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Stereoselective Route towards 2,5-Disubstituted Piperidine Alkaloids. Synthesis of (+)-Pseudoconhydrine and (±)-*epi*-Pseudoconhydrine

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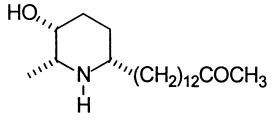
Abstract—This paper describes a new general approach towards functionalized piperidine alkaloids, based on the stereo- and regioselective palladium(0)-catalyzed nucleophilic ring-opening of vinyl epoxides by nitrogen nucleophiles. The latter reaction provides access to stereodefined *anti* and *syn* aminoalcohol derivatives, 1-benzyloxy-5-(*p*-toluenesulfonamido)-3-alken-2-ols (**5**), which were transformed to (+)-pseudoconhydrine (**3**) and (±)-*epi*-pseudoconhydrine (**9**), respectively, via protection (silyl ether), hydrogenation, debenzylation and cyclization. Detosylation–deprotection gave the final products in good yields and high stereoisomeric purity.

Introduction

Piperidine alkaloids are widespread in nature and many compounds of this family exhibit interesting biological activity.[1] Cassein (**1**)[2] isolated from *Cassia excelsa* and spectalin (**2**)[3] from *Cassia spectabilis* are members of this family that have been subject to synthetic studies. Pseudoconhydrine (**3**) has been isolated along with coniine (**4**) from Poison Hemlock, *Conium maculatum*.[4] Syntheses of compound **3** in its racemic[5] and enantiomerically pure[6] form using different strategies have been reported previously.



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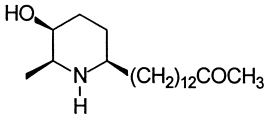

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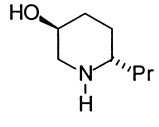

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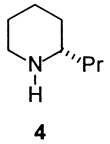

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While there are several known routes towards piperidine alkaloids, most of them suffer from lack of generality. It was therefore of interest to develop new general approaches that give access to all stereoisomers via a single common route. The strategy outlined in the present work provides a route to 2,5-disubstituted piperidine alkaloids of either *cis* or *trans* stereochemistry using 1-benzyloxy-5-(*p*-toluenesulfonamido)-3-alken-2-ols (**5**) as key intermediates. The absolute stereochemistry is introduced early in the sequence via Sharpless epoxidation.

The use of amidoalkenols with the general structure **5** as building blocks in the synthesis of 2,5-disubstituted pyrrolidine derivatives (**6**) and indolizidine alkaloids (**7**) has previously been demonstrated in our laboratory[7] (Scheme 1). Amidoalkenols of *anti* (**5a**) and *syn* (**5b**) stereochemistry are readily available by a common route, starting from either *cis* or *trans*-1-benzyloxy-2,3-epoxybutan-4-ol (**8a** or **8b**), respectively. The versatility of intermediates **5** is further demonstrated in this paper by the synthesis of (+)-pseudoconhydrine (**3**) from **5a**, and (±)-*epi*-pseudoconhydrine (**9**) from **5b** (Scheme 1).

Results and Discussion

Amidoalkenol **5a** with alkyl side chains of varying length is readily available from *trans* epoxyalcohol **8a**.[7a] The key step in the synthesis of **5a** is the Pd(0)-catalyzed regio- and stereoselective ring-opening of vinylepoxide **10a** by NaNHTs.[8] The reaction involves an external attack by $TsNH^-$ on an intermediate (π-allyl)palladium complex.[7a,8a,9] Protection of the hydroxy group of **5a** as a TBDMS ether using standard conditions[10] gave the ether **11a** in 91% yield, and subsequent hydrogenation employing

