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Synthesis of chiral *trans*-fused 2-methyl-5-hydroxyldecahydroquinoline

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ABSTRACT

A practical asymmetric synthesis of the *trans*-fused 2-methyl-5-hydroxyldecahydroquinolines **8a** and **8b** is reported. Double Michael addition of enone **4** with (*S*)-phenylethylamine generated separable C2-methylated decahydroquinolinones **5a** and **5b**, which were converted to **8a** and **8b** via several functional group transformations.

1. Introduction

Decahydroquinoline (DHQ) alkaloids constitute a large family of biologically and pharmaceutically active natural products containing a bicyclic heterocycle backbone in which a piperidine ring is fused with a cyclohexane ring in cis or trans orientation. The parent member of DHQ alkaloids is *cis*-195A (**1**) (Fig. 1), previously known as pumiliotoxin C and originally isolated from the skin of the tropical rain forest frog *Dendrobates pumilio*.[1] This compound differs structurally from true pumiliotoxins and has much lower toxicity. Therefore, the name pumiliotoxin C is no longer used in order to avoid confusion with the true pumiliotoxins.[2] With alkyl substituents at positions C2 and C5 on the bicyclic backbone, it is considered the prototype of 2,5-disubstituted-DHQs, a large subclass of the DHQ family.[3] More than 50 such disubstituted compounds have been reported in poison frog, marine flatworms, bufanoid toads, and myrmicine ants.[4] In addition to *cis*-195A, our laboratory is interested in *cis*-195J because it is the only 2,5-disubstituted-DHQ with a methyl substitution at the C2 position.[5] The C2-methyl 2,5-disubstituted-DHQ moiety is present in more complex nitrogen-containing natural products, such as the galbulimima alkaloids (−)-GB 13 and (+)-GB 16.[6]

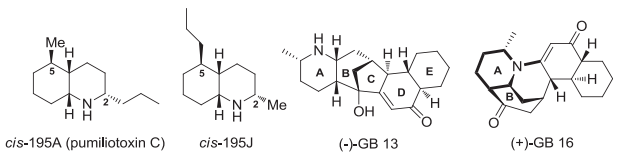

Fig. 1. Structure of atropurpuran **1** and its fragments **2** and **3**.

Although significant advances have been made in the asymmetric syntheses of 2,5-disubstituted-DHQs by Blechert,[7] Amat,[8] and Bradshaw,[9] much less work has been done on the synthesis of C2-methylated 2,5-disubstituted-DHQ. In 2010, in their total synthesis of (−)-GB 13 and (−)-himgaline, Ma and co-workers reported a versatile preparation of C2-methylated *cis*-2,5-disubstituted-DHQ from (*S*)-3-aminobutan-1-ol and cyclohexane-1,3-dione via consecutive condensation, cyclization, and asymmetric hydrogenation.[10] Since chiral (*S*)-3-aminobutan-1-ol is expensive for scale-up, our group aimed to develop a practical, stereoselective method to synthesize the *trans*-fused 2-methyl-5-hydroxyl-DHQ building blocks from commercially available, inexpensive chemicals. These compounds would not only serve as starting materials for the syntheses of complex natural products such as (−)-GB 13 and (+)-GB 16, but also may use as building blocks in construction of compound libraries with new scaffold for medicinal chemistry studies.

