JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

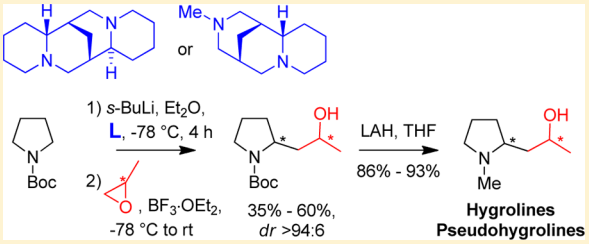
# Total Synthesis of Hygrolines and Pseudohygrolines

Marc Liniger, Katja Estermann, and Karl-Heinz Altmann*

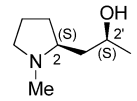
ETH Zürich, Department of Chemistry and Applied Biosciences, Institute of Pharmaceutical Sciences, HCI H405, Wolfgang-Pauli Str. 10, CH-8093 Zürich, Switzerland

Supporting Information

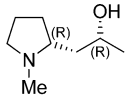
**ABSTRACT:** A concise two-step synthesis of all four diastereoisomeric hygrolines ((−)-hygroline (**1**), (+)-hygroline (**2**), (−)-pseudohygroline (**3**), (+)-pseudohygroline (**4**)) has been developed based on the (−)-sparteine (**5**)- or (+)-sparteine surrogate **11**-mediated enantioselective lithiation of *N*-Boc pyrrolidine (**6**), followed by reaction of the chiral anion with (*S*)- or (*R*)-propylene oxide. Reduction of the resulting *N*-Boc amino alcohols furnished hygrolines and pseudohygrolines in 30% to 56% overall yields with *dr*'s > 95:5.



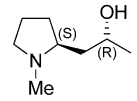

(−)-Hygroline ("hygroline", **1**) is a plant-derived natural product that was first isolated from the mother liquors of cocaine preparations obtained from *Erythroxylum coca* extracts by Späth and Kittel in 1943.[1] In 1953, Galinovsky and Zuber reported the first synthesis of **1**, together with the synthesis of its (2′*R*)-isomer **3**, *via* catalytic hydrogenation of (−)-hygrine[2] bistartrate and subsequent fractional precipitation (in a rather elaborate process).[3] Starting from (+)-hygrine bistartrate the same process led to (+)-hygroline (**2**) and (+)-pseudohygroline (**4**); the absolute configuration of all four isomers was later confirmed by Lukes et al.[4]



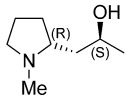

(-)-Hygroline (**1**)




(+)-Hygroline (**2**)




(-)-Pseudohygroline (**3**)




(+)-Pseudohygroline (**4**)

Subsequent to the work of Galinovsky and Zuber, **2**[5,6] and **4**[7] were also isolated from natural sources and thus established to be natural products. In contrast, to the best of our knowledge, (−)-pseudohygroline (**3**) has not been found in nature so far. A number of total syntheses of (pseudo)hygrolines have been reported (racemic as well as stereoselective), with the total number of steps ranging from 4 to 11 and overall yields from 13 to 40%.[8−17]

Our interest in the synthesis of hygrolines arose from unrelated SAR work on resorcylic acid lactones (RAL), where we required efficient stereoselective access to *N*-protected-*N*-desmethyl variants of hygroline (**1**) and pseudohygroline (**4**) as building blocks for (RAL) analog synthesis. However, instead of relying on existing, but rather lengthy, protocols for the synthesis of *N*-protected 2-(2-hydroxypropyl) pyrrolidines, we decided to explore the possibility of the stereoselective opening of homochiral propylene oxides with a C2 lithiated pyrrolidine to introduce both stereocenters simultaneously. This idea was essentially driven by the availability of methodology that allows the generation of enantiopure carbanions based on chiral lithium complexes with (−)-sparteine (**5**), which we felt would be perfectly suited for our problem.[18] In particular, Deng and Mani have reported the (−)-sparteine (**5**)-mediated enantioselective lithiation of *N*-Boc pyrrolidine (**6**) and the subsequent reaction of the resulting chiral anion with ethylene oxide to produce *N*-Boc 2-(2-hydroxethyl) pyrrolidine in 83% yield with a remarkable *er* of 91:9.[19]

Employing a modification of the protocol developed by Deng and Mani, which involved lithiation of **6**[20] with 1.2 equiv of the *preformed* *s*-BuLi/(−)-sparteine (**5**) complex for 4 h at −78 °C[21] and subsequent reaction with 2 equiv of (*R*)-propylene oxide (**7a**) and 2 equiv of $BF_3{\cdot}OEt_2$ at −78 °C and warming to 0 °C, the desired secondary alcohol **8** was obtained with excellent diastereoselectivity (*dr* = 96.5:3.5)[22] based on GC of the crude reaction mixture (Scheme 1).

While the compound could not be purified to homogeneity by flash column chromatography (FC), careful fractional high-vacuum distillation furnished **8** in high purity (>95%) and 35% yield (50% based on recovered starting material (brsm)) and with a *dr* of 98:2. If the reaction mixture was allowed to warm to rt instead of 0 °C, the yield increased to 45%, but the *dr* of the distilled product decreased slightly (to 96:4; 94:6 before distillation).

