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Hydrogenation condition for sequential processes to (+)-trifluoromethyl monomorine

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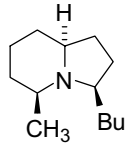
Abstract—(+)-Trifluoromethyl monomorine has been synthesized under mild hydrogenation condition by initiating reductive cleavage of the oxazoline ring followed by deprotection and intramolecular reductive amination reaction. The precursors could be prepared concisely by condensation and palladium-catalyzed coupling reaction.

Since isolation of the indolizidine alkaloid monomorine, a trail pheromone of the Pharaoh's ant, from *Monomorium pharaonis L.* by Ritter,[1] many synthetic ways have been developed for the skeleton with the correct arrangement of chiral centers adjacent to the nitrogen atom.[2]



(+)-Monomorine

Recently, we have published intramolecular reductive amination approaches for the indolizidine skeleton.[3] As an extension of the sequential strategy, we hoped to synthesize a trifluoromethyl-substituted monomorine derivative and find new biological properties.

The previous results for the construction of the 2,6-disubstituted piperidine derivatives by reductive conditions have indicated that proper arrangement of the functional groups would secure the synthesis of the new derivative in one pot under the similar condition.[2c,4] Stereochemistry at C6 of **2**, which is believed to be established by *endo* facial hydrogenation of **3**, controls the stereochemistry at C2 of **2** when it is reduced, and the following reductive amination of the deprotected piperidine intermediate would afford the expected product **1** (Eq. 1).

Intermediate **5** was prepared by condensation of **6** with (*S*)-(+)-phenylglycinol, and was transformed to triflate **4** by reaction with *N*-(5-chloro-2-pyridinyl)triflimide using the known procedure.[4] Coupling of **4** with 1-heptyne-3-ol **7** using $PdCl_2(PPh_3)_2$, and CuI as catalysts afforded **3** in 65% yield as an inseparable ca. 1:1 mixture. Hydrogenation of **3** over hydrogen (50 psi) using PtO_2 as a catalyst afforded a mixture of **8**, which could be separated to yield epimers **8a** and **8b** in 33% and 35% yields, respectively (Scheme 1).

In order to prepare the required precursor **2**, the mixture **8** was oxidized using Dess–Martin periodinane. The yield was 91% and the enantiomeric purity was proved to be >98% by chiral HPLC. For the desired transformation of **2**, hydrogenation under 1 atm of H_2 for 1 h at room temperature was enough to afford 62% of (+)-trifluoromethyl monomorine **1**, $[\alpha]_D^{23}$ 12.5° (*c* 0.75, $CHCl_3$), as a sole product after purification (Scheme 2).

As the synthesis of the new monomorine derivative **1** could not be confirmed by comparison with authentic sample, although spectra (^1H and ^{13}C NMR, IR, HRMS) supported it, we decided to synthesize **1** via a different route and match them. Instead of reductive amination reaction for the last transformation, we considered that S_N2 type reaction of **9a** would afford the

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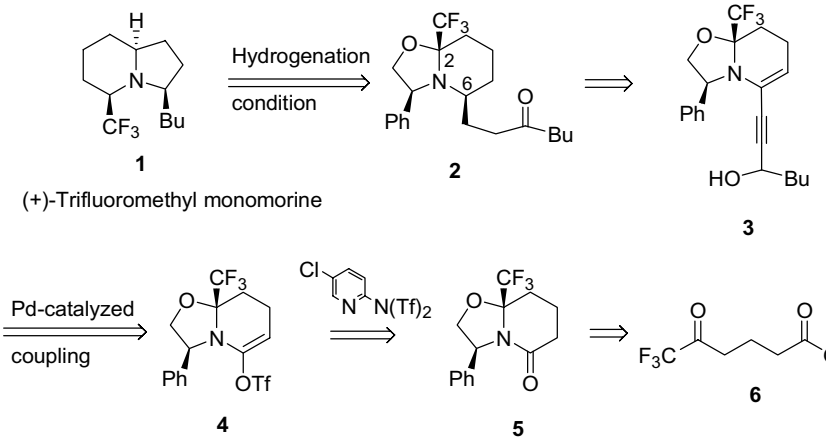
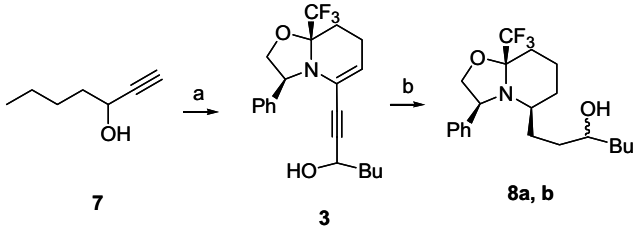
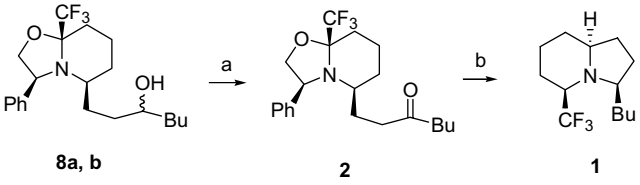


