JOC The Journal of Organic Chemistry

Article

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Divergent Method to *trans*-5-Hydroxy-6-alkynyl/alkenyl-2-piperidinones: Syntheses of (−)-Epiquinamide and (+)-Swainsonine

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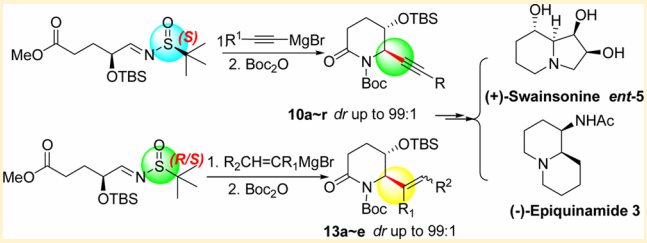
Supporting Information

ABSTRACT: An efficient diastereoselective approach to access *trans*-5-hydroxy-6-alkynyl/alkenyl-2-piperidinones has been developed through nucleophilic addition of α-chiral aldimines using alkynyl/alkenyl Grignard reagents. The diastereoselectivity of alkenyl in C-6 position of 2-piperidinone was controlled by α-alkoxy substitution, while the alkynyl was controlled by the coordination of the α-alkoxy substitution and stereochemistry of sulfinamide. The utility of this straightforward cascade process is demonstrated by the asymmetric synthesis of the (−)-epiquinamide and (+)-swainsonine.



INTRODUCTION

Chiral functionalized piperidines are common framework shared by many bioactive alkaloids, azasugars and pharmaceutical agents (Figure 1).[1] In past decades, tremendous efforts

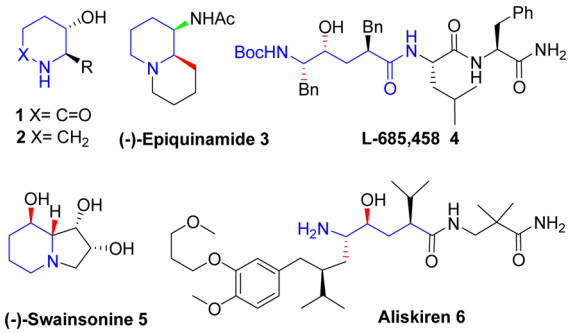


Figure 1. Structures of several bioactive products.

have been devoted to the stereoselective preparation of *trans*- or *cis*-5-hydroxy-6-substituted-2-piperidinones **1** and the corresponding amines **2** (2-substituted-3-piperidinols). Although a number of powerful approaches have been reported,[2,3] direct construction of 5-hydroxy-6-alkynyl/alkenyl-2-piperidinones **1** and 2-alkynyl/alkenyl-3-piperidinols **2** is still quite limited. In 2009, Pyne and co-workers first demonstrated the synthesis of *cis*/*trans*-5-hydroxy-6-alkynyl-2-piperidinones using $BF_3{\cdot}Et_2O$-catalyzed coupling reactions of *N*-acyliminium ions and potassium alkynyltrifluoroborates.[4] In 2012, Caprio and co-workers prepared *trans*-2-alkynyl-3-hydroxy *N*-hydroxypiperidines through nucleophilic addition of organometallic reagents to cyclic nitrone.[3a]

Following the pioneering work of Ellman and Davis, asymmetric addition of imines bearing chiral auxiliaries (e.g., *N*-*tert*-butanesulfinamide and *N*-toluenesulfinamide) with organometallic reagents has become a versatile and practical way for the efficient synthesis of chiral amines.[5−7] However, the application of alkynyl anions for this nucleophilic addition is very rare. Ellman and Qing's group achieved the addition of lithium acetylides to *N*-*tert*-butanesulfinyl ketimines using $AlMe_3$ as a mandatory additive,[8a,c] whereas Hou and co-workers investigated the addition of various alkynes using LiHMDS as a base.[8b] Recently, Lin and co-workers reported the addition of corresponding Grignard reagents to *N*-*tert*-butanesulfinyl imines.[9] While making efforts to extend the nucleophilic addition of chiral imines into the divergent synthesis of bioactive natural products,[10] we found that enantioenriched *N*-*tert*-butanesulfinyl iminoacetates could undergo *tert*-butyl migration-addition upon the treatment with organozinc reagents.[11] In addition, we discovered an intramolecular tandem sequence to afford *trans*-5-hydroxy-6-alkyl/aryl-2-piperidinone skeleton by reacting α-chiral aldimines **7** with alkyl or aryl Grignard reagents (Figure 2, eq 1).[12] Under the optimized reaction conditions, the substitutions of C-5 and C-6 were predominantly in *trans*-2,3-form and the stereochemistry at C-6 position was solely controlled by α-OTBS group. Encouraged by this novel cascade reaction, we

Received: April 10, 2015
Published: May 14, 2015

DOI: 10.1021/acs.joc.5b00803
J. Org. Chem. 2015, 80, 5824−5833

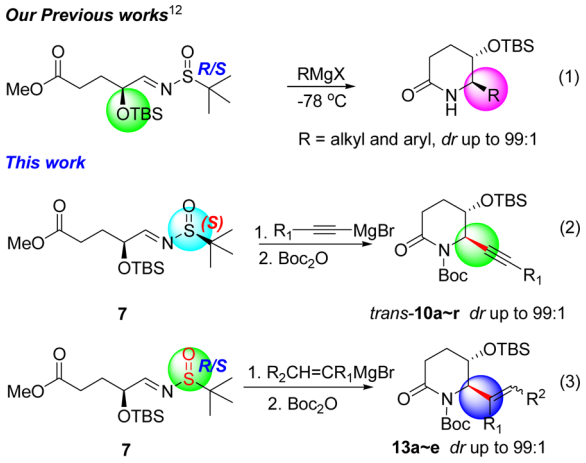


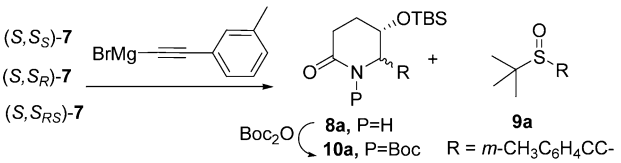
Figure 2. Our protocol to access *trans*-5-hydroxy-6-alkynyl/alkenyl-2-piperidinones.

began to investigate the nucleophilic addition using alkynyl or alkenyl magnesium reagents, which would provide one of the most straightforward methods to *trans*-5-hydroxy-6-alkynyl/alkenyl-2-piperidinones. Herein we report our results of this one-pot cascade process starting from α-chiral aldimines and alkynyl/alkenyl magnesium reagents (Figure 2, eq 2 and 3), as well as its application in the asymmetric syntheses of (−)-epiquinamide **3** and (+)-swainsonine *ent*-**5**.

RESULTS AND DISCUSSION

Our investigation started with the intramolecular cascade reaction of α-chiral aldimines (S,S_{RS})-7[12] and *m*-methylphenylethynyl magnesium bromide. As shown in Table 1, no desired addition-cyclization product **8a** was generated at −78 °C. However, when the reaction mixture was warmed to room temperature, the desired lactam **8a** was observed, which was coeluted with the sulfoxide byproduct **9a** in flash silica gel chromatography. Fortunately, complete separation was achieved when the lactam-NH was protected as *N*-Boc, and

Table 1. Optimization of the Tandem Process



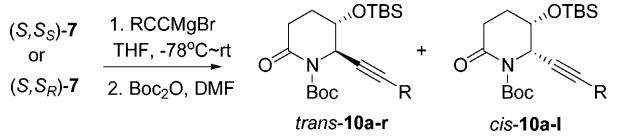
entry[a]	imine	solvent	LA	yield %[c]	*trans*/*cis*[d]
1[b]	(S,S_{RS})-7	THF	–	NR	–
2	(S,S_{RS})-7	THF	–	49	74:26
3	(S,S_S)-7	THF	–	73	99:1
4	(S,S_R)-7	THF	–	32	15:85
5	(S,S_R)-7	THF	$In(OTf)_3$	NR	–
6	(S,S_R)-7	THF	$AlMe_3$	NR	–
7	(S,S_R)-7	THF	$ZnCl_2$	NR	–
8	(S,S_{RS})-7	DCM	–	28	99:1
9	(S,S_{RS})-7	Et_2O	–	44	99:1

[a]The reactions were performed with α-chiral substituted aldimines 7 (1.0 mmol), *m*-methylphenylethynyl magnesium bromide (3 mL, 1.0 M in THF) at −78 °C to rt, then the crude product was treated with Boc_2O (2.0 mmol), DMAP (1.0 mmol) and TEA (5.0 mmol) in DMF for 24 h. [b]The reaction temperature was −78 °C. [c]Isolated yield. [d]*dr* was determined by HPLC or ^1H NMR.

the imide **10a** was obtained in 49% yield (over two steps). It is worth mentioning that the crude **8a** was found to be unstable, especially in $CDCl_3$ solution, while the *N*-Boc imide **10a** showed excellent stability. Despite the acceptable yield of **10a**, the diastereoselectivity of this cascade reaction was very low (*dr* = 74:26) (Table 1, entry 2). Interestingly, when optically pure (S,S_S)- and (S,S_R)-aldimines 7 were subjected to the above conditions respectively, (S,S_S)-aldimine 7 gave the desired product as a *trans* isomer in 73% yield with high diastereoselectivity (*dr* = 99:1) (Table 1, entry 3), while (S,S_R)-7 produced a mixture of two isomers in 32% yield with moderate diastereoselectivity (*trans*:*cis* = 15:85) (Table 1, entry 4). We attempted to improve the stereoselectivity for the substrate (S,S_R)-7 using different Lewis acids, such as $In(OTf)_3$[13] and $AlMe_3$,[8a,c] but the efforts turned out to be fruitless (Table 1, entries 5−7). Different solvents were also examined for the reaction of (S,S_{RS})-7 and *m*-methylphenylethynyl magnesium bromide, both DCM and Et_2O proved to be less favored (Table 1, entries 8−9).

