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Enantioselective syntheses of both enantiomers of *cis*-pyrrolidine 225H

Hong Shu, April R. Noble, Suhong Zhang, Lei Miao, Mark L. Trudell *

Department of Chemistry, University of New Orleans, New Orleans, LA 70148, USA

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ABSTRACT

The efficient and expeditious syntheses of both enantiomers of the amphibian alkaloid *cis*-225H have been achieved. Utilizing a common *cis*-2,5-disubstituted pyrrolidine building block derived from (+)-2-tropinone, the enantioselective syntheses have established the absolute configuration of these alkaloids as (+)-(2*R*,5*S*) and (−)-(5*S*,2*R*).

1. Introduction

Alkaloids isolated from amphibian skin extracts are represented by over 20 structural classes with over 800 unique compounds identified as of 2005.[1] The amphibian alkaloids have provided valuable leads toward the development of new therapeutic agents and have been attractive targets for synthesis.[2] The unsymmetrical 2,5-disubstituted pyrrolidine alkaloids (**1**) are a unique class of alkaloids in that these simple monocyclic amines have been isolated from two very distinct sources.[1] Initially, the 2,5-disubstituted pyrrolidine alkaloids were isolated from the venom of several ant species and thought to serve as a chemical defense mechanism against predators.[3] More recently, the 2,5-disubstitited pyrrolidine alkaloids have been found in the skin extracts of various neotropical amphibian species.[4] With few exceptions, the 2,5-disubstituted pyrrolidine alkaloids are rare in amphibian species and when present are only obtained in trace amounts. However, the 2,5-disubstituted pyrrolidine alkaloid 197B (**2**) was found to be the major alkaloid in the skin extracts of one population of Columbian frog (*Dendrobates histrionicus*).[4] The source of these anuran alkaloids has been presumed to be dietary[3d], although feeding studies have shown that pyrrolidine alkaloids are not readily accumulated in amphibian skin.[5] This suggests that a rather remarkable ecological and perhaps evolutionary relationship exists between ant and frog species living in neotropical environments (Fig. 1).

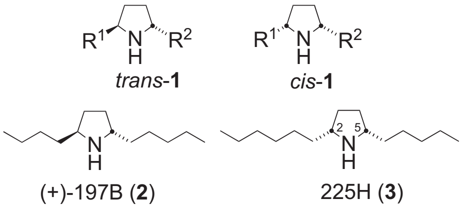

Figure 1. Pyrrolidine Alkaloids.

Among, the 2,5-disubstituted pyrrolidine alkaloids that have been isolated, the trans-isomers (e.g., **2**) have been shown to be exclusively found in ant extacts[3] and predominate over the cis-isomers in anuran extracts.[1,4] As such the *trans*-2,5-disubstituted pyrrolidine alkaloids have been the subject of numerous studies, ranging from the development of synthetic methods[6] and total synthesis[7] to pharmacological evaluation.[2] However, due to the paucity of the cis-isomers (e.g., 225H, **3**), these alkaloids have not been fully characterized and the absolute configurations of these molecules are unknown.[1] In addition, these alkaloids have not received much attention from the synthetic community.[8] As part of program aimed at CNS drug discovery based upon novel molecular scaffolds it was of interest to develop an enantioselective synthetic approach that would allow for the unequivocal determination of the absolute configuration of both enantiomers of the 2,5-disubstituted pyrrolidine alkaloid *cis*-225H **3** and *ent*-**3**. Herein we describe the synthesis of both enantiomers of *cis*-225H from a common intermediate.

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* Corresonding author. E-mail address: mtrudell@uno.edu (M.L. Trudell).

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2. Results and discussion

Previous work in our laboratory has shown that the pyrrolidine derivative **4**, was a useful chiral building block for the construction of amphibian alkaloid skeletons containing a *cis*-pyrrolidine subunit.[9] The orthogonal reactivity of the side chain functional groups and the nitrogen atom protecting group of **4** offered easy access to more complicated ring systems. In addition, we had shown previously that the *S*-configuration at C5 of **4** was inert to a wide variety of functional group transformations and could be exploited without worry of epimerization. Readily prepared from (+)-(1*R*)-2-tropinone (**5**)[10], the versatility of **4** for enantioselective synthesis seemed well suited for the preparation of both enantiomers of *cis*-225H (**3** and *ent*-**3**, Fig. 2).

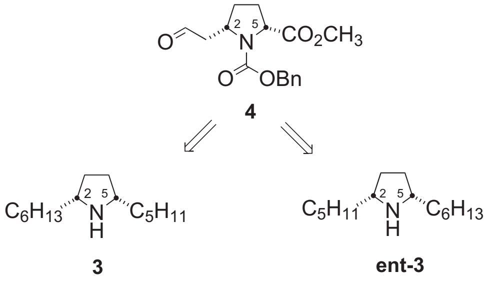
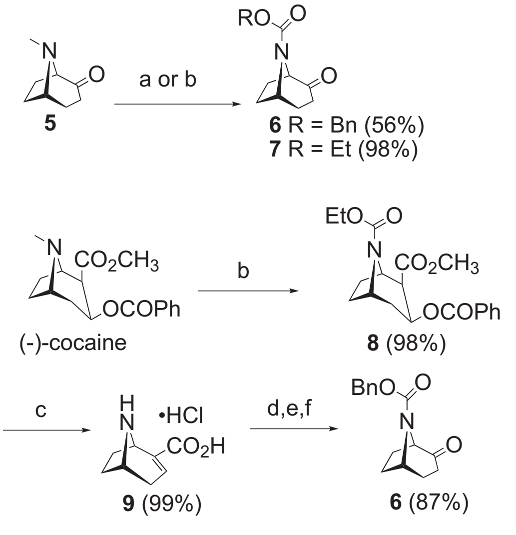


Figure 2. Retrosynthetic approach.

