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Asymmetric synthesis of *erythro*- and *threo*-2-(1-hydroxyalkyl)piperidines via iodocyclocarbamation of 1-acyl-2-alkenyl-1,2,3,6-tetrahydropyridines

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Abstract

An iodocyclocarbamation procedure has been developed for the stereoselective preparation of *erythro*- and *threo*-2-(1-hydroxyalkyl)piperidines. This methodology was utilized in the asymmetric synthesis of two piperidine alkaloids, (+)-α-conhydrine and (+)-β-conhydrine.

Keywords: asymmetric synthesis; pyridinium salts; dihydropyridones; alkaloids; iodocyclocarbamation.

Biologically active alkaloids containing a 2-(1-hydroxyalkyl)piperidine unit **1** are abundant in nature.[1] The indolizidine alkaloids castanospermine **2**, slaframine **3**, and swainsonine **4** fall into this category and have attracted considerable attention from the synthetic community due to their antiviral and antitumor activities.[2] As part of a program directed at exploring the scope of *N*-acyldihydropyridones as chiral building blocks,[3] strategies for the stereocontrolled preparation of substituted piperidines of the type **1** were investigated. For initial development of an appropriate methodology, the well-characterized piperidine alkaloids β-conhydrine **5** and α-conhydrine **6** were chosen as targets.

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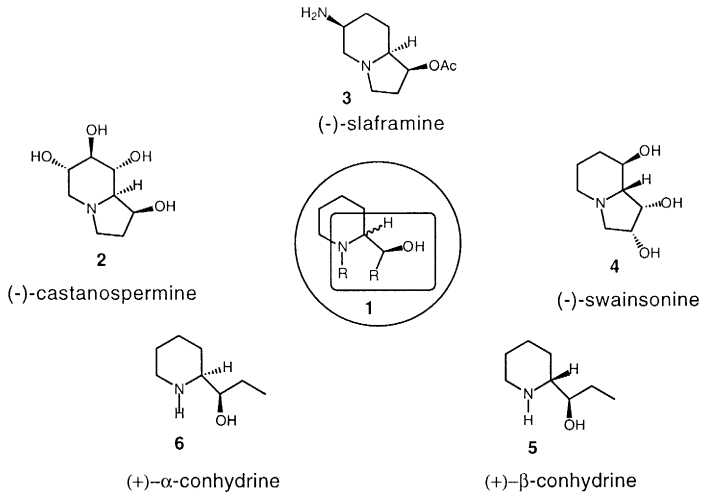
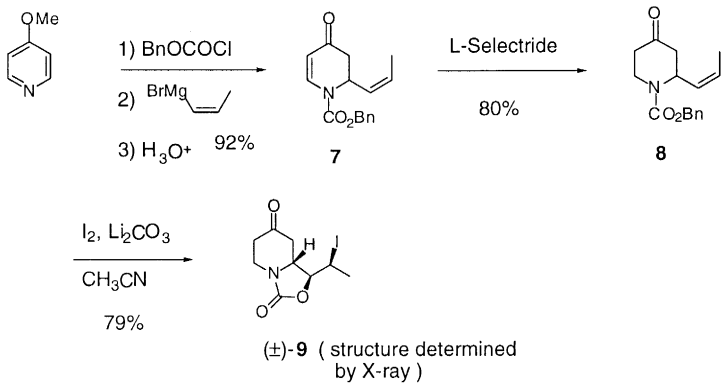


The iodocyclocarbamation reaction[4] was investigated as a method to regio- and stereoselectively introduce the required oxygen–carbon bond on the C-2 side chain of an appropriate piperidine derivative. To examine the feasibility of this approach, a racemic substrate was prepared (Scheme 1).

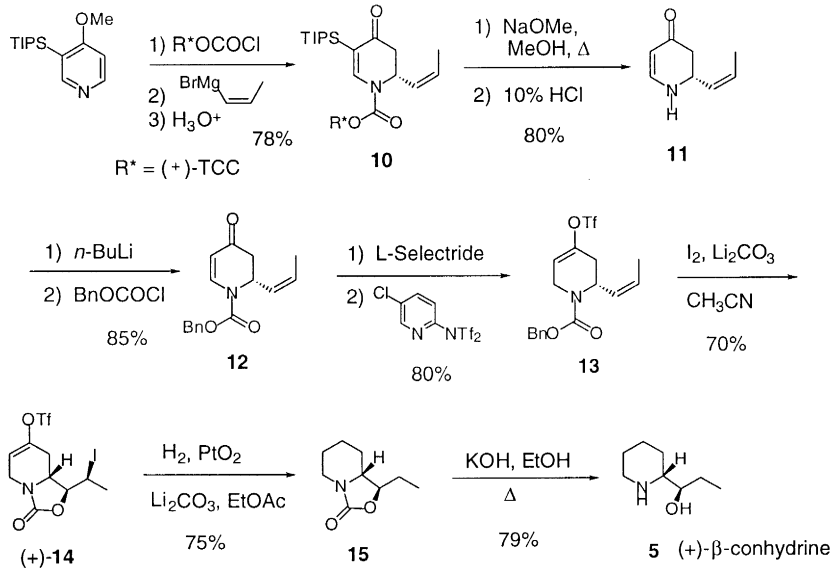


Scheme 1.

