Communications

Hydroarylation for the Facile Synthesis of 2-Substituted Tetrahydroquinoline: A Concise Synthesis of (+)-(*S*)-Angustureine

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Tetrahydroquinolines constitute important structural features present in a number of biologically active alkaloids. Especially, 2-substituted tetrahydroquinoline[1] has drawn medicinal chemists' attention as a privileged structure. Angustureine, one member of 2-substituted tetrahydroquinoline alkaloids, was first isolated[2] by Jacquemond-Collet and his co-workers in 1999 from *Galipea officinalis*, which has been used in traditional herbal medicine to treat a fever of dyspepsia, dysentery and chronic diarrhea.[3] Recently, anti-tuberculous,[4] anti-malarial,[5] and cytotoxic[5] activities have been reported for angustureine.

In the context to develop efficient synthetic methods for diversity oriented synthesis of tetrahydroquinolines, herein, we report a concise synthesis of (+)-(*S*)-angustureine and hydroarylation strategy. As outlined in Figure 1, our synthetic stratagem includes the introduction of a chiral side chain by Mitsunobu reaction[6] and the subsequent hydroarylation to dihydroquinoline. This approach is flexible and applicable to the preparation of other 2-substituted tetrahydroquinolines, as well. To this end, we chose the aniline as our starting point (Scheme 1). *N*-methanesulfonyl protection of aniline, followed by Mitsunobu inversion[6] of the (*R*)-(+)-1-octyn-3-ol (**4**) (98% ee) with the resulting methanesulfonanilide **3** in the presence of DEAD/PPh_3, afforded *N*-propargylaniline **5**. The Mesyl-NH group served as an efficient nucleophile for Mitsunobu reaction as well as an arene-free protecting group in the next hydroarylation step.

With the hydroarylation precursor **5** in hand, we have explored the feasibility of intramolecular hydroarylation under a variety of catalytic conditions (Table 1). We first

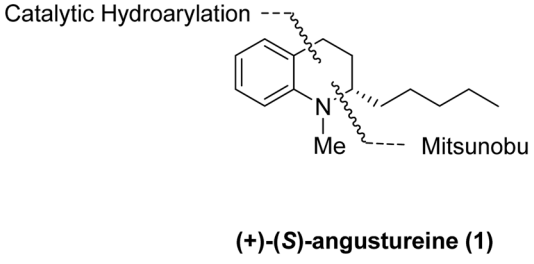
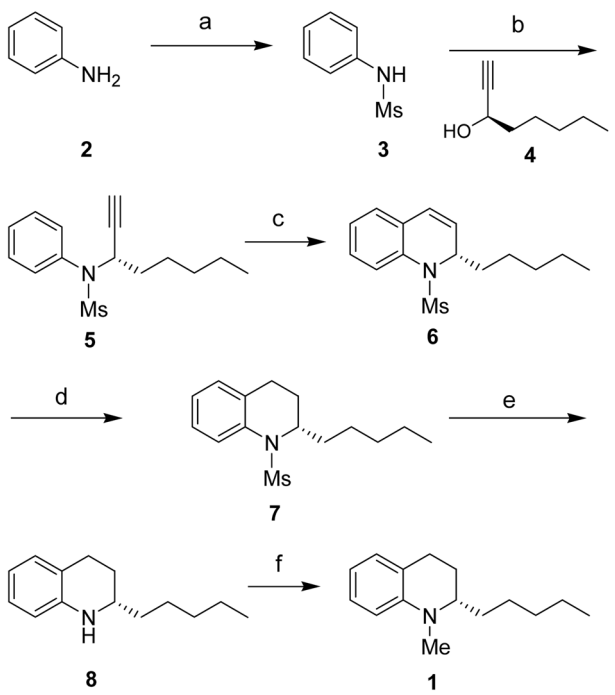


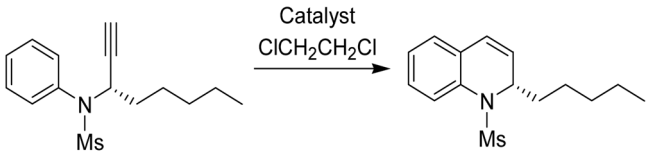
Figure 1. Key Features in Synthesis of (+)-(*S*)-Angustureine.



Scheme 1. Synthesis of (+)-(*S*)-Angustureine (**1**). (a) MsCl, Pyridine, CH_2Cl_2, 0 °C, 1 h, 92%; (b) (*R*)-(+)-1-Octyn-3-ol (**4**), DEAD, Ph_3P, THF, rt, 1 h, 100%; (c) See table 1; (d) H_2, Pd/C, EtOH, rt, 3 h, 85%; (e) Red-Al, toluene, 80 °C, 0.5 h, 99%; (f) K_2CO_3, THF, CH_3I, reflux, 24 h, 99%.

tested the reaction with $AuCl_3$ in the presence and absence of AgOTf.[7] The catalysts were not active enough to complete the reaction within an acceptable reaction condition (80 °C, 18 h) (entries 1 and 2). $Hg(OTf)_2$-$(TMU)_3$ complex,[8] which was reported as an efficient catalyst for the cyclization of activated arylalkynes, produced a unidentified byproduct as a major product with a small amount of dihydroquinoline **6** (entry 4). Then, we investigated platinum catalysts. We were pleased to find that $PtCl_4$ was an effective catalyst to provide dihydroquinoline **6**[9] in a respectable yield (entry 8). None of undesired exomethylene regioisomer or 4H-dihydroquinoline was detected. Generally, the hydroarylation of unactivated arylpropargylamine, especially

