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# Total Synthesis of (+)-Dihydrocuscohygrine and Cuscohygrine

Christian Stapper and Siegfried Blechert*

*Institut für Chemie, Technische Universität Berlin, Strasse des 17. Juni 135, D-10623 Berlin, Germany*

*blechert@chem.tu-berlin.de*

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The first enantioselective synthesis of (+)-dihydrocuscohygrine **1** and cuscohygrine **2** is presented. **1** was obtained in nine steps and 30% overall yield with a ruthenium-catalyzed tandem ring rearrangement metathesis key step starting from enantiomerically pure cycloheptene-1,3,5-triol derivative **6**. The unknown absolute configuration of natural dihydrocuscohygrine **1** could be determined as (*S*,*S*)-(−). Cuscohygrine **2** was obtained by Jones oxidation of **1** in quantitative yield but unfortunately with complete epimerization.

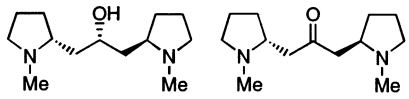
## Introduction

The development of methods for the preparation of chiral heterocyclic ring systems is a challenge in natural product synthesis. In this field, olefin metathesis[1] has gained increasing importance during the past decade. Recent examples demonstrate the wide spread applicability of ruthenium-catalyzed metathesis reactions in the synthesis of highly substituted heterocycles. In this reaction, the chirality embedded in the carbocyclic starting compound is completely transferred into the product side chain. The catalyst systems developed so far are compatible with many functional groups present in the substrate molecules. Besides the most frequently used *ring-closing metathesis* (RCM) combinations of RCM and the *ring-opening metathesis* (ROM) are also suitable for natural product synthesis. We herein report the first stereoselective synthesis of the pyrrolidine alkaloids (+)-dihydrocuscohygrine **1** and cuscohygrine **2** (Scheme 1) via a tandem ring rearrangement metathesis key step.

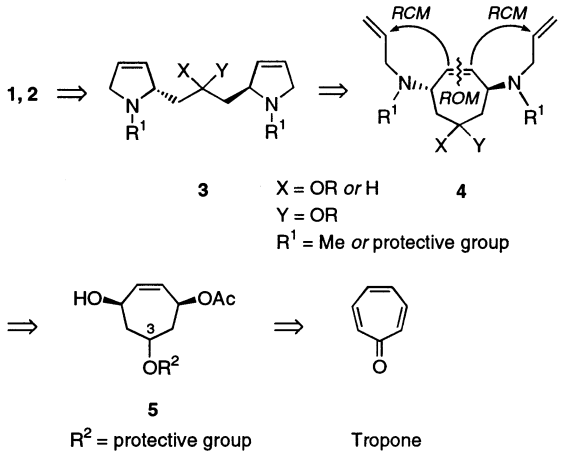
Cuscohygrine **2** was isolated in 1889 from the leaves of *Erythroxylon coca* and its structure established by Liebermann.[2a,b] Later, it was reported to be also a minor component of many other *Solanaceae* alkaloids.[2c] Like related alkaloids, cuscohygrine **2** epimerizes readily so that it has never been obtained as optically active material. In contrast, natural dihydrocuscohygrine **1**, isolated by Turner[3] in 1981, occurs in different *Solanaceae* spp. as the (−)-enantiomer. Its relative configuration was established by $^1$H NMR, $^{13}$C NMR, and MS in comparison with synthetic material obtained by reduction of cuscohygrine, but the absolute configuration of (−)-dihydrocuscohygrine **1** was unknown up to now.

A *tandem ring rearrangement metathesis*, a RCM−ROM−RCM sequence, was planned as the key step of the synthesis of dihydrocuscohygrine **1** and cuscohygrine **2**. Therefore, both alkaloids had to be derived from the protected bis-dihydropyrrole system **3** containing double bonds that are formed in the metathesis reaction (Scheme 2). From **3** the natural products should then be accessible by deprotection, *N*-methylation, and double bond hydrogenation. At this stage the carbonyl group was planned to be protected as an acetal to avoid epimerization. In the key step, **3** should be accessible from **4** by a RCM−ROM−RCM-sequence, a *tandem ring rearrangement*. **4** should in turn be obtained from enantiomerically pure triol derivative **5** via a sequential stereoselective substitution of both the allylic alcohol and the allylic acetate. Compounds such as **5** can be obtained in a few steps from commercially available tropone.[4] Enzymatic desymme-

**SCHEME 1**




**SCHEME 2**




(1) For recent reviews, see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (b) Fürstner, A. *Angew. Chemie* **2000**, *112*, 3140. (c) Blechert, S. *Pure Appl. Chem.* **1999**, *71*, 1393. (d) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, 4413.

(2) (a) Liebermann, C. *Ber.* **1889**, *22*, 675. (b) Liebermann, C.; Cybulski, G. *Ber.* **1895**, *28*, 578. (c) Leete, E. *Phytochemistry* **1983**, *22*, 699.

(3) Turner, C. E.; Elsohly, M. A.; Hanus, L.; Elsohly, H. N. *Phytochemistry* **1981**, *20*, 1403.