Next, we turned our attention to investigate the scope and limitation of alkynyl Grignard reagents for this tandem addition-cyclization with α-chiral aldimines 7. A variety of substituted alkynyl Grignard reagents were examined under the above optimal conditions, as summarized in Table 2. As for the reactions with (S,S_S)-aldimine 7, various substituents at

Table 2. Reactions with Different Alkynyl Grignard Reagents with 7



entry[a]	R	7	10a−r	yield %[b]	*trans*/*cis*[c]
1	3-Me-C_6H_4-	(S,S_S)	*trans*-**10a**	73	99:1
2	2−Cl-C_6H_4-	(S,S_S)	*trans*-**10b**	65	99:1
3	3−Br-C_6H_4-	(S,S_S)	*trans*-**10c**	63	99:1
4	4-Me-C_6H_4-	(S,S_S)	*trans*-**10d**	71	99:1
5	4−F-C_6H_4-	(S,S_S)	*trans*-**10e**	66	99:1
6	4−Cl-C_6H_4-	(S,S_S)	*trans*-**10f**	63	99:1
7	4−Br-C_6H_4-	(S,S_S)	*trans*-**10g**	62	99:1
8	4-$MeOC_6H_4$-	(S,S_S)	*trans*-**10h**	69	99:1
9	4-propylC_6H_4-	(S,S_S)	*trans*-**10i**	65	99:1
10	C_6H_5-	(S,S_S)	*trans*-**10j**	66	99:1
11	$TBSOCH_2CH_2$-	(S,S_S)	*trans*-**10k**	67	99:1
12	$CH_3(CH_2)_3CH_2$-	(S,S_S)	*trans*-**10l**	64	99:1
13	CH_2SPh	(S,S_S)	*trans*-**10m**	66	99:1
14	CH_2OBn	(S,S_S)	*trans*-**10n**	57	99:1
15	CH_2OTBS	(S,S_S)	*trans*-**10o**	62	99:1
16	*tert*-butyl	(S,S_S)	*trans*-**10p**	69	99:1
17	$Si(CH_3)_3$	(S,S_S)	*trans*-**10q**	58	99:1
18	H	(S,S_S)	*trans*-**10r**	71	99:1
19	3-Me-C_6H_4-	(S,S_R)	*cis*-**10a**	32	15:85
20	4−Cl-C_6H_4-	(S,S_R)	*cis*-**10f**	28	13:87
21	$TBSOCH_2CH_2$-	(S,S_R)	*cis*-**10k**	23	5:95
22	$CH_3(CH_2)_3CH_2$-	(S,S_R)	*cis*-**10l**	27	22:78

[a]The reactions were performed with α-chiral aldimines (S,S_S)-7 or (S,S_R)-7 (1.0 mmol), alkynyl Grignard reagents (3 mL, 1.0 M in THF) in dry THF (5 mL) at −78 °C to rt for overnight, then the crude product was treated with Boc_2O (2.0 mmol), DMAP (1.0 mmol) and TEA (5.0 mmol) in DMF for 24 h. [b]Isolated yield. [c]*dr* was determined by HPLC or ^1H NMR.

DOI: 10.1021/acs.joc.5b00803
J. Org. Chem. 2015, 80, 5824−5833

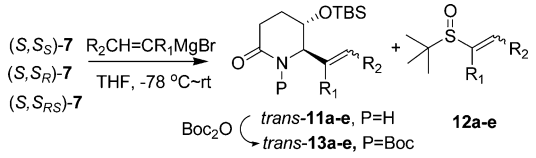
phenylacetylene Grignard reagents were tolerated. Regardless of their electron properties and substitution positions at the phenyl ring, the tandem sequence proceeded smoothly with high diastereoselectivities in 62−73% yields (Table 2, entries 1−10). Alkyl or substituted alkyl substituents of acetylene Grignard reagents were also screened, and they showed excellent tolerance as well (Table 2, entries 11−16). It is worth mentioning that silyl substituted alkyne and simple acetylene (R = H) Grignard reagents could provide the desired products in high diastereoselectivities (Table 2, entries 17−18). As for the reactions with the chiral imine (S,S_R)-**7**, both aryl and alkyl susbtituted acetylene Grignard reagents still provided the *cis*-lactams in poor yields and diastereoselectivities (Table 2, entries 19−22).

The stereochemistry of the products *trans*-**10a−r** was unambiguously assigned as *trans*-form by X-ray crystallography of compound *trans*-**10f** (see Supporting Information). The remaining isomers were assigned *trans*-form based on the compounds having a coupling constant of similar magnitude (J for protons H_5 (C*H*OTBS) and H_6 (C*H*-alkyne).

Then, we turned our attention to investigate the tandem process of α-chiral aldimines (S,S_{RS})-**7** with alkenyl Grignard reagents. When (S,S_{RS})-**7** was treated with vinylmagnesium bromide at −78 °C, the desired product **11a** was obtained. Because **11a** was inseparable from the byproduct sulfoxide **12a** by flash silica gel chromatography, the crude amide **11a** was converted to its imide **13a**, which was isolated in 26% yield (over two steps) with high diastereoselectivity (dr > 99:1) (Table 3, entry 1). When the reaction temperature of nucleophilic addition step was slowly warmed to rt overnight, the yield of corresponding imide **13a** was greatly improved to 64% with high diastereoselectivity (dr > 99:1) (Table 3, entry 2). In order to understand the influence of chiral sulfinyl auxiliary on the stereoselectivity outcome, both (S,S_S)-**7** and (S,S_R)-**7** were applied to this tandem reaction, respectively. In both cases, the desired *trans* isomer was obtained with very high diastereoselectivities (dr > 99:1), and (S,S_S)-**7** offered slightly better yield than (S,S_R)-**7** (Table 3, entries 3 and 4). Probably the steric hindrance of (S,S_R)-**7** slightly affected the nucleophilic attack of Grignard reagent to S−N bond during the step to cleave auxiliary.[12] With optimal conditions in hand, a survey of different substituted alkenyl Grignard reagents were examined for (S,S_{RS})-**7**, as summarized in Table 3. When alkyl substituted vinylmagnesium bromide was used, the tandem addition-cyclization proceeded smoothly with high diastereoselectivity and in 61% yield (Table 3, entry 5). Although phenyl and *para*-methylphenyl substituted vinyl Grignard reagents could provide similar yields compared to vinylmagnesium bromide (Table 3, entries 6−7), the α-naphthyl substituted vinylmagnesium bromide led to lower yield for the desired lactams **13e** (Table 3, entry 8). It is worth mentioning that all products **13b−e**, as mixtures of Z/E isomers (ca. 1:1), showed excellent diastereoselectivities. These results indicated that the generation of stereogenic center at the C-6 position was solely controlled by α-OTBS group[7d] in this tandem sequence starting from α-chiral aldimines **7** and alkenyl Grignard reagents.

With chiral lactams **11a** in hand, we focused on the total synthesis of (−)-epiquinamide **3**, an alkaloid isolated from the skin of Ecuadorian frog *Epipedobates tricolor* in 2003.[14a,b] (−)-Epiquinamide **3** represents a new structural class of nicotinic agonist, selective for nicotinic receptor containing the β_2-subunit,[14c] and is considered to be a lead compound in the development of new therapeutics for neuronal receptors. Recently, the initially isolated group has found that the synthetic epiquinamide was inactive at nicotinic receptors.[14d] Because of its scarcity from natural sources (240 μg from 183 frogs) and inaccurately potential use in drug development, both enantiomers of epiquinamide **3** have attracted considerable attention and several asymmetric routes have been reported in past years.[15] As a continuation of our program for asymmetric synthesis of natural products including epiquinamide **3**,[15l] our synthesis started with the crude lactam **11a**, which was derived from the tandem process of (S,S_{RS})-**7** with vinylmagnesium bromide. Upon the treatment with lithium aluminum hydride ($LiAlH_4$) and subsequent protection with di-*tert*-butyl dicarbonate (Boc_2O), *N*-Boc piperidine **14** was obtained in 48% yield. After the hydroxyl group in **14** was converted to TBS ether, *N*-Boc group was cleaved by trifluoroacetic acid (TFA) and the resultant amine was coupled with but-3-enoic acid using diethyl phosphorocyanidate (DEPC)[16] to give the corresponding amide **16** in 79% overall yield. The subsequent ring closure using Grubbs second-generation catalyst[17] successfully afforded the bicyclic compound **17** in 97% yield. Upon the reduction of the carbon−carbon double bond and cleavage of O-TBS protection group, the alcohol **18** was obtained in 84% yield. The X-ray crystallography of **18** further confirmed the formation of *trans* isomer during the nucleophilic attack and cyclization step (see Supporting Information). Oxidation of **18** with Dess−Martin periodinane (DMP)[18] gave the desired ketone **19** in quantitative yield. Oxime formation with $NH_2OMe{\cdot}HCl$, followed by subsequent reduction with $BH_3{\cdot}THF$ and acetylation (Ac_2O, NaOH), led to the desired (−)-epiquinamide **3** {$[\alpha]_D^{25}$ = −20.3 (c 0.65, $CHCl_3$), lit.[15b] $[\alpha]_D^{20}$ = −25 (c 0.26, $CHCl_3$); lit.[15d] $[\alpha]_D^{25}$ = −22 (c 0.5, $CHCl_3$}) in 67% isolated yield. The spectroscopic and physical data of the synthetic (−)-epiquinamide **3** were identical to the reported data.[15b,d] Thus, epiquinamide **3** was synthesized in 6.2% overall yield by 19 steps from the L-glutamic acid (Scheme 1).

Table 3. Reactions with Different Alkenyl Grignard Reagents with 7

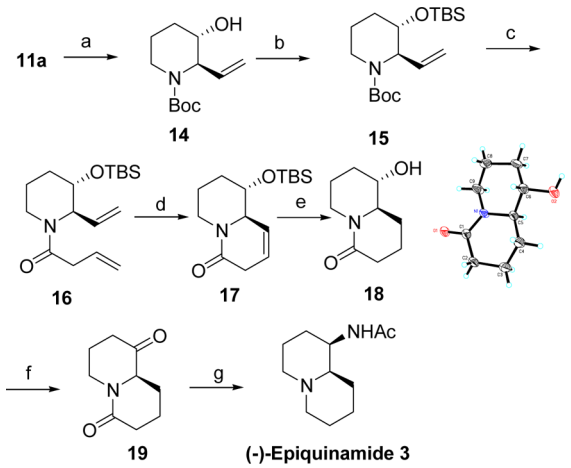


entry[a]	7	R_1	R_2	13a−e	yield %[c]	*trans*/*cis*[d]
1[b]	(S,S_{RS})	H	H	**13a**	26	99:1
2	(S,S_{RS})	H	H	**13a**	64	99:1
3	(S,S_S)	H	H	**13a**	71	99:1
4	(S,S_R)	H	H	**13a**	55	99:1
5	(S,S_{RS})	Et-	H	**13b**	61	99:1
6	(S,S_{RS})	H	C_6H_5-	**13c**	55	99:1
7	(S,S_{RS})	H	*p*-$CH_3C_6H_4$-	**13d**	62	99:1
8	(S,S_{RS})	H	α-Naphthyl-	**13e**	47	99:1

[a]The reactions were performed with α-chiral substituted aldimines **7** (1.0 mmol), alkenyl Grignard reagents (3 mL, 1.0 M in THF) in dry THF (5 mL) at −78 °C to rt for overnight, then the crude product was treated with Boc_2O (2.0 mmol), DMAP (1.0 mmol) and TEA (5.0 mmol) in DMF for 24 h. [b]The reaction temperature was −78 °C. [c]Isolated yield. [d]dr was determined by HPLC or ^1H NMR, and E/Z isomers were isolated by silica gel chromatography.