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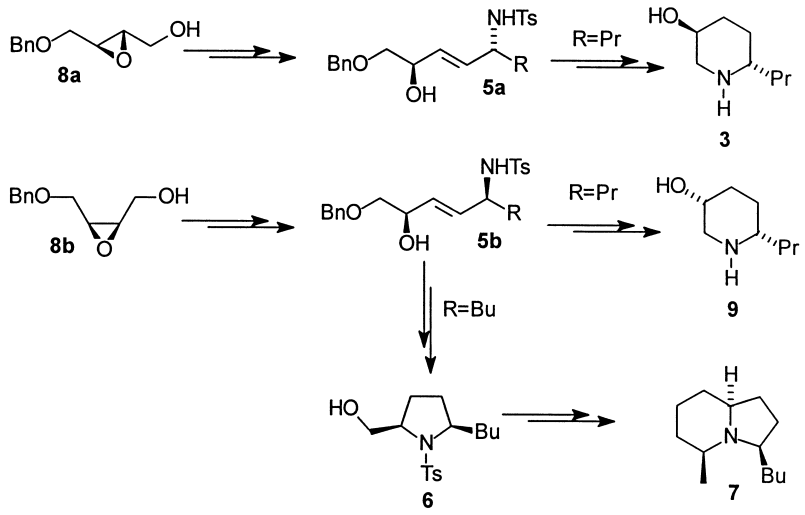
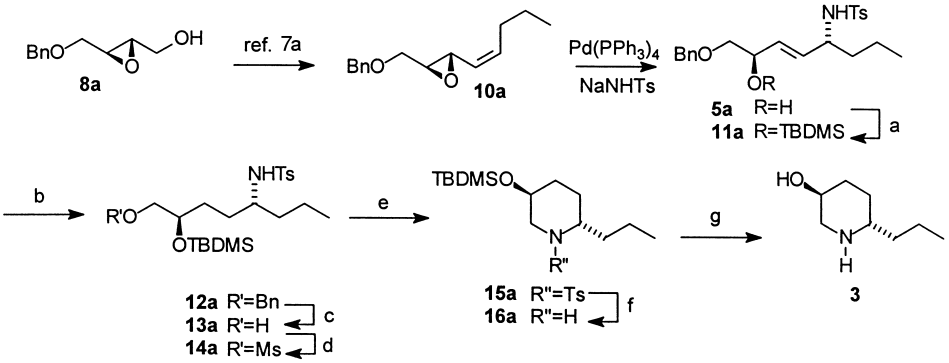
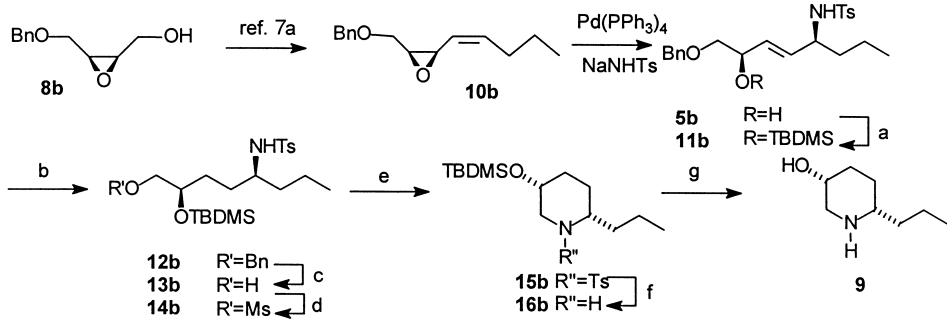


Scheme 1.



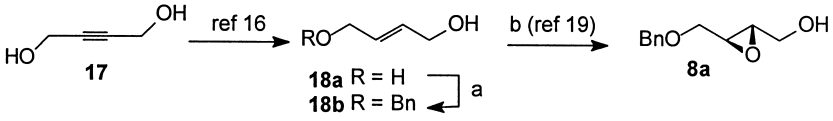
Scheme 2. (a) TBDMSCl, imidazole, (b) PtO_2, EtOH, H_2 (c) Pd/C, MeOH, H_2, (d) MsCl, Et_3N, THF, (e) K_2CO_3, MeOH, (f) Na(Hg), Na_2HPO_4, MeOH, (g) HCl, EtOH.



Scheme 3. (a) TBDMSCl, imidazole, (b) PtO_2, EtOH, H_2 (c) Pd/C, MeOH, H_2, (d) MsCl, Et_3N, THF, (e) K_2CO_3, MeOH, (f) Na(Hg), Na_2HPO_4, MeOH, (g) HCl, EtOH.

