N, 9.00%.

4.2.2. (1*R*,2*S*,2*S*)-(–)-*N*-[2-(*tert*-Butyldimethylsilyloxy)-1-(3-[1,3]dioxolan-2-yl-propyl)-butyl]-*N*-(2-methoxymethyl-pyrrolidin-1-yl)-amine, 15. Iodide **12** (1.94 g, 8 mmol) was dissolved in dry Et_2O (4 mL) and a solution of *tert*-butyllithium (1.6 M, 2.0 equiv.) in hexane (10 mL, 16.0 mmol) was slowly added at −78°C. After stirring for 30 min at –78°C, the solution was allowed to warm to room temperature and stirred for an additional hour. The resulting mixture was cooled again to −78°C and dissolved in dry THF (20 mL). A solution of hydrazone **14** (630 mg, 2.0 mmol) in dry THF (2 mL) was slowly added and the reaction mixture was stirred at –78°C for 16 h. After stirring for 1 h at −20°C the reaction was quenched with saturated $NaHCO_3$ solution (15 mL). The aqueous phase was extracted with Et_2O (3×10 mL), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash column chromatography of the residue on silica gel eluting with pentane–Et_2O (1:1) gave **15** (760 mg, 88%). R_f (silica, pentane–Et_2O 1:1): 0.5. d.e. >96% (^{13}C NMR). $[\alpha]_D^{24}$ −44.0 (*c* 1.11, $CHCl_3$). ^1H NMR (300 MHz): δ 0.06 (s, 6H, $Si(CH_3)_2$), 0.88 (t, $J=7.4$, 3H, CH_2CH_3), 0.90 (s, 9H, $C(CH_3)_3$), 1.35–2.10 (m, 10H, $NCHHCH_2CH_2$, $NCHCH_2CH_2CH_2$), 1.44 (m, 2H, CH_2CH_3), 2.51 (m, 1H, NCH), 3.28–3.88 (m, 6H, NCH, $NCHCH_2O$, $NCHCH_2CH_2CH_2$, CHOSi), 3.34 (s, 3H, OCH_3), 3.85 (m, 2H, OCH_2CH_2O), 3.96 (m, 2H, OCH_2CH_2O), 4.86 (t, $J=4.9$, 1H, $CH(OCH_2)_2$). ^{13}C NMR (75 MHz): δ −4.57 ($SiCH_3$), −4.08 ($SiCH_3$), 11.19 (CH_2CH_3), 18.09 ($C(CH_3)_3$), 20.85, 20.91 ($(CH_2O)_2CHCH_2CH_2$), 23.27 (NCH_2CH_2), 25.97 ($C(CH_3)_3$), 26.04 ($NCHCH_2$), 29.26 (NCHCHOSi), 30.44 (CH_2CH_3), 34.52 ($(CH_2O)_2$-$CHCH_2CH_2CH_2$), 56.62 (NCH_2), 59.00 (CH_2OCH_3), 62.95 ($NCHCH_2$), 64.79 ($(CH_2O)_2CH$), 74.32 (CHOSi), 74.73 (CH_2OCH_3), 104.63 ($(CH_2O)_2CH$). MS (EI): *m*/*z* (%) 430 (6, $M^{+\bullet}$), 258 (15), 257 (100), 114 (6), 85 (6), 73 (14), 70 (9). IR (film): *v* 3298, 2954, 2927, 2856, 1742, 1464, 1373, 1241, 1129, 1103, 1048, 837, 776. HR-MS calcd for $C_{22}H_{46}N_2O_4Si^{+\bullet}$: 430.3227. Found: 430.3226.

