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An efficient synthesis of optically pure (*S*)-2-functionalized 1,2,3,4-tetrahydroquinoline

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Abstract—Using a copper-catalyzed coupling reaction of amino acid and aryl halide, followed by intramolecular cyclization of *N*-aryl-1-hydroxyl-3-propylamines under the Swern's condition as the key steps, (*S*)-2-hydroxymethyl-1,2,3,4-tetrahydroquinoline was synthesized as an example of optically pure 2-functionalized 1,2,3,4-tetrahydroquinolines.
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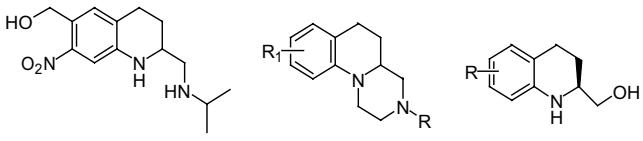
Substituted tetrahydroquinolines are the core structures in many important pharmacological agents and drug molecules, such as anti-arrhythmic and cardiovascular agents, anti-cancer drugs, immunosuppressants, ligands for 5-HT1A and NMDA receptors.[1–8] In fact 2-substituted tetrahydroquinoline oxamniquine (**1**) has been used in clinic to treat Manson's schistosomiasis since 1979. For these reasons, many efforts have been made to synthesize tetrahydroquinoline derivatives.[9–12] Recently, we found that N-substituted 2,3,4,4a,5,6-hexahydro-1H-pyrazine[1,2-*a*]quinolines (**2**) are quite potent ligands for the dopamine 3 (D_3) receptor.[13] Although the racemic form of **2** can be synthesized efficiently using previously published methods,[14,15] the synthesis of the optically pure form of **2** has not been reported. The key intermediate to obtain the optically pure form of **2** is the chiral 2-hydroxymethyl tetrahydroquinoline **3**. Herein, we report an efficient method to synthesize the optically pure substituted 2-hydroxymethyl tetrahydroquinoline **3** (Fig. 1).



1 Oxamniquine **2** **3**

Figure 1. Examples of important tetrahydroquinoline derivatives.

Our initial idea was to use copper-catalyzed coupling reaction of amino acid and aryl halide, which was initially developed by Ma et al.[16] and modified by Hayes and co-workers,[17] followed by intramolecular acylation as the key reactions to synthesize (*S*)-2-hydroxymethyl-7-methoxy-1,2,3,4-tetrahydroquinoline (Scheme 1). 3-Bromoanisole was treated with L-aspartic acid under Hayes' condition, followed by esterification to obtain *N*-aryl-aspartic diester **4** in a yield of 65% (two steps). Compound **4** was then reduced by $NaBH_4$, and the resulting diol **5** was reacted with triphosgene to produce oxazolidinone **6** and **7** (approximately 3:1 ratio). The major product **6** was oxidized by Jone's reagent, followed by intramolecular acylation to yield the desired cyclization product **9**. Unfortunately, the yield of Jone's oxidation was quite poor (<15%), which might be due to the instability of the oxazolidinone under the very strong acidic condition, so a large quantity of **9** could not be obtained. Although the following intramolecular acylation, reduction and deprotection worked very well, an alternative method had to be developed to obtain **11** in satisfactory yield.

Since the major problem in Scheme 1 was the low yield of Jone's oxidation, we planned to produce the

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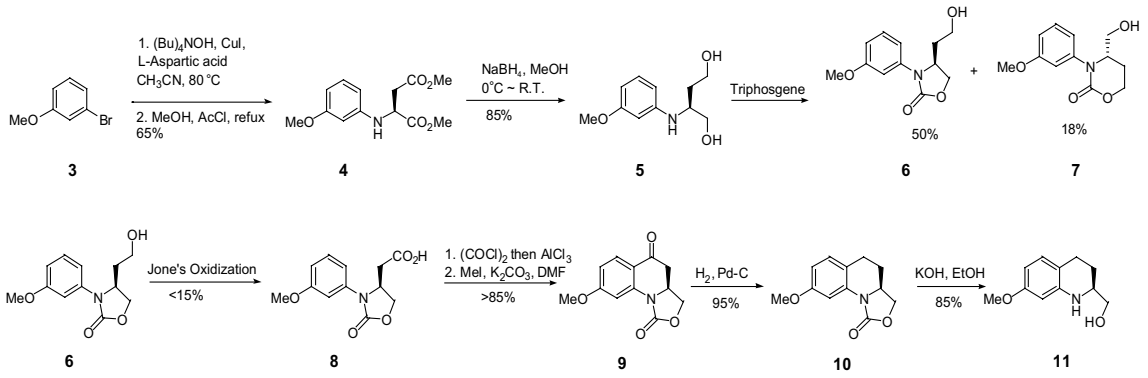
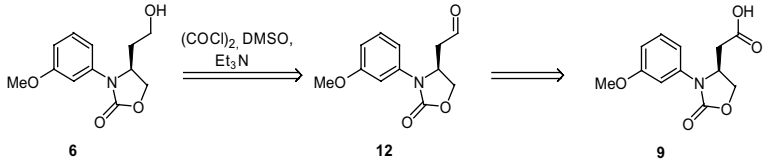


Scheme 1.



