Functionalization of *N*-tosyl-2-pyridinone with silyl ketene acetal catalyzed by Lewis acid, and synthetic studies of corynantheidol

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Dedicated to Professor Keiichiro Fukumoto on his 70th birthday
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Abstract

The reaction of *N*-tosyl-2-pyridinone with *tert*-butyldimethylsilyl ketene acetal, catalyzed by a Lewis acid, has been investigated. While both the C-4 Michael adduct **3** and the bicyclic compound **5** were isolated from aluminum chloride- or trimethylaluminum- catalyzed reactions, the former was afforded as the sole product from diethylaluminum chloride- or trimethylsilyl trifluoromethanesulfonate- catalyzed reactions. During investigation of a synthesis of corynantheidol, a method for construction of the key intermediate **30** was accomplished *via*, (1), the efficient conversion of the enamine moiety to an alkenyl bromide (**20**→**22**), followed by the Sonogashira coupling reduction (**22**→**23**); (2), selective reduction of the acetylene and intramolecular cyclization (**25**→**26**); (3), the coupling reaction with the indole unit (**27**→**30**).

Keywords: *N*-Tosyl-2-pyridinone, Lewis acid, Michael reaction, corynantheidol

Introduction

Owing to their valuable biological activities, nitrogen-containing compounds have long been of interest to organic chemists and biochemists and are present in many types of pharmaceuticals. In particular, six-membered ring systems having nitrogen atoms in their rings are found abundantly in nature as substructure(s) of alkaloids or aza-sugars.[1] Therefore, many efforts had been made over recent decades to construct such ring systems and, in particular, to develop enantio- and/or diastereo-selective synthetic methods for functionalized piperidine rings.[2]

The stereoselective construction of multi-functional piperidine ring systems, the utilization of pyridinium salts or dihydropyridine derivatives has been well investigated recently,[2,3] including the Mukaiyama–Michael addition reaction,[4,5] alkylation reactions,[6,7] and reductive alkylation

reactions.[8] In these areas, elegant methods for the functionalization of pyridine rings using chiral 1-acylpyridinium salts as substrates have been developed by Comins' research group,[5,6] and the syntheses of many biologically active natural products were also reported.[9]

In comparison with the significant efforts in studies of the 4-alkoxypyridine derivatives, the researches involving the reactivity of the 2-oxypyridine (2-pyridinone) derivatives have mainly been limited to the Diels–Alder reactions[10,11] and, to the best of our knowledge, the introduction of the acetate units into oxygenated pyridine derivatives has been reported only once.[5]

As part of our continuous program for the development of new methodologies for heterocyclic compounds,[12] we focused our attention on the utilization of the activated 2-pyridinone derivatives. Herein, we report the regioselective functionalization of *N*-tosyl-2-pyridinone **1**[11,13] with *tert*-butyldimethylsilyl ketene acetal **2**, activated by a Lewis acid, and its application in the synthetic study of corynantheidol **4** (Figure 1).

