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$BF_3{\cdot}Et_2O$ catalyzed diastereoselective nucleophilic reactions of 3-silyloxypiperidine *N,O*-acetal with silyl enol ether and application to the asymmetric synthesis of (+)-febrifugine

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ABSTRACT

The asymmetric $BF_3{\cdot}Et_2O$ catalyzed nucleophilic reactions of 3-silyloxypiperidine *N,O*-acetal **10** with silyl enol ethers derived from ketones are described. (+)-Febrifugine **1**, an antimalarial alkaloid, was successfully synthesized based on this nucleophilic substitution. In addition, *N,O*-acetal **10** was synthesized from L-benzyl glutamate in 11 steps.

1. Introduction

Alkaloids containing 3-hydroxy 2-substituted piperidine rings exist abundantly in nature. Most of them show interesting biological activities.[1] Among them, febrifugine **1** and isofebrifugine **2** (Fig. 1) are antimalarial alkaloids isolated from Chinese medicinal plants *Dichroa febrifuga* Lour (Chang Shan)[2] and related *hydrangea* plants.[3] Febrifugine **1** is approximately 100 times as effective as quinine against *Plamodia lophurae* in ducks.[2a] The absolute configurations of these alkaloids were elucidated by Kobayashi et al.[4] During the past ten years or so, the synthesis of these two alkaloids and their analogues has attracted considerable attention.[4,5] Halofuginone **3**, a pharmaceutical candidate developed from febrifugine, is currently under phase II clinical trials for treatment of scleroderma in human.[6]

Among the reported asymmetric approaches to febrifugine, one of the most straightforward approaches to construct the 2-substituted 3-hydroxy piperidine is the stereoselective reaction of 3-hydroxy-piperidine *N*-acyliminium ions with the nucleophiles.[5k,m] While there are some reports on the diastereoselective C-2 functionalization onto the six-membered system, the control of diastereoselectivity between the 2- and 3-positions has been far from satisfactory.[5k,m,7] For example the $TiCl_4$-catalyzed nucleophilic substitution reaction of 3-acetoxy-2-methoxy-*N*-methoxycarbonylpiperidine derivatives with the silyl enol ether of acetone gave moderate diastereoselectivity.[7a] Correia group reported that 3-acetoxy-*N*-ethoxycarbonyl-2-methoxypiperidine reacted with trimethylsilyl cyanide (TMSCN) in the presence of $BF_3{\cdot}OEt_2$ to afford the corresponding adduct as a 1:1.3 mixture of cis/trans diastereomers.[7b] Later on, Kobayashi's group[5k] reported the $Sc(OTf)_3$-catalyzed nucleophilic substitution reaction of 3-acyloxypiperidines and 3-(4-methoxybenzyloxy)piperidines with moderate diastereoselectivities. Johnson[7c] and Blaauw[7d,e] showed that the reaction of multifunctionalized *N*-Cbz-piperidine system provided only the trans product. Craig's group studied the alkylation reactions of multifunctionalized *N*-tosylpiperidine system.[7f] Recently, Huang[5m] and Chang[7g] have independently investigated the allylation of 3-silyloxy and 3-methoxy 2-piperidinone with allyltrimethylsilane reagents, the major products are in 2,3-cis-diastereomers, although in moderate diastereoselectivities.

Very recently, we have reported an asymmetric synthesis of 3-hydroxy 2,6-disubstituted piperidines.[8] On pursuing our efforts on developing efficient asymmetric methods for synthesis of 2-substituted 3-hydroxy piperidine alkaloids, we now report a highly diastereoselective (up to 96:4) method for the nucleophilic substitution of 3-silyloxy-2-acyloxypiperidine with silyl enol ether in the presence of $BF_3{\cdot}OEt_2$. The total synthesis of (+)-febrifugine **1** using the key step is described.

As shown in Scheme 1, the nucleophilic substitution reaction of *N,O*-acetal **10** with silyl enol ether derived from acetone in high stereoselectivity would be a desirable goal for the synthesis of

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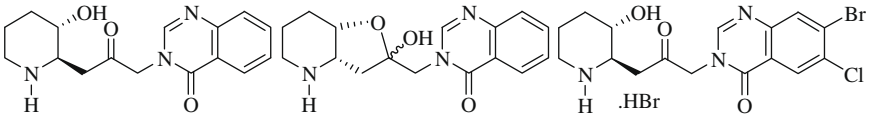
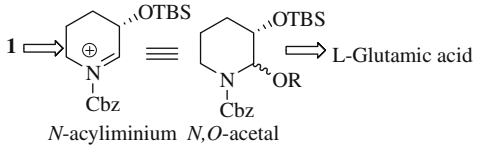


Figure 1.