PtO_2 and 1 atm. of H_2[11] gave **12a** in 97% yield. The benzyl group of **12a** was removed by hydrogenolysis[10] over palladium on carbon to give **13a** in 93% yield. Mesylation and subsequent cyclization employing K_2CO_3 in MeOH[12] afforded the tosyl piperidine **15a** in 81% yield. The *N*-tosyl protective group was removed with Na/NH_3 in EtOH[13] to give the free amine **16a** in 85% yield. Stirring of **16a** in EtOH containing 1% HCl (10 equiv.) afforded (+)-**3** as its HCl salt in 98% yield.[14] The free base was released by treatment with 2 M NaOH (Scheme 2). (+)-Pseudoconhydrine (**3**) was characterized and spectral data were in accordance with those previously reported.[6e]

The same reaction sequence was employed to convert the racemic *syn* aminoalcohol derivative **5b** to (±)-**9** (Scheme 3). The *syn* amidoalcohol **5b** was obtained from palladium-catalyzed ring opening of the (*cis*, *Z*)-epoxide **10b** by NaNHTs.[7a] The detosylation step in this sequence was



Scheme 4. (a) Ag_2O, BnBr, CH_2Cl_2, (b) (−)-DET (7%), Ti(*i*-PrO)$_4$ (6%), *t*-BuOOH, CH_2Cl_2.

carried out using Na(Hg).[15] The (±)-*epi*-pseudoconhydrine (**9**) was characterized as its hydrochloride salt which is known in the literature.[6b]

For an efficient synthesis of the target compounds it is necessary to have easy access to **8a** and **8b**. The latter compounds are prepared from (*E*)- and (*Z*)-2-butene-1,4-diol, respectively. The (*E*)-2-butene-1,4-diol (**18a**) was prepared by reduction of the alkyne moiety in **17** with $LiAlH_4$.[16,17] Monobenzylation of the (*Z*)-2-butene-1,4-diol under the previously employed standard conditions (1 equiv. NaH, BnBr, THF) worked satisfactorily and afforded the monoether in 70% yield. However, the corresponding monobenzylation of (*E*)-2-butene-1,4-diol (**18a**) in THF was sluggish and gave a poor yield of the monoether (<20%). For an efficient synthesis of pseudoconhydrine ((+)-**3**) it was therefore necessary to improve the synthesis of **8a** and hence the monoalkylation of **18a** to **18b**. A change of solvent to DMF led to some improvement of the yield (50%). Recently, the use of Ag_2O together with BnBr was successfully used to monobenzylate diols.[18] Reaction of **18a** with 1.1 equiv. BnBr in the presence of 1.0 equiv. Ag_2O in CH_2Cl_2 (RT)[19] dramatically improved the yield (84%) as well as the simplicity of the reaction.

Sharpless epoxidation[20] using standard conditions, 7% (−)-diethyltartrate ((−)-DET) and 6% Ti(*i*-PrO)$_4$, gave the epoxide as an oil in 87% yield and 93% ee. To improve the enantiomeric excess by recrystallization, the product was converted to the 2,4-dichlorobenzoate. The ester was successfully recrystallized and hydrolyzed (NaOH in MeOH, RT, overnight) to give the epoxide **8a** in more than 99.5% ee (Scheme 4).

Conclusions

The piperidine alkaloids (+)-pseudoconhydrine (**3**) and (±)-*epi*-pseudoconhydrine (**9**) were synthesized employing **5a** and **5b**, respectively, as stereodefined key intermediates. By using a slight modification of this method 5-hydroxy-2,6-dialkylpiperidines such as cassein (**1**) and spectaline (**2**) should also be available.

The possibility of forming stereodefined 5- and 6-membered ring structures from the same precursor makes amidoalkenols **5** powerful tools for the synthesis of these heterocyclic compounds.

Experimental

General

^{1}H (^{13}C NMR)-spectra were recorded at 400 (100.6) MHz using chloroform-d$_1$ (7.26 ppm ^{1}H, 77 ppm ^{13}C) as internal standard unless otherwise stated. Accurate mass measurements were preformed with a JEOL SX 102 mass spectrometer with *m*-nitrobenzylalcohol as matrix. IR spectra were obtained on a Perkin–Elmer FTIR spectrometer. Optical rotations were measured using Perkin–Elmer 241 polarimeter. GC–MS were measured with a Thermo Quest GCQ plus. The (*Z*)-2-butene-1,4-diol and 2-butyne-1,4-diol are commercially available. The enantiomeric purity of epoxide **8a** was determined by HPLC analysis using a Chiragel OD-H column, flow rate 0.5 ml/min, 80/20, hexane/2-propanol.

