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Synthesis of Octahydro- and Decahydroquinolines by a One-Pot Cascade Reaction of Tetrasubstituted Enecarbamate

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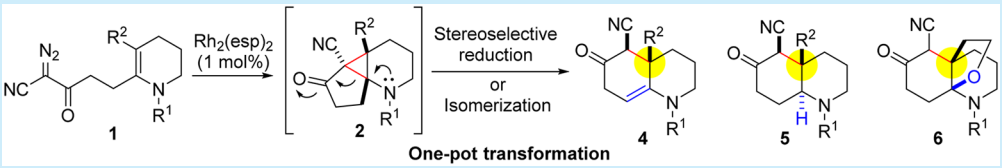
Supporting Information



ABSTRACT: A transition-metal-catalyzed cyclopropanation followed by ring opening was investigated for the synthesis of octahydroquinolines **4** and decahydroquinolines **5** having a quaternary carbon center at the angular position, which are core structures of the fawcettimine-type alkaloids. A tandem reaction was also established for the synthesis of decahydroquinolines **5** and the tricyclic compound **6** through an iminium ion intermediate, readily produced by acidic treatment of cyclopropane **2**.

Fawcettimine, isolated from *Lycopodium fawcettii* by Burnell and co-workers in 1959, is one of the representative *Lycopodium* alkaloids (Figure 1).[1] It is one of more than 80

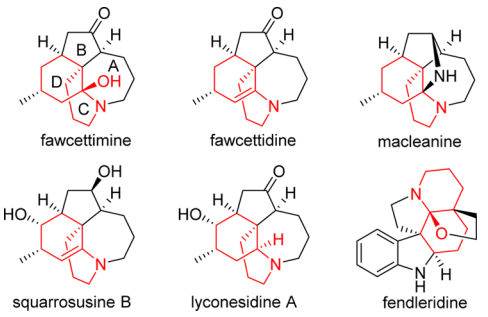
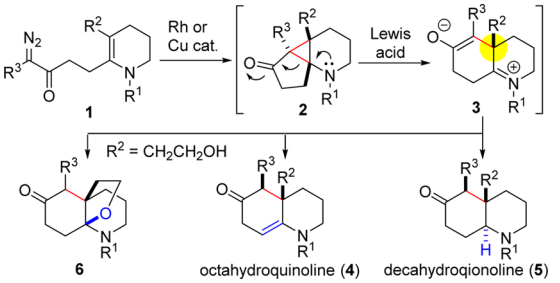


Figure 1. Fawcettimine-type alkaloids and a natural product containing both octa- and decahydroquinoline skeletons.

congeners reported to date, which include fawcettidine,[1,2] macleanine,[3] and squarrosusine B,[4] each of which belong to the fawcettimine class of alkaloids. Recently, new members of this alkaloid class, such as lyconesidines,[5] have been found in related species. Among these compounds, a complex tetracyclic skeleton is common, and the structural diversity mainly derives from the oxidation level and substituents on the B and D rings.[6] Because of its unique tetracyclic structure, many groups are engaged in synthetic studies of the fawcettimine-type alkaloids.[7,8] The main focus of these studies has been the synthesis of the hydrindane skeleton (B and D rings), and they are based on Heathcock and Inubushi's pioneering work.[8p,q] As an exceptional strategy, Dake and Kozak reported Pt(II)-catalyzed cyclization to construct an octahydroquinoline skeleton having a quaternary carbon (C and D rings),[8n] while Dake's synthesis proposed the possibility of an octahydroquinoline skeleton as a useful intermediate. Additionally, the skeleton has been found in various alkaloids such as fendleridine.[9] Therefore, the development of a concise synthetic method for these skeleta would contribute to the synthesis of not only fawcettimine-type alkaloids but also related natural products.