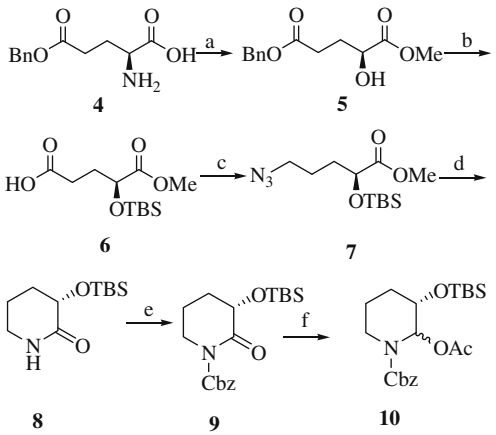


Scheme 1. Synthetic strategy of (+)-febrifugine **1**.

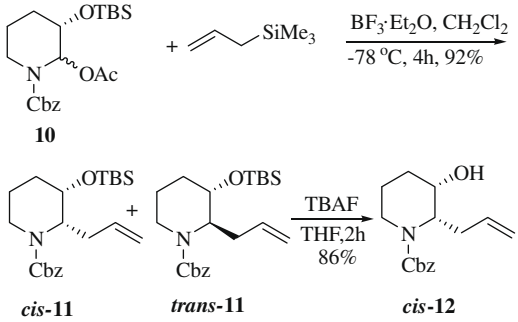
(+)-febrifugine **1.** For this purpose, a reliable method for the preparation of 3-silyloxy-2-acyloxypiperidine **10** from L-glutamic acid is required.

In order to find a general method to prepare *N,O*-acetals such as **10**, we selected L-Glu(OBn)-OH **4** as a starting material. Thus, treatment of L-Glu(OBn)-OH **4** with an aqueous solution of $NaNO_2$ under acid conditions[9] followed by in situ methanolysis (MeI, DMF) afforded ester **5** in 63% overall yield. Protection of the secondary alcohol of **5** as its TBS ether (TBSCl, imidazole) and reductive removal of the benzyl ester (Pd/C, MeOH) gave acid **6** in 71% overall yield. Upon reduction ($BH_3{\cdot}SMe_2$) and tosylation, the resulting ester was directly treated with sodium azide in the presence of pyridine to generate azide **7** in 68% overall yield. Upon hydrogenation (5%Pd/C, MeOH) of the azide group in **7**, spontaneous cyclization occurred to afford the known lactam[10] **8** in 75% yield. Lactam **8** was treated successively with *n*-butyllithium and benzyl carbonochloridate to afford imide **9** in high yield. Reduction ($NaBH_4$, MeOH) of the imide carbonyl and subsequent reaction with acetic anhydride gave *N,O*-acetal **10** in 58% overall yield from **8** (Scheme 2).

Treatment of *N,O*-acetal **10** with 2.0 equiv of $BF_3{\cdot}Et_2O$ in the presence of allyltrimethylsilane at −78 °C gave a mixture of *cis*-**11** and *trans*-**11**, with the ratio determined by HPLC to be 90:10. Although the allylated product **11** and its isomer were not separable in this stage by chromatography on silica gel, we were delighted to find that the two diastereoisomers were easily separated after removal of silyl-protecting group with TBAF yielding the known (2*S*,3*S*)-**12** as the major diastereomers {$[\alpha]_D^{25}$ +77.2 (*c* 0.4, EtOH); lit[5f] $[\alpha]_D^{24}$ +76.2 (*c* 1.0, EtOH); lit[5m] $[\alpha]_D^{20}$ +77.1 (*c* 1.0, EtOH)} in 86 % yield (Scheme 3). It is worth mentioning that when TMSOTf was used as catalysts, a disappointing 82:18 mixture of *cis*-**11**/*trans*-**11** was obtained in 83% combined yield.