Compound 18b. To a stirred solution of the diol **18a** (0.53 g, 6.0 mmol) in CH_2Cl_2 (11 ml) was added freshly prepared Ag_2O (1.39 g, 6.0 mmol) and BnBr (0.78 ml, 6.6 mmol). The reaction was stirred for 15 h and filtered through a short silica gel pad, which was washed with diethyl ether. Evaporation of the solvent followed by flash chromatography (SiO_2, pentane:ether (75:25)) gave 0.90 g (84%) of the monoalkylated product **18b**. Spectral data were in accordance with those previously reported.[16]

Compound 5a was prepared using the procedure previously described.[7a] $Pd(PPh_3)_4$ (33 mg, 0.028 mmol), NaNHTs (110 mg, 0.57 mmol), and NH_2Ts (100 mg, 0.57 mmol) were combined and an argon atmosphere was applied. CH_3CN (5 ml) was added and a yellow color appeared. A solution of **10a** (110 mg, 0.47 mmol) in 0.5 ml CH_3CN was added and the reaction was stirred at 40°C for 6 h. 170 mg (90%) of **5a** was isolated: ^{1}H NMR ($CDCl_3$) δ 7.70 (d, J=8.4 Hz, 2H, Ts), 7.31 (m, 5H, Ph), 7.21 (d, J=8.4 Hz, 2H, Ts), 5.40 (m, 2H, CH=CH), 5.08 (d, J=8.1 Hz, 1H, NH), 4.50 (s, 2H, $PhCH_2$), 4.12 (m, 1H, CHOH), 3.72 (quintet, J=7.3 Hz 1H, CHNHTs), 3.29 (dd, J=3.3, 9.5 Hz, 2H, $BnOCH_2$), 3.15 (dd, J=7.7, 9.5 Hz, 2H, $BnOCH_2$), 2.52 (d, J=3.3 Hz, 1H, OH), 2.36 (s, 3H, Ts), 1.20–1.50 (several m, 4H), 0.80 (t, J=7.3 Hz, 3H, Me). ^{13}C NMR ($CDCl_3$) δ 142.7, 138.0, 137.5, 131.4, 129.7, 129.1 (2C), 128.1 (2C), 127.5, 127.4 (2C), 126.9 (2C), 73.7, 73.1, 70.2, 55.2, 37.7, 21.4, 18.5, 13.8. $[\alpha]_D^{23}=-12°$ (c=1.15, $CHCl_3$).

Compound 11a. To a stirred solution of amidoalcohol **5a** (0.35 g, 0.87 mmol) in DMF (3.5 ml) at 0°C was added imidazole (0.19 g, 2.78 mmol) and TBDMSCl (0.20 g, 1.30 mmol). The mixture was stirred at 0°C for 2 h and at RT for an additional 2 h. The reaction mixture was then partitioned between ether and brine, then dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (SiO_2, pentane:ether (1:1)) to afford 0.41 g, (91%) of the product. ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J=7.9 Hz, 2H, Ts), 7.34 (m, 5H, Ph), 7.31 (d, J=7.9 Hz, 2H, Ts), 5.40 (m, 2H, CH=CH), 4.97 (d, J=7.8 Hz, 1H, NH), 4.48 (d, J=2.0, 2H, $PhCH_2$), 4.15 (m, 1H,

CHOTBDMS), 3.76 (quintet, J=6.5 Hz 1H, CHNHTs), 3.19 (m, 2H, $BnOCH_2$) 2.39 (s, 3H, Ts) 1.20–1.50 (several m, 4H), 0.85 (m, 12H, *t*-BuSi+Me), 0.00 (s, 3H, MeSi), −0.03 (s, 3H, MeSi). ^{13}C NMR ($CDCl_3$) δ(142.8, 138.2, 138.1, 131.7, 130.1, 129.4 (2C), 128.2 (2C), 127.4 (2C), 127.3 (2C), 127.0, 74.9, 73.3, 71.7, 55.1, 38.2, 25.9, 21.6, 18.6, 18.4, 13.8, −4.6. IR 3273, 2929, 2857, 1453, 1161, 1094, 698. HRMS Calcd for $C_{28}H_{43}O_4NSiS$+Na: 540.2580, found: 540.2597. $[\alpha]_D^{22}$=−15° (c=1.2, $CHCl_3$).