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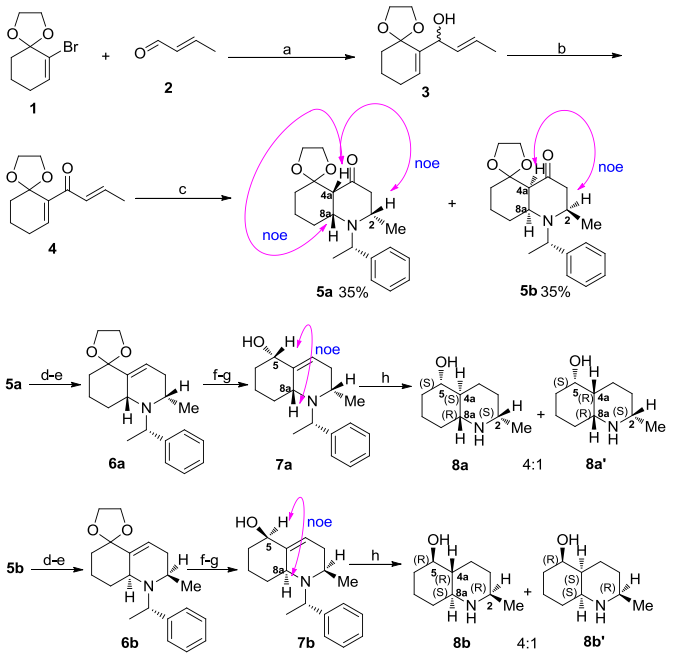
Here we report a practical method for synthesizing *trans*-fused 2-methyl-5-hydroxyl-DHQs **8a** and **8b** that relies on double Michael addition of enone **4** with (*S*)-phenylethylamine. This generates C2-methylated decahydroquinolinones **5a** and **5b**. Further functionalization of **5a** affords *trans*-fused 2-methyl-5-hydroxyldecahydroquinoline **8a** and *cis*-fused 2-methyl-5-hydroxyldecahydroquinoline **8a**′. Similar functionalization of **5b** provides *trans*-fused 2-methyl-5-hydroxyldecahydroquinoline **8b** and *cis*-fused 2-methyl-5-hydroxyldecahydroquinoline **8b**′.

2. Results and discussion

In our approach (Scheme 1), bromide **1**[11] was first treated with *t*-BuLi at −78 °C to generate an organolithium reagent, which then underwent nucleophilic addition to (*E*)-crotonaldehyde **2** to afford alcohol **3** in 85% yield. IBX oxidation of **3** generated enone **4** in 90% yield. A key double Michael addition of enone **4** with (*S*)-phenylethylamine proceeded smoothly under basic conditions of K_2CO_3 in methanol, providing a 1:1 mixture of C2-methylated *cis*-decahydroquinoline **5a** in 35% yield and **5b** in 35% yield. The two compounds were separable by silica gel chromatography. In **5a**, NOE correlations were detected between proton at C4a and protons at C2 and C8a, indicating an all-cis relationship among C2−H, C4a−H, and C8a−H. A similar NOE correlation between proton at C4a and C2 was found in **5b**, indicating a cis relationship. While no NOE correlation was found between the protons at C4a and C8a at **5b**, the cis relationship was further confirmed based on the structure of **8b** at a late stage of synthesis.



Scheme 1. Reagents and conditions: (a) *t*-BuLi, THF, −78 °C, 85%; (b) IBX, DMSO, rt, 90%; (c) (*S*)-phenylethylamine, K_2CO_3, MeOH, **5a** in 35% and **5b** in 35%; (d) $NaBH_4$, MeOH; (e) $SOCl_2$, pyridine, 0 °C→rt, 81% in two steps; (f) *p*-TsOH, acetone/H_2O (v/v 10:1), rt; (g) $NaBH_4$, MeOH, 0 °C, 86% for two steps; (h) 10% Pd/C, H_2, MeOH, 95%, **8a**/**8a**′ 4:1 (IBX, 2-iodoxybenzoic acid; *p*-TsOH, *p*-toluenesulfonic acid).