Scheme 2. Reagents and conditions: (a) (i) $NaNO_2$ AcOH/H_2O (*V*/*V* = 2:8), 0 °C, 3 h; (ii) $NaHCO_3$, MeI, DMF, rt, 18 h, two steps 63%; (b) (i) TBSCl, imid, DMAP, DMF, rt overnight, 85%; (ii) 10% Pd/C H_2, rt, 12 h, 83%; (c) (i) $BH_3{\cdot}SMe_2$, THF, 0 °C–rt, 16 h; (ii) TsCl, Py, DMAP,CH_2Cl_2, rt, 36 h; (iii) NaN_3 DMF, rt, 12 h, three steps 68%; (d)5% Pd/C, H_2, CH_3OH, rt, 36 h, 75%; (e) *n*-BuLi, CbzCl, THF,−78 °C, 1 h, 81%; (f) (i) $NaBH_4$, CH_3OH, 0 °C, 40 min; (ii) Ac_2O, TEA, DMAP, CH_2Cl_2, rt, overnight, two steps 71%.



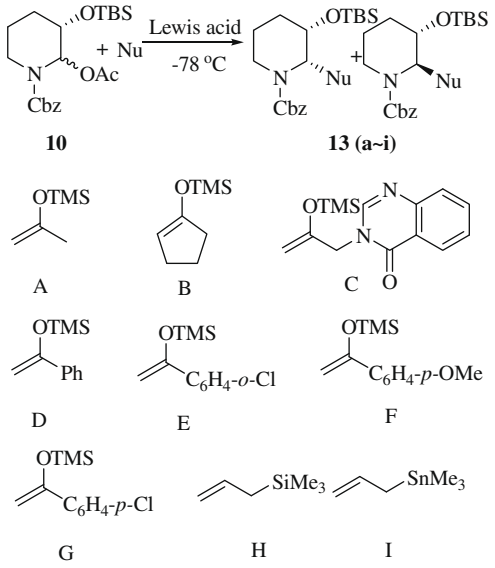
Scheme 3. Structure determination of **11**.

Encouraged by the highly cis-diastereoselective reaction of *N,O*-acetal **10** with allyltrimethylsilane, we then investigated the reaction of **10** with various silyl enol ethers derived from ketones as carbon nucleophiles. The results are summarized in Table 1. To our delight when **10** was treated with silyl enol ether in the presence of 2.0 equiv of $BF_3{\cdot}Et_2O$ in dichloromethane at −78 °C for 4 h, **13a** was generated with excellent cis-selectivity (96:4) in 78 % yield.[11] On the other hand, the reaction induced by a catalytic amount of TMSOTf or stoichiometric amount of $TiCl_4$ in dichloromethane afforded product **13a** in moderate yield with diastereomeric ratios of 76:24 and 55:45, respectively. The silyl enol ether derived from cyclopentanone also reacted with *N,O*-acetal **10** to give a single product **13b** in 71% yield, although the stereostructure

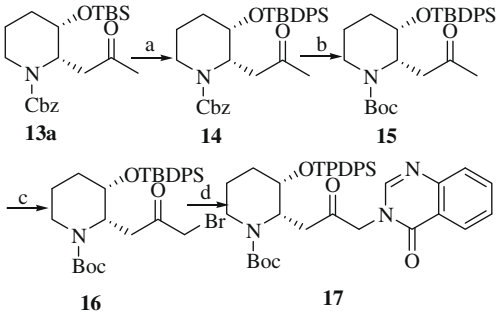
Table 1
Nucleophilic substitution reaction of 3-silyoxy *N,O*-acetal

Entry	Nu	Lewis acid	Product	Yield[a] (cis/trans)[b] (%)
1	A	$BF_3{\cdot}Et_2O$	**13a**	78 (96:4)
2	A	TBSOTf	**13a**	63 (76:24)
3	A	$TiCl_4$	**13a**	53 (55:45)
4	B	$BF_3{\cdot}Et_2O$	**13b**	71
6	C	$BF_3{\cdot}Et_2O$	**13c**	NR
7	C	TMSOTf	**13c**	53 (52:48)
8	D	$BF_3{\cdot}Et_2O$	**13d**	85 (83:17)
9	D	TMSOTf	**13d**	73 (73:24)
10	E	$BF_3{\cdot}Et_2O$	**13e**	74 (74:26)
11	F	$BF_3{\cdot}Et_2O$	**13f**	81 (63:37)
12	G	$BF_3{\cdot}Et_2O$	**13g**	70 (66:34)
13	H	$BF_3{\cdot}Et_2O$	**11**	92 (90:10)
14	H	TMSOTf	**11**	83 (82:18)
15	H	$TiCl_4$	**11**	67 (57:43)
16	I	$BF_3{\cdot}Et_2O$	**11**	89 (91:9)

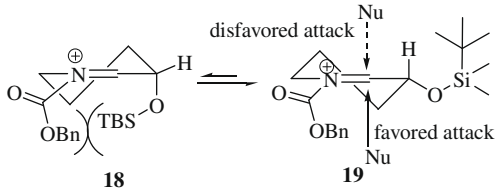
[a] Isolated yields after column chromatography.
[b] The cis/trans ratio was determined from the HPLC data of crude reaction mixture.