Compound 11b. To a stirred solution of amidoalcohol **5b** (0.30 g, 0.75 mmol) in DMF (2.5 ml) at 0°C was added imidazole (0.16 g, 2.4 mmol) and TBDMSCl (0.16 g, 1.1 mmol). The procedure outlined for **11a** afforded 0.34 g, (87%) of **11b**. ^{1}H NMR ($CDCl_3$) δ 7.71 (d, 2H, Ts), 7.32 (m, 5H, Ph), 7.22 (d, 2H, Ts), 5.45 (m, 2H, CH=CH), 4.49 (d, J=2.0, 2H, $PhCH_2$), 4.34 (d, J=8.0 Hz, 1H, NH), 4.19 (m, 1H), 3.79 (m, 1H), 3.23 (dd, J=9.0, 6.5, 1H), 3.19 (dd, J=9.0, 5.0, 1H), 2.39 (s, 3H, Ts), 1.20–1.50 (several m, 4H), 0.92 (m, 12H, *t*-BuSi+Me), 0.02 (s, 3H, MeSi), −0.03 (s, 3H, MeSi). ^{13}C NMR ($CDCl_3$) δ 143.7, 138.2 (2C), 132.0, 130.3, 129.5 (2C), 128.4, 128.3, 127.7 (2C), 127.5 (2C), 127.1, 74.9 (2C), 71.5, 55.0, 38.3, 36.4, 31.4, 25.8, 25.7, 18.5, 18.2, 13.6, −4.6. IR 3269, 2956, 2928, 2856, 1669, 1455, 1387, 1160, 1094, 814, 697.

Compound 12a. Compound **11a** (0.41 g, 0.79 mmol) was dissolved in 21 ml of EtOH. PtO_2 (13 mg, 0.056 mmol) was added and a hydrogen pressure of 1 atm. was applied. The reaction mixture was stirred at RT for 3 h, then filtered through celite and concentrated to give 0.40 mg (97%) of **12a**. ^{1}H NMR ($CDCl_3$) δ 7.74 (d, J=8.0 Hz, 2H, Ts), 7.32 (m, 5H, Ph), 7.25 (d, J=8.0 Hz, 2H, Ts), 4.44 (s, 2H, $PhCH_2$), 3.69 (m, 1H, CHOTBDMS), 3.26 (m, 3H, CHNHTs+$BnOCH_2$), 2.40 (s, 3H, Ts) 1.20–1.60 (several m, 8H), 0.84 (s, 9H, *t*-BuSi), 0.78 (t, 3H, Me), 0.00 (s, 3H, MeSi), −0.02 (s, 3H, MeSi). ^{13}C NMR ($CDCl_3$) δ 142.8, 138.3, 138.2, 129.4 (2C), 128.2 (2C), 127.5 (2C), 127.4 (2C), 126.9, 74.3, 73.2, 71.2, 54.2, 37.3, 30.54, 30.46, 25.9, 21.5, 18.4, 18.2, 13.9, −4.3, −4.7. IR 3278, 3030, 2955, 2828, 2856, 1496, 1454, 1252, 1161, 1094, 698, 664. HRMS Calcd for $C_{28}H_{45}O_4NSiS$+H: 520.2939, found: 520.2928. $[\alpha]_D^{22}$=−12° (c=0.8, $CHCl_3$).