(4) (a) Johnson, C. R.; Golebiowski, A.; Steensma, D. H.; Scialdone, M. A. *J. Org. Chem.* **1993**, *53*, 7185. (b) Johnson, C. R.; Golebiowski, A.; Steensma, D. H *J. Am. Chem. Soc.* **1992**, *114*, 9414.

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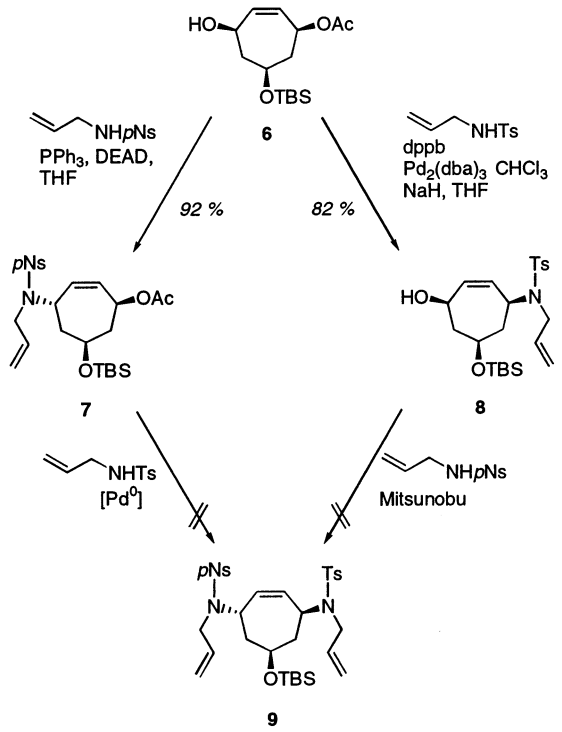
**SCHEME 3**




trization of the corresponding *meso*-diol should provide a simple entry to an enantiomerically pure precursor. A real concern with this approach was the ease of base-catalyzed epimerization of cuscohygrine **2** during the isolation procedure.

## Results

Alcohol **6** was considered to be a suitable starting material.[4b] Due to the orthogonality of the two *O*-protecting groups, **6** is a variably applicable building block in our synthesis. The absolute configuration at C-3 may be neglected, because the hydroxyl group would be oxidized to a ketone during the synthesis. The first allyl amino side chain was introduced by a Mitsunobu reaction with *N*-nosyl protected allylamine under inversion of the configuration (Scheme 3).

Thus, the amine **7** was obtained in good yield and high diastereoselectivity (>98% de, determined by $^1$H NMR). Several attempts to introduce the second allyl amino side chain into **7** via an $\eta^3$-allyl-Pd(0)-substitution with allylamine or *N*-protected allylamine to give **9** failed. The starting material was inert under the reaction conditions. We suppose that a boat conformation of the cycloheptene (confirmed by molecular modeling studies) ring may suppress the backside attack of the bulky Pd catalyst to the double bond. This assumption is supported by the fact that variations of neither the Pd catalyst [$Pd(PPh_3)_4$, $Pd_2(dba)_3$·$CHCl_3$/dppb or dppe, $Pd(dba)_2$/dppb or dppe] nor the nucleophile (allylamine, sodium azide, tosyl amide) resulted in the formation of substitution products. Changing the order of the sequence also did not give the desired product: the first allyl amino side chain was successfully introduced by $\eta^3$-allyl-Pd(0)-substitution of the acetate, affording **8** in good yield, but the subsequent Mitsunobu reaction with *N*-nosyl allylamine failed. Obviously, the allylic hydroxyl group is also too inert for Mitsunobu type reactions. This was confirmed by several attempts to *O*-acylate **8** with acetic anhydride or methyl chloroformate. Even at elevated temperatures, only the starting material was recovered. Only mesylation was effected by stirring **8** in pyridine at room temperature for 24 h. A route via two subsequent allylic $S_N2$-type reactions under net retention was then taken into account: Conversion of the allylic alcohol into the corresponding halide under inversion followed by an allylic nucleophilic substitution with a *N*-nucleophile should afford the desired bis(allylamino)cycloheptene derivative. We assumed that due to the bulky *N*-nosyl allyl amino side chain the $S_N2'$-type attack of the nucleophile should be sterically hindered. Both allylic substitutions should give the $S_N2$ product. The acetate **7** was cleaved in good yield with potassium cyanide in methanol, yielding the alcohol **10**.[5]

Several methods of converting alcohol **10** into the chloride or bromide under inversion were tested. The best results were obtained by stirring **10** with 1.5 equiv of MsCl in pyridine at room temperature overnight. The chloride **11** was prepared under total inversion of the configuration in good yield (Scheme 4). NMR spectroscopic studies (NOE- and H,H-correlation) on **11** showed that only the $S_N2$ product was formed, no $S_N2'$ product could be detected. Tests with solvents, usually more feasible for bimolecular substitution reactions, like DMF or acetonitrile gave much poorer results in diastereoselectivity.