Scheme 4. Lewis acid catalyzed nucleophilic substitution reaction.



Scheme 5. Structure determination of **13a**. Reagents and conditions: (a) (i)TBAF, THF, rt, 2 h; (ii) TBDPSCl, imidazole, DMF, rt, 12 h, two steps 67%; (b) 10%Pd/C, MeOH, Boc_2O, triethylamine, rt, overnight, 87%. (c) (i) LiHMDS, THF, TMSCl; (ii) NBS, $NaHCO_3$, two steps 75%; (d) 4-hydroxyquinazoline, KOH, EtOH, refluxed, 83%.



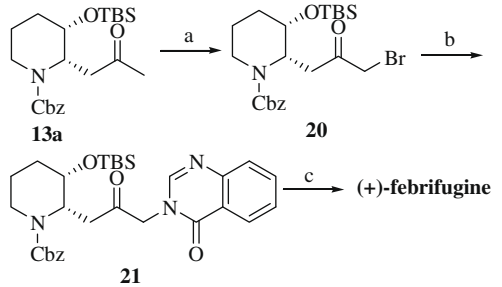
Scheme 6.

was not determined at this stage. To our disappointment, the reaction of **10** with the quinazolinone-containing silyl enol ether[12] did not occur under the same conditions, even at room temperature. Other conditions such as using acetonitrite as polar solvent to stabilize the iminium ion intermediate[13] and to promote the coupling reaction, and $BF_3{\cdot}Et_2O$ used as Lewis acid, the reaction still did not take place. However, it was found that 2.0 equiv of TMSOTf at −30 °C to rt led to **13c** with 52:48 dr in 53% yield (entry 7). We then investigated the reactions of **10** with other silyl enol ethers derived from acetophenones, all reactions proceeded smoothly to give the coupling products **13d–g** in moderate diastereoselectivities (entries 8–12) (Scheme 4).

In most cases, the alkylation products are mixtures of rotamers at room temperature, and unseparable by chromatography on silica gel. So it is hard to determine their stereochemistry by NOE or by the known rules of this reaction system. Considering that both cis and trans **13a** could be converted to the (+)-febrifugine **1** and (+)-isofebrifugine **2,** and there is a equilibrium between these alkaloids,[14] it would be difficult to determine the stereochemistry of **13a** according to the reported total synthesis of (+)-febrifugine. However, the *cis*-**13a** was reported to be convertible to the known 2-*epi*-febrifugine **17** derivative.[5i] This is a helpful information for the determination of the stereochemistry of cis/trans **13**. Thus, reaction of **13a** in the presence of TBAF in tetrahydrofuran followed by in situ protection (TBDPSCl, imidazole) afforded ether **14** in 67% overall yield. Upon palladium-catalyzed hydrogenation (10%Pd/C, MeOH) of ether **14**, the resulting amine was simultaneously reacted with di-*tert*-butyldicarbonate in the presence of triethylamine to give **15** in one-pot with 87% yield. Following a routine work[15] **15** was converted into brominated compound **16**, and treatment of **16** with 4-hydroxyquinazoline in the presence of potassium hydroxide gave 2-*epi*-febrifugine **17** derivative {$[\alpha]_D^{25}$ +12.8 (*c* 0.4,$CHCl_3$); lit[5i] $[\alpha]_D^{25}$ +13.7 (*c* 0.38, $CHCl_3$)} in 62 % yield (Scheme 5). Thus, **13a** was unambiguously established as cis isomer. Base on this result, the configurations of **13e–h** were determined by HPLC analysis in comparison with the results of **13a** and **11**.