Attempts to improve the efficiency of the epoxide opening reaction by increasing the excess of **7a** or/and $BF_3{\cdot}Et_2O$ were unsuccessful.[23] In a separate set of experiments, epoxide opening of **7a** was also investigated after racemic lithiation of **6** with *s*-BuLi and TMEDA, either directly or after transmetalation, and in the presence or absence of $BF_3{\cdot}OEt_2$.

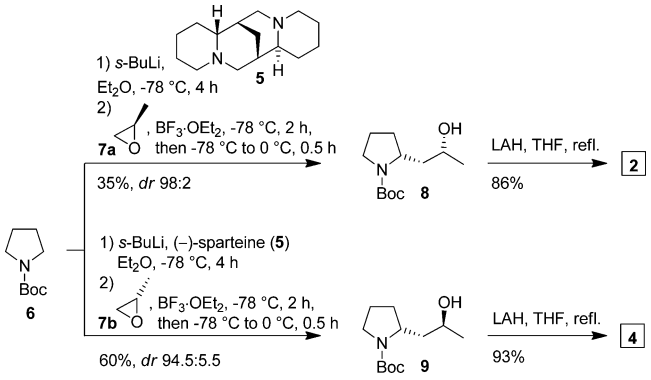
**Received:** August 7, 2013
**Published:** October 8, 2013



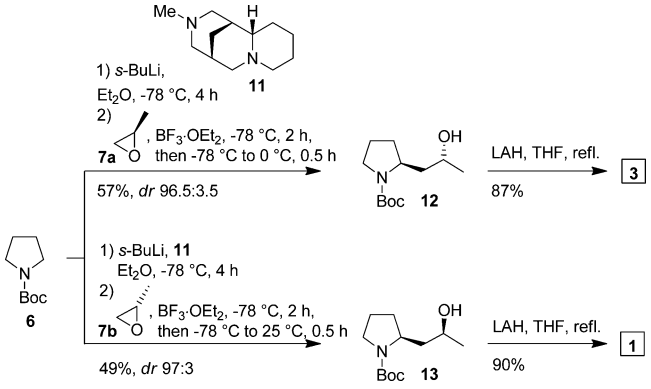


dx.doi.org/10.1021/jo4017343 | J. Org. Chem. 2013, 78, 11066−11070

**Scheme 1. Synthesis of (+)-Hygroline (2) and (+)-Pseudohygroline (4)**




**Scheme 2. Synthesis of (−)-Pseudohygroline (3) and (−)-Hygroline (1)**




Transmetalations included the transformation of the organolithium intermediate into an organozinccuprate,[24] a lower[25] or higher[26,27] order cyanocuprate, or a mixed higher order cyanocuprate.[28] None of these conditions led to epoxide opening;[29] at the same time, direct quenching of the organolithium intermediate with TMSCl[30] gave 2-TMS-pyrrolidine in 84% yield, thus excluding any insufficiencies in the deprotonation step.

Reduction of **8** with 5 equiv of LAH in refluxing THF furnished, after simple acid–base extraction, (+)-hygroline (**2**) in 86% yield (Scheme 1). The latter was obtained with a *dr* of 98:2, which was identical with the *dr* of the Boc-protected precursor **8**. As for all other hygroline isomers, **2** proved to be volatile under reduced pressure and care had to be taken in the solvent evaporation step after extractive workup, in order to minimize loss of product (which can be substantial).

Employing the same protocol as for the reaction with **7a**, **6** was converted into protected amino alcohol **9** by reaction with (*S*)-propylene oxide (**7b**) in 60% yield (64% brsm) and with a *dr* of 94.5:5.5 (Scheme 1);[31] in contrast to the reaction with **7a**, **6** was almost completely consumed in the reaction with **7b**, which is reflected in the higher yield of amino alcohol **9** (compared to **8**). Treatment of **9** with LAH then furnished (+)-pseudohygroline (**4**) in 93% yield (*dr* 96:4) after extractive workup; the material was contaminated with minor impurities (<5%) that could not be removed by distillation.

Compared to the synthesis of **2** and **4**, access to (−)-hygroline (**1**) and (−)-pseudohygroline (**3**) would have required the use of (+)-sparteine (**10**)[32] as a chiral base. The latter is also naturally occurring, but it is significantly less abundant than its (−)-isomer **5**. However, it has been demonstrated that (+)-sparteine (**10**) can be replaced by the (+)-sparteine surrogate **11**,[33−35] which possesses a similar three-dimensional architecture as **10** and can be prepared in three steps from (−)-cytisine.[36,37]

Diamine **11** was successfully applied to the synthesis of (−)-pseudohygroline (**3**), using the previously optimized protocol for epoxide opening. Thus, amino alcohol **12** was obtained in 57% yield (65% brsm) with a *dr* of 96.5:3.5 (97.5:2.5 before distillation) (Scheme 2); subsequent LAH reduction gave (−)-pseudohygroline (**3**) in 50% overall yield from **6** (*dr* 97:3). Lastly, **6** was elaborated into (−)-hygroline (**1**) *via* reaction with **7b** in the presence of **11** in 44% overall yield (*dr* 96.5:3.5, Scheme 2).