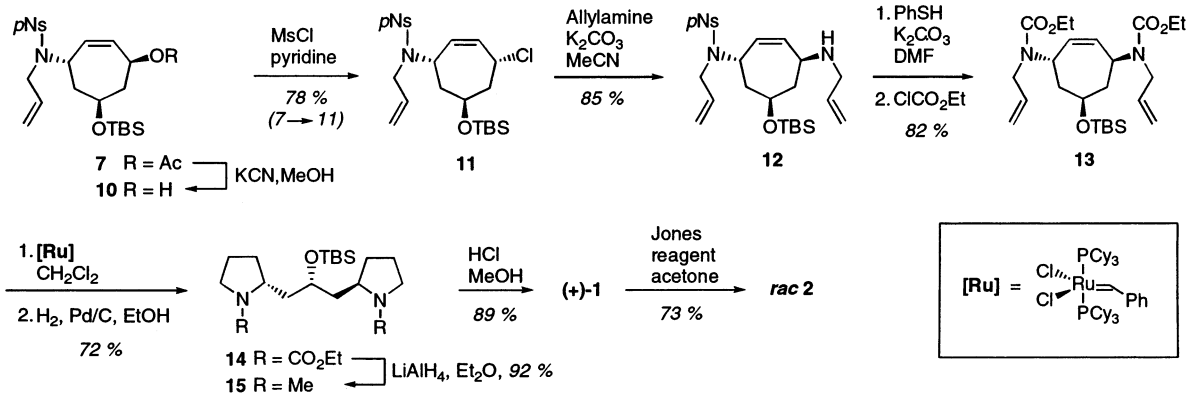
The subsequent nucleophilic substitution of allyl chloride **11** with allylamine was carried out under classic $S_N2$ conditions with a large excess of amine (15 equiv) and $K_2CO_3$ in acetonitrile at 70 °C. This afforded **12** in good yield and a diastereoselectivity higher than 30:1, as determined by the $^1$H NMR spectrum. Since *N*-nosyl protecting groups gave only poor results in the metathesis reactions, we used carbamate protecting groups. Carbamates proved to be good protecting groups in olefin metathesis reactions.[6] As alkyl carbamates are also proper synthetic equivalents for *N*-methyl groups, a change of the protective groups from nosyl to ethylcarbamate was carried out at this stage. The deprotection−protection sequence was performed with 1.5 equiv of thiophenol and an excess of $K_2CO_3$ in DMF at 70 °C followed by the addition of ethylchloroformate at 0 °C, affording **13** in 82% yield. TBS−ether cleavage with TBAF in THF followed by Jones oxidation at 0 °C and even at −78 °C yielded only tropone, due to immediate elimination of the amines. Therefore, the oxidation had to occur at a later stage.

The tandem metathesis of **13** was then carried out with 5 mol % of Grubbs catalyst **[Ru]** in boiling $CH_2Cl_2$. After 36 h the reaction was complete (determined by TLC). Upon column chromatography of the crude material, decomposition took place to a large extent. Several modifications of the workup procedure did not improve the result. Decomposition occurred already during the evaporation of the solvent. $^1$H NMR spectroscopic analysis of the crude product showed broad signals between

(5) Mori, K.; Tominaga, M.; Takigawa, T.; Matsui, M. *Synthesis* **1973**, 790.

(6) For further examples of the use of *N*-carbamate protecting groups instead of *N*-nosyl groups, see: Stragies, R.; Blechert, S. *Synlett* **1998**, 169.

**SCHEME 4**




the olefinic and the aromatic region due to isomers of the product. We found that decomposition products of the catalyst **[Ru]** were responsible for the isomerization. Attempts to remove the catalyst remainders with lead tetraacetate resulted in complete decomposition of the product. Therefore, we hydrogenated (Pd/C) the crude product immediately after the metathesis reaction had been completed. The saturated product **14** was obtained in 72% yield over two steps but was still highly colored due to decomposition products of the catalyst. $^1$H NMR spectroscopic analysis of **14** was difficult due to rotation isomerization of the two carbamate groups. However, the combustion analysis and the high-resolution MS supported the proposed empirical formula. Reduction of the dicarbamate **14** with $LiAlH_4$ gave the bis-*N*-methylpyrrolidine **15**, which was fully characterized. The choice of the solvent was crucial in this reaction: whereas THF gave rise to a highly colored product, a completely colorless oil could be obtained with diethyl ether as solvent in 92% yield. In the latter case, the ruthenium impurities were adsorbed on the aluminum hydroxide precipitate during the work up and could be filtered off. The bis-methylpyrrolidine **15** thus obtained was diastereomerically pure according to its $^1$H NMR spectrum. *O*-Deprotection[7] with concentrated HCl in methanol (yield 89%) completed the synthesis of **1**, which was obtained in >98% purity (GC) and 30% overall yield from **7**. $^1$H NMR and IR spectroscopical data were congruent with the literature data[3], but the optical rotation of the synthetic dihydrocuscohygrine **1** $[\alpha]^{20}_D = +105$ ° (*c* 2.05, acetone) differs both in sign and in magnitude from the reported data,[3] $[\alpha]^{20}_D = -68$ ° (*c* 2.5, acetone). The data demonstrate that natural (−)-dihydrocuscohygrine is the (*S*,*S*)-enantiomer.