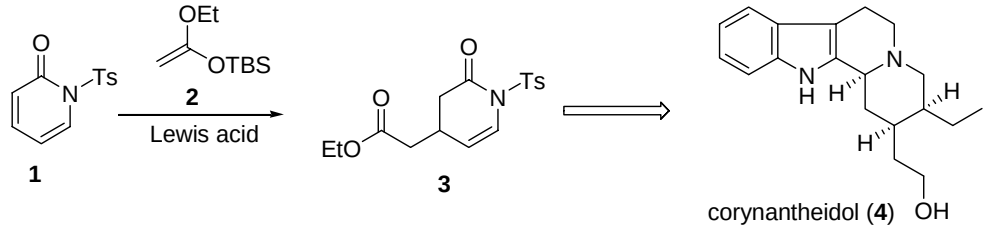


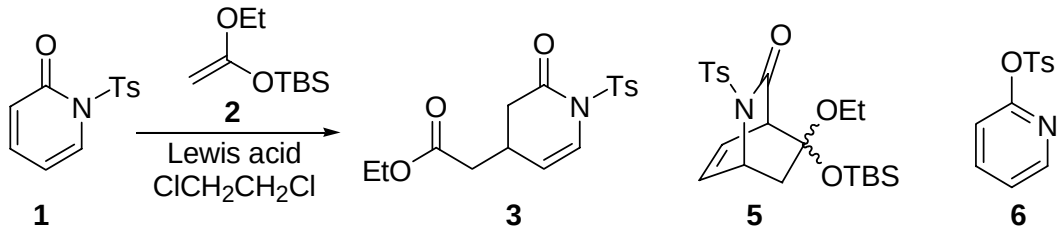
Figure 1

Results and Discussion

N-Tosyl-2-pyridinone, **1**, was synthesized by reaction of the lithium salt of pyridinone with *p*-toluenesulfonyl chloride according to the reported procedure.[11] The results of the reactions between **1** and the *tert*-butyldimethylsilyl ketene acetal **2** in the presence of various Lewis acids are summarized in Table 1. However, neither thermal conditions (toluene, 90°C, 110 h), nor treatment of **1** and **2** with zinc chloride or boron trifluoride diethyl etherate promoted any reactions, and **1** was completely recovered. Stannic chloride promoted only the migration of the tosyl group from the nitrogen- to oxygen atom to give **6** exclusively (Table 1: entry 1). However, when **1** was allowed to react with **2** in the presence of 10 mol % of aluminum chloride, the C-4 Michael adduct **3** was obtained, although the yield (22%) was disappointing (Table 1: entry 2). The yield of **3** was greatly improved by changing the catalyst to diethylaluminum chloride or trimethylaluminum: **3** was produced as the sole product by the former catalyst, and the unexpected bicyclic compound **5** was isolated in the latter case (Table 1: entries 3 and 4). The best condition tested used 10 mol % of tert-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) at -40°C, where 89% of **3** was isolated as the single product (Table 1: entry 5). The structure of **3** was established from spectra and by conversion into the δ-lactam derivatives **8** by catalytic hydrogenation. Although the bicyclic compound **5** was given as a single product, which

was confirmed by the ^{13}C-NMR spectrum, the stereochemistry of the ethyl silyl acetal moiety was difficult to determine from the ^{1}H-NMR spectrum. Thus, the structure of **5** was confirmed by the NMR analysis (^{1}H, ^{13}C, and ^{1}H-COSY) of **9** which was obtained by hydrolysis of the acetal moiety (Scheme 1). When the reaction in the presence of 10 mol % of TBSOTf was terminated without treatment with H_2O (evaporation of the solvent and the reagents), the silyl enol ether **7** was identified by ^{1}H-NMR. Therefore, our proposed reaction mechanisms catalyzed by TBSOTf may involve: (1) activation of the carbonyl group by the TBS group (**1**→**10**), (2) Michael addition at C4 (**10**→**11**), and (3) elimination of the TBS group to produce TBSOTf (**11**→**7**) as illustrated in Scheme 1. As the aluminum reagents for these reactions functioned as catalysts, the silyl group migration reaction (**12**→**7**) might participate in the catalytic cycle, although we do not have any evidence. On the other hand, for production of the bicyclic compound **5**, it could also be that the silyl group's migration reaction was impossible for the intermediate **15**, for steric reasons, and then the reaction might progress *via* the tandem Michael–Claisen type pathway, but not through the Diels–Alder process (Scheme 1).

Table 1. Reaction of *N*-tosyl-pyridinone **1** with *tert*-butyldimethylsilyl ketene acetal **2**