In order for the above epoxide opening reactions to be successful, the exact molarity of the *s*-BuLi solution had to be established by titration and (−)-sparteine (**5**) and (+)-sparteine surrogate **11** had to be distilled over calcium hydride before use; the concentration of commercial *s*-BuLi solutions varied significantly, and the ligands were hygroscopic and air sensitive. The ligands were easily recovered from the crude reaction mixtures *via* acid extraction with aqueous 5% phosphoric acid.

In summary, hygrolines **1** and **2** and pseudohygrolines **3** and **4** have been prepared in two steps from *N*-Boc pyrrolidine (**6**) in 30% to 56% yield and with excellent stereoselectivities. The syntheses are based on the enantioselective deprotonation of **6** with *s*-BuLi/sparteine (**5**) or diamine **11** in combination with epoxide opening of homochiral propylene oxides to introduce the stereocenters at C2 and C2′. Purification of intermediates and final products was achieved solely by distillation and simple extractive workup, respectively. All products were obtained in excellent optical purity, based on the comparison of optical rotations with literature values and chiral GC analysis.

While we are not pursuing this line of investigation ourselves, we believe that the method developed here as part of the synthesis of hygrolines and pseudohygrolines should also be applicable to other terminal epoxides, thus providing access to various 2(2-hydroxyalkyl or aryl)-pyrrolidines in high diastereo- and enantioselectivity.

## EXPERIMENTAL SECTION

***tert*-Butyl Pyrrolidine-1-carboxylate (6).** To a solution of $Boc_2O$ (10.0 g, 45.8 mmol, 1.0 equiv) in $CH_2Cl_2$ (150 mL) was added pyrrolidine (4.60 mL, 55.1 mmol, 1.2 equiv) at 0 °C. After stirring at rt for 2 h, the reaction mixture was concentrated and the residue was purified by Kugelrohr distillation to afford **6** (7.33 g, 93%) as a colorless oil. Analytical data were identical with those reported in the literature.[20] $R_f$ = 0.52 (hexane/EtOAc, 2:1). Bp 104−106 °C (0.05 mbar). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$/ppm): 3.30 (br s, 4H), 1.82 (br s, 4H), 1.45 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$/ppm): 154.7, 78.9, 45.9, 45.6, 28.5, 25.7, 25.0.

**(*R*)-*tert*-Butyl 2-((*R*)-2-Hydroxypropyl)pyrrolidine-1-carboxylate (8).** To a solution of (−)-sparteine (**5**) (13.4 g, 57.2 mmol, 1.2 equiv) in $Et_2O$ (90 mL) was added dropwise *s*-BuLi (37.8 mL, 57.1 mmol, 1.2 equiv, 1.51 M in cyclohexane, plus 10 mL of $Et_2O$ for washing) at −78 °C. The homogeneous solution was stirred at −78 °C for 10 min, and a solution of *N*-Boc pyrrolidine (**6**) (8.40 mL, 47.9 mmol, 1.0 equiv) in $Et_2O$ (10 mL) was added dropwise. After stirring at −78 °C for 4 h, a precooled solution (−78 °C) of (*R*)-propylene oxide (**7a**) (6.70 mL, 95.8 mmol, 2.0 equiv) in $Et_2O$ (10 mL) was added dropwise followed by the dropwise addition of a solution of $BF_3{\cdot}OEt_2$ (11.8 mL, 95.6 mmol, 2.0 equiv) in $Et_2O$ (10 mL) over 20 min. After stirring at −78 °C for 2 h, the reaction mixture was allowed to warm to 0 °C over a period of 45 min. The reaction was quenched by the addition of water (15 mL), and the solution was diluted with


dx.doi.org/10.1021/jo4017343 | J. Org. Chem. 2013, 78, 11066−11070

$Et_2O$ (70 mL). The biphasic mixture was washed with 5% aq $H_3PO_4$ (2 × 100 mL) and brine (50 mL). The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue (10.8 g, *dr* 97:3) was submitted to high vacuum distillation (<0.001 mbar) to give **8** (3.85 g, 35%, 50% brsm, *dr* 98:2) as a colorless oil along with recovered starting material **6** (2.47 g, 30%). Bp 110−112 °C (<0.001 mbar). $R_f$ = 0.45 (hexane/EtOAc, 2:1). $[\alpha]_D^{24}$ = +6.4° (*c* = 1.005, $CHCl_3$) (lit.[15] $[\alpha]_D^{23}$ = +10.9° (*c* = 0.7, $CHCl_3$)). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$/ppm): 4.89 (br s, 1H), 4.15−3.98 (m, 1H), 3.68−3.53 (m, 1H), 3.26−3.13 (m, 2H), 1.94−1.69 (m, 3H), 1.55−1.44 (m, 1H), 1.44−1.18 (m, 2H), 1.36 (s, 9H), 1.06 (d, *J* = 6.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$/ppm): 156.3, 79.5, 63.4, 53.6, 46.3, 45.4, 30.9, 28.2, 23.3, 22.4. IR (neat, $\nu$/cm$^{-1}$): 3443brs, 2969m, 2931w, 2880w, 1692s, 1671s, 1479w, 1455w, 1396s, 1365s, 1304w, 1254w, 1165s, 1132m, 1109s, 1052w, 774w. HRMS (ESI): *m*/*z* calcd for $C_{12}H_{24}NO_3$ $[M + H]^+$, 230.1751; found, 230.1748. GC (Restek, Rtx 5Sil MS, 45 °C → 4 °C/min →220 °C, 20 min He): $t_r$/min = 32.9; chiral GC (BGB, BGB 176SE, 50 °C → 2 °C/min →180 °C He): $t_r$/min = 49.5.