Table 1. Catalytic Hydroarylation of *N*-propargyl methanesulfonanilide **5**



5 **6**

Entry	Catalyst	Temperature	Time (h)	Yield (%)[a]
1	$AuCl_3$ (10 mol%)	80 °C	18	5[b]
2	$AuCl_3$ (10 mol%), AgOTf (48 mol%)	80 °C	18	12[b]
3	$Hg(OTf)_2$-$(TMU)_3$ (10 mol%)	rt	24	0[b]
4	$Hg(OTf)_2$-$(TMU)_3$ (10 mol%)	80 °C	18	11[c]
5	$PtCl_2$ (10 mol%)	rt	17	0[b]
6	$PtCl_2$ (10 mol%)	70 °C	18	0[b]
7	$PtCl_4$ (10 mol%)	rt	72	32[b]
8	**$PtCl_4$ (10 mol%)**	**70 °C**	**2**	**72**

[a]Isolated yield. [b]Remaining starting material was recovered. [c]A unidentified byproduct was isolated as a major product.

terminal alkynes, suffers from low activities.[10] Although Au(III),[7] Hg(II),[8] and Pt(II)[11] provided a few examples of activated-arylpropargylamine hydroarylations, the result with the unactivated substrate **5** was not satisfactory. To our best knowledge, our result constitutes the first example of a catalytic hydroarylation with unactivated *N*-propargylaniline to provide dihydroquinoline effectively.[11]

Reduction of the dihydroquinoline **6** was effected in 85% yield under standard catalytic hydrogenation conditions (5% Pd/C, EtOH). Removal of Ms protecting group of **7** was best achieved using Red-Al in toluene, ultimately affording the tetrahydroquinoline **8** in 99% yield. Finally, *N*-methylation completed the synthesis of (+)-(*S*)-angustureine. The spectroscopic data[12] measured from **1** are in full accord with the published data[13] of the compound.

In conclusion, we have accomplished a concise six-step synthesis of (+)-(*S*)-angustureine in overall 55% yield. The key features include an introduction of a chiral side chain by Mitsunobu reaction and an efficient Pt-catalyzed hydroarylation to dihydroquinoline. Given the result described above, research to expand hydroarylation into diversity oriented synthesis is currently in progress.

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9. *Representative procedure for $PtCl_4$-catalyzed hydroarylation to dihydroquinoline* ***6****:* A solution of *N*-propargyl methanesulfonanilide **5** (28 mg, 0.1 mmol) in anhydrous dichloroethane (1 mL, 0.1 M) was added to $PtCl_4$ (3.4 mg, 0.01 mmol). The reaction reaction mixture was stirred at 70 °C for 2 h under N_2. The solvent was then removed *in vacuo*. Column chromatography on silica gel (6 : 1 hexane/EtOAc) afforded pure dihydroquinoline **6** (20 mg; 72% yield). TLC: R_f 0.27 (6 : 1 hexane/EtOAc). $[\alpha]_D^{25}$ = +287 (*c* 1.0, MeOH). ^{1}H–NMR (400 MHz, $CDCl_3$): δ 7.61 (d, 1H, *J* = 7.2), 7.27 (td, 1H, *J* = 7.2, 1.6), 7.22 (td, 1H, *J* = 7.2, 1.6), 7.14 (dd, 1H, *J* = 7.2, 1.6), 6.53 (d, 1H, *J* = 9.6), 6.08 (dd, 1H, *J* = 9.6, 5.6), 4.72 (m, 1H), 2.65 (s, 3H), 1.49–1.34 (m, 4H), 1.32–1.17 (m, 4H), 0.85 (t, 3H, *J* = 7.2). ^{13}C–NMR (100 MHz, $CDCl_3$): δ 133.1, 130.1, 128.6, 128.5, 127.8, 126.9, 126.8, 125.0, 55.4, 37.7, 33.2, 31.5, 25.0, 22.6, 14.2. HRMS (FAB): calcd for $C_{15}H_{22}NO_2S$ ($[M+H]^+$), 280.1371; found, 280.1374.
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12. TLC: R_f 0.53 (8 : 1 hexane/EtOAc). $[\alpha]_D^{25}$ = +6.1 (*c* 1.0, CH_2Cl_2), {lit. $[\alpha]_D^{26}$ = +4.4 (*c* 1.0, CH_2Cl_2)}. ^{1}H–NMR (400 MHz, $CDCl_3$): δ 7.08 (t, 1H, *J* = 7.2), 6.97 (d, 1H, *J* = 7.2), 6.58 (t, 1H, *J* = 7.2), 6.53 (d, 1H, *J* = 7.2), 3.24 (m, 1H), 2.93 (s, 3H), 2.81 (m, 1H), 2.66 (td, 1H, *J* = 16.0, 4.0), 1.89 (m, 2H), 1.63-1.27 (m, 8H), 0.90 (t, 3H, *J* = 7.2). ^{13}C–NMR (100 MHz, $CDCl_3$): δ 145.6, 128.8, 127.3, 122.1, 115.4, 110.6, 59.2, 38.2, 32.2, 31.4, 26.0, 24.6, 23.8, 22.9, 14.2. HRMS (FAB): calcd for $C_{15}H_{23}N$ (M^+), 217.1830; found, 217.1832.
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