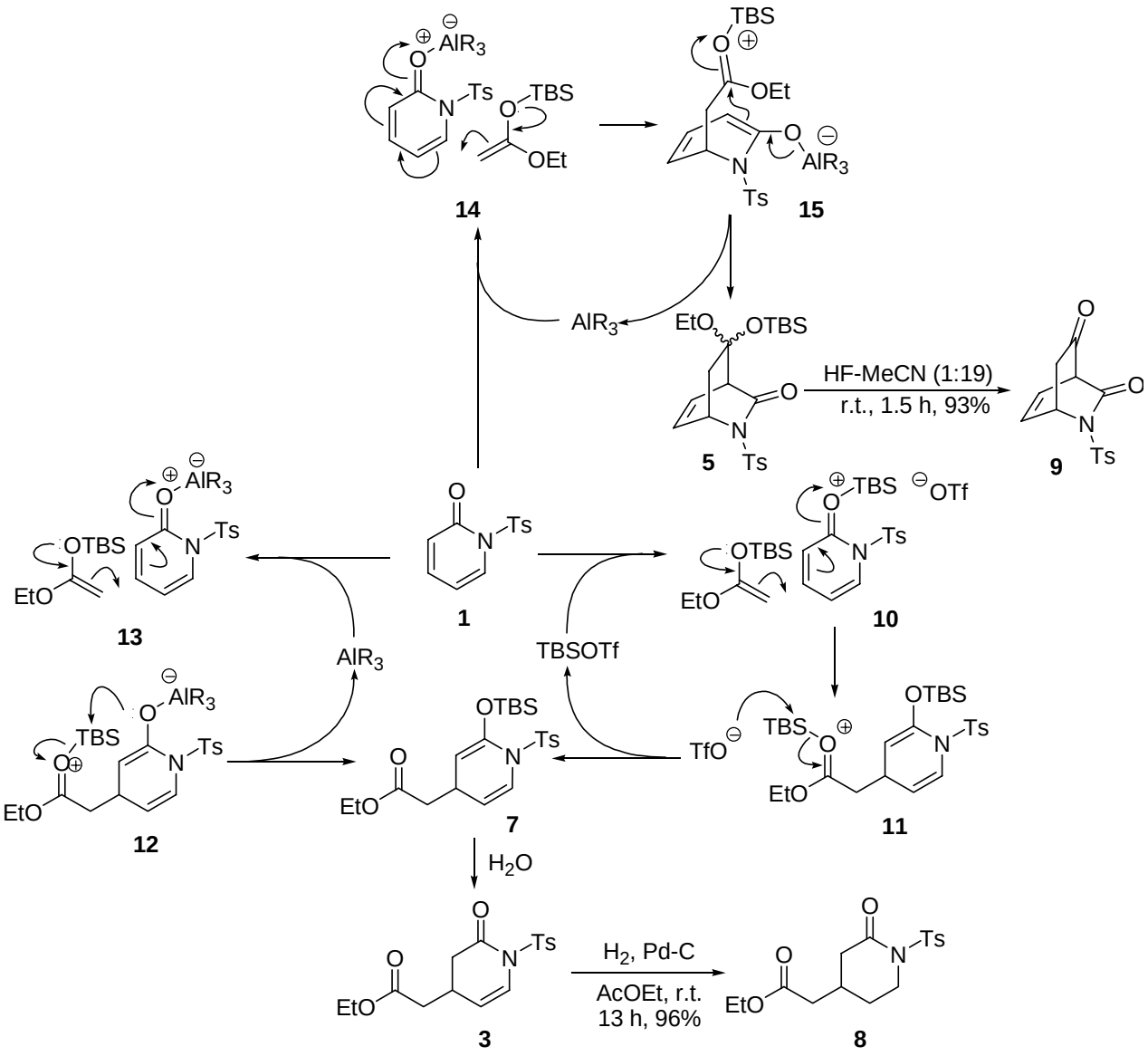
Entry	Lewis acid (mol %)	Temp (°C)	Time (h)	Yield (%)		
				3	**5**	**6**
1	$SnCl_4$ (110)	-78 – r.t.	42	0	0	66
2	$AlCl_3$ (10)	-40 – 0	72	22 [a]	0	0
3	Et_2AlCl (10)	-40	24	72	0	0
4	Me_3Al (10)	-40	16	83	4	0
5 [b]	TBSOTf (10)	-78 – -20	24	89	0	0

[a] **1** (16%) was recovered. [b] Dichloromethane was used as solvent.

We have now established an efficient synthetic method for preparing **3** in large quantities, and our next aim is to synthesize natural products from **3**.

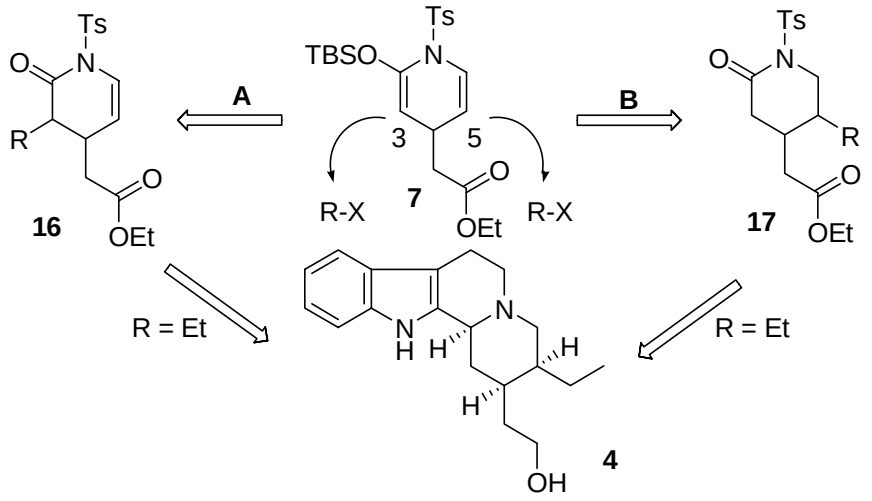
Corynantheidol **4** was isolated and characterized by Shellard and Houghton in 1973.[14] Total syntheses of this indole alkaloid were reported by several research groups, both as the racemate [15] and the optically active form.[16] The Michael adduct **3** possesses the unique property that both C3 and C5 can be functionalized by an electrophile, although the oxidation states of the carbon atoms at the 2- and 6- positions are different from each other. Thus, we postulated that **3** should

be able to convert into the D- ring system of corynantheidol **4** through two different routes according to the strategy mentioned above, namely, an alkylation reaction at the C3 position using the silyl enol ether moiety (**A**: **7**→**16**→**4**) or at the C5 position by enamine alkylation (**B**: **7**→**17**→**4**) (Scheme 2).