The Grignard reagent prepared from *cis*-bromopropene was added to 4-methoxypyridine and benzyl chloroformate in THF at −78°C to provide dihydropyridone **7** in high yield.[5] Conjugate reduction with L-Selectride (1 equiv., THF, −78°C, 1 h) gave piperidinone **8**, which was subjected to conditions for iodocyclocarbamation. Anhydrous iodine (1.5 equiv.) and lithium carbonate (5 equiv.) were added to **8** in acetonitrile (0°C, 7 h). After workup and purification, the cyclic carbamate **9** was isolated as a white solid in 79% yield. The relative stereochemistry of **9** was confirmed by single crystal X-ray analysis.

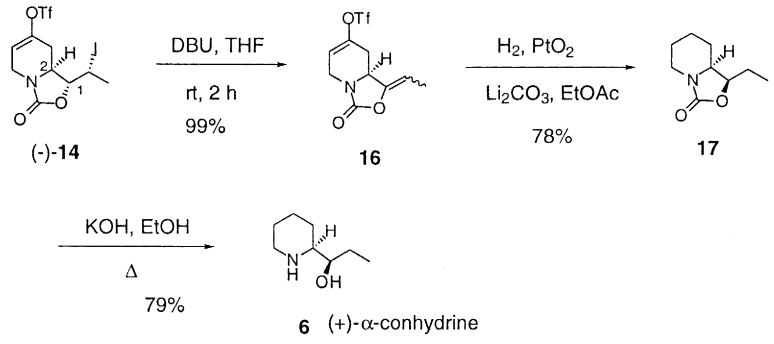
The relative stereochemistry obtained in the formation of **9** corresponds to that required for β-conhydrine **5**. Based on these results, an asymmetric synthesis of **5** was accomplished as shown in Scheme 2. A THF solution of *cis*-propenylmagnesium bromide was added to a mixture of 4-methoxy-3-(triisopropylsilyl)pyridine[6] and the chloroformate of (+)-TCC[7] to give *N*-acyldihydropyridone **10** in 78% yield. Analysis of the crude product revealed that the reaction proceeded in 91% de. One-pot removal of the chiral auxiliary and TIPS group gave enantiopure dihydropyridone **11** in 80% yield along with 94% recovery of the chiral auxiliary, (+)-TCC. Treatment of **11** with *n*-BuLi and benzyl chloroformate provided the intermediate **12**. Conjugate reduction of **12** with L-Selectride followed by addition of *N*-(5-chloro-2-pyridyl)triflimide[8] afforded vinyl triflate **13**, which was subjected to the

iodocyclocabamation reaction conditions used in the preparation of **9**. The crude reaction product (≥97% de) was purified by radial PLC (SiO_2, EtOAc/hexanes) to give a 70% yield of cyclic carbamate (+)-**14**. Catalytic hydrogenation in the presence of PtO_2 reduced **14** to oxazolidinone **15** in 75% yield. Hydrolysis of **15** with KOH afforded a 75% yield of (+)-β-conhydrine **5** ($[\alpha]_D^{28}$ +8.0 (*c* 0.85, EtOH); lit.[9] $[\alpha]_D^{20}$ +8.6 (*c* 1.0, EtOH)). The ^1H and ^{13}C NMR data of **5** were in agreement with literature values.[10,11]



Scheme 2.

A route to α-conhydrine **6** from the antipode of (+)-**14** was investigated. The absolute stereochemistry at the C-2 stereocenter of α-conhydrine is opposite to that found in β-conhydrine, so (−)-TCC was used to prepare (−)-**14**. In order for (−)-**14** to be converted to α-conhydrine, the stereocenter at C-1 needed to be inverted. We were successful in finding a concise solution to this problem as shown in Scheme 3. Dehydrohalogenation of **14** was carried out with DBU in THF to afford a 99% yield of enol carbamate **16**. Catalytic hydrogenation of **16** occurs from the convex face (22:1) to give the desired oxazolidinone **17**,[10] which was hydrolyzed with base to afford (+)-α-conhydrine **6** ($[\alpha]_D^{28}$ + 9.0 (*c* 0.85, EtOH); lit.[10] $[\alpha]_D^{20}$ + 8.9 (EtOH)). Our synthetic material exhibited spectral data in agreement with literature values.[12,13]



Scheme 3.

In conclusion, a synthetic route has been developed for the preparation of both *erythro*- and *threo*-2-(1-hydroxyalkyl)piperidine derivatives. This methodology was applied to the asymmetric synthe-

sis of (+)-α-conhydrine and (+)-β-conhydrine in overall yields of 18 and 17%, respectively.[14] The strategy should be amenable to the enantioselective synthesis of other alkaloids containing the 2-(1-hydroxyalkyl)piperidine subunit.

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11. (+)-β-Conhydrine **5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.24–3.18 (dt, 1H, J=3.4, 7.9 Hz), 3.08 (d, 1H, J=12.0 Hz), 2.64–2.55 (dt, 1H, J=2.8, 11.9 Hz), 2.41–2.34 (m, 1H), 1.81–1.12 (m, 10H), 0.98 (t, 3H, J=7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.4, 61.1, 46.6, 29.1, 26.4, 24.5, 10.2.
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13. (+)-α-Conhydrine **6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75–3.60 (m, 2H), 3.50 (br s, 1H), 2.03 (br s, 1H), 1.55–1.05 (m, 9H), 0.92–0.85 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.5, 54.5, 44.0, 26.9, 25.8, 24.3, 10.5.
14. The structure assigned to each new compound is in accord with its IR and ^{1}H and ^{13}C NMR spectra and elemental analysis or high-resolution mass spectra.