4.2.3. (–)-α-Conhydrine *ent*-1. Hydrazine **15** (760 mg, 1.76 mmol) was dissolved in dry THF (4 mL) at room temperature and treated by slow addition of a solution of BH_3·THF (1 M, 10.0 equiv.) in THF (17.6 mL, 17.6 mmol). After heating under reflux for 15 h, the reaction mixture was allowed to cool to room temperature and carefully quenched with aqueous HCl (3 M, 18 mL). After addition of CH_2Cl_2 (16 mL) and stirring for 4 h at room temperature, the solvents were removed in vacuo. The residue was dissolved in EtOH (20 mL) and $NaBH_4$ (684 mg, 18 mmol, 10.0 equiv.) were slowly added at room temperature. After 2 h the reaction mixture was quenched with aqueous HCl (3 M, 2 mL) and conc. NH_3 was added to a basic pH value. H_2O (18 mL) and CH_2Cl_2 (20 mL) was added and after separation of the organic layer the aqueous portion was extracted with CH_2Cl_2 (4×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The isomer ratio was determined and flash column chromatography of the residue on silica gel eluting with CH_2Cl_2–MeOH (1:1) gave *ent*-**1** (140 mg, 55%). R_f (AcOEt–MeOH–conc. NH_3 4:4:0.25): 0.3. d.e., e.e. =>96% (^1H, ^{13}C NMR). $[\alpha]_D^{27}$ −8.6 (*c* 0.68, EtOH). Mp 118°C. ^1H NMR (500 MHz): δ 0.98 (t, $J=7.5$, 3H, CH_2CH_3), 1.22–1.53 (m, 5H, CH_2CH_3, NCH_2CHHCH_2), 1.60 (m, 2H, NCH_2CHH, NCHCHH), 1.86 (m, 1H, NCHCHH), 2.56 (d/t, $J=$ 10.7/2.7, 1H, NCH), 2.72 (t/d, $J=12.0/2.7$, 1H, NCHH), 3.05 (br s, 2H, NH; OH), 3.12 (m, 1H, NCHH), 3.42 (m, 1H, CHO). ^{13}C NMR (125 MHz): δ 10.61 (CH_2CH_3), 24.40 ($NCHCH_2$), 25.13 ($NCHCH_2CH_2$), 25.52 (CH_2CH_3), 26.47 (NCH_2CH_2), 46.99 (NCH_2), 60.29 (NCH), 75.71 (OCH). MS (EI): *m*/*z* (%) 143 (1, $M^{+\bullet}$), 85 (5), 84 (100), 56 (13), 55 (6). IR ($CHCl_3$): *v* 3289 (NH), 3112 (OH), 2974, 2953, 2927, 2852, 2805, 2739, 2679, 1726, 1476, 1448, 1350, 1252, 1235, 1214, 1151, 1128, 1106, 1085, 1059, 1035, 1005, 978, 953, 894, 853, 811, 754, 596. Anal. calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 66.89, H, 12.02; N, 9.93%.

4.3. Synthesis of oxazolidin-2-one 18

4.3.1. (5*S*,4*R*)-(+)-4-([1,3]-Dioxolan-2-yl-propyl)-5-ethyl-oxazolidin-2-one, 18. Iodide **12** (1.16 g, 4.8 mmol) was dissolved in dry Et_2O (2.5 mL) and cooled to −78°C a solution of *tert*-butyllithium (1.6 M, 2.0 equiv.) in hexane (6 mL, 9.6 mmol) was slowly added. After 30 min stirring at that temperature, the solution was allowed to warm to room temperature and stirred for an additional hour. The resulting mixture was cooled again to −78°C and dissolved in dry THF (16 mL). A solution of hydrazone **14** (520 mg, 1.66 mmol) in dry THF (2 mL) was slowly added and the reaction mixture was stirred at –78°C for 16 h and allowed to warm up to −30°C. After cooling to −78°C MocCl (1.23 mL, 16.6 mmol, 10.0 equiv.) was added rapidly. reaction mixture was stirred at –78°C for 15 h, then allowed to warm to room temperature and quenched with saturated $NaHCO_3$ solution (15 mL). The aqueous phase was extracted with Et_2O (3×15 mL), the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. After filtration through silica gel washing with pentane–Et_2O the crude product was first concentrated in vacuo and then dissolved in dry THF (5 mL). A solution of TBAF (1 M) in THF (5 mL, 5.0 mmol) was added at room temperature. The mixture was stirred for 1 day at room temperature and then concentrated in vacuo at 35°C. The residue was filtered through silica gel, washed with pentane–Et_2O and concentrated in vacuo. The crude product was dissolved in THF (10 mL) and added to a solution of Li (116 mg, 16.6 mmol, 10.0 equiv.) in NH_3 (40 mL) at −78°C. The solution was allowed to warm to −33°C and stirred at –33°C for 40 min. The reaction