Scheme 2.

carboxylic acid **9** by another strategy. 4-(2-Hydroxy-ethyl)-3-(3-methoxy-phenyl)-oxazolidin-2-one **6** should be able to be oxidized under Swern's condition[18] to yield the aldehyde **12** easily, and the aldehyde **12** could be oxidized to get the carboxylic acid **9** in a satisfactory yield (Scheme 2). Unexpectedly, under Swern's condition,[18] the desired aldehyde **12** was not obtained. Instead, cyclization products **13**, **14**, **15** and **16** were produced, and the total yield was about 75% (Scheme 3, according to ^{1}H NMR, **13**:**14** = 10:1 and **15**:**16** = 10:1). This unexpected result might be attributed to the high reactivity of the disubstituted phenyl ring in **6**. Compound **13** was purified by recrystallization (to remove the minor product **14**) and the structure was determined by ^{1}H NMR, ^{13}C NMR and X-ray crystallographic analyses (Fig. 2).

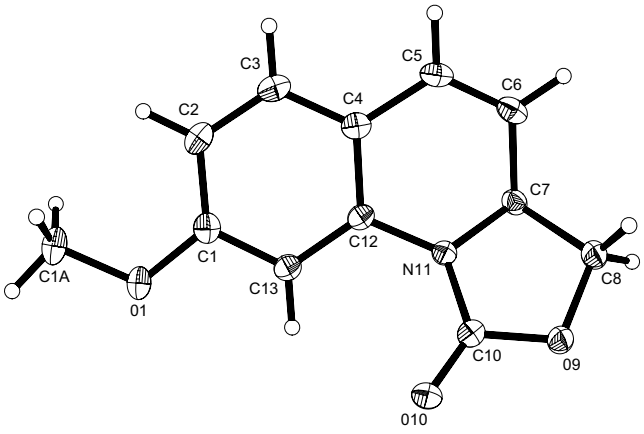
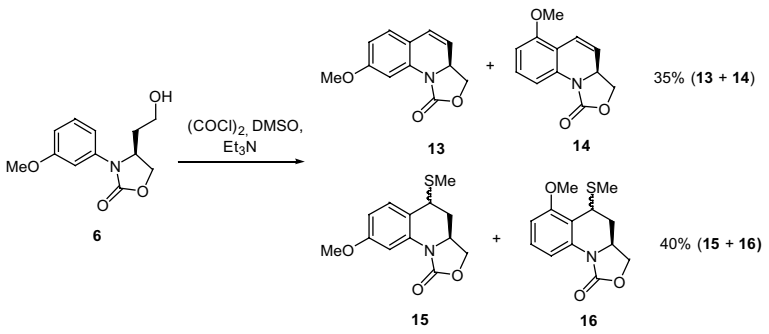
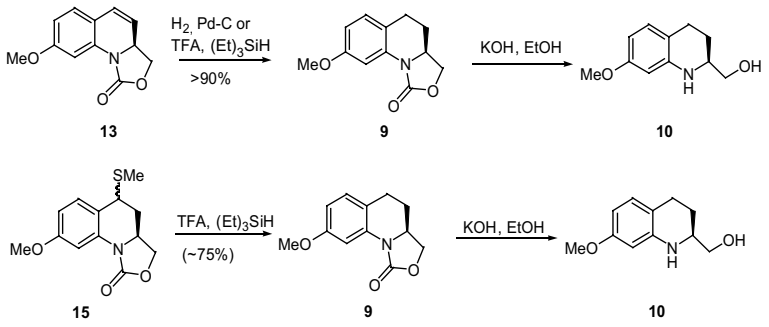


Figure 2. X-ray structure of compound **13**. Thermal ellipsoids are at the 50% probability level, H atoms are shown as circles of an arbitrary radius.

Both the reduction of double bond in compound **13** by hydrogenation and the removal of the methylthio group in **15** by Et_3SiH in trifluoroacetic acid produced compound **9** in excellent yields (Scheme 4). Finally, deprotection using the same reaction condition as shown in Scheme 1 led to (*S*)-2-hydroxymethyl-tetrahydroquinoline, which can be used to synthesize optically pure



Scheme 3.



Scheme 4.

N-substituted 2,3,4,4a,5,6-hexahydro-1H-pyrazine[1,2-*a*]quinolines as a class of novel D_3 ligands.

In summary, using a copper-catalyzed coupling reaction of amino acid and aryl halide, followed by intramolecular cyclization of *N*-aryl-1-hydroxyl-3-propylamine derivatives under the Swern's condition as the key steps, a new and efficient method was developed to synthesize optically pure 2-hydroxymethyl tetrahydroquinoline. Further applications of this method for the synthesis of novel optically pure D_3 ligands and other compounds with interesting biological properties are underway in our laboratory and will be reported in due course.

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