(1)



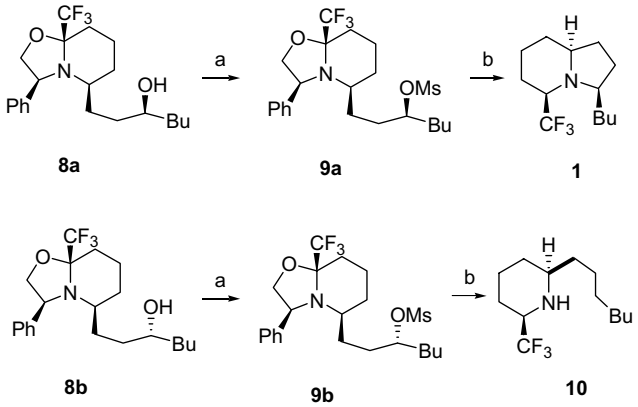
Scheme 1. Reagents and conditions: (a) **4**, $PdCl_2(PPh_3)_2$, CuI, THF–$(i\text{-}Pr)_2NH$, rt, 65%; (b) H_2 (50 psi), Pt_2O, toluene, 33% and 35%, respectively.



Scheme 2. Reagents and conditions: (a) Dess–Martin periodinane, CH_2Cl_2, 91%; (b) H_2, $Pd(OH)_2$, EtOH, rt, 62%.

same products **1**, on the other hand **9b** might afford the epimeric compound.[5,6] For this verification, the separated isomers **8a** and **8b** were mesylated to **9a** and **9b** in 89% and 94% yields, respectively. When compound **9a** was subjected to the same hydrogenation condition, compound **1** was obtained in 58% yield, and therefore the synthesis could be confirmed.[7] However, **9b** afforded unanticipated piperidine **10** $[\alpha]_D^{23}$ 16.1° (*c* 1.00, $CHCl_3$) in 53% yield under the hydrogenation condition (Scheme 3).[8]

In conclusion, we have described the concise hydrogenation-condition sequential route to a new derivative, (+)-trifluoromethyl monomorine. The precursors **2** and **3**, have been prepared by condensation of **6** and (+)-phenylglycinol followed by palladium coupling reactions. It is noteworthy in this approach (+)-phenylglycinol group of **2** has served as a chiral template for the selective



Scheme 3. Reagents and conditions: (a) (i) MsCl, Et_3N, CH_2Cl_2, rt, 89% for **9a** and 94% for **9b**; (b) H_2, $Pd(OH)_2$, EtOH, rt, 58% for **1** and 53% for **9**.

hydrogenation, and made the synthetic process possible with minimum functional group protection. Search for new biological activities of the new derivative is under study.

Acknowledgements

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6. The stereochemistry of the side chain of **8a**, **8b**, **9a**, and **9b** was assumed retrospectively by the comparison result.
7. *Compound* **1**: ^{1}H NMR (500 MHz, $CDCl_3$) 0.88 (t, 3H), 1.16–1.18 (m, 2H), 1.76–1.90 (m, 4H), 2.19–2.22 (m, 1H), 2.73–2.80 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 14.06, 22.71, 23.61, 26.53, 29.15, 29.65, 29.98, 30.25, 37.79, 61.75, 64.10, 64.30, 67.30. EIMS 249 (M^+, 7), 192 (M^+–butyl, 100), HRMS calcd for $C_{13}H_{22}NF_3$ found 249.1704, found 249.1729.
8. *Compound* **10**: ^{1}H NMR (500 MHz, $CDCl_3$) 0.88 (t, 3H), 1.02–1.09 (m, 1H), 1.67 (d, 1H, J = 12.1 Hz), 1.80–1.90 (m, 2H), 2.47–2.53 (m, 1H), 3.11–3.16 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 14.07, 22.63, 23.30, 24.84, 25.76, 29.20, 29.69, 31.56, 31.78, 37.08, 56.48, 58.44, 58.66. EIMS 251 (M^+, 3), 152 (M^+–heptyl, 100), HRMS calcd for $C_{13}H_{24}NF_3$ found 251.1861, found 251.1880. The formation of **10** was assumed to proceed via elimination followed by hydrogenation of the side chain before S_N2 cyclization, however, the explanation why cyclization was slowed down or inhibited is still under investigation.