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An alternative synthesis and x-ray crystallographic confirmation of (–)-stepholidine

Satishkumar V Gadhiya^{a,b}, Chunhua Hu^c, and Wayne W Harding^{a,b,d}

^aDepartment of Chemistry, Hunter College, City University of New York, 695 Park Avenue, New York 10065, USA

^bPh.D. Program in Chemistry, The Graduate Center of The City University of New York, 365 5th Avenue, New York 10016, USA

^cMolecular Design Institute, Department of Chemistry, New York University, 100 Washington Square, New York 10003, USA

^dPh.D. Program in Biochemistry, The Graduate Center of The City University of New York, 365 5th Avenue, New York 10016, USA

Abstract

A formal enantioselective synthesis of (–)-stepholidine that provides an alternative preparation of key lactone intermediate **2** is described. The stereostructure of (–)-stepholidine prepared via this method was confirmed by x-ray diffraction.

Graphical abstract

Keywords

Stepholidine; THPB; Tetrahydroprotoberberine; Dopamine; X-ray crystallography

Tetrahydroprotoberberine (THPB) alkaloids are an important class of biologically active compounds. Several THPBs have been reported to possess strong affinity for dopamine receptors.^{1,2} Dopamine receptor ligands are sought after as biological tools and as potential

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Supplementary Material

Description of syntheses and NMR spectral data for all new compounds.

therapeutics for a range of neuropsychiatric disorders. Hence, the pharmacological potential of THPBs has attracted the attention of synthetic and medicinal chemists for decades.

The naturally-occurring THPB (–)-stepholidine (**1**), possesses a remarkable pharmacological profile in having dopaminergic D1 agonist/D2 antagonist dual activity. This extremely rare profile is promising as a new therapeutic strategy to treat schizophrenia and psychostimulant abuse.^{3–7}

A common method to synthesize THPBs is via Mannich cyclization of a 1-benzyltetrahydroisoquinoline intermediate (usually formed via Bischler-Napieralski or Pictet-Spengler reactions), thus forming ring C at a late stage in the synthesis. However, this approach fails to afford high yields in the synthesis of THPBs that have a 9,10 dioxxygenated substitution pattern, as displayed by **1**.^{8–11} One approach to solve this issue is to use a sulfinyl or trimethylsilyl group to direct cyclization in *ipso* fashion.^{12,13}

An alternative approach to the synthesis of 9,10-dioxxygenated aporphines involves the use of a suitable tetra-substituted phenyl intermediate, in which the phenyl ring later becomes ring D of the THPB core. The degree of success of this approach hinges on an efficient preparation of this tetra-substituted intermediate as well as its subsequent transformation to **1**. Yang et al utilized the lactone **2** (Figure 2) - prepared via a phenylacetic acid precursor for this purpose, in the first enantioselective synthesis of **1**.¹⁴ However, preparation of **2** was deemed inefficient and a bottleneck in the synthesis. Later the same group utilized the *o*-tolunitrile intermediate **3** to provide the ring D motif via reaction of the lithiated derivative of **3** with a chiral sulfinimine.¹⁵ The yield for this key step was quite low due to problematic self-condensation. In a third approach, the bromoacid **4** was used as the key tetra-substituted intermediate.¹⁶ In this case the preparation of acid **4** and its eventual transformation to **1** (though straightforward) required several synthetic steps.

Of the three methods to prepare **1** described above, the first synthesis is particularly attractive based on the length of the synthesis and ease of synthesis in general. Since the major obstacle in this synthesis was the formation of **2**, we considered alternative approaches to intercept this key intermediate in the synthesis. In this manuscript we report an alternative preparation of **2** as a key intermediate in Yang's synthesis of **1**. In addition, we have confirmed the structure of **1** prepared by this method via x-ray crystallography.