Now, we turned our attention to the synthesis of cuscohygrine **2**. Our plan was to oxidize dihydrocuscohygrine **1** under acidic conditions. Basic conditions and long reaction times would result in epimerization of **2**. After a series of test reactions,[8] the Jones oxidation turned out to be the method of choice. The oxidation of **1** with an excess of Jones reagent in acetone was complete after 30 min according to TLC and GC. Careful basification of the reaction mixture with KOH at 0 °C and immediate extraction of the product with precooled solvents gave pure **2**, which turned out to be a diastereomeric mixture of *meso*- and *d*,*l*-cuscohygrine **2** according to $^{13}$C NMR analysis owing to very fast epimerization. Trapping the product as the dihydrochloride immediately after extraction at 0 °C also gave rise to a mixture of epimeric dihydrochlorides. Various changes in the neutralization conditions or workup procedure did not improve the results. Even slightly basic conditions after neutralization with $NaHCO_3$ and a single extraction at −10 °C with a large volume of $CHCl_3$ followed by immediate acidification at −10 °C with HCl gas only afforded an optically inactive epimeric mixture. Attempts to convert the ketone into an acetal in situ by adding an excess of methanol and trimethylorthoformate in dichloromethane also failed. We then focused our attention on the oxidation of the dihydrochloride of **1**. But no feasible reaction conditions could be found. The dihydrochloride was only slightly soluble in chloroform, but no oxidation took place under a variety of conditions.[9] At this stage no further efforts were made to obtain enantiomerically pure cuscohygrine **2**.

## Conclusion

The short and efficient stereoselective synthesis of (*R*,*R*)-dihydrocuscohygrine **1** clarified the absolute configuration of natural (*S*,*S*)-dihydrocuscohygrine. Via a ruthenium-catalyzed ring rearrangement metathesis as key step the chirality was transferred from an enantiomerically pure carbocycle **11** into two pyrrolidine heterocycles **14**. This strategy can be extended to the synthesis of related alkaloids. We are currently investigating further applications of this methodology for the synthesis of other ring sizes and stereocenters.

## Experimental Details

Each reaction with air- and moisture-sensitive components was performed under a $N_2$ atmosphere, metathesis reactions were carried out in a glovebox. Tetrahydrofuran was distilled from sodium/benzophenone, and dichloromethane was distilled from calcium hydride. $^1$H NMR (200 or 500 MHz) and $^{13}$C NMR spectra (50 or 125 MHz) were recorded in $CDCl_3$ relative to TMS. Mass spectra were obtained at an ionizing potential of 70 eV. IR spectra were measured by attenuated total reflectance (ATR). GC−MS analyses were performed with He as

(7) Cunico, R. F.; Bedell, L. *J. Org. Chem.* **1980**, *45*, 4797.

(8) Attempted oxidation conditions (results): PCC (incomplete after 24 h), PCC on alumina (incomplete after 24 h), PDC (no reaction), Dess−Martin-periodinane (complete after 15 h, complete epimerisation), tritylium tetrafluoroborate (no reaction).

(9) Attempted oxidation conditions: PCC, PDC, Jones' reagent.

carrier gas. Optical rotations were determined on a polarimeter as solutions in a 10 cm unit cell at 589 nm. $R_f$ values indicated refer to TLC on 0.2 mm analytical plates coated with silica gel. MTBE = methyl *tert*-butyl ether. Chemicals were purchased and used without further purification.

***p*-Nosylamide 7**. To a solution of acetate **6**[4] (3.5 g, 11.7 mmol), allyl-*p*-nosylamide[10] (4.23 g, 17.5 mmol), and $PPh_3$ (9.17 g, 35.1 mmol) in THF (100 mL) was added diisopropylazodicarboxylate (4.71 g, 23.4 mmol) dropwise at 0 °C. After stirring for 18 h at room temperature, the solution was concentrated in vacuo and the residue was purified by flash chromatography (silica, cyclohexane/MTBE 3:1) to give **7** as light yellow oil (5.01 g, 82% yield). $R_f$ = 0.50 (cyclohexane/MTBE 1:1). $^1$H NMR (200 MHz): $\delta$ 8.28−8.38 (m, 2H), 7.94−8.06 (m, 2H), 5.60−5.91 (m, 2H), 5.09−5.40 (m, 4H), 4.84−4.96 (m, 1H), 4.12−4.28 (m, 1H), 3.90−4.05 (m, 1H), 3.62−3.78 (m, 1H), 1.70−2.25 (m, 4H), 2.03 (s, 3H), 0.85 (s, 9H), 0.03 (s, 6H). $^{13}$C NMR (125 MHz): $\delta$ 170.00, 149.71, 146.87, 135.01, 134.58, 132.77, 128.25, 124.20, 118.41, 69.95, 64.37, 53.41, 47.66, 42.21, 41.78, 25.60, 21.06, 17.84, − 4.96, − 4.90. IR: $\nu$ 3105, 3082, 3035, 1739, 1531, 1350, 1240, 837, 777 cm$^{-1}$. MS *m*/*z* (%) 509 (1), 467 (40), 117 (100), 75 (97). HR-MS calcd for $C_{23}H_{33}N_2O_7SSi$ 509.1778 $[M - CH_3]^+$, obsd 509.1775. $[\alpha]^{20}_D$ = −77° (*c* 0.28, $CHCl_3$). Anal. Calcd for $C_{24}H_{36}N_2O_7SSi$: C, 54.96; H, 6.87; N, 5.34. Found: C, 54.96; H, 7.13; N, 5.56.