In order to recover (−)-sparteine (**5**), the combined aqueous extracts were basified with 50% NaOH and extracted with $Et_2O$ (3 × 100 mL). The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The recovered diamine was stored at −20 °C under an argon atmosphere and distilled before reuse.

**(+)-Hygroline (2).** To a solution of **8** (414 mg, 1.81 mmol, 1.0 equiv) in THF (26 mL) was added cautiously $LiAlH_4$ (343 mg, 9.03 mmol, 5.0 equiv) at 0 °C. The heterogeneous reaction mixture was refluxed for 14 h; it was then allowed to cool to 0 °C, and aq HCl (1 M, 15 mL) was added. The layers were separated, and the aqueous layer (pH 1) was washed with $CH_2Cl_2$ (2 × 10 mL). The aqueous solution was basified with aq NaOH (4 M) and extracted with $CH_2Cl_2$ (4 × 10 mL). The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford (+)-hygroline (**2**) (223 mg, 86%, *dr* 98:2) as a yellowish oil which solidified upon storage in the freezer. Mp 30−32 °C. $[\alpha]_D^{24}$ = +47.4° (*c* = 1.035, EtOH) (lit.[10] $[\alpha]_D^{25}$ = +49.6° (*c* = 1.28, EtOH)). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$/ppm): 6.54 (br s, 1H), 4.14 ($m_c$, 1H), 3.06 ($m_c$, 1H), 2.56 ($m_c$, 1H), 2.33 (s, 3H), 2.18−2.08 (m, 1H), 1.95−1.64 (m, 5H), 1.41 (td, *J* = 2.4, 14.6 Hz, 1H), 1.13 (d, *J* = 6.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$/ppm): 64.8, 64.5, 57.0, 40.5, 37.0, 28.2, 23.6, 23.3. IR (neat, $\nu$/cm$^{-1}$): 3304brs, 2964s, 2927m, 2876m, 2843m, 2790s, 1456s, 1374m, 1291w, 1208m, 1186m, 1135s, 1117m, 1069s, 1037m, 951m, 931m, 901m. HRMS (ESI): *m*/*z* calcd for $C_8H_{18}NO$ $[M + H]^+$, 144.1383; found, 144.1384. Chiral GC (BGB, BGB 176SE, 50 °C → 2 °C/min →140 °C He): $t_r$/min = 26.5.

**(*R*)-*tert*-Butyl 2-((*S*)-2-Hydroxypropyl)pyrrolidine-1-carboxylate (9).** To a solution of (−)-sparteine (**5**) (4.92 g, 20.1 mmol, 1.2 equiv) in $Et_2O$ (33 mL) was added dropwise at −78 °C *s*-BuLi (15.6 mL, 20.9 mmol, 1.2 equiv, 1.34 M in cyclohexane). The homogeneous solution was stirred for 10 min, and then a solution of *N*-Boc-pyrrolidine (**6**) (3.10 mL, 17.7 mmol, 1.0 equiv) in $Et_2O$ (8 mL) was added dropwise. After stirring at −78 °C for 4 h, a precooled solution (−78 °C) of (*S*)-propylene oxide (**7b**) (2.50 mL, 35.7 mmol, 2.0 equiv) in $Et_2O$ (4.5 mL) was added dropwise followed by the dropwise addition of a solution of $BF_3{\cdot}OEt_2$ (4.40 mL, 35.7 mmol, 2.0 equiv) in $Et_2O$ (4.5 mL) over a period of 15 min. After stirring for 2 h at −78 °C, the reaction mixture was allowed to warm to 0 °C over 30 min, the reaction was quenched at 0 °C with water (40 mL), and then the mixture was diluted with $Et_2O$ (40 mL). The biphasic mixture was washed with 5% aq $H_3PO_4$ (2 × 60 mL) and brine (30 mL). The combined aqueous layers were back-extracted with $Et_2O$ (70 mL), and the organic extract was washed with 5% aq $H_3PO_4$ (15 mL) and brine (10 mL). The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue (6.07 g, *dr* 94.5:5.5) was submitted to high vacuum distillation (<0.001 mbar) to give **9** (2.45 g, 60%, 64% brsm, *dr* 94.5:5.5) as a colorless oil along with recovered starting material **6** (173 mg, 6%). Bp 114−116 °C (<0.001 mbar). $R_f$ = 0.21 (hexane/EtOAc, 2:1). $[\alpha]_D^{24}$ = +58.4° (*c* = 1.015, $CHCl_3$) (lit.[15] $[\alpha]_D^{23}$ = +78.5° (*c* = 1.00, $CHCl_3$)). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$/ppm): 4.02−3.89 (m, 1H), 3.89−3.76 (m, 1H), 3.35−3.21 (m, 2H), 2.01−1.89 (m, 1H), 1.89−1.69 (m, 3H), 1.68−1.55 (m, 1H), 1.50−1.35 (m, 1H), 1.43 (s, 9H), 1.21−1.11 (m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, rotamers 2:1 (*), $\delta$/ppm): 155.4, 79.4, 66.2, 65.7*, 55.5, 54.5*, 46.2, 45.8*, 45.4, 44.3*, 32.1, 31.1*, 28.4, 23.9, 23.6, 22.8*. IR (neat, $\nu$/cm$^{-1}$): 3427brs, 2969m, 2931w, 2876w, 1691s, 1669s, 1478w, 1454w, 1392s, 1365s, 1251w, 1166s, 1106s, 1026w, 965w, 921w, 898w, 855w, 772m. HRMS (ESI): *m*/*z* calcd for $C_{12}H_{23}NNaO_3$ $[M + Na]^+$, 252.1570; found, 252.1575. GC (Restek, Rtx 5Sil MS, 45 °C → 4 °C/min →220 °C, 20 min He): $t_r$/min = 33.7; chiral GC (BGB, BGB 176SE, 50 °C → 2 °C/min →180 °C He): $t_r$/min = 51.8.