DOI: 10.1021/acs.joc.5b00803
J. Org. Chem. 2015, 80, 5824−5833

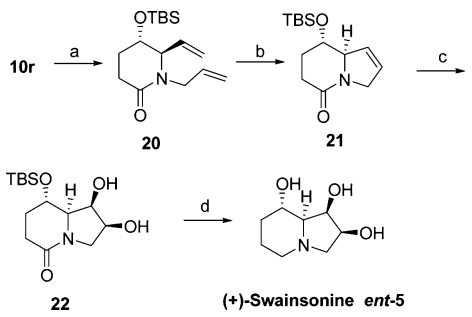
Scheme 1. Asymmetric Synthesis of (−)-Epiquinamide 3[a]



[a]Reagents and conditions: (a) (1) $LiAlH_4$, THF, reflux, overnight; (2) Boc_2O, TEA, $NaHCO_3$, DCM, 12 h, 48% (2 steps); (b) TBSCl, DMAP, imidazole, DMF, 24 h, quantitative yield; (c) (1) TFA, DCM, 0 °C, 3.5 h; (2) *but*-3-enoic acid, DEPC, TEA, DMF 0 °C to rt, overnight, 79% (2 steps); (d) Grubbs 2nd, CH_2Cl_2, reflux, 12 h, 97%; (e) Pd/C, MeOH, H_2, rt, 5 h, then 6 N HCl, overnight, 84%; (f) DMP, DCM, 0.5 h, rt, quantitative yield; (g) (1) $NH_2OMe{\cdot}HCl$, pyridine, 0.5 h; (2) borane (1 M in THF), THF, 50 °C, 4 h; (3) Ac_2O, 1 M NaOH, dioxane, rt, 3 h, 67% (3 steps).

Another example for the application of this tandem process α-chiral aldimine **7** with alkynyl Grignard reagents was demonstrated by the asymmetric synthesis of natural product (+)-swainsonine *ent*-**5**, which was isolated from the fungus rhizoctonia legumincola,[19] other plant and fungi.[20] (+)-Swainsonine *ent*-**5** exhibited lysosomal α-mannosidase, mannosidase II inhibitory properties,[21] and is being tested as a new treatment for cancer, HIV, and immunological.[22] Furthermore, this attractive molecule was the first glycoprotein processing inhibitor selected for clinical evaluation as an anticancer drug.[23] In the past decades, due to its important bioactivities and attractive structure, swainsonine has become a classic target for the demonstration of new synthetic methods and/or strategies relevant to indolizidine synthesis.[24−26] The facile preparation of chiral δ-lactam **10r** allowed us to construct indolizidine skeleton through ring-closing metathesis. As shown in Scheme 2, crude δ-lactam **10r** was hydrogenated by hydrogen in the presence of Lindlar catalyst (Pd-$BaSO_4$, quinoline) and subsequently alkylated with allyl bromide to give the bis-olefin **20** in 67% yield. The subsequent ring closure successfully afforded the bicyclic intermediate **21** using Grubbs second-generation catalyst[17] in 93% yield. Next, the dihydroxylation of alkene **21** with NMO in the presence of 0.1 equiv $K_2Os_2O_2(OH)_4$ resulted in the desired *cis*-diol **22** as the single isomer in 94% yield. Finally, **22** was subjected to reduction with $LiAlH_4$ at 60 °C and desilylation with HCl/MeOH, affording (+)-Swainsonine *ent*-**5** {$[\alpha]_D^{25}$ = +84.6 (*c* 1.20, CH_3OH), lit.[25a] $[\alpha]_D^{24}$ = +83.3 (*c* 0.5, CH_3OH); lit.[25b] $[\alpha]_D^{21}$ = +84.3 (*c* 1.02, H_2O); mp 143−144 °C; lit.[25a] mp 143−145 °C} in 87% yield. The spectroscopic and physical data of the synthetic (+)-swainsonine *ent*-**5** and its hydrochloride salt were identical to the reported data.[25]

Scheme 2. Asymmetric Synthesis of (+)-Swainsonine *ent*-5[a]



[a]Reagents and conditions: (a) (1) 5% Pd-$BaSO_4$, quinoline, MeOH, 0 °C, 3 h; (2) AllylBr, NaH, DMF, 0 °C to rt, 67% (2 steps); (b) Grubbs 2nd, CH_2Cl_2, reflux, 12 h, 93%; (c) $K_2Os_2O_2(OH)_4$, NMO, *t*-BuOH/H_2O, overnight, 94%; (d) (1) LAH, THF, reflux, overnight; (2) 1 M HCl−MeOH overnight, rt, 87% (2 steps).

CONCLUSION

In summary, we established a convenient and one-pot method for highly diastereoselective synthesis of *trans*-5-hydroxy-6-alkynyl-2-piperidinones **10a−r** by the reactions of (S,S_S)-**7** with alkynyl Grignard reagents. As for the tandem process of (S,S_{RS})-**7** with alkenyl Grignard reagents, the desired *trans*-5-hydroxy-6-alkenyl-2-piperidinones **13a−e** were also obtained and the stereochemistry at stereogenic center of C-6 was solely controlled by α-alkoxy substitution. The synthetic application of this methodology was demonstrated by the concise syntheses of (−)-epiquinamide **3** and (+)-swainsonine *ent*-**5**. Especially, (+)-swainsonine *ent*-**5** was synthesized in 14 steps from cheap L-glutamic acid in 16.8% overall yield.

EXPERIMENTAL SECTION

General Methods. THF was distilled from sodium/benzophenone. Reactions were monitored by thin layer chromatography (TLC) on glass plates coated with silica gel with fluorescent indicator. Flash chromatography was performed on silica gel (300−400) with Petroleum/EtOAc as eluent. Optical rotations were measured on a polarimeter with a sodium lamp. HRMS were measured on a LCMS-IT-TOF apparatus. IR spectra were recorded using film on a Fourier Transform Infrared Spectrometer. NMR spectra were recorded at 400 or 500 MHz, and chemical shifts are reported in δ (ppm) referenced to an internal TMS standard for ^{1}H NMR and $CDCl_3$ (77.0 ppm) for ^{13}C NMR.

General Procedure for Synthesis of 10a−r and 13a−e. To a solution of compound **7** (363 mg, 1.00 mmol) in anhydrous THF (5 mL) was treated with a solution of alkynyl/alkenyl Grignard reagents (3 mL, 1 M in THF) at −78 °C to rt overnight. The mixture was quenched with a saturated NH_4Cl aqueous solution and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine, dried, filtrated and concentrated. The crude, Boc_2O (436 mg, 2.00 mmol) and DMAP (122 mg, 1.00 mmol) were stirred in DMF (5 mL) before TEA (0.7 mL, 5.00 mmol) was dropped, then the reaction mixture was stirred for 24h. The mixture was quenched with a saturated NH_4Cl aqueous solution and extracted with EtOAc (30 mL × 4). The combined organic layers were washed with water (30 mL × 2) and brine, dried, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 15/1) to give **10a−r** and **13a−e**.

(2*R*,3*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-6-*oxo*-2-(2-*m*-tolylethynyl)piperidine-1-carboxylate *trans*-10a. Yellow oil (322 mg, 73%); $[\alpha]_D^{25}$ = −17.0 (*c* 1.52, $CHCl_3$); IR (film) ν_{max} 2958, 2930, 2895, 2857, 1775, 1723, 1473, 1367, 1292, 1251, 1145, 1107, 1087, 1002, 889, 837, 779 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.13 (m, 4H), 5.12 (dd, *J* = 3.0, 1.8 Hz, 1H), 4.33−4.28 (m, 1H), 2.77 (ddd, *J* = 18.0, 10.4, 7.4 Hz, 1H), 2.61 (ddd, *J* = 17.4, 7.4, 3.2 Hz, 1H), 2.51−2.41 (m, 1H), 2.34 (s, 3H), 1.90−1.81 (m, 1H), 1.57 (s, 9H), 0.91 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H) ppm; ^{13}C NMR

DOI: 10.1021/acs.joc.5b00803
J. Org. Chem. 2015, 80, 5824−5833

(100 MHz, $CDCl_3$) δ 170.3, 151.9, 138.0, 132.2, 129.6, 128.7, 128.2, 121.8, 85.4, 85.2, 83.2, 67.9, 54.6, 29.9, 28.0, 26.1, 25.6, 21.1, 17.9, −4.9, −5.0 ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{25}H_{37}NO_4SiNa$ 466.2390, found 466.2403.

(2*R*,3*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(2-(2-chlorophenyl)ethynyl)-6-oxopiperidine-1-carboxylate *trans*-10b. Colorless oil (301 mg, 65%); $[\alpha]_D^{25}$ = −25.7 (*c* 1.78, $CHCl_3$); IR (film) ν_{max} 2954, 2932, 2896, 2855, 1780, 1724, 1473, 1367, 1293, 1252, 1146, 1112, 1008, 888, 838, 779, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47−7.38 (m, 2H), 7.31−7.19 (m, 2H), 5.17 (dd, *J* = 3.0, 1.8, Hz, 1H), 4.37−4.33 (m, 1H), 2.76 (ddd, *J* = 17.8, 10.2, 7.4 Hz, 1H), 2.64 (ddd, *J* = 17.2, 7.6, 3.2 Hz, 1H), 2.59−2.49 (m, 1H), 1.91−1.82 (m, 1H), 1.56 (s, 9H), 0.90 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 151.9, 136.3, 133.4, 129.8, 129.3, 126.5, 122.0, 90.8, 83.3, 82.1, 67.9, 54.6, 29.9, 28.0, 26.2, 25.6, 17.9, −4.8, −5.0 ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{24}H_{34}ClNO_4SiNa$ 486.1843, found 486.1848.

(2*R*,3*S*)-*tert*-Butyl 2-(2-(3-bromophenyl)ethynyl)-3-(*tert*-butyldimethylsilyloxy)-6-oxopiperidine-1-carboxylate *trans*-10c. Colorless oil (319 mg, 63%); $[\alpha]_D^{25}$ = −14.1 (*c* 1.70, $CHCl_3$); IR (film) ν_{max} 2954, 2931, 2879, 2854, 1775, 1723, 1589, 1556, 1471, 1369, 1293, 1252, 1145, 1108, 1086, 1008, 887, 838, 779, 684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58−7.55 (m, 1H), 7.50−7.46 (m, 1H), 7.36−7.32 (m, 1H), 7.22−7.17 (m, 1H), 5.11 (dd, *J* = 2.8, 2.0 Hz, 1H), 4.32−4.28 (m, 1H), 2.77 (ddd, *J* = 18.0, 10.4, 7.2 Hz, 1H), 2.59 (ddd, *J* = 17.2, 7.2, 3.2 Hz, 1H), 2.47−2.37 (m, 1H), 1.91−1.82 (m, 1H), 1.56 (s, 9H), 0.90 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 152.0, 134.4, 131.9, 130.3, 129.8, 124.0, 122.1, 87.0, 83.7, 83.4, 67.8, 54.5, 29.9, 28.0, 26.2, 25.6, 17.9, −4.8, −5.0 ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{24}H_{34}{}^{79}BrNO_4SiNa$ 530.1338, found 530.1334, $[M + Na]^+$ Calcd for $C_{24}H_{34}{}^{81}BrNO_4SiNa$ 532.1318, found 532.1319.