**Tosylamide 8**. To a mixture of acetate **6** (610 mg, 2.03 mmol), *N*-allyl-*N*-tosylamide[11] (500 mg, 2.37 mmol), and NaH (90 mg 60% suspension in mineral oil, 2.25 mmol) was added dry THF (15 mL). DMF (4−5 mL) was then added to the suspension until the solution became clear. Under $N_2$ atmosphere $[Pd_2(dba)_3]{=}CHCl_3$ (52 mg, 0.051 mmol, 2.5 mol %) and dppb (90 mg, 0.21 mmol, 10 mol %) were added as solids. The solution was stirred for 30 min at 50 °C. After addition of water (50 mL), the solution was extracted with MTBE (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (silica, cyclohexane/MTBE 3:1), affording **8** (755 mg, 82%) as yellow oil. $R_f$ = 0.27 (cyclohexane/MTBE 3:1). $^1$H NMR (200 MHz): $\delta$ 7.64−7.72 (m, 2H), 7.21−7.31 (m, 2H), 5.89−6.10 (m, 1H), 5.57−5.70 (m, 1H), 5.38−5.50 (m, 1H), 5.24−5.36 (m, 1H), 5.08−5.17 (m, 1H), 4.74−4.80 (m, 1H), 4.02−4.22 (m, 4H), 3.90−4.02 (m, 1H), 2.20−2.60 (m, 3H), 2.40 (s, 3H), 1.70−1.84 (m, 1H), 0.84 (s, 9H), 0.05 (s, 6H). $^{13}$C NMR (125 MHz): $\delta$ 143.00, 137.72, 136.27, 131.45, 129.45, 127.98, 126.20, 116.51, 72.55, 67.88, 62.29, 47.67, 41.52, 34.73, 25.59, 21.43, 17.78, − 5.21, − 5.33. IR: $\nu$ 3488, 3081, 3035, 1598, 1338, 1255, 1159, 1091, 1025, 837, 712 cm$^{-1}$. MS *m*/*z* (%) 433 (2) $[M^+ - OH]$, 394 (21), 183 (100), 91 (88). HR-MS calcd for $C_{23}H_{35}NO_3SSi$ $[M^{+\ -}$ OH): 433.2107, obsd 433.2101. $[\alpha]_D^{20}$ = −103° (*c* 0.47, $CHCl_3$). Anal. Calcd for $C_{23}H_{37}NO_4SSi$: C, 61.20; H, 8.20; N, 3.14; Found: C, 61.28; H, 8.00; N, 3.11.

**Alcohol 10**. *p*-Nosylamide **7** (4.95 g, 9.45 mmol) and KCN (20 mg, 0.3 mmol) were dissolved in MeOH (50 mL) and stirred for 18 h at room temperature. The solution was concentrated in vacuo. Purification of the residue by flash chromatography (silica, cyclohexane/MTBE 1:1) afforded **10** as pale yellow oil (4.33 g, 95% yield). $R_f$ = 0.20 (cyclohexane/MTBE/MeOH 5:5:1). $^1$H NMR (200 MHz): $\delta$ 8.30−8.37 (m, 2H), 7.96−8.05 (m, 2H), 5.68−5.93 (m, 2H), 4.98−5.32 (m, 4H), 4.18−4.37 (m, 2H), 3.91−4.04 (m, 1H), 3.60−3.76 (m, 1H), 2.20−2.60 (br s, 1H), 1.85−2.14 (m, 4H), 0.93 (s, 9H), 0.10 (s, 6H). $^{13}$C NMR (125 MHz): $\delta$ 149.95, 146.91, 136.76, 134.99, 132.65, 128.45, 124.40, 118.40, 67.46, 67.02, 54.22, 48.06, 42.58, 42.27, 25.83, 18.06, − 4.97, − 4.81. IR: $\nu$ 3540, 3427, 3105, 3082, 3026, 1531, 1350, 832, 736 cm$^{-1}$. MS *m*/*z* (%) 425 (100), 333 (77). HR-MS calcd for $C_{18}H_{25}N_2O_6SSi$ 425.1203 $[M - C_4H_9]^+$, obsd 425.1210. $[\alpha]^{20}_D$ = −12° (*c* 0.34, $CHCl_3$). Anal. Calcd for $C_{22}H_{34}N_2O_6SSi$: C, 54.77; H, 7.05; N, 5.81. Found: C, 54.36; H, 7.12; N, 6.01.