Compound 12b. Compound **11b** (0.16 g, 0.3 mmol) was dissolved in 8 ml EtOH. PtO_2 (5 mg, 0.02 mmol) was added and a hydrogen pressure of 1 atm. was applied. The reaction was stirred at RT for 20 min, then filtered through celite and concentrated to give 0.15 g, (92%) of **12b**. ^{1}H NMR ($CDCl_3$) δ 7.79 (d, J=8.0 Hz, 2H, Ts), 7.40–7.25 (m, 7H, Ts and Ph), 4.39 (s, 2H, $PhCH_2$), 4.32 (d, J=8.2 Hz, 1H, NH), 3.73 (m, 1H, CHOTBDMS), 3.33 (dd, J=9.5, 5.5 Hz, 1H), 3.26 (m, 1H), 3.25 (dd, J=9.5, 5.5 Hz, 1H), 2.42 (s, 3H, Ts) 1.20–1.60 (several m, 8H), 0.89 (s, 9H, *t*-BuSi), 0.79 (t, 3H, Me), 0.03 (s, 3H, MeSi), 0.02 (s, 3H, MeSi). ^{13}C NMR ($CDCl_3$) δ 143.0, 138.5, 132.0, 130.3 (2C), 129.5 (2C), 128.3 (2C), 127.5 (2C), 127.1, 75.0, 73.3, 71.5, 55.1, 38.3, 36.4, 31.4, 25.8, 21.5, 18.5, 18.2, 13.6, −4.7, −4.9. IR 3276, 3030, 2955, 2928, 2856, 1496, 1454, 1252, 1160, 1094, 819, 698.

Compound 13a. Compound **12a** (80 mg, 0.15 mmol) was dissolved in MeOH (3 ml), and 5% palladium on carbon (33 mg) was added. A hydrogen pressure of 1 atm. was applied, and the reaction was stirred at RT for 1 h. After filtration and concentration 60 mg (93%) of compound **13a** was recovered. ^{1}H NMR ($CDCl_3$) δ 7.74 (d, J=8.4 Hz, 2H, Ts), 7.28 (d, J=8.4 Hz, 2H, Ts), 4.55 (d, J=8.4, 1H), 3.60 (m, 1H), 3.39 (m, 2H), 3.20 (m, 2H, $BnOCH_2$), 2.41 (s, 3H, Ts), 1.90 (br s, 1H) 1.20–1.60 (several m, 8H), 0.86 (m, 9H, *t*-BuSi), 0.76 (t, 3H, Me), 0.04 (s, 3H, MeSi), 0.01 (s, 3H, MeSi). ^{13}C NMR ($CDCl_3$) δ(143.0, 138.2, 129.4 (2C), 126.9 (2C), 72.5, 66.0, 54.1, 37.3, 30.7, 29.6, 25.9, 21.6, 18.6, 18.1, 13.9, −4.3, −4.4. IR 3510, 3285, 2956, 2929, 2857, 1599, 1462, 1322, 1254, 1159, 1094, 836. HRMS Calcd for $C_{21}H_{39}O_4NSiS$+Na: 452.2267, found: 452.2265. $[\alpha]_D^{22}$=−6° (c=1.3, $CHCl_3$). The product was of >99.5% ee as determined by HPLC analysis using a Chiragel OD-H column (flow rate 0.5 ml/min, 90/10, hexane/2-propanol).

Compound 13b. Compound **12b** (147 mg, 0.28 mmol) was dissolved in MeOH (5 ml), and 5% palladium on carbon (101 mg) was added. A hydrogen pressure of 1 atm. was applied, and the reaction was stirred at RT for 3.5 h. After filtration and concentration 110 mg (90%) of compound **13b** was recovered. ^{1}H NMR ($CDCl_3$) δ 7.75 (d, 2H, Ts), 7.29 (d, 2H, Ts), 4.21 (d, J=8.0, 1H), 3.45 (m, 1H), 3.36 (m, 1H), 3.24 (m, 1H), 3.14 (m, 1H), 2.42 (s, 3H, Ts), 1.69 (m, 1H) 1.20–1.50 (several m, 7H), 0.9 (m, 9H, *t*-BuSi), 0.79 (t, J=7.0, 3H, Me), 0.05 (s, 3H, MeSi), 0.02 (s, 3H, MeSi). ^{13}C NMR ($CDCl_3$) δ 143.2, 138.6, 129.6 (2C), 127.1 (2C), 72.5, 66.2, 53.9, 37.4, 30.6, 29.4, 25.8, 21.4, 18.5, 18.1, 13.8, −4.2, −4.9. IR 3510, 3282, 2956, 2929, 2857, 1599, 1460, 1322, 1254, 1159, 1094, 835.