With *cis*-fused DHQ **5a** in hand, we proceeded to carry out sequential functional group transformations to synthesize *trans*-fused 2-methyl-5-hydroxyldecahydroquinoline **8a**. The C4 carbonyl group in **5a** was transformed into a double bond via $NaBH_4$ reduction and subsequent elimination of the resulting hydroxyl group using $SOCl_2$/pyridine. This afforded alkene **6a** in 81% yield over two steps. Deprotection of the acetal group in **6a** with *p*-TsOH in a 10:1 mixture of acetone/H_2O, followed by stereoselective reduction of the resulting carbonyl group with $NaBH_4$, afforded a single stereomer **7a** in 86% yield over two steps. NOE correlation was detected in **7a** between the protons at C5 and C8a. Further stereoselective hydrogenation of the double bond with 10% Pd/C and hydrogen gas gave a 4:1 mixture of *trans*-fused 2-methyl-5-hydroxyldecahydroquinoline **8a** and *cis*-fused 2-methyl-5-hydroxyldecahydroquinoline **8a**′ in 95% yield. The stereochemical outcome of **8a** being a major stereomer probably resulted from a coordination effect of the C5-hydroxyl group with the palladium catalyst. This interaction induced the hydrogen attack to the double bond from the same lower face of the hydroxyl group. Compounds **8a** and **8a**′ were separated from each other by silica gel chromatography. The absolute configuration of **8a** was assigned to be (2*S*,4a*S*,8a*R*,5*S*) based on the fact that the ^1H NMR spectrum, ^{13}C NMR spectrum, and specific rotation were identical between our synthetic **8a** and the compound prepared by Ma's group.[10] Since the hydrogenation reaction caused **8a** and **8a**′ to differ stereochemically at C4a, the absolute stereochemistry of diastereomer **8a**′ was assigned to be (2*S*,4a*R*,8a*R*,5*S*).

Compounds **8b** and **8b**′ were synthesized using a similar approach as for **8a** and **8a**′ (Scheme 1). Since **8b** is an enantiomer of **8a**, with both compounds presenting identical ^1H and ^{13}C NMR spectra but opposite specific rotation, we deduced the absolute stereochemistry of **8b** to be (2*R*,4a*R*,8a*S*,5*R*). Similarly, **8b**′ had the same ^1H and ^{13}C NMR spectra but opposite specific rotation as **8a**′, leading us to deduce the absolute stereochemistry of **8b**′ to be (2*R*,4a*S*,8a*S*,5*R*).

3. Conclusion

We have developed a practical method for synthesizing chiral *trans*-fused 2-methyl-5-hydroxyl-DHQs **8a** and **8b**. The key double Michael addition reaction of enone **4** with (*S*)-phenylethylamine generated separable C2-methylated decahydroquinolinones **5a** and **5b**. Further functionalization of **5a** provided the *trans*-fused 2,5-disubstituted decahydroquinoline **8a** and its diastereomer **8a**′ in a 4:1 ratio. Compounds **8b** and **8b**′ were prepared using the same procedure as for **8a** and **8a**′. Further application of synthesized 2-methyl-5-hydroxyl-DHQs **8a** and **8b** as starting materials and building blocks in the synthesis of natural products and nitrogen-containing polycyclic compounds is under exploration in our laboratory.

4. Experimental section

4.1. General procedure

All commercially available reagents were used without further purification. All solvents were dried and distilled before use: tetrahydrofuran was dried over sodium-benzophenone; pyridine was distilled from calcium hydride; dimethyl sulfoxide was distilled under reduced pressure after drying over calcium hydride; Methanol was dried over activated 4 Å molecular sieves. Chromatography was conducted by using 200−300 mesh silica gel. All new compounds gave satisfactory spectroscopic analyses (IR, ^1H NMR, ^{13}C NMR, HRMS). IR spectra were recorded on an FT IR spectrometer. NMR spectra were recorded on a 400 and 600 MHz NMR spectrometer. HRMS spectra were obtained by the FAB method.

4.2. Synthesis of alcohol 3

To a solution of bromide **1** (20.0 g, 91.7 mmol) in anhydrous THF (200 mL) at −78 °C was slowly added *t*-BuLi (1.3 M solution in pentane, 137.6 mmol). After 5 min, aldehyde (8.4 g, 119.3 mmol) was added and the mixture was stirred for 30 min at the same temperature. The reaction mixture was then quenched by addition

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