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Formal syntheses of (−)- and (+)-aphanorphine from (2*S*,4*R*)-4-hydroxyproline

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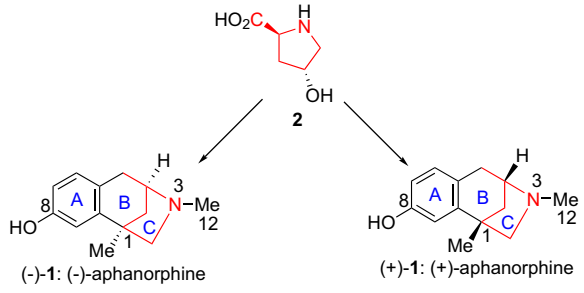
Abstract—We describe the efficient formal syntheses of both natural (−)-aphanorphine and unnatural (+)-aphanorphine from the same commercially available amino acid, (2*S*,4*R*)-4-hydroxyproline. The tricyclic framework was constructed by intramolecular Friedel–Crafts reaction. (1*R*,4*S*)-1-Methyl-8-methoxy-3-(4-toluenesulfonyl)-2,3,4,5-tetrahydro-1,4-methano-3-benzazepine (**8**) was synthesized in six steps from sulfonamide **3**; (−)-aphanorphine methyl ether **24** was obtained in seven steps from lactone **10**. Intramolecular etherification of **18** proceeded with excellent stereoselectivity in the presence of $BF_3 \cdot OEt_2$, which has paved an efficient synthetic route to a series of medicinally attractive heterocycles.

1. Introduction

(−)-Aphanorphine [(−)-**1**, Scheme 1], a novel alkaloid isolated by Shimizu and Clardy from the freshwater blue-green alga *Aphanizomenon flos-aquae* nearly two decades ago,[1] has stimulated tremendous synthetic attention[2] owing to its potential biological activity and unique structure containing tricyclic 3-benzazepine framework that resembles benzomorphane analgesics[3,4] such as pentazocine. Although a number of synthetic strategies have been reported for natural (−)-aphanorphine, unnatural (+)-aphanorphine, and (±)-aphanorphine in the literature,[2] currently there still exists strong demand for developing simpler and more efficient synthetic approaches for these molecules for the purpose of biological studies. Our previous synthesis of (−)-aphanorphine[2r] featured the formation of ring B at the final stage by Friedel–Crafts alkylative cyclization, while in most other strategies ring B was constructed prior to ring C. Moreover, carbohydrates,[5a] terpenes,[5b] and especially amino acids,[5c] have been widely used in the total synthesis of natural products. As shown in Scheme 1, (2*S*,4*R*)-4-hydroxyproline (**2**) was considered as an excellent starting point to secure the advanced tricyclic intermediates for constructing both enantiomers of aphanorphine, which would lead to novel, formal syntheses of (−)-aphanorphine and (+)-aphanorphine based on the 'chiral pool' strategy. Although we were not the first to 'extract' the chiron from **2** in the synthesis of aphanorphine, the previous approach[2m] made use of an initial enolate benzylation of a derivative of **2** and decarboxylation at a later stage, which adversely affected the overall synthetic efficiency in terms of atom economy and stereoselectivity. Moreover, our present research should be of great significance in terms of diversity-oriented synthesis. Some preliminary results along this line have been reported by our laboratory.[2s,y] Herein, we wish to describe the full account of our findings regarding the syntheses of natural (−)-aphanorphine and unnatural (+)-aphanorphine from (2*S*,4*R*)-4-hydroxyproline (**2**).



Scheme 1. Proposed synthesis of (−)- and (+)-aphanorphine.

Keywords: Alkaloid; Aphanorphine; Asymmetric synthesis; Configuration inversion; Intramolecular Friedel–Crafts reaction.
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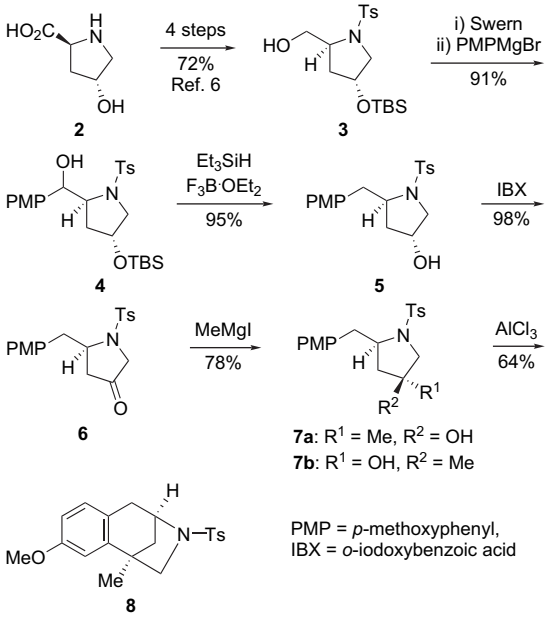
2. Results and discussion