Compound 15a. To a stirred solution of alcohol **13a** (0.162 g, 0.38 mmol) in THF (4.5 ml) at 0°C, were added Et_3N (109 μl, 0.76 mmol) and MsCl (47 μl, 0.60 mmol). The resulting solution was stirred at 0°C for 1 h and at RT for 2 h. The reaction mixture was partitioned between ether and water, and the organic phase was dried (Na_2SO_4). Concentration afforded the crude mesylate **14a**, which was dissolved in MeOH (7 ml). K_2CO_3 (0.46 g, 3.3 mmol) was added and the mixture was stirred at RT for 23 h. The solvent was evaporated and H_2O (10 ml) was added, this water phase was extracted EtOAc (3×15 ml). Drying and concentration afforded an oil, which was purified by flash chromatography (SiO_2, pentane:ether (75:25)) to afford 0.13 g, (81%) of the product **15a**. ^{1}H NMR ($CDCl_3$) δ 7.79 (d, J=8.0 Hz, 2H, Ts), 7.21 (d, J=8.0 Hz, 2H, Ts), 3.85 (m, 1H, CHN), 3.72–3.69 (m, 3H, CH_2N+CHOTBDMS), 3.14 (dd, 1H, J=1.8, 13.9), 2.38 (s, 3H, Ts), 1.95 (m, 1H), 1.10–1.70 (several m, 7H), 0.85 (m, 12H, *t*-BuSi+Me), 0.01 (s, 3H, MeSi), 0.00 (s, 3H, MeSi). ^{13}C NMR ($CDCl_3$) δ 142.2, 138.4, 129.0 (2C), 127.4 (2C), 64.6, 52.5, 46.6, 31.1, 26.1, 25.9, 21.5, 20.9, 19.9, 18.4, 14.1, −4.8 (2C). IR 3428, 2956, 2857, 1463, 1327, 1148, 1094, 835. HRMS Calcd for $C_{21}H_{37}O_3NSiS$+H: 412.2342, found: 412.2232. $[\alpha]_D^{22}$=−8° (c=1.1, $CHCl_3$).

Compound 15b. The procedure outlined for **15a** was employed. To **13b** (0.141 g, 0.33 mmol) in THF (4 ml) at 0°C, was added Et_3N (90 μl, 0.65 mmol) and MsCl (40 μl, 0.52 mmol) and the resulting crude product was dissolved in MeOH (6 ml) and K_2CO_3 (400 mg, 2.9 mmol) was added, this afforded 0.107 g (79%) of product **15b**. ^{1}H NMR

($CDCl_3$) δ 7.72 (d, 2H, Ts), 7.30 (d, 2H, Ts), 3.97 (m, 1H), 3.69 (dd, J=13.5, 5.0 Hz, 1H), 3.33 (m, 1H), 2.71 (dd, J=13.5, 10.7 Hz, 1H), 2.45 (m, 1H), 2.42 (s, 3H, Ts), 1.20–1.70 (several m, 8H), 0.91 (m, 12H, *t*-BuSi+Me), 0.04 (s, 3H, MeSi), 0.01 (s, 3H, MeSi). ^{13}C NMR ($CDCl_3$) δ 142.9, 138.9, 129.5 (2C), 127.6 (2C), 66.8, 51.8, 46.6, 31.6, 29.0, 26.7, 25.7, 21.4, 19.6, 18.0, 13.8, −4.7, −4.9 (2C). IR 3286, 2956, 2857, 1355, 1175, 1160, 959, 914, 837, 665.