mixture was quenched with NH_4Cl (2.5 g). NH_3 was removed at room temperature and the residue was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. After the isomer ratio was determined, flash column chromatography of the residue on silica gel eluting with Et_2O–MeOH (1:1) gave **18** (180 mg, 48%). R_f (Et_2O): 0.3. d.e., e.e. >96% (^1H, ^{13}C NMR). $[\alpha]_D^{26}$ +8.8 (*c* 0.97, $CHCl_3$). ^1H NMR (400 MHz): δ 1.04 (tr, $J=7.4$, 3H, CH_2CH_3), 1.35–1.80 (m, 8 H, $CH_2CH_2CH_2$, CH_2CH_3), 3.75 (m, 1H, CHN), 3.83 (m, 2H, OCH_2CH_2O), 3.95 (m, 2H, OCH_2CH_2O), 4.50 (m, 1H, CHO), 4.84 (t, $J=4.5$, 1H, $CH(OCH_2)_2$), 6.63 (s, 1H, NH). ^{13}C NMR (100 MHz): δ 10.69 (CH_2CH_3), 20.65 ($(CH_2O)_2CHCH_2CH_2$), 22.66 (CH_2CH_3), 29.93 ($NCHCH_2$), 33.56 ($(CH_2O)_2CHCH_2$), 55.78 (NCH), 65.10, 65.12 ($(CH_2O)_2CH$), 81.96 (OCH), 104.25 ($(CH_2O)_2CH$), 160.14 (C=O). MS (CI): *m*/*z* (%) 230 (32, $M^{+\bullet}+1$), 169 (10), 168 (100). IR ($CHCl_3$): *v* 3298 (NH), 2950, 2880, 1750 (C=O), 1461, 1396, 1238 1142, 1096, 1032, 947, 756. Anal. calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.21, H, 8.33; N, 5.97%.

4.4. X-Ray crystallographic analysis

Suitable crystals of *ent*-**1** ($C_8H_{17}NO$) were obtained from Et_2O at room temperature by slow evaporation of the solvent. The compound crystallizes in monoclinic space group $P\ 2_1$ (4) with the cell parameters $a=5.293(8)$, $b=8.676(12)$, $c=9.411(13)$ Å, and $\beta=96.52(4)°$. At a cell volume of $V=429.4(11)$ Å^3, $Z=2$, and $M_r=143.23$, we obtain a calculated density of $\rho_{cal}=1.108$ g/cm^3. A total number of 5702 reflections ($-7\le h\le 7$, $-11\le k\le 11$, $-12\le l\le 12$, $\Theta_{max}=28.3°$) have been collected at room temperature on a Bruker SMART APEX diffractometer employing graphite-monochromated Mo Kα radiation ($\lambda=0.71073$ Å). Data have been corrected for Lorentz- and polarization- but not for absorption effects ($\mu=0.072$ mm^{-1}). The structure has been solved by direct methods as implemented in the Xtal3.7 set of crystallographic routines,[19] employing GENSIN[20] for the generation of structure invariant relation ships and GENTAN[21] for the general tangent phasing procedure. 846 observed reflections ($F>4\sigma(F)$) have been included in the final full-matrix least-squares refinement on *F* involving 91 parameters and converging at $r(r_w)=0.075$ (0.064, $w=1/[\sigma^2(F)+0.0004\cdot F^2]$ a residual electron density of –0.36/+0.30 e Å^{-3}, and a goodness of fit of $S=1.718$. Most hydrogen atoms could not be located in a difference Fourier map and have been calculated in idealized positions. Their equivalent displacement parameters have been fixed at $1.5U$ of the relevant heavy atom. All hydrogen parameters have been kept constant in the refinement process.

CCDC 178847 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/ retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