(2*R*,3*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-6-*oxo*-2-(2-*p*-tolylethynyl)piperidine-1-carboxylate *trans*-10d. Colorless oil (314 mg, 71%); $[\alpha]_D^{25}$ = −16.4 (*c* 1.10, $CHCl_3$); IR (film) ν_{max} 2957, 2926, 2897, 2854, 2367, 2340, 1769, 1722, 1508, 1459, 1369, 1292, 1250, 1146, 1106, 1002, 889, 840, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.29 (m, 2H), 7.16−7.11 (m, 2H), 5.11 (dd, *J* = 3.2, 2.0 Hz, 1H), 4.32−4.29 (m, 1H), 2.76 (ddd, *J* = 18.0, 10.4, 7.6 Hz, 1H), 2.60 (ddd, *J* = 17.2, 7.2, 3.2 Hz, 1H), 2.50−2.41 (m, 1H), 2.36 (s, 3H), 1.89−1.80 (m, 1H), 1.56 (s, 9H), 0.91 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 151.9, 138.9, 131.6, 129.1, 120.0, 85.4, 85.0, 83.2, 67.9, 54.7, 29.9, 28.0, 26.1, 25.6, 21.5, 18.0, −4.8, −5.0 ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{25}H_{37}NO_4SiNa$ 466.2390, found 466.2378.

(2*R*,3*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(2-(4-fluorophenyl)ethynyl)-6-oxopiperidine-1-carboxylate *trans*-10e. White solid (295 mg, 66%), mp 83−84 °C; $[\alpha]_D^{25}$ = −13.9 (*c* 0.72, $CHCl_3$); IR (film) ν_{max} 2958, 2928, 2854, 1775, 1715, 1505, 1472, 1368, 1293, 1248, 1144, 1105, 1089, 1013, 832, 776 cm^{-1}; ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.14 ppm; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.36 (m, 2H), 7.06−6.98 (m, 2H), 5.11 (dd, *J* = 3.0, 1.8 Hz, 1H), 4.32−4.29 (m, 1H), 2.77 (ddd, *J* = 18.0, 10.4, 7.2 Hz, 1H), 2.60 (ddd, *J* = 17.2, 7.2, 3.2 Hz, 1H), 2.49−2.39 (m, 1H), 1.91−1.82 (m, 1H), 1.56 (s, 9H), 0.93−0.89 (m, 9H), 0.15 (s, 3H), 0.14 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 162.7 (d, *J* = 248.7 Hz), 152.0, 133.7 (d, *J* = 8.3 Hz), 118.2 (d, *J* = 3.1 Hz), 115.6 (d, *J* = 21.9 Hz), 85.4, 84.2, 83.3, 67.9, 54.6, 29.9, 28.0, 26.1, 25.6, 18.0, −4.9, −5.0 ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{24}H_{34}FNO_4SiNa$ 470.2139, found 470.2130.

(2*R*,3*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(2-(4-chlorophenyl)ethynyl)-6-oxopiperidine-1-carboxylate *trans*-10f. White solid (292 mg, 63%), mp105−106 °C; $[\alpha]_D^{25}$ = −14.1 (*c* 1.42, $CHCl_3$); IR (film) ν_{max} 2953, 2930, 2895, 2857, 1775, 1723, 1487, 1364, 1292, 1249, 1146, 1108, 1090, 1016, 889, 837, 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.28 (m, 4H), 5.11 (dd, *J* = 3.0, 1.8 Hz, 1H), 4.32−4.27 (m, 1H), 2.77 (ddd, *J* = 18.2, 10.6, 7.4 Hz, 1H), 2.59 (ddd, *J* = 17.6, 7.4, 3.2 Hz, 1H), 2.47−2.37 (m, 1H), 1.90−1.81 (m, 1H), 1.55 (s, 9H), 0.90 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 152.0, 134.8, 132.9, 128.7, 120.5, 86.7, 84.1, 83.3, 67.8, 54.6, 29.9, 28.0, 26.1, 25.6, 17.9, −4.9, −5.0 ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{24}H_{34}ClNO_4SiNa$ 486.1843, found 486.1845.

(2*R*,3*S*)-*tert*-Butyl 2-(2-(4-bromophenyl)ethynyl)-3-(*tert*-butyldimethylsilyloxy)-6-oxopiperidine-1-carboxylate *trans*-10g. Pale yellow solid (314 mg, 62%), mp 87−88 °C; $[\alpha]_D^{25}$ = −11.6 (*c* 1.86, $CHCl_3$); IR (film) ν_{max} 2953, 2931, 2895, 2860, 1780, 1723, 1484, 1369, 1293, 1250, 1145, 1106, 1009, 887, 843, 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49−7.44 (m, 2H), 7.30−7.25 (m, 2H), 5.10 (dd, *J* = 2.8, 2.0 Hz, 1H), 4.33−4.27 (m, 1H), 2.77 (ddd, *J* = 18.0, 10.8, 7.2 Hz, 1H), 2.58 (ddd, *J* = 17.6, 7.2, 3.2 Hz, 1H), 2.47−2.37 (m, 1H), 1.90−1.81 (m, 1H), 1.56 (s, 9H), 0.90 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 150.8, 132.0, 130.5, 121.9, 119.8, 85.7, 83.0, 82.2, 66.6, 53.5, 28.7, 26.8, 25.0, 24.4, 16.8, −6.0, −6.2 ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{24}H_{34}{}^{79}BrNO_4SiNa$ 530.1338, found 530.1346; Calcd for $C_{24}H_{34}{}^{81}BrNO_4SiNa$ 532.1318, found 532.1333.

(2*R*,3*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(2-(4-methoxyphenyl)ethynyl)-6-oxopiperidine-1-carboxylate *trans*-10h. Colorless oil (317 mg, 69%); $[\alpha]_D^{25}$ = −14.4 (*c* 1.22, $CHCl_3$); IR (film) ν_{max} 2954, 2931, 2899, 2860, 1774, 1723, 1610, 1510, 1468, 1367, 1291, 1249, 1146, 1107, 1030, 1008, 886, 836, 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.32 (m, 2H), 6.88−6.83 (m, 2H), 5.11 (dd, *J* = 3.2, 2.0 Hz, 1H), 4.32−4.27 (m, 1H), 3.83 (s, 3H), 2.76 (ddd, *J* = 18.0, 10.4, 7.4 Hz, 1H), 2.60 (ddd, *J* = 17.2, 7.2, 3.2 Hz, 1H), 2.51−2.40 (m, 1H), 1.89−1.80 (m, 1H), 1.56 (s, 9H), 0.90 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 157.9, 150.0, 131.2, 112.1, 112.0, 83.2, 82.3, 81.2, 66.0, 53.3, 52..8, 27.9, 26.0, 24.1, 23.6, 16.0, −6.8, −7.0 ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{25}H_{37}NO_5SiNa$ 482.2339, found 482.2345.

(2*R*,3*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-6-*oxo*-2-(2-(4-propylphenyl)ethynyl)piperidine-1-carboxylate *trans*-10i. Colorless oil (306 mg, 65%); $[\alpha]_D^{25}$ = −14.8 (*c* 1.25, $CHCl_3$); IR (film) ν_{max} 2956, 2930, 2895, 2858, 2361, 1775, 1723, 1473, 1369, 1293, 1250, 1145, 1107, 1009, 887, 838, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.31 (m, 2H), 7.16−7.11 (m, 2H), 5.12 (dd, *J* = 2.8, 2.0 Hz, 1H), 4.32−4.28 (m, 1H), 2.76 (ddd, *J* = 18.0, 10.4, 7.4 Hz, 1H), 2.66−2.55 (m, 3H), 2.51−2.41 (m, 1H),1.89−1.80 (m, 1H), 1.69−1.60 (m, 2H), 1.56 (s, 9H), 0.94 (t, 3H), 0.91 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 151.4, 143.1, 131.1, 128.0, 118.7, 84.9, 84.5, 82.7, 67.5, 54.2, 37.4, 29.4, 27.5, 25.5, 25.1, 23.8, 17.5, 13.2, −5.3, −5.5 ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{27}H_{41}NO_4SiNa$ 494.2703, found 494.2719.

(2*R*,3*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-6-*oxo*-2-(2-phenylethynyl)piperidine-1-carboxylate *trans*-10j. White solid (283 mg, 66%), mp 62−63 °C; $[\alpha]_D^{25}$ = −15.7 (*c* 1.29, $CHCl_3$); IR (film) ν_{max} 2953, 2931, 2895, 2855, 1780, 1723, 1367, 1293, 1250, 1145, 1106, 1013, 891, 836, 779, 756, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45−7.30 (m, 5H), 5.13 (dd, *J* = 3.0, 1.8 Hz, 1H), 4.35−4.30 (m, 1H), 2.77 (ddd, *J* = 18.0, 10.8, 7.6 Hz, 1H), 2.61 (ddd, *J* = 17.6, 7.2, 3.2 Hz, 1H), 2.50−2.40 (m, 1H), 1.90−1.81 (m, 1H), 1.57 (s, 9H), 0.91 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 151.9, 131.7, 128.7, 128.3, 122.0, 85.6, 85.2, 83.2, 67.9, 54.6, 29.8, 28.0, 26.1, 25.6, 17.9, −4.9, −5.0 ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{24}H_{35}NO_4SiNa$ 452.2233, found 452.2241.

(2*R*,3*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(4-(*tert*-butyldimethylsilyloxy)but-1-ynyl)-6-oxopiperidine-1-carboxylate *trans*-10k. Colorless oil (342 mg, 67%); $[\alpha]_D^{25}$ = −13.7 (*c* 0.95, $CHCl_3$); IR (film) ν_{max} 2954, 2930, 2857, 1775, 1724, 1368, 1294, 1253, 1148, 1105, 1006, 837, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.90−4.85 (m, 1H), 4.17 (dd, *J* = 6.4, 3.2 Hz, 1H), 3.72−3.67 (m, 2H), 2.70 (ddd, *J* = 18.0, 10.4, 7.2 Hz, 1H), 2.53 (ddd, *J* = 17.2, 7.2, 3.2 Hz, 1H), 2.43−2.33 (m, 3H), 1.81−1.73 (m, 1H), 1.54 (s, 9H), 0.91 (s, 9H), 0.88 (s, 9H), 0.10 (s, 6H), 0.08 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 152.1, 83.1, 83.0, 77.9, 68.0, 61.6, 54.2, 29.9, 28.0, 25.9, 25.8, 25.6, 23.1, 18.3, 17.9, −4.9, −5.0, −5.3 ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{26}H_{49}NO_5Si_2Na$ 534.3047, found 534.3045.

DOI: 10.1021/acs.joc.5b00803
J. Org. Chem. 2015, 80, 5824−5833

(2*R*,3*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(*hept*-1-ynyl)-6-oxopiperidine-1-carboxylate *trans*-10l. Colorless oil (271 mg, 64%); $[\alpha]_D^{25}$ = −10.5 (*c* 0.97, $CHCl_3$); IR (film) ν_{max} 2958, 2930, 2858, 1775, 1723, 1407, 1366, 1293, 1252, 1150, 1103, 1005, 887, 840, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.90−4.85 (m, 1H), 4.18−4.14 (m, 1H), 2.71 (ddd, *J* = 18.0, 10.4, 7.4 Hz, 1H), 2.53 (ddd, *J* = 17.2, 7.2, 3.2 Hz, 1H), 2.43−2.33 (m, 1H), 2.21−2.14 (m, 2H), 1.80−1.73 (m, 1H), 1.54 (s, 9H), 1.52−1.45 (m, 2H), 1.40−1.26 (m, 4H), 0.94−0.89 (m, 3H), 0.88 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 152.0, 86.1, 82.9, 68.1, 54.3, 31.0, 29.8, 28.1, 27.9, 25.8, 25.6, 22.1, 18.6, 17.9, 13.9, −4.9, −5.0 ppm; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ Calcd for $C_{23}H_{41}NO_4SiNa$ 446.2703, found 446.2711.