(−)-Sparteine (**5**) was recovered as described above (*cf.* preparation of **8**).

**(+)-Pseudohygroline (4).** To a solution of **9** (410 mg, 1.79 mmol, 1.0 equiv) in THF (26 mL) was added $LiAlH_4$ (339 mg, 8.94 mmol, 5.0 equiv) cautiously at 0 °C. The heterogeneous reaction mixture was refluxed for 14 h; it was then allowed to cool to rt, and aq HCl (1 M, 25 mL) was added at 0 °C. The aqueous layer (pH 1) was washed with $CH_2Cl_2$ (2 × 15 mL), basified with aq NaOH (50%), and extracted with $CH_2Cl_2$ (5 × 25 mL). The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford (+)-pseudohygroline (**4**) (239 mg, 93%, *dr* 96:4, *er* > 99%) as a yellowish oil. $[\alpha]_D^{24}$ = +103° (*c* = 1.02, EtOH) (lit.[10] $[\alpha]_D^{25}$ = +95.4° (*c* = 0.94, EtOH)). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$/ppm): 5.23 (br s, 1H), 3.91 ($m_c$, 1H), 3.04 ($m_c$, 1H), 2.70 ($m_c$, 1H), 2.39−2.28 (m, 1H), 2.35 (s, 3H), 2.01 (ddd, J = 8.0, 12.5, 16.1 Hz, 1H), 1.81−1.69 (m, 2H), 1.51−1.30 (m, 3H), 1.15 (d, *J* = 6.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$/ppm): 67.4, 65.8, 55.4, 43.0, 42.9, 30.5, 24.2, 22.8. IR (neat, $\nu$/cm$^{-1}$): 3293brs, 2963s, 2928m, 2874m, 2840m, 2781m, 1446m, 1371m, 1323w, 1218w, 1181w, 1132s, 1074m, 1029s, 957w, 936w, 820w. HRMS (ESI): *m*/*z* calcd for $C_8H_{18}NO$ $[M + H]^+$, 144.1383; found, 144.1385. GC (BGB, BGB 176SE, 50 °C → 2 °C/min →140 °C He): $t_r$/min = 31.0.

**(*S*)-*tert*-Butyl 2-((*R*)-2-Hydroxypropyl)pyrrolidine-1-carboxylate (12).** To a solution of (+)-sparteine surrogate **11** (8.05 g, 41.4 mmol, 1.2 equiv) in $Et_2O$ (65 mL) was added *s*-BuLi (30.0 mL, 41.4 mmol, 1.2 equiv, 1.38 M in cyclohexane, plus 10 mL $Et_2O$ for washing) dropwise at −78 °C. The homogeneous solution was stirred for 10 min, and then a solution of *N*-Boc pyrrolidine (**6**) (6.05 mL, 34.5 mmol, 1.0 equiv) in $Et_2O$ (7 mL) was added dropwise. After stirring at −78 °C for 4 h, a precooled solution (−78 °C) of (*R*)-propylene oxide (**7a**) (4.20 mL, 60.0 mmol, 1.74 equiv) in $Et_2O$ (7 mL) was added dropwise followed by the dropwise addition of a solution of $BF_3{\cdot}OEt_2$ (7.40 mL, 60.1 mmol, 1.74 equiv) in $Et_2O$ (5 mL) over a period of 20 min. After stirring at −78 °C for 2 h, the reaction mixture was allowed to warm to 0 °C over 45 min. The reaction was quenched by the addition of water (66 mL), and the mixture was diluted with $Et_2O$ (70 mL). The biphasic mixture was washed with 5% aq $H_3PO_4$ (2 × 100 mL) and brine (50 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue (7.82 g, *dr* 97.5:2.5) was submitted to high vacuum distillation (<0.001 mbar) to give **12** (4.48 g, 57%, 65% brsm, *dr* 96.5:3.5) as a colorless oil along with recovered starting material **6** (702 mg, 12%). Bp 114−116 °C (<0.001 mbar). $R_f$ = 0.21 (hexane/EtOAc, 2:1). $[\alpha]_D^{24}$ = −56.9° (*c* = 1.04, $CHCl_3$) (lit.[17] $[\alpha]_D^{28}$ = −80.2° (*c* = 0.1, $CHCl_3$)). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$/ppm): 3.99−3.87 (m, 1H), 3.87−3.73 (m, 1H), 3.39−3.18 (m, 2H), 1.92 ($m_c$, 1H), 1.86−1.68 (m, 3H), 1.68−1.51 (m, 1H), 1.45−1.31 (m, 1H), 1.40 (s, 9H), 1.21−1.07 (m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, rotamers 2:1 (*), $\delta$/ppm): 155.4, 79.4, 66.2, 65.6*, 55.4, 54.5*, 46.2, 45.8*, 45.3, 44.2*, 32.0, 31.1*, 28.4, 23.9, 23.6, 22.8*. $^1$H NMR (400 MHz, DMSO-$d_6$, $\delta$/ppm) (1:1 mixture of rotamers): 4.32 (s, 1H), 3.93−3.74 (m, 1H), 3.71−3.51 (m, 1H), 3.30−3.08 (m, 2H), 1.95−1.57 (m, 5H), 1.39 (s, 9H), 1.32−1.14 (m, 1H), 1.06 (d, *J* = 6.1 Hz, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$/ppm) (1:1 mixture of rotamers (*)): 153.3, 77.8, 63.5, 54.0, 45.9, 45.6*, 43.5, 42.9*, 30.3, 29.4*, 28.1, 24.1, 23.1, 22.4*. IR (neat, $\nu$/cm$^{-1}$): 3418brs, 2969m, 2935w, 2881w, 1691s, 1670s, 1478w, 1455w, 1401s, 1366m, 1252w, 1169s, 1110m, 1061w, 774w. HRMS (ESI): *m*/*z* calcd for