Compound 16a. A solution of **15a** (93 mg, 0.23 mmol) in EtOH (2 ml) was added to liquid ammonia (6 ml) with stirring at −78°C. To this mixture was added sodium (0.3 g, 13 mmol) in small portions. The reaction was allowed to reach RT. After 24 h the mixture was diluted with ether (15 ml) and quenched with aqueous NH_4Cl (sat) (1 ml). The aqueous phase was separated, backextracted with ether (2×15 ml) and dried over Na_2SO_4. Concentration in vacuo afforded 50 mg (85%) of **16a** as the only product. This colorless oil was used directly in the next step. ^{1}H NMR ($CDCl_3$) δ 3.55 (m, 1H), 3.10 (m, 1H), 2.5 (m, 2H) 1.90 (m, 1H), 1.70 (m, 2H) 1.20–1.00 (several m, 6H), 0.90 (m, 12H, *t*-BuSi+Me), 0.00 (s, 6H, MeSi). ^{13}C NMR ($CDCl_3$) δ 69.4, 55.6, 54.5, 38.9, 34.7, 31.6, 25.9, 19.5, 18.2, 14.3, −4.5. GCMS (CI, CH_4) 258 (M+1, 100%), 242 (M−CH_3, 89%), 214 (M−C_3H_7, 16%), 200 (M−*t*-Bu, 31%), 126 (M−OTBDMS, 55%). IR 3339, 2956, 2928, 2857, 1463, 1257, 1098. HRMS Calcd for $C_{14}H_{31}ONSi$+H: 258.2254, found: 258.2255. $[\alpha]_D^{22}$=+3° (c=0.9, $CHCl_3$).

Compound 16b. To a solution of **15b** (100 mg, 0.24 mmol) and Na_2HPO_4 (287 mg, 2.0 mmol) in dry MeOH (2 ml) at RT was added Na(Hg) (6%, 796 mg). The mixture was heated to 50°C and stirred for 18 h. The reaction was allowed to reach RT, filtered through celite and the filter cake rinsed with EtOAc. Brine was added and the organic layer was separated. The aqueous phase was backextracted three times with EtOAc, and the combined organic layers were dried (Na_2SO_4). Concentration afforded 50 mg (81%) of **16b**. ^{1}H NMR ($CDCl_3$) δ 3.71 (m, 1H), 2.85 (dd, J=13.0, 2.5 Hz, 1H), 2.70 (dd, J=13.0, 1.7 Hz, 1H) 2.41 (m, 1H), 1.72–1.15 (several m, 11H), 0.85 (m, 12H, *t*-BuSi+Me), 0.03 (s, 3H, MeSi) 0.01 (s, 3H, MeSi). ^{13}C NMR ($CDCl_3$) δ 65.2, 55.5, 52.7, 39.3, 31.7, 27.2, 25.8, 19.1, 18.0, 14.2, −4.8, −4.9.

(+)-Pseudoconhydrine 3. The silyl ether **16a** (25 mg, 0.10 mmol) was stirred for 2 h in 3.5 ml of a 1% solution of HCl in EtOH (95%) (10 equiv. of HCl). After concentration, the hydrochloride salt of **3** was isolated and washed with CH_2Cl_2 to give 17 mg (98%). $[\alpha]_D^{21}$=+3.67° (c=0.52, MeOH). lit.[6f] $[\alpha]_D^{21}$=+3.56° (c=0.40, MeOH). ^{1}H NMR (CD_3OD) δ 3.82 (m, 1H), 3.33 (m, 1H), 3.07 (m, 1H) 2.73 (t, J=11 Hz, 1H), 2.10 (m, 2H), 1.68–1.36 (m, 6H), 0.98 (t, J=7.3 Hz 3H). Treatment of the salt with 2 M NaOH (1 ml) and extraction with ether (3×1.5 ml) released the free amine **3**, which after removing of the solvent was obtained as a crystalline compound. $[\alpha]_D^{22}$=+11.2°(c=0.23, EtOH). (lit.[6e] $[\alpha]_D^{29}$=+11.1°(c=1.0, EtOH). Spectral data were in accordance with those previously reported.[6e]

(±)-*epi*-Pseudoconhydrine 9. The silyl ether **16b** (5 mg, 0.02 mmol) was stirred for 2 h in 0.7 ml of a 1% solution of HCl in EtOH (95%) (10 equiv. of HCl). After concentration the hydrochloride salt of **9** was isolated in 94% yield (3.3 mg). Spectral data of the hydrochloride salt were in accordance with those reported in Ref. 6b. Treatment with 2 M NaOH (1 ml) and extraction with ether (3×1.5 ml) gave the free amine **9**.

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