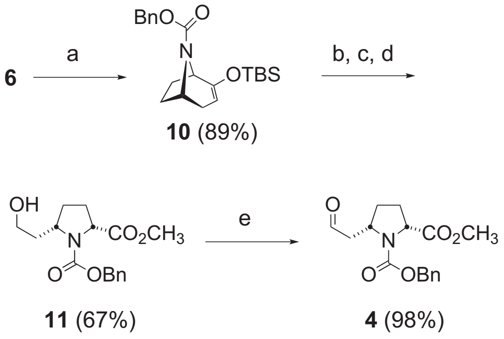
Starting from (+)-2-tropinone (**5**) it was our intent to prepare **4** by direct demethylation/acylation with benzyl chloroformate (CbzCl) followed by subsequent conversion into the *cis*-pyrrolidine derivative. The (+)-tropinone **5** was readily obtained from (−)-cocaine[10] or via resolution of (±)-2-tropinone with L-tartaric acid.[11] As we had previously shown, the direct demethylation/acylation of **5** only gave a modest yield (56%) of the desired Cbz-2-tropinone **6**.[9] This was disappointing since the corresponding ethyl carbamate **7**, could be obtained in 98% yield employing ethyl chloroformate under similar conditions (Scheme 1). Although **7** was a viable starting point, the ethyl carbamate would not provide the overall efficiency that was desired, due to deprotection chemistry that would be required late in the synthetic sequence.



Scheme 1. Reagents and conditions: (a) CbzCl, K_2CO_3, toluene, reflux. (b) EtOCOCl, K_2CO_3, toluene, reflux. (c) 12 N HCl, reflux. (d) DMAP, $(PhO)_2PON_3$, Na_2CO_3, CH_2Cl_2. (e) 1 N HCl, reflux. (f) CbzCl, Na_2CO_3, CH_3OH/H_2O.

Since the demethylation step was clearly problematic with CbzCl, we elected to explore an alternative route to **6**. We envisaged that a separate demethylation step prior to introduction of the Cbz-group would give higher overall yields of **6**. In the revised synthetic route (Scheme 1), demethylation was attempted first. Treatment of confiscated grade cocaine[12] with ethyl chloroformate provided **8** in 98% yield. Subsequent hydrolysis and concomitant dehydration of **8** in concentrated HCl at reflux for 12 h afforded noranhydroecognine·HCl (**9**) in quantitative yield. The carboxylic acid moiety of **9** was then reacted with diphenylphosphoryl azide catalyzed by 4-dimethylaminopyridine in dichloromethane giving the intermediate acyl azide, which then underwent a Curtius rearrangement in 1 N HCl at reflux. The crude mixture was treated with CbzCl to furnish **6** in 84% overall yield. The yield of this one-pot three-step heterogeneous reaction was closely related to the dryness of the intermediate **9**. Thoroughly drying the acid **9** and grinding it into a fine powder was found to greatly facilitate the formation of the acyl azide and as a result led to a higher overall yield of the Cbz-2-tropinone **6**.

With **6** in hand, our attention was focused on the preparation of pyrrolidine **4**. The tropinone **6** was treated with a THF solution of NaH followed by the addition of TBSCl to furnish silyl enol ether **10** in 89% yield. Compared with the methyl enol ether employed in earlier studies,[9] the silyl enol ether was more stable toward chromatography and was readily purified prior to the ozonolysis step. Ozone was slowly bubbled through a solution of enol ether **10** in dichloromethane/methanol (9:1) at −78 °C. Treatment of the intermediate ozonide with sodium borohydride followed by addition of diazomethane (from Diazald®) furnished the pyrrolidine **11**, in 67% yield over the three steps. Subsequent Swern oxidation of **11** provided the *cis*-pyrrolidine **4** in 98% yield (Scheme 2).



Scheme 2. Reagents and conditions: (a) TBSCl, NaH, THF, 0 °C. (b) O_3, CH_2Cl_2/CH_3OH, −78 °C. (c) $NaBH_4$, 0 °C. (d) CH_2N_2, Et_2O, 0 °C. (e) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N.

The conversion of the intermediate ozonide to the alcohol derivative **11** and subsequent oxidation to **4** was preferable to the direct conversion of **10** into the aldehyde moiety (e.g., using dimethylsufide or triphenylphosphine to reduce the ozonide). This indirect method gave more reliable yields and furnished **4** with fewer byproducts and impurities. This revised synthetic route gave the pyrrolidine building block **4** in a 49% overall yield from (−)-cocaine and was a significant improvement over our previous method.[9]

The pyrrolidine **4** existed as a mixture (3:1) of conformational isomers due to hindered rotation about the N–Cbz bond (rotamers). Since the presence of rotamers significantly complicated the NMR spectrum it was practical to advance subsequent intermediates to a point where the conformational isomers did not contribute to the complexity of the molecule before a meaningful structural characterization was made.