dx.doi.org/10.1021/jo4017343 | J. Org. Chem. 2013, 78, 11066−11070

$C_{12}H_{23}NNaO_3$ [M + Na]$^+$: 252.1570, found: 252.1567. GC (Restek, Rtx 5Sil MS, 45 °C → 4 °C/min →220 °C, 20 min He): $t_r$/min = 33.7; chiral GC (BGB, BGB 176SE, 50 °C → 2 °C/min →180 °C He): $t_r$/min = 53.3.

Diamine **11** was recovered as described above for **5** (*cf.* preparation of **8**).

**(−)-Pseudohygroline (3).** To a solution of **12** (409 mg, 1.78 mmol, 1.0 equiv) in THF (26 mL) was added $LiAlH_4$ (338 mg, 8.92 mmol, 5.0 equiv) cautiously at 0 °C. The heterogeneous reaction mixture was refluxed for 14 h; it was then allowed to cool to 0 °C and aq HCl (1 M, 15 mL) was added. The aqueous layer (pH 1) was washed with $CH_2Cl_2$ (2 × 10 mL), basified with aq NaOH (4 M), and extracted with $CH_2Cl_2$ (4 × 10 mL). The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford (−)-pseudohygroline (**3**) (223 mg, 87%, *dr* 97:4; *er* 98:2) as a colorless oil. $[\alpha]_D^{24}$ = −102° (*c* = 1.07, EtOH) (lit.[10] $[\alpha]_D^{25}$ = −97.0° (*c* = 1.01, EtOH)). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$/ppm): 5.30 (br s, 1H), 3.91 (m$_c$, 1H), 3.04 (m$_c$, 1H), 2.70 (m$_c$, 1H), 2.40−2.27 (m, 1H), 2.35 (s, 3H), 2.01 (m$_c$, 1H), 1.81−1.68 (m, 2H), 1.51−1.30 (m, 3H), 1.15 (d, *J* = 6.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$/ppm): 67.4, 65.7, 55.4, 43.0, 42.9, 30.5, 24.2, 22.8. IR (neat, $\nu$/cm$^{-1}$): 3285brs, 2963s, 2927m, 2853m, 2840m, 2783m, 1456m, 1419w, 1371m, 1323w, 1215m, 1180m, 1132s, 1073m, 1029s, 957m, 937w, 818m. HRMS (ESI): *m*/*z* calcd for $C_8H_{18}NO$ [M + H]$^+$: 144.1383, found: 144.1384. Chiral GC (BGB, BGB 176SE, 50 °C → 2 °C/min →140 °C He): $t_r$/min = 31.3.