Considering a synthesis of various analogues, we envisioned that an intramolecular cyclopropanation of tetrahydropyridine **1** followed by a ring opening would give both octa- and decahydroquinoline **4** and **5**, respectively (Scheme 1). That is,

Scheme 1. Synthetic Strategy for Diverse Decahydro- and Octahydroquinolines



by introducing an electron-withdrawing group as a substituent (R^3 = EWG), a ring-opening of cyclopropane **2** would readily produce an iminium intermediate **3**,[10] which would be converted to **4** and **5** by a proton transfer and stereoselective reduction, respectively. It was expected that various substituents could be introduced into the obtained compounds **4** and **5** by using ketone functionality for the synthesis of fawcettimine-type alkaloids. Moreover, the iminium intermediate **3**, derived from a substrate having a hydroxyethyl group (R^2 = CH_2CH_2OH), would be intramolecularly trapped with an alcohol to give a

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tricyclic compound **6**, which can be found in a fendleridine skeleton. While there are many reports about cyclopropanation of monosubstituted enamides and ene carbamates,[11,12] the number of reports decreases as the number of substituents increases. In the case of tetrasubstituted enamides and ene carbamates, pyrolysis of tosylhydrazone[13a] and formation of carbene from chloroform via treatment of a strong base[13b] were only employed for cyclopropanation.[14] Thus, there is no example of the use of a transition-metal−carbene complex. Herein, we report synthesis of octahydroquinolines **4**, decahydroquinolines **5**, and tricyclic compound **6** having a quaternary carbon center at the angular position via a transition-metal-catalyzed cyclopropanation of tetrasubstituted ene carbamate and a ring-opening.

Initially, cyclization precursors **1a−h** were synthesized from 2-piperidone in six to eight steps including Heck or Suzuki−Miyaura coupling, 1,4-reduction,[15] and diazotransfer[16] (Scheme 2). We then investigated transition-metal-catalyzed cyclopropanation of tetrasubstituted ene carbamate **1a**. When compound **1a** was treated with $Cu(OTf)_2$, diketone **12** was obtained in 70% yield via a ring-opening of cyclopropane followed by hydrolysis (Table 1, entry 1). Although $Cu(hfacac)_2$ could be used for suppressing a ring-opening of cyclopropane, a part of the desired product **2a** was converted to octahydroquinoline **4a**, which was a mixture of keto and enol tautomers owing to the presence of an acidic proton (entry 2). In contrast, the use of rhodium catalysts, including $Rh_2(OAc)_4$, $Rh_2(cap)_4$,[17] and $Rh_2(esp)_2$,[18] was effective for suppressing the undesired side reactions (entries 3−5). Specifically, $Rh_2(esp)_2$ gave hexasubstituted cyclopropane **2a** in 57% yield without compounds **4a** and **12** (entry 5). For reproducible isolation of the product **2a**, addition of triethylamine into an eluent for silica gel column chromatography was important because **2a** was not stable on silica gel.

We next focused on the selective transformation of the hexasubstituted cyclopropane **2a** into octahydroquinoline **4a** and decahydroquinoline **5a**. When compound **2a** was treated with trifluoroacetic acid (TFA) or $BF_3{\cdot}OEt_2$, ring-opening of cyclopropane was followed by a proton transfer to give compound **4a** in excellent yields (Table 2, entries 1 and 2).

Scheme 2. Synthesis of Tetrasubstituted Enecarbamate 1

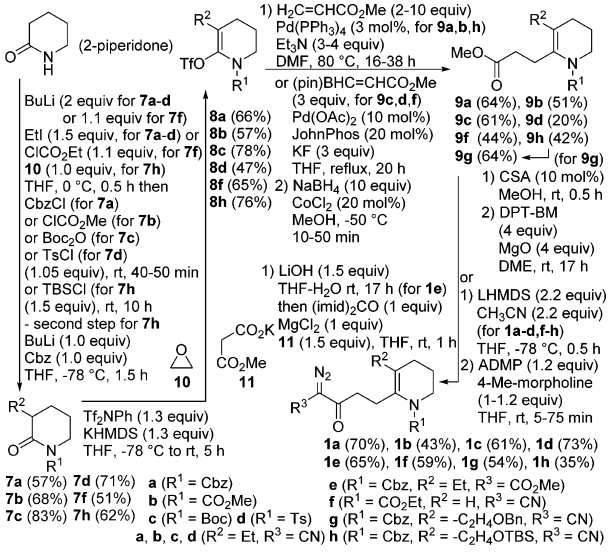
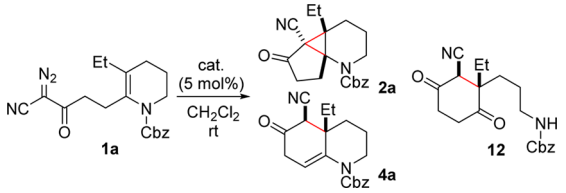