**Chloride 11**. To a solution of alcohol **10** (4.25 g, 8.82 mmol) in pyridine (25 mL) was added mesyl chloride (1.81 g, 15.9 mmol) dropwise under cooling (ice bath) and stirring. After stirring at room temperature for 18 h, the solvents were distilled off, and the residue was suspended in ethyl acetate (100 mL) and filtered through silica. The filtrate was concentrated in vacuo. **11** was obtained as a light yellow oil (3.75 g, 85% yield). $R_f$ = 0.53 (cyclohexane/MTBE 1:1). $^1$H NMR (500 MHz): $\delta$ 8.30−8.38 (m, 2H), 7.95−8.05 (m, 2H), 5.75−5.86 (m, 2H), 5.40−5.46 (m, 1H), 5.19−5.27 (m, 1H), 5.10−5.18 (m, 1H), 4.97−5.04 (m, 1H), 4.82−4.87 (m, 1H), 4.18−4.27 (m, 1H), 3.93−4.00 (m, 1H), 3.69−3.76 (m, 1H), 2.03−2.20 (m, 3H), 1.85−1.94 (m, 1H), 0.92 (s, 9H), 0.03 (s, 6H). $^{13}$C NMR (125 MHz): $\delta$ 149.97, 146.86, 135.26, 134.68, 133.98, 128.46, 124.39, 118.65, 66.87, 53.73, 53.63, 48.22, 43.96, 42.05, 25.83, 18.11, −4.85, −4.79. IR: $\nu$ 3106, 3084, 1531, 1350, 1166, 837, 734 cm$^{-1}$. MS *m*/*z* (%) 485 (<1), 443 (100), 299 (24), 69 (39). HR-MS calcd for $C_{21}H_{30}N_2O_5ClSSi$ 485.1333 $[M - CH_3]^+$, obsd 485.1331. $[\alpha]^{20}_D$ = +71° (*c* 0.23, $CHCl_3$). Anal. Calcd for $C_{22}H_{33}N_2O_5ClSSi$: C, 52.75; H, 6.59; N, 5.59. Found: C, 52.84; H, 6.34; N, 5.66.

**Diamine 12**. Chloride **11** (3.60 g, 7.19 mmol), allylamine (2.05 g, 36 mmol), and $K_2CO_3$ (1.49 g, 10.8 mmol) were stirred in acetonitrile (25 mL) at 70 °C for 18 h. Then brine (100 mL) was added and the solution was extracted with MTBE (3 × 50 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo, and the residue was purified by flash-chromatography (silica, cyclohexane/MTBE 1:1 (2% $Et_2NH$)), giving **12** as a pale yellow oil (3.23 g, 86% yield). $R_f$ = 0.50 (cyclohexane/MTBE/$Et_2NH$ 10:10:1). $^1$H NMR (200 MHz): $\delta$ 8.28−8.36 (m, 2H), 7.96−8.05 (m, 2H), 5.68−6.02 (m, 3H), 5.08−5.39 (m, 5H), 4.83−4.97 (m, 1H), 4.08−4.24 (m, 1H), 3.87−4.03 (m, 1H), 3.62−3.77 (m, 1H), 3.24−3.40 (m, 3H), 2.00−2.20 (m, 2H), 1.64−1.92 (m, 1H), 0.90 (s, 9H), 0.04 (s, 6H). $^{13}$C NMR (125 MHz): $\delta$ 149.87, 147.20, 138.06, 136.47, 134.98, 132.06, 128.44, 124.33, 118.34, 116.30, 66.54, 54.13, 52.19, 49.52, 47.85, 42.47, 42.07, 25.85, 18.05, −4.75, − 4.65. IR: $\nu$ 3335, 3104, 3081, 1723, 1531, 1349, 1255, 1165, 836, 735 cm$^{-1}$. MS *m*/*z* (%) 522 (16), 407 (16), 203 (52), 73 (100). HR-MS calcd for $C_{25}H_{40}N_3O_5SSi$ 522.2458 $[MH]^+$, obsd 522.2455. $[\alpha]^{20}_D$ = −41° (*c* 0.60, $CHCl_3$). Anal. Calcd for $C_{25}H_{39}N_3O_5SSi$: C, 57.58; H, 7.49; N, 8.06. Found: C, 58.56; H, 7.08; N, 7.56.

**Dicarbamate 13**. Diamine **12** (2.20 g, 4.22 mmol) and $K_2CO_3$ (2.91 g, 21.1 mmol) were suspended in DMF (15 mL). PhSH (930 mg, 8.22 mmol) was added and the suspension was stirred at 70 °C for 30 min. The mixture was then cooled to 0 °C and ethylchloroformate (1.37 g, 12.6 mmol) was added dropwise under stirring over 25 min. The mixture was stirred for 30 min at 0 °C and then for 2 h at room temperature. The mixture was poured into water (150 mL) and extracted with MTBE (50 mL). The aqueous phase was saturated with NaCl and extracted with MTBE (2 × 50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (silica, cyclohexane/MTBE 5:1 to 3:1) yielded dicarbamate **13** as light yellow oil (1.66 g, 82% yield). $R_f$ = 0.32 (cyclohexane/MTBE 3:1). $^1$H NMR (200 MHz): (rotameric mixture) $\delta$ 5.64−5.88 (m, 2H), 5.38−5.62 (m, 2H), 4.94−5.18 (m, 4H), 4.28−4.84 (m, 2H), 3.96−4.20 (m, 5H), 3.51−3.92 (m, 4H), 2.08−2.40 (m, 1H), 1.82−2.02 (m, 2H), 1.64−1.80 (m, 1H), 1.19 (t, *J* = 7 Hz, 3H), 1.18 (t, *J* = 7 Hz, 3H), 0.80 (s, 9H), −0.04 (s, 6H). $^{13}$C NMR (50 MHz): (rotameric mixture) $\delta$ 155.61, 135.91, 135.27, 134.85, 133.27, 115.94, 116.18, 66.18, 61.09, 60.93, 51.85, 51.08, 48.00, 46.12, 42.07, 25.53, 17.74, 14.42, −5.08, −4.93. IR: $\nu$ 3081, 1699, 1411, 1250, 837, 774 cm$^{-1}$. MS *m*/*z* (%) 480 (5), 423 (85), 294 (44), 186 (100). HR-MS calcd for $C_{25}H_{44}N_2O_5Si$ 480.3020, obsd 480.3023. $[\alpha]^{20}_D$ = −56.3° (*c* 0.70, $CHCl_3$). Anal. Calcd for $C_{25}H_{44}N_2O_5Si$: C, 62.50; H, 9.17; N, 5.83. Found: C, 62.54; H, 9.18; N, 5.95.