2.1. (A) Formal synthesis of (−)-aphanorphine: synthesis of 8 from 2

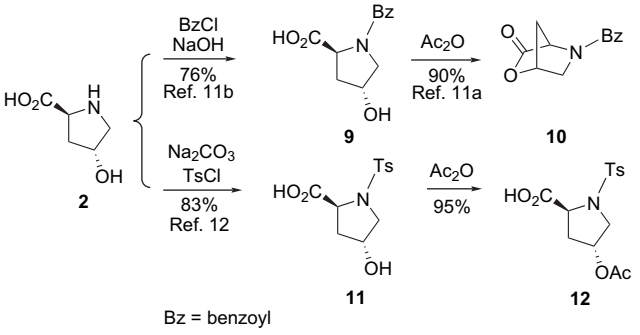
As outlined in Scheme 2, the synthesis of (−)-aphanorphine ((−)-**1**) commenced from alcohol **3**, an intermediate[6] obtainable from **2** in 72% yield by a four-step process. Swern oxidation[7a] of **3** gave a crude aldehyde, which in turn was arylated[8] with 4-methoxyphenylmagnesium bromide to furnish **4** in 91% yield as a single pure compound. Exposure[9] of alcohol **4** to triethylsilane in the presence of $BF_3\cdot OEt_2$ in dichloromethane produced **5** in high yield (95%), as a result of benzylic reductive dehydroxylation with concomitant O-desilylation. Oxidation[7b] with IBX (i.e., *o*-iodoxybenzoic acid) of **5** afforded ketone **6** in 98% yield. Nucleophilic methylation of **6** with methylmagnesium iodide[10] produced the tertiary alcohols **7a/7b** (equally utilizable, 78%). The diastereomeric ratio was measured by ^{1}H NMR integral analysis to be 4:1, presumably favoring **7a** based on steric consideration. By following the previously published protocol from this laboratory,[2r] $AlCl_3$-promoted Friedel–Crafts alkylative cyclization of alcohols **7a/7b** was effected to furnish the desired intermediate **8** as colorless needles (64%). The sample of **8** was in high enantiopurity (99.8% ee), as determined by HPLC analysis [Chiralpak AD column: 250×4.6 mm, UV detector: 254 nm, eluant: hexanes/2-propanol (4:1), flow rate: 0.7 mL/min], indicating that essentially no epimerization ever took place. The $[\alpha]_D^{20}$ of **8** was found to be −14.2 (*c* 0.93, $CHCl_3$) {lit.[2r] $[\alpha]_D^{20}$ −13.4 (*c* 0.969, $CHCl_3$)}. Other spectroscopic data of **8** were also in agreement with those disclosed in the literature.[2r] Thus a new formal synthesis of alkaloid (−)-aphanorphine ((−)-**1**) has been completed, since **8** could further be manipulated to give (−)-**1** in three additional steps (desulfurization, N-methylation, and 8-O-demethylation).



Scheme 2. Synthesis of **8**.

2.2. (B) Formal synthesis of (+)-aphanorphine: synthesis of 24 from 2

The synthesis of unnatural (+)-aphanorphine from (2*S*,4*R*)-4-hydroxyproline (**2**) featured configuration inversion at C-2 of the amino acid. Chemoselective N-benzoylation (BzCl, NaOH, Et_2O, 0 °C and then room temperature, 24 h, 76%) of **2** produced amide **9** (Scheme 3).[11a] Agitation of **9** in acetic anhydride heated at 90 °C for 5 h effected the requisite lactonization and configuration inversion at C-2 in the same step to provide bicycle **10** in 90% yield, by taking advantage of an efficient protocol developed recently by Rosa and Croce.[11b] Interestingly, treatment of sulfonamide **11**[12] (prepared in 83% yield by selective N-tosylation of **2** with TsCl in the presence of Na_2CO_3) with acetic anhydride at 90 °C for 8 h resulted only in the acylation of the secondary hydroxyl and the acetate **12** was obtained in 95% yield as a colorless solid. The desirable lactonization with configuration inversion at C-2 failed to take place just because the substituent on the nitrogen atom was switched from Bz (in **9**) to Ts (in **11**).



Scheme 3. Cyclization of **9**.

Treating[13] a mixture of lactone **10** and Me(MeO)NH·HCl (120 mol %) in tetrahydrofuran with *p*-methoxyphenylmagnesium bromide (370 mol %) at −10 °C furnished γ-hydroxy-α-amido ketone **14** (27%) along with diamide **13** (55%) and diol **15** (17%) (Scheme 4; Table 1, entry 1). The yield of **14** was increased to 41% when the reaction was run at −78 °C (entry 2). Since additional **14** could be formed from the Weinreb amide **13** in moderate yield (64%) by reacting with excess *p*-methoxyphenylmagnesium bromide (at −35 °C and then room temperature), phenyl ketone **14** could be obtained from lactone **10** in 76% overall yield. For comparison, direct addition of *p*-methoxyphenylmagnesium bromide (130 mol %) to lactone **10** at −78 °C (i.e., without the involvement of Me(MeO)NH·HCl) gave **14** in only 44% yield.

Ketone deoxygenation of **14** was then vigorously pursued (Scheme 5). Initially, a stepwise reduction strategy (i.e., via the benzylic alcohol intermediate) was explored. For instance, reduction of **14** with $NaBH_4$[14] in MeOH at 0 °C for 1 h smoothly formed the diol **18** (88%) essentially as a single diastereomer (dr=70:1). The configuration of the newly generated stereocenter of this diol was assigned based on the Cram rule. To our surprise, exposure of **18** to triethylsilane in the presence of $BF_3\cdot OEt_2$ in dichloromethane (at 0 °C and then room temperature) effected intramolecular etherification rather than benzylic reductive dehydroxylation. In