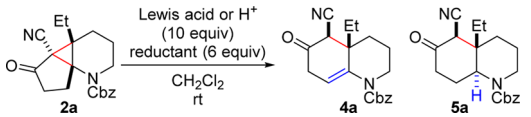
Table 1. Transition-Metal-Catalyzed Cyclopropanation of Tetrasubstituted Enecarbamate 1a



			yield[a] (%)		
entry	cat.	time	**2a**	**4a**	**12**
1	$Cu(OTf)_2$	10 h	0	0	70
2	$Cu(hfacac)_2$[b]	24 h	13	33	0
3	$Rh_2(cap)_4$	2.5 h	42	0	0
4	$Rh_2(OAc)_4$	30 min	52	0	0
5	$Rh_2(esp)_2$[c]	15 min	57	0	0

[a]Isolated yield. [b]60 mol %. [c]0.1 mol %. Tf = triflate, hfacac = hexafluoroacetylacetonato, cap = caprolactamate, esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid.

Table 2. Selective Formation of Octahydroquinoline 4a and Decahydroquinoline 5a



				yield[a] (%)	
entry	Lewis acid or H^+	reductant	time	**4a**	**5a**
1	TFA[b]	none	30 min	96	0
2	$BF_3{\cdot}OEt_2$[b]	none	30 min	95	0
3	TFA	Et_3SiH	2 h	56	0
4	TFA	Ph_3SiH	5 h	40	0
5	TFA	$NaBH_3CN$	2 h	17	0
6	TFA	$NaBH(OAc)_3$	2 h	22[c]	72[c]
7	$BF_3{\cdot}OEt_2$[d]	$NaBH(OAc)_3$[e]	11 h	23[c]	31[c]
8	$Ti(OiPr)_4$	$NaBH(OAc)_3$	15 min	29[f]	0
9	$AlCl_3$	$NaBH(OAc)_3$	3 h	59	0
10	$Sc(OTf)_3$	$NaBH(OAc)_3$	2 h	28	0
11	$MgBr_2{\cdot}OEt_2$	$NaBH(OAc)_3$	3 h	60	0

[a]Isolated yield. [b]1 equiv. [c]The yield was calculated by ^1H NMR. [d]6 equiv. [e]10 equiv. [f]The starting material was recovered (31%). TFA = trifluoroacetic acid.

These results indicated that cyclopropane **2a** was readily cleaved to produce an iminium ion such as **3**. Thus, reduction of the iminium ion was examined for obtaining decahydroquinoline **5a**. When compound **2** was treated with Et_3SiH, Ph_3SiH, or $NaBH_3CN$ under acidic conditions (TFA), these reductions did not proceed (entries 3−5). In sharp contrast, use of $NaBH(OAc)_3$ was effective, and the reaction gave the desired product **5a** in 72% yield along with a small amount of **4a** (entry 6). Several Lewis acids were also examined instead of TFA. In the case of $BF_3{\cdot}OEt_2$, the reaction gave **5a**, but the yield was low (31%, entry 7). In contrast, a combination of $NaBH(OAc)_3$ and other Lewis acids, including $Ti(OiPr)_4$, $AlCl_3$, $Sc(OTf)_3$, and $MgBr_2{\cdot}OEt_2$, gave only octahydroquinoline **4a** in low to moderate yields (entries 8−11). Therefore, $BF_3{\cdot}OEt_2$ was employed for opening the cyclopropane ring to access compound **4**, and a combination of TFA and $NaBH(OAc)_3$ was determined to provide the best conditions for the synthesis of compound **5**. Reduction of the iminium intermediate **3a**