(2*R*,3*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-6-*oxo*-2-(3-(phenylthio)prop-1-ynyl)piperidine-1-carboxylate *trans*-10m. Colorless oil (314 mg, 66%); $[\alpha]_D^{25}$ = −17.5 (*c* 1.68, $CHCl_3$); IR (film) ν_{max} 2956, 2928, 2893, 2856, 1775, 1723, 1583, 1473, 1368, 1294, 1252, 1144, 1105, 1089, 1003, 891, 837, 776, 744, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44−7.39 (m, 2H), 7.36−7.30 (m, 2H), 7.29−7.23 (m, 1H), 4.86−4.82 (m, 1H), 4.05−4.02 (m, 1H), 3.68−3.58 (m, 2H), 2.62 (ddd, *J* = 18.0, 10.4, 7.6 Hz, 1H), 2.36 (ddd, *J* = 17.6, 7.6, 3.2 Hz, 1H), 2.11−2.02 (m, 1H), 1.68−1.59 (m, 1H), 1.52 (s, 9H), 0.86 (s, 9H), 0.07 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 151.9, 134.5, 130.5, 128.9, 127.1, 83.1, 81.3, 80.1, 67.7, 54.0, 29.7, 27.9, 25.8, 25.5, 22.8, 17.9, −4.9, −5.1 ppm; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ Calcd for $C_{25}H_{37}NO_4SSiNa$ 498.2110, found 498.2128.

(2*R*,3*S*)-*tert*-Butyl 2-(3-(benzyloxy)prop-1-ynyl)-3-(*tert*-butyldimethylsilyloxy)-6-oxopiperidine-1-carboxylate *trans*-10n. Pale yellow solid (270 mg, 57%), mp 50−51 °C; $[\alpha]_D^{25}$ = −10.9 (*c* 1.23, $CHCl_3$); IR (film) ν_{max} 2954, 2931, 2898, 2857, 2356, 1775, 1723, 1609, 1472, 1457, 1367, 1293, 1252, 1147, 1087, 1005, 893, 837, 779, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.30 (m, 5H), 4.99−4.95 (m, 1H), 4.58 (s, 2H), 4.24−4.21 (m, 1H), 4.20 (d, *J* = 1.6 Hz, 1H), 2.74 (ddd, *J* = 18.0, 10.8, 7.2 Hz, 1H), 2.55 (ddd, *J* = 17.6, 7.2, 3.2 Hz, 1H), 2.42−2.32 (m, 1H), 1.86−1.77 (m, 1H), 1.55 (s, 9H), 0.89 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 152.1, 137.2, 128.5, 128.1, 128.0, 83.3, 83.2, 81.4, 71.8, 67.7, 57.3, 54.1, 29.8, 28.0, 26.0, 25.6, 17.9, −4.9, −5.0 ppm; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ Calcd for $C_{26}H_{39}NO_5SiNa$ 496.2495, found 496.2496.

(2*R*,3*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(3-(*tert*-butyldimethylsilyloxy)prop-1-ynyl)-6-oxopiperidine-1-carboxylate *trans*-10o. Colorless oil (308 mg, 62%); $[\alpha]_D^{25}$ = −12.5 (*c* 0.97, $CHCl_3$); IR (film) ν_{max} 2955, 2929, 2895, 2854, 1775, 1724, 1463, 1364, 1293, 1252, 1147, 1086, 1008, 891, 835, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.96−4.93 (m, 1H), 4.32 (d, *J* = 1.6 Hz, 1H), 4.23−4.18 (m, 1H), 2.72 (ddd, *J* = 18.0, 10.4, 7.2 Hz, 1H), 2.53 (ddd, *J* = 17.2, 7.2, 3.2 Hz, 1H), 2.43−2.33 (m, 1H), 1.84−1.75 (m, 1H), 1.54 (s, 9H), 0.91 (s, 9H), 0.88 (s, 9H), 0.12 (s, 6H), 0.10 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 151.9, 84.0, 83.1, 81.3, 67.7, 54.0, 51.6, 29.8, 27.9, 25.9, 25.7, 25.6, 18.2, 17.9, −4.9, −5.1, −5.2 ppm; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ Calcd for $C_{25}H_{47}NO_5Si_2Na$ 520.2890, found 520.2895.

(2*R*,3*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(3,3-dimethylbut-1-ynyl)-6-oxopiperidine-1-carboxylate *trans*-10p. Colorless oil (282 mg, 69%); $[\alpha]_D^{25}$ = −7.5 (*c* 1.19, $CHCl_3$); IR (film) ν_{max} 2969, 2931, 2895, 2858, 1780, 1723, 1479, 1364, 1287, 1251, 1147, 1105, 1008, 891, 832, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.85 (dd, *J* = 3.0, 1.8 Hz, 1H), 4.16−4.12 (m, 1H), 2.69 (ddd, *J* = 18.0, 10.4, 7.6 Hz, 1H), 2.54 (ddd, *J* = 17.6, 7.6, 3.2 Hz, 1H), 2.40−2.29 (m, 1H), 1.80−1.72 (m, 1H), 1.54 (s, 9H), 1.20 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 151.8, 94.1, 82.9, 75.3, 68.1, 54.3, 30.8, 29.8, 28.0, 27.4, 25.7, 25.6, 17.9, −4.9, −5.0 ppm; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ Calcd for $C_{22}H_{39}NO_4SiNa$ 432.2546, found 432.2551.

(2*R*,3*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-6-*oxo*-2-(2-(trimethylsilyl)ethynyl)piperidine-1-carboxylate *trans*-10q. White solid (247 mg, 58%), mp 42−43 °C; $[\alpha]_D^{25}$ = −10.4 (*c* 0.98, $CHCl_3$); IR (film) ν_{max} 2958, 2926, 2895, 2860, 2169, 1780, 1725, 1473, 1369, 1287, 1251, 1145, 1106, 1040, 1003, 974, 842, 777, 648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.88 (dd, *J* = 2.8, 2.0 Hz, 1H), 4.23−4.18 (m, 1H), 2.71 (ddd, *J* = 18.0, 10.4, 7.2 Hz, 1H), 2.56 (ddd, *J* = 17.2, 7.2, 3.2 Hz, 1H), 2.41−2.31 (m, 1H), 1.83−1.74 (m, 1H), 1.55 (s, 9H), 0.90−0.86 (m, 9H), 0.19−0.16 (m, 9H), 0.13−0.10 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 151.7, 101.9, 90.3, 83.2, 67.9, 54.8, 29.8, 27.9, 25.8, 25.6, 17.9, −0.2, −4.9, −5.0 ppm; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ Calcd for $C_{21}H_{39}NO_4Si_2Na$ 448.2315, found 448.2305.

(2*R*,3*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-ethynyl-6-oxopiperidine-1-carboxylate *trans*-10r. Colorless oil (251 mg, 71%); $[\alpha]_D^{25}$ = −8.7 (*c* 1.18, $CHCl_3$); IR (film) ν_{max} 3248, 2955, 2928, 2895, 2855, 1775, 1724, 1606, 1471, 1369, 1332, 1295, 1252, 1147, 1108, 1010, 887, 840, 777, 726, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.89 (dd, *J* = 5.2, 2.4 Hz, 1H), 4.25−4.20 (m, 1H), 2.73 (ddd, *J* = 18.0, 10.8, 7.6 Hz, 1H), 2.55 (ddd, *J* = 17.6, 7.2, 3.2 Hz, 1H), 2.43 (d, *J* = 2.4 Hz, 1H), 2.42−2.35 (m, 1H), 1.86−1.70 (m, 1H), 1.54 (s, 9H), 0.88 (s, 9H), 0.11 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 150.1, 81.5, 78.6, 71.8, 65.8, 52.0, 27.9, 26.1, 24.0, 23.7, 16.1, −6.7, −6.9 ppm; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ Calcd for $C_{18}H_{31}NO_4SiNa$ 376.1920, found 376.1916.

(2*S*,3*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-6-*oxo*-2-(2-*m*-tolylethynyl)piperidine-1-carboxylate *cis*-10a. Yellow oil (142 mg, 32%); $[\alpha]_D^{25}$ = −5.5 (*c* 1.62, $CHCl_3$); IR (film) ν_{max} 2955, 2930, 2857, 1775, 1727, 1463, 1368, 1291, 1252, 1149, 882, 838, 779 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25−7.10 (m, 4H), 5.14 (dd, *J* = 4.8, 1.2 Hz, 1H), 4.10 (ddd, *J* = 10.4, 5.2, 4.4 Hz, 1H), 2.84 (ddd, *J* = 17.6, 8.4, 4.4 Hz, 1H), 2.52 (ddd, *J* = 16.8, 8.4, 7.6 Hz, 1H), 2.32 (s, 3H), 2.28−2.19 (m, 1H), 2.00−1.90 (m, 1H), 1.55 (s, 9H), 0.93 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 151.3, 137.9, 132.3, 129.3, 128.8, 128.1, 122.5, 85.3, 84.5, 83.7, 67.9, 53.4, 32.0, 28.0, 26.7, 25.7, 21.2, 18.0, −4.5, −4.7 ppm; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ Calcd for $C_{25}H_{38}NO_4Si$ 444.2570, found 444.2551.

(2*S*,3*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(2-(4-chlorophenyl)ethynyl)-6-oxopiperidine-1-carboxylate *cis*-10f. Yellow oil (130 mg, 28%); $[\alpha]_D^{25}$ = −5.5 (*c* 1.63, $CHCl_3$); IR (film) ν_{max} 2954, 2930, 2849, 1775, 1728, 1489, 1368, 1292, 1252, 1150, 1003, 882, 837, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.31 (m, 2H), 7.30−7.25 (m, 2H), 5.14 (dd, *J* = 4.8, 1.2 Hz, 1H), 4.11 (ddd, *J* = 10.0, 5.2, 4.4 Hz, 1H), 2.82 (ddd, *J* = 17.6, 8.0, 4.4 Hz, 1H), 2.53 (ddd, *J* = 17.2, 8.4, 7.6 Hz, 1H), 2.28−2.16 (m, 1H), 2.00−1.90 (m, 1H), 1.55 (s, 9H), 0.92 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 151.3, 134.4, 133.0, 128.6, 121.1, 86.0, 83.9, 83.8, 67.7, 53.4, 32.0, 28.0, 26.9, 25.6, 18.0, −4.7, −4.8 ppm; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ Calcd for $C_{24}H_{35}ClNO_4Si$ 464.2024, found 464.2024.