(10) Prepared according to Beckwith, A. L. J.; Meijs, G. F. *J. Org. Chem.* **1987**, *52*, 1922.

(11) Prepared according to Lee, C.-W.; Oh, K. S.; Kim, K. S.; Ahn, K. H. *Org. Lett.* **2000**, *2*, 1213.

**Bispyrrolidine Dicarbamate 14**. Dicarbamate **13** (1.61 g, 3.35 mmol) and [**Ru**] (140 mg, 0.17 mmol, 5 mol %) were refluxed under $N_2$ (Glovebox) in absolute $CH_2Cl_2$ (100 mL) for 36 h. The solution was concentrated in vacuo, and the residue was dissolved in MeOH (50 mL). Pd on charcoal (10%) was added and the suspension was stirred under $H_2$ at room temperature overnight. The catalyst was then filtered off, the filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (silica, cyclohexane/MTBE 1:1) to afford **14** as light brown oil (1.10 g, 72% yield). $R_f$ = 0.27 (cyclohexane/MTBE 1:1). $^1$H NMR (200 MHz): $\delta$ 3.92−4.16 (q, $J$ = 7 Hz, 5H), 3.50−3.83 (m, 2H), 3.18−3.42 (m, 4H), 1.74−2.12 (m, 12H), 1.19, 1.20 (2 t, $J$ = 7 Hz, 6H), 0.84 (br s, 9H), 0.00, 0.01 (2 s, 6H). $^{13}$C NMR (50 MHz): $\delta$ 154.90, 68.66, 60.53, 55.23, 54.00, 49.97, 49.12, 42.02, 40.00, 30.79, 30.21, 25.71, 23.62, 22.84, 17.81, 14.69, −4.37, −4.76. IR: $\nu$ 1698, 1415, 1379, 1109, 836, 772 cm$^{-1}$. MS $m/z$ (%) 441 (2), 399 (35), 142 (100). HR-MS calcd for $C_{22}H_{41}N_2O_5Si$ 441.2785, obsd 441.2782. $[\alpha]^{20}_D$ = +48.0° ($c$ 0.74, $CHCl_3$). Anal. Calcd for $C_{23}H_{44}N_2O_5Si$: C, 60.53; H, 9.65; N, 6.14. Found: C, 60.58; H, 9.48; N, 6.30.

**Dimethyl Bispyrrolidine 15**. $LiAlH_4$ (420 mg, 11 mmol) was suspended under $N_2$ in absolute diethyl ether (30 mL). To this suspension was added **14** (1.25 g, 2.74 mmol) in absolute diethyl ether (5 mL) dropwise at 0 °C. The mixture was stirred for 45 min at room temperature. The excess of $LiAlH_4$ was quenched with ethyl acetate (5 mL) at 0 °C. 50% KOH solution was added to precipitate the aluminum salts, which were filtered off. The filtrate was concentrated in vacuo, giving **15** as a colorless oil (857 mg, 92%). $R_f$ = 0.64 (cyclohexane/$CHCl_3$/$Et_2NH$ 5:4:1). $^1$H NMR (200 MHz): $\delta$ 3.60−3.74 (m, 1H), 3.00−3.22 (m, 2H), 2.35, 2.30 (2 s, 6H), 1.60−2.25 (m, 12H), 1.34−1.56 (m, 4H), 0.87 (s, 9H), 0.04 (s, 3H), 0.06 (s, 3H). $^{13}$C NMR (50 MHz): $\delta$ 69.07, 63.06, 63.12, 56.70, 56.92, 42.77, 40.89, 40.15, 30.88, 30.93, 25.81, 21.75, 21.95, 17.93, −3.91, −4.78. IR: $\nu$ 1472, 1462, 1255, 836, 773 cm$^{-1}$. MS $m/z$ (%) 340 (<1), 240 (9), 84 (100). HR-MS calcd for $C_{19}H_{40}N_2OSi$ 340.2910 $[M]^+$, obsd 340.2911. $[\alpha]^{20}_D$ = +115° ($c$ 1.54, $CHCl_3$). Anal. Calcd for $C_{19}H_{40}N_2OSi$: C, 67.06; H, 11.76; N, 8.24. Found: C, 66.66; H, 11.45; N, 8.10.