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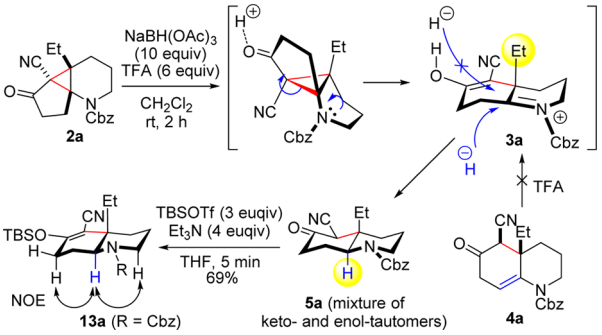
proceeded with excellent stereoselectivity because the reductant attacked from the less hindered face (Scheme 3). Because **5a** was

Scheme 3. Stereoselectivity of the Reduction of Iminium Intermediate 3a



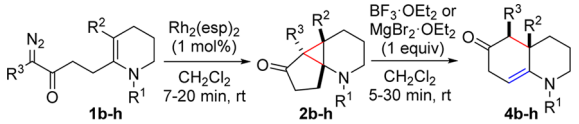
a mixture of keto and enol tautomers, the stereochemistry of the *trans*-fused ring system was determined by NOESY experiments after formation of *tert*-butyldimethylsilyl (TBS) enol ether **13a** (Scheme 3). For the synthesis of compound **5a**, compound **4a** was also treated under the optimized reduction conditions (TFA and $NaBH(OAc)_3$, rt). However, the reaction did not proceed to give **5a**. This result indicated that the iminium ion **3a** was not produced from compound **4a** under these mild conditions.

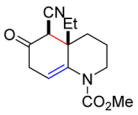
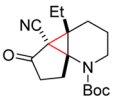
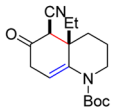
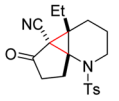
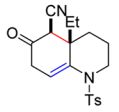
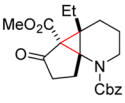
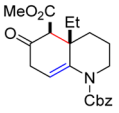
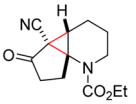
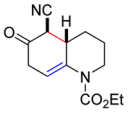
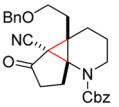
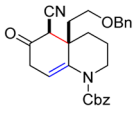
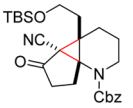
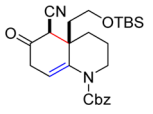
To determine the scope and limitations, the optimized conditions were applied for the synthesis of several octahydroquinolines **4b–h** (Table 3). Cyclopropanation of substrates **1b** and **1c** having CO_2Me and Boc groups as protecting groups gave compounds **2b** and **2c** in moderate yields, respectively (entries 1 and 2). Compound **2b** readily converted to octahydroquinoline **4b** when treated with $BF_3{\cdot}OEt_2$. In the case of **2c**, $MgBr_2{\cdot}OEt_2$ was used instead of $BF_3{\cdot}OEt_2$ for suppressing the undesired deprotection of the Boc group. Compound **4c** was obtained in excellent yield. Interestingly, the reaction of **1d** with its tosyl group gave **4d** in 76% yield without acidic treatment, as the corresponding cyclopropane **2d** was easily cleaved (entry 3). The reaction of *β*-keto-*α*-diazoester **1e** did not give compound **2e**. Thus, a nitrile group is essential for this cyclopropanation (entry 4). The reaction of **1f** did not give cyclopropane **2f** because C–H insertion was competitive (entry 5). Benzyl (Bn) and TBS groups were compatible under these reactions, and octahydroquinolines **4g** and **4h** were obtained in 80% and quantitative yields, respectively (entries 6 and 7).

Because compound **2** was not stable as described above, a one-pot cyclopropanation/reductive ring-opening was attempted for the synthesis of decahydroquinolines **5**. Treatment of **1a** with $Rh_2(esp)_2$ was followed by reductive ring opening using TFA and $NaBH(OAc)_3$ to give decahydroquinoline **5a** in 48% yield, which was comparable to the yield of the stepwise procedure (Table 4, entry 1). Methoxycarbonyl and Boc groups were compatible under these conditions (entries 2 and 3). In the case of substrates having Bn and TBS groups, the desired decahydroquinolines **5g** and **5h** were obtained as major products, respectively, while the reductive ring opening competed with formation of octahydroquinolines **4g** and **4h**.