(2*S*,3*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(4-(*tert*-butyldimethylsilyloxy)but-1-ynyl)-6-oxopiperidine-1-carboxylate *cis*-10k. Colorless oil (118 mg, 23%); $[\alpha]_D^{25}$ = −3.8 (*c* 1.38, $CHCl_3$); IR (film) ν_{max} 2955, 2930, 2857, 1776, 1727, 1474, 1368, 1292, 1254, 1143, 883, 838, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.84 (dd, *J* = 4.8, 2.0 Hz, 1H), 3.93 (ddd, *J* = 10.4, 5.2, 4.4 Hz, 1H), 3.66−3.61 (m, 2H), 2.72 (ddd, *J* = 17.6, 8.4, 4.4 Hz, 1H), 2.46−2.33 (m, 3H), 2.16−2.05 (m, 1H), 1.87−1.78 (m, 1H), 1.47 (s, 9H), 0.85 (s, 9H), 0.83 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H), 0.00 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 151.4, 83.4, 82.4, 76.5, 67.7, 61.9, 52.8, 32.0, 28.0, 26.5, 25.9, 25.7, 23.2, 18.3, 18.0, −4.6, −4.8, −5.3 ppm; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ Calcd for $C_{26}H_{50}NO_5Si_2$ 512.3228, found 512.3225.

(2*S*,3*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(*hept*-1-ynyl)-6-oxopiperidine-1-carboxylate *cis*-10l. Colorless oil (114 mg, 27%); $[\alpha]_D^{25}$ = −4.7 (*c* 0.93, $CHCl_3$); IR (film) ν_{max} 2957, 2931, 2858, 1776, 1727, 1463, 1368, 1291, 1254, 1145, 882, 838, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.89 (dd, *J* = 4.8, 2.0 Hz, 1H), 3.98 (ddd, *J* = 10.4, 5.2, 4.4 Hz, 1H), 2.78 (ddd, *J* = 17.6, 8.4, 4.4 Hz, 1H), 2.47 (ddd, *J* = 17.6, 8.4, 7.6 Hz, 1H), 2.23−2.10 (m, 3H), 1.94−1.83 (m, 1H), 1.53 (s, 9H), 1.51−1.44 (m, 2H), 1.40−1.25 (m, 4H), 0.91 (s, 9H), 0.90−0.85 (m, 3H), 0.11 (s, 3H), 0.09 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 151.4, 85.9, 83.4, 75.4, 67.8, 52.9,

DOI: 10.1021/acs.joc.5b00803
J. Org. Chem. 2015, 80, 5824−5833

32.0, 30.9, 28.2, 28.0, 26.5, 25.7, 22.2, 18.7, 18.0, 14.0, −4.6, −4.8 ppm; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{23}H_{42}NO_4Si$ 424.2883, found 424.2882.

(2*R*,3*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-6-*oxo*-2-vinylpiperidine-1-carboxylate 13a. White solid (227 mg, 64%), mp 47−48 °C; $[\alpha]_D^{25}$ = +36.3 (c 0.93, $CHCl_3$); IR (film) ν_{max} 2953, 2932, 2855, 1770, 1721, 1370, 1252, 1090, 1003, 838, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (ddd, J = 16.8, 10.4, 4.8 Hz, 1H), 5.16−5.08 (m, 2H), 4.65−4.60 (m, 1H), 3.95−3.92 (m, 1H), 2.63 (ddd, J = 18.8, 11.2, 7.6 Hz, 1H), 2.31 (ddd, J = 17.6, 7.2, 2.4 Hz, 1H), 1.93−1.83 (m, 1H), 1.67−1.58 (m, 1H), 1.39 (s, 9H), 0.79 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 152.4, 135.8, 116.7, 82.6, 67.3, 64.7, 29.5, 27.9, 25.6, 24.8, 17.9, −4.9, −5.0 ppm; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{18}H_{34}NO_4Si$ 356.2257, found 356.2254.

(2*R*,3*S*)-*tert*-Butyl 2-(*but*-1-*en*-2-yl)-3-(*tert*-butyldimethylsilyloxy)-6-oxopiperidine-1-carboxylate 13b. Colorless oil (234 mg, 61%); $[\alpha]_D^{25}$ = +37.0 (c 1.41, $CHCl_3$); IR (film) ν_{max} 2956, 2926, 2855, 1772, 1720, 1452, 1368, 1253, 1151, 1107, 1087, 1007, 893, 838, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00−4.96 (m, 1H), 4.95−4.92 (m, 1H), 4.62−4.57 (m, 1H), 4.10 (ddd, J = 4.8, 2.8, 2.0 Hz, 1H), 2.73 (ddd, J = 18.8, 11.6, 7.6 Hz, 1H), 2.43 (ddd, J = 18.0, 7.2, 2.0 Hz, 1H), 2.17−2.01 (m, 2H), 2.00−1.90 (m, 1H), 1.70−1.62 (m, 1H), 1.47 (s, 9H), 1.15−1.08 (m, 3H), 0.89 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 152.0, 148.8, 109.6, 82.2, 66.9, 65.3, 29.0, 27.5, 26.5, 25.2, 23.8, 17.6, 11.7, −5.2, −5.3 ppm; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{20}H_{38}NO_4Si$ 384.2570, found 384.2563.

(2*R*,3*S*,*E*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-6-*oxo*-2-styrylpiperidine-1-carboxylate *E*-13c. White solid (118 mg, 28%), mp 147−148 °C; $[\alpha]_D^{25}$ = +9.0 (c 1.12, $CHCl_3$); IR (film) ν_{max} 2926, 2854, 1754, 1253, 1151, 1074, 986, 836, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.25 (m, 5H), 6.53 (dd, J = 16.0, 1.2 Hz, 1H), 6.09 (dd, J = 16.0, 6.0 Hz, 1H), 4.91−4.86 (m, 1H), 4.14−4.09 (m, 1H), 2.79 (ddd, J = 18.4, 11.2, 7.6 Hz, 1H), 2.49 (ddd, J = 17.6, 6.8, 2.4 Hz, 1H), 2.11−2.01 (m, 1H), 1.84−1.75 (m, 1H), 1.50 (s, 9H), 0.92 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 152.4, 136.1, 132.0, 128.7, 128.0, 126.9, 126.5, 82.9, 67.8, 64.6, 29.6, 27.9, 25.6, 25.2, 18.0, −4.8, −4.9 ppm; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{24}H_{38}NO_4Si$ 432.2570, found 432.2567.

(2*R*,3*S*,*Z*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-6-*oxo*-2-styrylpiperidine-1-carboxylate *Z*-13c. Colorless oil (117 mg, 27%); $[\alpha]_D^{25}$ = +97.2 (c 1.29, $CHCl_3$); IR (film) ν_{max} 2955, 2930, 2849, 1770, 1718, 1367, 1292, 1252, 1149, 1107, 1088, 893, 837, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.27 (m, 5H), 6.59 (d, J = 11.6 Hz, 1H), 5.48 (dd, J = 11.6, 8.8 Hz, 1H), 5.29−5.24 (m, 1H), 4.08−4.04 (m, 1H), 2.78 (ddd, J = 19.2, 11.6, 8.0 Hz, 1H), 2.51 (ddd, J = 18.0, 7.6, 2.4 Hz, 1H), 2.13−2.02 (m, 1H), 1.86−1.77 (m, 1H), 1.33 (s, 9H), 0.86 (s, 9H), 0.002−0.004 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 152.1, 136.1, 131.8, 130.3, 128.6, 128.4, 127.7, 82.7, 67.7, 60.8, 29.5, 27.7, 25.7, 25.6, 17.9, −4.9, −5.0 ppm; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{24}H_{38}NO_4Si$ 432.2570, found 432.2569.

(2*S*,3*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-6-*oxo*-2-(2-*m*-tolylethynyl)piperidine-1-carboxylate *E*-13d. White solid (138 mg, 31%), mp 115−116 °C; $[\alpha]_D^{25}$ = +9.5 (c 1.17, $CHCl_3$); IR (film) ν_{max} 2954, 2930, 2844, 1770, 1719, 1368, 1252, 1150, 1106, 1086, 1008, 986, 837, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.22 (m, 2H), 7.15−7.10 (m, 2H), 6.47 (d, J = 16.0 Hz, 1H), 6.01 (dd, J = 16.0, 6.0 Hz, 1H), 4.87−4.82 (m, 1H), 4.10−4.06 (m, 1H), 2.76 (ddd, J = 18.4, 11.2, 7.6 Hz, 1H), 2.46 (ddd, J = 17.6, 6.8, 2.4 Hz, 1H), 2.33 (s, 3H), 2.09−1.99 (m, 1H), 1.81−1.72 (m, 1H), 1.48 (s, 9H), 0.90 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 152.3, 137.9, 133.2, 131.8, 129.3, 126.3, 125.7, 82.7, 67.8, 64.5, 29.6, 27.9, 25.6, 25.1, 21.1, 17.9, −4.9, −5.0 ppm; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{25}H_{40}NO_4Si$ 446.2727, found 446.2718.

(2*S*,3*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-6-*oxo*-2-(2-*m*-tolylethynyl)piperidine-1-carboxylate *Z*-13d. Pale yellow oil (138 mg, 31%); $[\alpha]_D^{25}$ = +81.8 (c 1.65, $CHCl_3$); IR (film) ν_{max} 2953, 2926, 2855, 1770, 1718, 1468, 1367, 1252, 1150, 1107, 1090, 1008, 838, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.14 (m, 4H), 6.52 (d, J = 12.0 Hz, 1H), 5.40 (dd, J = 11.6, 9.2 Hz, 1H), 5.26−5.22 (m, 1H), 4.07−4.03 (m, 1H), 2.76 (ddd, J = 19.2, 11.6, 8.0 Hz, 1H), 2.49 (ddd, J = 17.6, 7.2, 2.0 Hz, 1H), 2.35 (s, 3H), 2.10−2.00 (m, 1H), 1.83−1.75 (m, 1H), 1.30 (s, 9H), 0.85 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 152.0, 137.4, 133.1, 131.6, 129.5, 129.2, 128.3, 82.5, 67.5, 60.8, 29.4, 27.6, 25.6, 25.5, 21.1, 17.8, −4.9, −5.0 ppm; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{25}H_{40}NO_4Si$ 446.2727, found 446.2725.

(2*R*,3*S*,*E*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(2-(naphthalen-1-yl)vinyl)-6-oxopiperidine-1-carboxylate *E*-13e. Pale yellow solid (114 mg, 24%), mp 105−106 °C; $[\alpha]_D^{25}$ = +12.1 (c 1.06, $CHCl_3$); IR (film) ν_{max} 2954, 2930, 2849, 1769, 1718, 1473, 1367, 1291, 1252, 1150, 1107, 1086, 1008, 970, 895, 837, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05−8.00 (m, 1H), 7.87−7.77 (m, 2H), 7.55−7.41 (m, 4H), 7.30 (d, J = 14.8 Hz, 1H), 6.11 (dd, J = 15.6, 5.6 Hz, 1H), 5.01−4.96 (m, 1H), 4.20−4.16 (m, 1H), 2.82 (ddd, J = 18.4, 11.2, 7.6 Hz, 1H), 2.53 (ddd, J = 17.6, 7.2, 2.4 Hz, 1H), 2.17−2.07 (m, 1H), 1.86−1.72 (m, 1H), 1.52 (s, 9H), 0.92 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 152.6, 133.9, 133.6, 131.0, 130.2, 129.4, 128.5, 128.4, 126.3, 126.0, 125.5, 123.8, 123.6, 83.0, 67.7, 64.8, 29.6, 28.0, 25.7, 25.2, 18.0, −4.7, −4.9 ppm; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{28}H_{40}NO_4Si$ 482.2727, found 482.2731.