**Dihydrocuscohygrine 1**. TBS-ether **15** (550 mg, 1.62 mmol) was stirred in EtOH/concentrated HCl (2:1, 10 mL) overnight. The solution was diluted with water (60 mL) and washed with MTBE (3 × 10 mL). Then the aqueous solution was brought to pH 14 with 30% NaOH and extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated in vacuo to give **1** as colorless oil (326 mg, 89% yield). $R_f$ = 0.43 (cyclohexane/$CHCl_3$/$Et_2NH$ 5:4:1). $^1$H NMR (200 MHz): $\delta$ 6.70 (br s, 1H), 3.92−4.07 (m, 1H), 2.96−3.12 (m, 2H), 2.48−2.62 (m, 1H), 2.26−2.42 (m, 1H), 2.31, 2.30 (2 s, 2 · 3H), 1.57−2.23 (m, 11H), 1.32−1.54 (m, 2H), 1.08−1.25 (m, 1H). $^{13}$C NMR (50 MHz): $\delta$ 66.99, 64.64, 63.10, 56.95, 56.84, 42.30, 40.54, 40.51, 36.59, 30.71, 28.45, 23.27, 21.84. IR: $\nu$ 3228, 1455, 1036, 903, 824 cm$^{-1}$. MS $m/z$ (%) 226 (12), 211 (7), 84 (100). HR-MS calcd for $C_{13}H_{26}N_2O$ 226.2045, obsd 226.2045. $[\alpha]^{20}_D$ = +105° ($c$ 2.05, acetone), lit.[3] $[\alpha]^{20}_D$ = −68° ($c$ 2.5, acetone). Anal. Calcd for $C_{13}H_{26}N_2O \cdot H_2O$: C, 63.93; H, 11.48; N, 11.48. Found: C, 64.11; H, 11.71; N, 11.16.

**Racemic Cuscohygrine 2**. To a stirred solution of (*R*,*R*)-Dihydrocuscohygrine **1** (30 mg, 0.13 mmol) in acetone (1 mL) was added Jones' reagent (0.2 mL, 1.8 M) at 0 °C. After 2 h the solution was cooled to 0 °C and ice-cold saturated $NaHSO_3$ solution (1 mL) was added. The solution was brought to pH 13 with ice-cold 5 N KOH. Then the solution was immediately extracted with precooled $CHCl_3$ (3 × 5 mL), and the combined organic layers were washed with cold brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure at room temperature gave **rac-2** as a colorless oil (22 mg, 73% yield). The product was immediately characterized. $R_f$ = 0.27 (cyclohexane/$CHCl_3$/$Et_2NH$ 5:4:1). $^1$H NMR (200 MHz): (diastereomeric mixture) $\delta$ 3.07−3.21 (m, 2H), 2.82−2.97 (m, 2H), 2.45−2.79 (m, 4H), 2.37 (s, 6H), 2.18−2.35 (m, 2H), 2.00−2.14 (m, 2H), 1.67−1.90 (m, 4H), 1.36−1.57 (m, 2H). $^{13}$C NMR (50 MHz): (diastereomeric mixture) $\delta$ 209.13, 209.00, 61.56, 61.45, 56.59, 48.28, 48.21, 40.34, 40.31, 31.15, 21.94. IR: $\nu$ 3234, 1710, 1456, 909 cm$^{-1}$. MS $m/z$ (%) 209 (2), 140 (8), 98 (7), 84 (100). HR-MS calcd for $C_{12}H_{21}N_2O$ 209.1654 $[M - CH_3]^+$, obsd 209.1654. Anal. Calcd for $C_{13}H_{24}N_2O \cdot 0.5\ H_2O$: C, 69.64; H, 10.71; N, 12.50. Found: C, 68.66; H, 11.03; N, 12.31.

**Cuscohygrine Dihydrochloride**. To a stirred solution of (*R*,*R*)-Dihydrocuscohygrine **1** (30 mg, 0.13 mmol) in acetone (1 mL) was added Jones' reagent (0.2 mL, 1.8 M) at 0 °C. After 2 h the solution was cooled to 0 °C and ice-cold saturated $NaHSO_3$ solution (1 mL) was added. The solution was brought to pH 13 with ice-cold 5 N KOH. Then the solution was immediately extracted with $CHCl_3$ (3 × 5 mL), and the combined organic layers were washed with cold brine and dried over $MgSO_4$. HCl gas (50 mL, dried over $H_2SO_4$) was bubbled through the solution at 0 °C. Evaporation of the solvent under reduced pressure at room temperature gave the dihydrochloride as a colorless solid (32 mg, 81% yield). $^1$H NMR (200 MHz, $CDCl_3$): (diastereomeric mixture) $\delta$ 3.70−3.84 (m, 2H), 3.60−3.68 (m, 2H), 3.20−3.34 (m, 2H), 2.97−3.18 (m, 4H), 2.94 (s, 3H), 2.93 (s, 3H), 2.36−2.47 (m, 2H), 1.98−2.18 (m, 4H), 1.73−1.85 (m, 2H). $^{13}$C NMR (50 MHz, $CDCl_3$): (diastereomeric mixture) $\delta$ 205.47, 64.52, 56.21, 55.96, 43.13, 43.06, 40.22, 29.55, 21.80. IR: $\nu$ 3414, 3234, 1722, 971, 864 cm$^{-1}$. MS $m/z$ (%) 209 (1), 140 (11), 98 (6), 84 (100). HR-MS calcd for $C_{12}H_{21}N_2O$ 209.1654 $[M - CH_3]^+$, obsd 209.1657. Anal. Calcd for $C_{13}H_{26}Cl_2N_2O \cdot 0.5\ H_2O$: C, 50.98; H, 8.82; N, 9.15. Found: C, 50.67; H, 8.79; N, 9.02.

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