**(*S*)-*tert*-Butyl 2-((*S*)-2-Hydroxypropyl)pyrrolidine-1-carboxylate (13).** To a solution of (+)-sparteine surrogate **11** (3.41 g, 17.5 mmol, 1.2 equiv) in $Et_2O$ (27 mL) was added *s*-BuLi (13.1 mL, 17.5 mmol, 1.2 equiv, 1.34 M in cyclohexane) dropwise at −78 °C. The homogeneous solution was stirred for 10 min, and then a solution of *N*-Boc pyrrolidine (**6**) (2.60 mL, 14.8 mmol, 1.0 equiv) in $Et_2O$ (7 mL) was added dropwise. After stirring at −78 °C for 4 h, a precooled solution (−78 °C) of (*S*)-propylene oxide (**7b**) (2.10 mL, 30.0 mmol, 2.0 equiv) in $Et_2O$ (5 mL) was added dropwise followed by the dropwise addition of a solution of $BF_3{\cdot}OEt_2$ (3.70 mL, 30.0 mmol, 2.0 equiv) in $Et_2O$ (5 mL) over a period of 15 min. After stirring for 2 h at −78 °C, the reaction mixture was allowed to warm to rt over a period of 1 h and then recooled to 0 °C; water was added (40 mL), and the mixture was diluted with $Et_2O$ (40 mL). The biphasic mixture was washed with 5% aq $H_3PO_4$ (2 × 7 mL) and brine (30 mL). The combined aqueous extracts were back-extracted with $Et_2O$ (80 mL), and the organic phase was washed with 5% aq $H_3PO_4$ (15 mL) and brine (10 mL). The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue (3.59 g, *dr* 93.5:6.5) was submitted to high vacuum distillation (<0.001 mbar) to give **13** (1.68 g, 49%, 53% brsm, *dr* 97:3) as a colorless oil along with recovered starting material **6** (194 mg, 8%). Bp 110−112 °C (<0.001 mbar). $R_f$ = 0.45 (hexane/EtOAc, 2:1). $[\alpha]_D^{24}$ = −5.7° (*c* = 1.01, $CHCl_3$) (lit.[17] $[\alpha]_D^{28}$ = −11.2° (*c* = 0.2, $CHCl_3$)). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$/ppm): 4.95 (br s, 1H), 4.24−4.02 (m, 1H), 3.75−3.57 (m, 1H), 3.36−3.15 (m, 2H), 2.01−1.69 (m, 3H), 1.61−1.49 (m, 1H), 1.49−1.23 (m, 2H), 1.40 (s, 9H), 1.18−1.04 (m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$/ppm): 156.5, 79.7, 63.5, 53.7, 46.4, 45.5, 31.0, 28.3, 23.4, 22.5. IR (neat, $\nu$/cm$^{-1}$): 3436brs, 2969m, 2931w, 2878w, 1692s, 1670s, 1478w, 1454w, 1393s, 1365s, 1304w, 1252w, 1163s, 1131m, 1107s, 1052w, 929w, 853w, 774m. HRMS (ESI): *m*/*z* calcd for $C_{12}H_{23}NNaO_3$ [M + Na]$^+$, 252.1570; found, 252.1571. GC (Restek, Rtx 5Sil MS, 45 °C → 4 °C/min →220 °C, 20 min He): $t_r$/min = 32.9; chiral GC (BGB, BGB 176SE, 50 °C → 2 °C/min →180 °C He): $t_r$/min = 50.3.

**(−)-Hygroline (1).** To a solution of **13** (405 mg, 1.77 mmol, 1.0 equiv) in THF (26 mL) was added $LiAlH_4$ (335 mg, 8.83 mmol, 5.0 equiv) cautiously at 0 °C. The heterogeneous reaction mixture was refluxed for 14 h; it was then allowed to cool to rt, and aq HCl (1 M, 25 mL) was added. The aqueous layer (pH 1) was washed with $CH_2Cl_2$ (2 × 15 mL), basified with aq NaOH (50%), and extracted with $CH_2Cl_2$ (5 × 25 mL). The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford (−)-hygroline (**1**) (229 mg, 90%, *dr* 96.5:3.5) as a yellowish oil which solidified upon storage in the freezer. Mp 30−32 °C. $[\alpha]_D^{24}$ = −46.9° (*c* = 1.00, EtOH) (lit.[10] $[\alpha]_D^{25}$ = −53.1° (*c* = 1.03, EtOH)). $^1$H NMR (400 MHz, $CDCl_3$, $\delta$/ppm): 6.49 (br s, 1H), 4.14 (m$_c$, 1H), 3.10−3.01 (m, 1H), 2.56 (m$_c$, 1H), 2.33 (s, 3H), 2.18−2.09 (m, 1H), 1.95−1.65 (m, 5H), 1.41 (td, *J* = 2.4, 14.6 Hz, 1H), 1.13 (d, *J* = 6.1 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$, $\delta$/ppm): 64.8, 64.6, 57.1, 40.5, 37.0, 28.3, 23.7, 23.4. IR (neat, $\nu$/cm$^{-1}$): 3281brs, 2964s, 2926m, 2876w, 2844m, 2790m, 1456s, 1374m, 1291w, 1208w, 1186m, 1135m, 1117m, 1069m, 1037m, 951w, 931w, 901m. HRMS (ESI): *m*/*z* calcd for $C_8H_{18}NO$ [M + H]$^+$, 144.1383; found, 144.1385. Chiral GC (BGB, BGB 176SE, 50 °C → 2 °C/min →140 °C He): $t_r$/min = 26.5.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

$^1$H, $^{13}$C NMR data and GC traces for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: karl-heinz.altmann@pharma.ethz.ch.


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We are indebted to Dr. Irmgard Werner and Sara Wyss for assistance with GC analyses. Dr. Bernhard Pfeiffer is acknowledged for NMR support, Kurt Hauenstein for practical advice, and the Laboratory of Organic Chemistry of the ETH Zürich for recording HRMS spectra.

## ■ REFERENCES


(1) Späth, E.; Kittel, F. *Ber. Dtsch. Chem. Ges. [Abteilung] B: Abhandlungen* **1943**, *76B*, 942.

(2) For the first isolation of hygrine (an amino ketone) from *coca* leaves, see: Wöhler, F. *Liebigs Ann. Chem.* **1862**, *121*, 372.