(2*R*,3*S*,*Z*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-(2-(naphthalen-1-yl)vinyl)-6-oxopiperidine-1-carboxylate *Z*-13e. Pale yellow oil (112 mg, 23%); $[\alpha]_D^{25}$ = +109.9 (c 1.26, $CHCl_3$); IR (film) ν_{max} 2954, 2930, 2860, 1769, 1716, 1468, 1367, 1293, 1251, 1150, 1087, 1006, 892, 838, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93−7.80 (m, 3H), 7.55−7.45 (m, 4H), 7.04 (d, J = 11.6 Hz, 1H), 5.77 (dd, J = 11.6, 8.0 Hz, 1H), 5.11−5.05 (m, 1H), 3.81−3.77 (m, 1H), 2.74 (ddd, J = 19.2, 11.6, 8.0 Hz, 1H), 2.49 (ddd, J = 17.6, 7.2, 1.6 Hz, 1H), 2.15−2.04 (m, 1H), 1.76−1.67 (m, 1H), 1.30 (s, 9H), 0.68 (s, 9H), 0.36 (s, 3H), −0.41 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 152.4, 133.7, 133.4, 132.4, 131.6, 130.6, 128.5, 128.2, 126.3, 126.1, 125.7, 125.4, 124.5, 82.3, 67.7, 60.7, 29.6, 27.7, 25.5, 17.7, −5.4, −5.5 ppm; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{28}H_{40}NO_4Si$ 482.2727, found 482.2737.

(2*R*,3*S*)-*tert*-Butyl 3-hydroxy-2-vinylpiperidine-1-carboxylate 14. A solution of crude compound **11a** (8.71 mmol) in THF (10 mL) was carefully dropped to a suspension of LAH (1.32 g, 34.78 mmol) in anhydrous THF (30 mL) at 0 °C. The mixture was heated to reflux overnight, and then the mixture was cooled to 0 °C and carefully diluted with THF (50 mL). The resulted mixture was carefully treated with $Na_2SO_4{\cdot}10H_2O$ and filtrated, the filtrate was concentrated to give crude intermediate without purification. The above crude product and Boc_2O (2.30g, 10.55 mmol) were dissolved in dry DCM (36 mL), then TEA (1.2 mL, 8.71 mmol) and an aqueous solution of 2 M $NaHCO_3$ (1.4 mL) was dropped. After being stirred for 12h, the mixture was quenched with a saturated aqueous solution of NH_4Cl. The mixture was separated and the aqueous phase was extracted with DCM (30 mL × 3). The combined organic layers were washed with brine, dried and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 4/1) to give **14** (950 mg) as a colorless oil in 48% overall yield. $[\alpha]_D^{25}$ = −10.4 (c 1.24, $CHCl_3$); IR (film) ν_{max} 3448, 2976, 2930, 1692, 1670, 1413, 1365, 1276, 1173, 1150, 1131, 1074, 985, 920, 876 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (ddd, J = 17.2, 10.4, 4.4 Hz, 1H), 5.26−5.20 (m, 1H), 5.15−5.07 (m, 1H), 4.74 (brs, 1H), 4.00−3.90 (m, 2H), 2.93−2.83 (m, 1H), 2.44 (brs, 1H), 1.92−1.79 (m, 1H), 1.76−1.70 (m, 1H), 1.68−1.58 (m, 1H), 1.45 (s, 9H), 1.44−1.39 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 133.6, 116.8, 79.8, 67.8, 67.5, 59.7, 39.3, 28.4, 26.2, 18.9 ppm; HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{12}H_{21}NO_3Na$ 250.1419, found 250.1413.

(2*R*,3*S*)-*tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-2-vinylpiperidine-1-carboxylate 15. To a cooled (0 °C) solution of **14** (875 mg, 3.85 mmol) TBSCl (867 mg, 5.78 mmol) and DMAP (470 mg, 3.85 mmol) in DMF (8 mL) was added imidazole (786 mg, 11.55

DOI: 10.1021/acs.joc.5b00803
J. Org. Chem. 2015, 80, 5824−5833

mmol) in one portion. After being stirred for 24 h, the mixture was quenched with a saturated aqueous solution of NH_4Cl. The resulted mixture was separated and the aqueous phase was extracted with EA (20 mL × 4). The combined organic layers were washed with water (20 mL × 2) and brine, dried and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 20/1) to give **15** (1.31 g) as a colorless oil in 100% yield. $[\alpha]_D^{25}$ = +6.5 (*c* 2.07, $CHCl_3$); IR (film) ν_{max} 2953, 2928, 2883, 2860, 2356, 1696, 1413, 1364, 1254, 1176, 1150, 1091, 1036, 829, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.72 (ddd, *J* = 17.2, 10.4, 4.6 Hz, 1H), 5.21−5.15 (m, 1H), 5.13−5.05 (m, 1H), 4.64 (brs, 1H), 4.05−3.97 (m, 1H), 3.86−3.83 (m, 1H), 2.85−2.76 (m, 1H), 2.00−1.85 (m, 1H), 1.60−1.54 (m, 2H), 1.43 (s, 9H), 1.33−1.26 (m, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 134.1, 116.3, 79.0, 68.4, 59.9, 39.0, 28.4, 27.4, 25.7, 19.0, 18.0, −5.0, −5.1 ppm; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ Calcd for $C_{18}H_{35}NO_3SiNa$ 364.2284, found 364.2277.

1-((2*R*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-vinylpiperidin-1-yl)but-3-en-1-one 16. A solution of Compound **15** (968 mg, 2.84 mmol) in DCM (20 mL) was treated with TFA (1.0 mL) at 0 °C for 3.5 h, then $NaHCO_3$ solid was added. The mixture was filtrated and the organic layer was concentrated to give oil, which was dissolved in DMF (8 mL) at 0 °C. TEA (2.4 mL, 17.35 mmol) and DEPC (1.28 mL, 8.52 mmol) were added, then *but*-3-enoic acid (0.74 mL, 8.52 mmol) was dropped slowly. After being stirred overnight, the mixture was quenched with a saturated NH_4Cl aqueous solution and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine, dried, filtrated and concentrated. The residue was purified by flash chromatography on silica gel (PE/EA = 10/1) to give **16** (694 mg) as a colorless oil in 79% yield. $[\alpha]_D^{25}$ = −9.6 (*c* 1.1, $CHCl_3$); IR (film) ν_{max} 2956, 2920, 2850, 1734, 1654, 1538, 1457, 1372, 1260, 1091, 1019, 866, 794 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, the mixtures of rotamers) δ 6.10−5.90 (m, 1H), 5.85−5.65 (m, 1H), 5.35−5.05 (m, 4.33H), 4.63−4.50 (m, 0.67H), 4.40−4.30 (m, 0.67H), 4.00−3.90 (m, 1H), 3.70−3.60 (m, 0.33H), 3.30−3.05 (m, 2.33H), 2.75−1.65 (m, 0.67H), 2.05−1.85 (m, 1H), 1.70−1.58 (m, 2H), 1.45−1.35 (m, 1H), 0.93−0.86 (m, 9H), 0.12−0.07 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 170.3, 133.5, 132.1, 131.8, 117.4, 116.9, 69.1, 68.4, 62.4, 57.2, 41.8, 39.3, 38.4, 37.2, 27.5, 25.7, 19.7, 18.9, 18.0, −4.8, −5.0 ppm; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ Calcd for $C_{17}H_{31}NO_2SiNa$ 332.2022, found 332.2012.

(9*S*,9*aR*)-9-(*tert*-Butyldimethylsilyloxy)-7,8,9,9a-tetrahydro-3*H*-quinolizin-4(6*H*)-one 17. Compound **16** (530 mg, 1.71 mmol) and Grubbs^{second} catalyst (73 mg) was refluxed in dry DCM (50 mL) for 12 h, then the mixture was concentrated. The crude was purified by flash chromatography on silica gel to give **17** (467 mg) as a colorless oil in 97% yield. $[\alpha]_D^{25}$ = +132.7 (*c* 1.74, $CHCl_3$); IR (film) ν_{max} 2954, 2929, 2895, 2857, 1650, 1463, 1254, 1106, 1084, 838, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.01−5.95 (m, 1H), 5.75−5.71 (m, 1H), 4.84−4.77 (m, 1H), 3.66−3.58 (m, 1H), 3.36−3.26 (m, 1H), 2.98−2.86 (m, 2H), 2.46−2.34 (m, 1H), 2.08−1.98 (m, 1H), 1.76−1.66 (m, 1H), 1.56−1.42 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 123.6, 121.6, 74.1, 63.8, 41.7, 34.8, 31.7, 25.7, 23.6, 18.0, −4.2, −4.8 ppm; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ Calcd for $C_{15}H_{27}NO_2SiNa$ 304.1709, found 304.1703.

(9*S*,9*aR*)-9-Hydroxy-hexahydro-1*H*-quinolizin-4(6*H*)-one 18. Compound **17** (432 mg, 1.54 mmol) and 10% Pd/C (50 mg) were stirred in MeOH (30 mL) for 5h under H_2 atmosphere, then 6 N HCl (4 mL) was dropped in one portion. After being stirred overnight, the resulted mixture was filtrated and concentrated. The residue was purified by flash chromatography on silica gel to give **18** (218 mg) as a white solid in 84% yield. mp 156−157 °C; $[\alpha]_D^{25}$ = +73.7 (*c* 0.58, $CHCl_3$); IR (film) ν_{max} 3291, 3064, 2945, 2924, 2854, 1599, 1473, 1446, 1418, 1355, 1312, 1273, 1259, 1157, 1073, 1030, 932, 349, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.76−4.69 (m, 1H), 3.35 (ddd, *J* = 15.2, 9.8, 5.0 Hz, 1H), 3.06 (ddd, *J* = 12.0, 6.6, 5.8 Hz, 1H), 2.90 (d, *J* = 5.2 Hz, 1H), 2.43−2.26 (m, 3H), 2.20−2.08 (m, 2H), 1.89−1.79 (m, 2H), 1.78−1.71 (m, 1H), 1.70−1.59 (m, 1H), 1.54−1.39 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 71.6, 62.4, 42.2, 34.1, 32.8, 25.3, 23.5, 18.3 ppm; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ Calcd for $C_9H_{15}NO_2Na$ 192.1000, found 192.0994.

(*R*)-Hexahydro-2*H*-quinolizine-1,6-dione 19. To solution of **18** (206 mg, 1.22 mmol) in dry DCM (10 mL) was treated with DMP (1.04 g, 2.44 mmol) at room temperature for 0.5 h. The reaction was carefully quenched with a solution of $NaHCO_3$ and $Na_2S_2O_3$, then the resulted mixture was separated and the aqueous layer was extracted with DCM (30 mL × 3). The combined organic layers were washed with brine, dried, filtered and concentrated. The residue was purified by flash chromatography on silica gel (DCM/CH_3OH = 50/1) to give **19** (203 mg) as a pale yellow oil in 100% yield. $[\alpha]_D^{25}$ = +7.7 (*c* 0.23, $CHCl_3$); IR (film) ν_{max} 1720, 1671, 1460, 1438, 1389, 1352, 1255, 1167, 1134, 1097, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.89−3.84 (m, 2H), 2.70−2.65 (m, 4H), 2.43−2.37 (m, 2H), 2.00−1.85 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 172.7, 77.2, 38.7, 32.8, 31.3, 23.0, 17.1 ppm; The HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ or $[M + Na]^+$ was unavailable due to instability of the compound **19** under MS ionization conditions.