The cis selectivity in forming **13a** can be rationalized by considering the two competitive conformations of **18** and **19** in the transition state (Scheme 6). Due to the 1,3-interaction[16] of the Cbz group with the steric bulky 3-silyloxy group, the more stable transition state **19** should be the favored conformation. Axial attack[17] of the nucleophile to **19** would happen from the same face as that of 3-silyloxy group, to generate a chair conformation having the cis-stereochemistry (*cis*-**13)**. This is in agreement with the results of the six-membered-ring oxocarbenium ions reported by Woerpel.[18]

Although (+)-febrifugine **1** can be easily synthesized from compound **17** in one step, this route is inefficient due to the requirement of the two times change of protective groups. Therefore, we then turned our attention to study the direct synthesis of **1** from **13a**. Treatment of **13a** with TMSOTf in the presence of *N,N*-diisopropylethylamine (DIPEA) followed by NBS afforded brominated compound **20** in 72% yield. The reaction of **20** with 4-hydroxyquinazoline in the presence of potassium hydroxide gave protected 2-*epi*-febrifugine **21** derivative in 85% yield. Finally, treatment of **21** in 6 N HCl solution under reflux for 4 h afforded the crude dihydrochloride salt of (+)-isofebrifugine **2**, which is stable under acidic conditions.[5f,5i] After basification of the crude dihydrochloride salt **2** with potassium carbonate, the crude was refluxed in MeOH for 4 h,[5i,19] and the product was recrystallized in ethanol to give (+)-febrifugine **1** {colorless solid, mp 139–141 °C (EtOH); lit.[2b] 138–140 °C; $[\alpha]_D^{25}$ +27.9 (*c* 0.52, EtOH); lit.[2b] $[\alpha]_D^{29}$ +28 (*c* 0.5, EtOH)} in 68% yield. The spectroscopic and physical data of the synthetic



Scheme 7. Total synthesis of (+)-febrifugine. Reagents and conditions: (a) TMSOTf, DIPEA, CH_2Cl_2,1 h, then $NaHCO_3$, NBS, 2 h, 72%; (b) 4-hydroxyquinazoline, KOH, EtOH, refluxed, 85%; (c) 6 N HCl, refluxed, 4 h, then EtOH, refluxed, 68%.

(+)-febrifugine **1** were identical with the reported data.[5] Thus, an efficient method for the synthesis of (+)-febrifugine was established via high diastereoselective nucleophilic substitution reaction of 3-silyloxy-2-acyloxypiperidine with silyl enol ether (Scheme 7).

2. Conclusion

In summary, nucleophilic reactions of 3-silyloxy-2-acyloxypiperidine with silyl enol ethers in the presence of $BF_3{\cdot}Et_2O$ as a catalyst were demonstrated to give high cis-diastereoselectivity. The structure was determined by comparing the two known compounds **12** and **17**. Using this method, a highly diastereoselective approach for the asymmetric synthesis of the antimalarial alkaloid (+)-febrifugine **1** was developed. In addition, a new route for the synthesis of *N*,*O*-acetal **10** from the cheap L-glutamic acid derivatives was also described.

Acknowledgments

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11. *General procedure for the synthesis of* **13a–h** *from* **10**: To a solution of **10** (1.40 mmol) and silyl enol ether (4.20 mmol) in dichloromethane (10 mL) cooled to −78 °C under argon atmosphere, a solution of $BF_3{\cdot}Et_2O$ (2.80 mmol) was added dropwise. After being stirred for 3.5 h at the same temperature, the reaction was quenched with a solution of $NaHCO_3$ aqueous and warmed to room temperature. The mixture was extracted with CH_2Cl_2 (15 mL × 3) and the combined organic layers were dried over anhydrous Na_2SO_4. Filtered and concentrated, the residue was purified by chromatography on silica gel to a mixture of two diastereoisomers **13a–h**. **13a** (78%, >96%, HPLC) as a colorless oil. $[\alpha]_D^{25}$ −42.31 (*c* 1.31, $CHCl_3$); IR (film): ν_{max} 2953, 2933, 1704, 1423, 1254, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers): δ 7.37–7.28 (m, 5H), 5.15 (br s, 2H), 4.90–4.85 (m, 1H), 4.04–4.01 (m, 1/2H), 3.92–3.89 (m, 1/2H), 3.78–3.71(m, 1H), 2.87–2.71 (m, 2H), 2.48–2.46 (m, 1H), 2.21 (br s, 3/2H), 2.06 (m, 3/2H), 1.71–1.68 (m, 2H), 1.64–1.45 (m, 2H), 0.94 (s, 9H), −0.18 (s, 3H), −1.20 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.8, 155.4, 136.5, 128.4, 127.9, 127.8, 69.2, 67.2, 53.0, 39.5, 38.2, 30.1, 28.5, 25.7, 23.7, 18.0, −0.05, −5.01 ppm; MS (ESI): 428.2 ($M+Na^+$); HRMS (MALDI/DHB) calcd for ($C_{22}H_{35}NO_4Si+Na^+$): 428.2233, found: 428.2256.
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