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References

1. Wertheim, T. *Liebigs. Ann. Chem.* **1856**, *100*, 328–330.
2. Späth, E.; Adler, E. *Monatsh. Chem.* **1933**, *63*, 127–140.
3. Galinovsky, F.; Mulley, H. *Monatsh. Chem.* **1948**, *79*, 426–429.
4. Fodor, G.; Bauerschmidt, E. *J. Heterocycl. Chem.* **1968**, *5*, 205–209.
5. Ratovelomanana, V.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1985**, *26*, 3803–3806.
6. For a recent example, see: Comins, D. L.; Williams, A. L. *Tetrahedron Lett.* **2000**, *41*, 2839–2842.
7. For recent examples, see: (a) Guerreiro, P.; Ratevelomanana-Vidal, V.; Genêt, J.-P. *Chirality* **2000**, *12*, 408–410; (b) Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron Lett.* **2000**, *41*, 4113–4116; (c) Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron* **2001**, *57*, 5393–5401; (d) Masaki, Y.; Imaeda, T.; Nagata, K.; Oda, H.; Ito, A.; *Tetrahedron Lett.* **1989**, *30*, 6395–6396.
8. (a) Enders, D.; Klatt, M. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: Chichester, 1995; Vol. 1, pp. 178–182; (b) Enders, D. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp. 275–339; (c) Enders, D.; Fey, P.; Kipphardt, H. *Org. Synth.* **1987**, *65*, 173–182, 183–202; (d) For a review, see: Job, A; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253–2329.
9. For a short review on the synthesis of some alkaloids, see: Enders, D.; Thiebes, C. *Pure Appl. Chem.* **2001**, *73*, 573–578.
10. For reviews on the 1,2-addition of organometallic reagents, see: (a) Denmark, S. E.; Nicaise, O. J.-C. *J. Chem. Soc., Chem. Commun.* **1996**, 999–1004; (b) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895–1946. (c) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407–1438; (d) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094; (e) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Synlett* **2000**, 442–454.
11. (a) Enders, D.; Reinhold, U. *Angew. Chem.* **1995**, *107*, 1332–1334; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1219–1222; (b) Enders, D.; Reinhold, U. *Liebigs Ann. Chem.* **1996**, 11–26; (c) Enders, D.; Kallfass, U.; Nolte, B. *Synlett* **2002**, 33–36.
12. (a) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404–5406; (b) Negishi, E.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406–5409.

13. Bobrova, N. I.; Belosludtsev, Yu.; Pivnitskii, K. K. *J. Org. Chem. USSR (Engl. Trans.)* **1989**, *25*, 1873–1878.
14. Pleshakov, M. G.; Vasil'ev, A. E.; Sarycheva, I. K.; Preobazhenskii, N. A. *J. Gen. Chem. USSR (Engl. Trans.)* **1961**, *31*, 1433–1435.
15. For recent examples of the BH_3·THF cleavage of hydrazines, see: (a) Enders, D.; Lochtmann, R.; Meiers, M.; Müller, S.; Lazny, R. *Synlett* **1998**, 1182–1184; (b) Enders, D.; Thiebes, C. *Synlett* **2000**, 1745–1748; (c) Enders, D.; Kirchhoff, J. H. *Synthesis* **2000**, 2099–2105.
16. (a) Enders, D.; Tiebes, J. *Liebigs Ann. Chem.* **1993**, 173–177; (b) Enders, D.; Schankat, J.; Klatt, M. *Synlett* **1994**, 795–800; (c) Enders, D.; Lochtmann, R.; Raabe, G. *Synlett* **1996**, 126–128; (d) Enders, D.; Meiers, M. *Angew. Chem.* **1996**, *108*, 2391–2393; *Angew. Chem., Int. Ed. Engl* **1996**, *35*, 2261–2263; (e) Enders, D.; Bartzen, D. *Liebigs Ann. Chem.* **1997**, 1115–1123.
17. Beak, P.; Zadjel, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 1010–1018.
18. For examples, see: (a) Cainelli, G.; Panunzio, M.; Contento, M.; Giacomini, D.; Mezzina, E.; Giovagnoli, D. *Tetrahedron* **1993**, *49*, 3809–3826; (b) Zietlow, A.; Steckhan, E. *J. Org. Chem.* **1994**, *59*, 5658–5661; (c) Jordá-Gregori, J. M.; González-Rosende, M. E.; Cava-Montesinos, P.; Sepúlveda-Arques, J.; Galeazzi, R.; Orena, M. *Tetrahedron: Asymmetry* **2000**, *11*, 3769–3777; (d) Andrés, J. M.; De Elena, N.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1503–1509.
19. Hall, S. R.; du Boulay, D. J.; Olthof-Hazekamp, R. In *XTAL3.7 System;* University of Western Australia: Perth, 2000.
20. Subramanian, V.; Hall, S. R. In *GENSIN. Xtal3.7 System*; Hall, R.; du Boulay, D. J.; Olthof-Hazekamp, R., Eds.; University of Western Australia: Perth, 2000.
21. Hall, S. R. In *GENTAN. Xtal3.7 System*; Hall, R.; du Boulay, D. J.; Olthof-Hazekamp, R., Eds.; University of Western Australia: Perth, 2000.