***N*-((1*R*,9*aR*)-Octahydro-1*H*-quinolizin-1-yl)acetamide (−)-epiquinamide 3.** $NH_2OMe{\cdot}HCl$ (72 mg, 0.86 mmol) was added to solution of **19** (120 mg, 0.72 mmol) in pyridine (3 mL). After being stirred for 0.5 h, the mixture was diluted with THF (8 mL) and treated with borane (2.88 mL, 1 M in tetrahydrofuran, 2.88 mmol) at 50 °C for 4 h. then the resulted mixture was concentrated to give the crude intermediate without further purification, which was dissolved in dioxane (5 mL). Ac_2O (0.41 mL, 4.32 mmol) and a 1 M aqueous solution of NaOH (5 mL) was added, respectively. After stirring for 3 h, an aqueous solution of 1 M NaOH (5 mL) was dropped and the resulted mixture was extracted with DCM (30 mL × 3). The combined organic layers were washed with brine, dried and concentrated. The residue was purified by flash chromatography on silica gel (DCM/CH_3OH = 10/1) to give (−)-epiquinamide **3** (94 mg) as a white solid in 67% overall yield. {$[\alpha]_D^{25}$ = −20.3 (*c* 0.65, $CHCl_3$), lit.[15b] $[\alpha]_D^{20}$ = −25 (*c* 0.26, $CHCl_3$); lit.[15d] $[\alpha]_D^{25}$ = −22 (*c* 0.5, $CHCl_3$)}; IR (film) ν_{max} 3307, 3063, 2935, 2856, 2803, 2764, 1652, 1537, 1443, 1372, 1289, 1128, 1055, 960, 607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.23 (brs, 1H), 3.95−3.90 (m, 1H), 2.82−2.73 (m, 2H), 2.05−1.99 (m, 4H), 1.98−1.92 (m, 2H), 1.90−1.83 (m, 1H), 1.77−1.65 (m, 2H), 1.64−1.57 (m, 1H), 1.52−1.35 (m, 4H), 1.34−1.21 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 64.3, 56.8, 48.1, 29.6, 29.1, 25.6, 24.0, 23.5, 20.6 ppm; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ Calcd for $C_{11}H_{21}N_2O$ 197.1654, found 197.1654.

(5*S*,6*R*)-1-Allyl-5-(*tert*-butyldimethylsilyloxy)-6-vinylpiperidin-2-one 20. To a solution of crude lactam **10r** (5.57 mmol) in MeOH (20 mL) was added 5% Palladium on barium sulfate (0.01 mmol) and quinoline (0.3 mmol) at 0 °C. Then the mixture was connected to a hydrogen balloon and stirred for 3h, the resulted mixture was filtered through silica gel and concentrated in vacuo to give crude **11a**, which was directly dissolved in DMF (10 mL) without further purification and carefully dropped to a solution containing NaH (60% in petrolatum 673 mg, 28 mmol) in dry DMF (30 mL) at 0 °C. The mixture was mixture was stirred for 0.5 h, allyl bromide (1.43 mL, 16.7 mmol) was dropped. After stirring overnight, the mixture was carefully quenched with a saturated NH_4Cl aqueous solution. The resulted mixture was extracted with EtOAc (40 mL × 4) and the combined organic layers were washed with water and brine. Dried and concentrated, the residue was purified by flash chromatography on silica gel (PE/EA = 5/1) to give a light yellow oil **20** (1.10 g) in 67% yield. $[\alpha]_D^{25}$ = +129.0 (*c* 0.20, $CHCl_3$); IR (film) ν_{max} 2954, 2929, 2857, 1654, 1460, 1411, 1259, 1097, 1078, 1008, 993, 837, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.67−5.61 (m, 1H), 5.61−5.56 (m, 1H), 5.20 (d, *J* = 6.8 Hz, 1H), 5.14−5.11 (m, 1H), 5.11−5.09 (m, 1H), 5.07−5.03 (m, 1H), 4.75−4.70 (m, 1H), 3.03 (dd, *J* = 10.4, 4.4 Hz, 1H), 2.59 (ddd, *J* = 12.8, 8.2, 4.8 Hz, 1H), 2.26 (ddd, *J* = 11.6, 4.2, 0.8 Hz 1H), 1.92−1.86 (m, 1H), 1.66−1.61 (m, 1H), 0.81 (s, 9H), 0.00 (s, 6H); ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 135.9, 132.7, 118.1, 116.8, 67.9, 66.0, 46.9, 26.9, 25.7, 24.4, 18.0, −4.8, −4.9 ppm; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ Calcd for $C_{16}H_{30}NO_2Si$ 296.2046, found 296.2024.

DOI: 10.1021/acs.joc.5b00803
J. Org. Chem. 2015, 80, 5824−5833

(8*S*,8a*R*)-8-(*tert*-Butyldimethylsilyloxy)-6,7,8,8a-tetrahydroindolizin-5(3*H*)-one 21. To solution of **20** (3.86 g, 13.08 mmol) and Grubbs^{second} catalyst (110 mg) in dry DCM (260 mL) was refluxed for 12h, then the mixture was concentrated. The crude was purified by flash chromatography on silica gel to give **21** (3.25 g) as a white solid in 93% yield. mp 98−100 °C; $[\alpha]_D^{25}$ = +28.0 (*c* 1.08, $CHCl_3$); IR (film) ν_{max} 3233, 2954, 2929, 2857, 1641, 1460, 1407, 1257, 1114, 837, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.88−5.82 (m, 2H), 4.43−4.37 (m, 1H), 4.10−4.06 (m, 1H), 3.99−3.94 (m, 1H), 3.48 (ddd, *J* = 9.2, 5.6, 3.2 Hz, 1H), 2.54 (ddd, *J* = 11.6, 5.6, 2.2 Hz, 1H), 2.38−2.31 (m, 1H), 1.98−1.92 (m, 1H), 1.71 (ddd, *J* = 14.8, 9.0, 6.0 Hz, 1H), 0.83 (s, 9H), 0.00 (s, 6H); ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 128.5, 126.7, 71.1, 69.1, 53.3, 30.2, 29.7, 25.7, 18.0, −4.3, −4.8 ppm; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ Calcd for $C_{14}H_{26}NO_2Si$ 268.1733, found 268.1719.

(1*R*,2*S*,8*S*,8a*R*)-8-(*tert*-Butyldimethylsilyloxy)-1,2-dihydroxyhexahydroindolizin-5(1*H*)-one 22. To a solution of **21** (2.86 g, 10.71 mmol) in *t*-BuOH/H_2O (60 mL, *V*/*V* = 3/1) was added *N*-methylmorpholine *N*-oxide (4.34 g, 32.13 mmol) and potassium osmate (VI) dihydrate (394 mg, 1.07 mmol). After being stirred overnight, the reaction mixture was quenched with a saturated aqueous solution of $NaHSO_3$ and stirred for another 1 h. Then the resulted mixture was concentrated and residue was diluted with water. The mixture was extracted with EtOAc (150 mL × 3) and the combined organic extracts were washed with brine. Dried, filtrated and concentrated, the residue was purified by flash chromatography on silica gel (EtOAc) to give **22** (3.03 g) as a white solid in 94% yield. Mp 150−152 °C; $[\alpha]_D^{25}$ = +77.2 (*c* 0.25, $CHCl_3$); IR (film) ν_{max} 3315, 2949, 2929, 2854, 1610, 1469, 1415, 1252, 1113, 870, 836, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.43−4.38 (m, 1H), 4.26−4.20 (m, 1H), 4.03−3.98 (m, 2H), 3.57 (dd, *J* = 8.0, 5.6 Hz, 1H), 3.39−3.36 (m, 1H), 3.26−3.21 (m, 2H), 2.37−2.29 (m, 1H), 2.28−2.20 (m, 1H), 1.90−1.84 (m, 1H), 1.69−1.61 (m, 1H), 0.78 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 70.7, 70.0, 67.1, 64.7, 49.6, 30.2, 29.5, 25.7, 17.9, −4.5, −4.9 ppm; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ Calcd for $C_{14}H_{28}NO_4Si$ 302.1788, found 302.1759.

(+)-Swainsonine *ent*-5. To a suspension of $LiAlH_4$ (537 mg, 14.14 mmol) in THF (60 mL), a solution of compound **22** (1.42 g, 4.72 mmol) in THF (10 mL) was dropped. Then the mixture was refluxed overnight. The mixture was cooled to 0 °C and diluted with THF (100 mL). Then $Na_2SO_4{\cdot}10H_2O$ was carefully added in several portions until the mixture was turned to white. The resulting mixture was filtrated and concentrated to give intermediate without further purification. Then, above crude intermediate was dissolved in 1 M HCl−MeOH and stirred overnight, the solvent was concentrated and the crude was purified by chromatography resin (Dowex 1 × 8−100, OH^- form) eluting with water (200 mL). The eluent was concentrated and filtered through chromatography on silica gel (eluent NH_4OH/*n*-BuOH/EtOH/DCM = 1:3:3:3) to give *ent*-**5** (706 mg) as a white solid in 87% overall yield. {$[\alpha]_D^{25}$ = +84.6 (*c* 1.20, CH_3OH), lit.[25a] $[\alpha]_D^{24}$ = +83.3 (*c* 0.5, CH_3OH); lit.[25b] $[\alpha]_D^{21}$ = +84.3 (*c* 1.02, H_2O); mp 143−144 °C; lit.[25a] mp 143−145 °C}. The *ent*-5 was easily converted to *ent*-**5** HCl. IR (film) ν_{max} 3295, 2914, 1733, 1717, 1653, 1457, 1384, 1025, 834, 685, 636 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 4.20 (ddd, *J* = 8.4, 6.0, 2.4 Hz, 1H), δ 4.11 (dd, *J* = 6.0, 3.6 Hz, 1H), δ 3.65 (ddd, *J* = 14.2, 9.6, 4.6 Hz, 1H), 2.78−2.72 (m, 2H), 2.40 (dd, *J* = 11.0, 7.8 Hz, 1H), 1.94−1.88 (m, 1H), 1.86−1.74 (m, 2H), 1.60−1.54 (m, 1H), 1.43−1.30 (m, 1H), 1.14−1.03 (m, 1H); ppm; ^{13}C NMR (100 MHz, D_2O) δ 72.3, 69.2, 68.6, 65.9, 60.1, 51.2, 32.0, 22.7 ppm; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ Calcd for $C_8H_{16}NO_3$ 174.1130, found 174.1130.

■ ASSOCIATED CONTENT

Supporting Information

^1H, ^{19}F and ^{13}C NMR spectra, details for computational calculations and X-ray structural data (CIF) of compounds *trans*-**10f** and **18**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00803.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (21472022, 21272041, 21072034, 20832005), Key Laboratory for Chemical Biology of Fujian Province for financial support. The authors also thank Dr. Xin-Sheng Lei for helpful suggestions.

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