(3) Galinovsky, F.; Zuber, H. *Monatsh. Chem.* **1953**, *84*, 798.

(4) Lukes, R.; Kovar, J.; Kloubek, J.; Blaha, K. *Collect. Czech. Chem. Commun.* **1960**, *25*, 483.

(5) Platonova, T. F.; Kuzovkov, A. D. *Meditsinskaya Promyshlennost SSSR* **1963**, *17*, 19.

(6) Fitzgerald, J. S. *Aust. J. Chem.* **1965**, *18*, 589.

(7) San Martin, A.; Rovirosa, J.; Gambaro, V.; Castillo, M. *Phytochemistry* **1980**, *19*, 2007.

(8) Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K. *J. Org. Chem.* **1986**, *51*, 2590.

(9) Murahashi, S.; Imada, Y.; Kohno, M.; Kawakami, T. *Synlett* **1993**, 395.

(10) Takahata, H.; Kubota, M.; Momose, T. *Tetrahedron: Asymmetry* **1997**, *8*, 2801.

(11) Louis, C.; Hootelé, C. *Tetrahedron: Asymmetry* **1997**, *8*, 109.

(12) Enierga, G.; Hockless, D. C.; Perlmutter, P.; Rose, M.; Sjoberg, S.; Wong, K. *Tetrahedron Lett.* **1998**, *39*, 2813.

(13) Knight, D. W.; Salter, R. *Tetrahedron Lett.* **1999**, *40*, 5915.

(14) Vanucci-Bacque, C.; Calvet-Vitale, S.; Fargeau-Bellassoued, M.-C.; Lhommet, G. *ARKIVOC* **2007**, 148.

(15) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Smith, A. D. *Tetrahedron* **2009**, *65*, 10192.

(16) Yadav, J. S.; Narasimhulu, G.; Mallikarjuna Reddy, N.; Subba Reddy, B. V. *Tetrahedron Lett.* **2010**, *51*, 1574.

(17) Bhat, C.; Tilve, S. G. *Tetrahedron Lett.* **2011**, *52*, 6566.

(18) For a review see: Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 2282.

(19) Deng, X.; Mani, N. S. *Tetrahedron: Asymmetry* **2005**, *16*, 661.

(20) **6** was obtained by reaction of pyrrolidine with $Boc_2O$ in a reproducible 93% yield after Kugelrohr distillation (multigram scale): Barker, G.; O'Brien, P.; Campos, K. R. *Org. Lett.* **2010**, *12*, 4176.
(21) In the original protocol by Deng and Mani, the base was added to a stirred solution of *N*-Boc-pyrrolidine (**6**) and (−)-sparteine (**5**). However, preformation of the *s*-BuLi/(−)-sparteine (**5**) complex has been shown to result in improved *dr*'s (although in a different context): Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708.
(22) Diastereomeric ratios were determined by gas chromatography.
(23) The protocol of Deng and Mani was used in these optimization experiments, which solely served to search for conditions that would improve the chemical yield of the transformation.
(24) Coldham, I.; Leonori, D. *J. Org. Chem.* **2010**, *75*, 4069.
(25) Marino, J. P.; Anna, L. J.; Fernandez de la Pradilla, R.; Martinez, M. V.; Montero, C.; Viso, A. *Tetrahedron Lett.* **1996**, *37*, 8031.
(26) Ng, J. S.; Behling, J. R.; Campbell, A. L.; Nguyen, D.; Lipshutz, B. *Tetrahedron Lett.* **1988**, *29*, 3045.
(27) Alexakis, A.; Jachiet, D.; Normant, J. F. *Tetrahedron* **1986**, *42*, 5607.
(28) Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E. *J. Organomet. Chem.* **1985**, *285*, 437.
(29) These findings are in agreement with similar observations by Deng and Mani, although the stereoselective allylation of **6** with allyl bromide after (−)-sparteine-mediated stereoselective lithiation has been reported: Coldham, I.; Leonori, D. *J. Org. Chem.* **2010**, *75*, 4069.
(30) Beak, P.; Lee, W. K. *Tetrahedron Lett.* **1989**, *30*, 1197.
(31) The separation of **9** from the starting material **6** proved to be more difficult than was the case for **8**, due to its lower boiling point. These difficulties may have been responsible for a significant loss in product *dr* during distillation that was observed in a first experiment (from 93.5:6.5 in the crude reaction mixture to 87.5:12.5 in the distilled product); in this case, some of the lower-boiling desired isomer **9** may have been removed together with the starting material **6**, thus leading to an accumulation of the undesired (*S,S*)-diastereoisomer of **9** in the product.
(32) Ebner, T.; Eichelbaum, M.; Fischer, P.; Meese, C. O. *Arch. Pharm.* **1989**, *322*, 399.
(33) Dearden, M. J.; McGrath, M. J.; O'Brien, P. *J. Org. Chem.* **2004**, *69*, 5789.
(34) O'Brien, P. *Chem. Commun.* **2008**, 655.
(35) Carbone, G.; O'Brien, P.; Hilmersson, G. *J. Am. Chem. Soc.* **2010**, *132*, 15445.
(36) Dearden, M. J.; Firkin, C. R.; Hermet, J.-P.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870.
(37) Dixon, A. J.; McGrath, M. J.; O'Brien, P. *Org. Synth.* **2006**, *83*, 141.