As depicted in Scheme 1, our synthesis of **2** commenced with compound **5** (which is easily obtained by protecting commercially available 4-bromoguaiacol with ethoxymethyl ether). Regioselective reaction of the intermediate benzyne derived from **5** with malonate anion at –78 °C afforded diester **6** in 56% yield.¹⁷ The ethoxymethyl group of **6** was exchanged for a benzyl protecting group in two high yielding steps. Here, **6** was refluxed in acidic methanol to effect deprotection of the ethoxymethyl group and this was followed by protection of resulting phenol as the benzyl ether to give **7**. Global hydrolysis of the ester functionalities of **7** and subsequent selective esterification of the aliphatic acid functionality, generated acid **8**. The acid **8** was converted to an intermediate activated ester via reaction with EDC/HOBt. This ester group was selectively reduced with NaBH₄ to provide an alcohol which was then cyclized to the lactone **2**. We also effected cyclization of **8** to **2** by selective reduction of the

carboxylic acid group of **8** with BH_3 , followed by lactonization with $p\text{-TsOH}$.¹⁸ However, despite the fact that this process was one step shorter, we found that the yield for the conversion was lower (65% for transformation of **8** to **2**), than the previously described activated ester method.

Thereafter the route developed by Yang was implemented to prepare **1**. The spectral data of **1** were in accordance with previously reported values.¹⁴

The key enantioselective reaction in the synthesis of **1** involves reduction of a dihydroisoquinoline intermediate to generate a chiral tetrahydroisoquinoline. As was previously reported, the determination of ee at this stage is difficult via chiral HPLC; ee was determined as 99.6% after the final step in the synthesis (removal of the benzyl groups under acidic conditions to give **1**). Chiral HPLC, though a very powerful tool, can be unreliable in structure/enantiopurity determination. Thus, to provide unequivocal stereostructural proof, we determined the 3-dimensional structure of **1** by single crystal X-ray diffraction. Figure 3 shows a representation of the x-ray structure, in which a water molecule co-crystallizes with **1**. The structure compares favorably with a previously reported crystal structure of **1**, isolated from the Chinese medicinal herb, *Stephania intermedia*.^{19, 20} This confirms the molecular structure of **1** and also validates the success of the method.

In conclusion, the synthesis of **1** was accomplished in 23% overall yield from compound **5** in a fourteen step sequence. This is comparable to Yang's first synthesis where a 24% yield of **1** was obtained in eleven steps (from a 4-benzyloxy-3-hydroxy phenylacetic acid precursor).¹⁴ This, route involves an alternative, reliable preparation of the vital intermediate compound **2**. The synthetic manipulations to afford **2** are straightforward, scalable and generally high yielding, (save for the moderately yielding first step; conversion of **5** to **6**). This synthetic pathway should be applicable to the generation of chiral analogues of **1** for bioactivity studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- A new synthesis of a key lactone intermediate required for the synthesis of (–)-stepholidine (1) was achieved
- (–)-Stepholidine was prepared in 23% overall yield in a fourteen-step synthetic sequence
- The stereostructure of (–)-stepholidine prepared by this method was confirmed by single crystal x-ray diffraction

Figure 1.
Structure of (-)-stepholidine (**1**)

Figure 2.
Structures of key intermediates **2**, **3** and **4**

Figure 3.
Crystal structure of (–)-stepholidine monohydrate ($1 \cdot \text{H}_2\text{O}$)

Scheme 1. Synthesis of key intermediate 2 and transformation to (-) stepholidine (1)

Reagents and conditions: a) Diisopropylamine, *n*-BuLi, dimethyl malonate, THF, -78 °C, 56%; b) i) Conc. HCl, MeOH, reflux; ii) K₂CO₃, Benzyl bromide, CH₃CN, reflux; 100%; c) i) 10% NaOH, EtOH, reflux; ii) SOCl₂, MeOH, rt, 98%; d) i) EDC, HOBT, DCM; ii) NaBH₄, THF, H₂O; iii) *p*-TsOH, CH₃CN, 81%;