This one-pot procedure for decahydroquinolines **5** was extended to a one-pot synthesis of tricyclic compound **6** (Scheme 4). Treatment of *β*-keto-*α*-diazonitrile **1i** with $Rh_2(esp)_2$ followed by $BF_3{\cdot}OEt_2$ gave compound **6** via cyclopropanation in 66% yield. It is interesting that the cyclopropanation was the preferable process rather than O–H

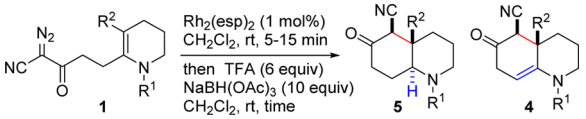
Table 3. Scope and Limitations of Synthesis of Octahydroquinoline 4



entry	first step	yield[a]	second step	yield[a]
1		**2b:** 60%		**4b:** 96%
2		**2c:** 50%		**4c:** quant[b]
3		**2d:** (-)		**4d:** 76%[c,d]
4		**2e:** 0%		**4e:** (-)
5		**2f:** 0%		**4f:** (-)
6		**2g:** 49%		**4g:** 80%
7		**2h:** 52%		**4h:** quant[b]

[a]Isolated yield. [b]$MgBr_2{\cdot}OEt_2$ was used instead of $BF_3{\cdot}OEt_2$. [c]Without acidic treatment. [d]The reaction time was 35 min. Bn = benzyl, TBS = *tert*-butyldimethylsilyl.

Table 4. One-Pot Cyclopropanation and Reductive Ring-Opening for Synthesis of Decahydroquinoline 5



entry	R^1	R^2	time	product	yield (%)[a] of **5** + **4**	ratio[b] of **5**:**4**
1[c]	Cbz	Et	2 h	**5a**	48	4.0:1
2[d]	CO_2Me	Et	50 min	**5b**	64	7.3:1
3[d]	Boc	Et	45 min	**5c**	77	6.5:1
4	Cbz	CH_2CH_2OBn	8 h	**5g**	47	3.3:1
5[d]	Cbz	CH_2CH_2OTBS	2 h	**5h**	43	3.8:1

[a]Isolated yield. [b]The ratio was calculated by ^1H NMR. [c]0.1 mol % of $Rh_2(esp)_2$ was used. [d]$Rh(OAc)_2$ was used instead of $Rh_2(esp)_2$.

insertion in the first step, and an iminium ion could be trapped without formation of ene carbamate in the second step. It was difficult to obtain compound **6** from octahydroquinoline **4i**

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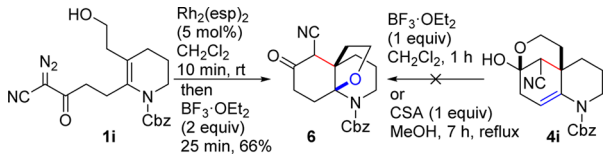
Scheme 4. One-Pot Synthesis of Tricyclic Compound 6



under mild conditions including treatment with $BF_3{\cdot}OEt_2$ or CSA.

In summary, we have investigated a concise synthesis of octahydroquinolines **4** and decahydroquinolines **5** having a quaternary carbon center at the angular position via a one-pot reaction involving cyclopropanation and ring opening. The use of Ts-protected ene−sulfonamide **1d** was found to be effective for direct access to **4**. One-pot procedures for the synthesis of decahydroquinolines **5** and tricyclic compound **6** were also established. These methods would be powerful because a quaternary carbon center and a six-membered carbocycle were constructed at once. Synthesis of related alkaloids based on the developed strategy for decahydroquinolines **5** is now underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02122.

Experimental procedures and spectral data (^1H and ^{13}C NMR, IR, and HRMS) (PDF)

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Notes

The authors declare no competing financial interest.

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