Scheme 1

We first tried the direct alkylation reaction of **7** under several reaction conditions (route **A**). However, both the usual alkylation of the silyl enol ether (dried TBAF and EtI in THF), and using silver acetate as an activator of the alkyl halide, were unsuccessful and only the hydrolyzed product **3** or the starting material **7** were recovered. Therefore, we decided to change the synthetic route from **A** to **B**.



Scheme 2

The selective reduction of the lactam carbonyl group of **3** by sodium borohydride in the presence of cerous chloride heptahydrate at -78 to -20°C produced the acetal **18** as inseparable diastereomeric mixtures. Formation of the acetal **18** under standard conditions (triethyl orthoformate, PPTS, EtOH, r.t.) gave two separable diastereomers **19** and **20** in 14 and 70% yield, respectively (Scheme 3). The stereochemistry of the major isomer **20** was determined by ^{1}H-NMR analysis. Between the possible two conformations, the conformer **20a** in which the axial position is occupied by an ethoxy group might be more favored, owing to the anomeric effect. The signal of the C3-βH appeared at 0.73 ppm as a triple doublet (J = 12.7 and 2.4 Hz), which showed the typical coupling pattern for the axial proton. Also, the unusually high field shift of this proton in comparison with the usual methylene signals, which is the result of shielding by the lone pair of the sp^2 nitrogen atom, might also be evidence for this conformation (Figure 2). Although both **19** and **20** seemed to be used for the synthesis of corynantheidol **4**, the major isomer **20** was used for the following sequences.

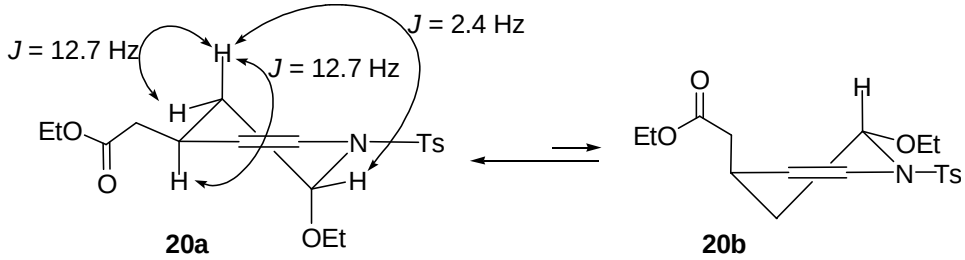
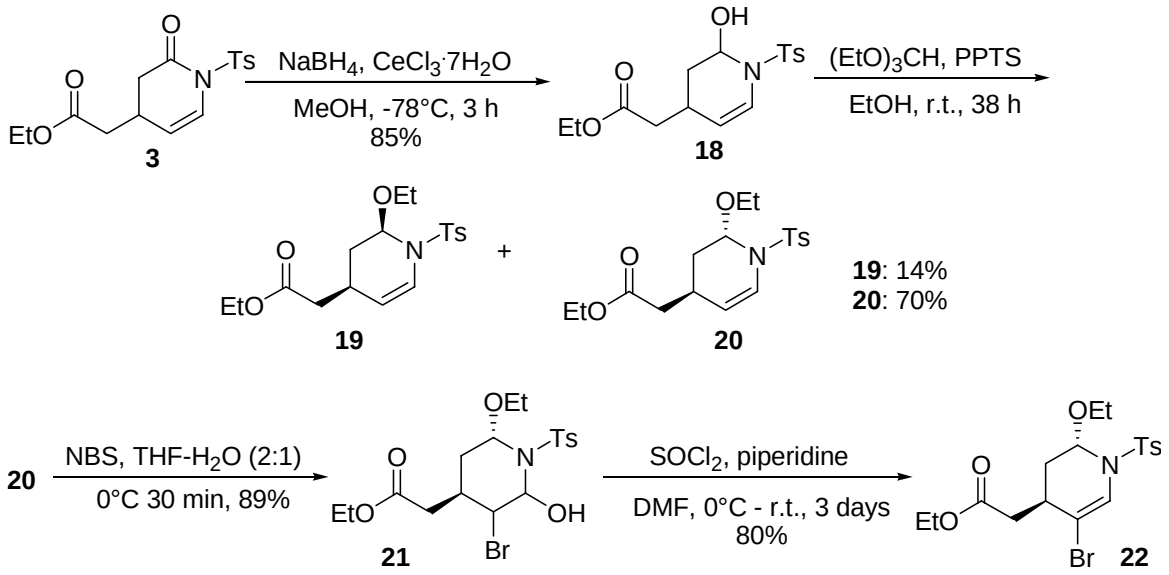


Figure 2. Conformation of the acetal **20**.

Because our efforts at alkylation at the C5 position were also all unsuccessful, we next planned to introduce the C2-unit by palladium-complex-catalyzed coupling between an alkenyl

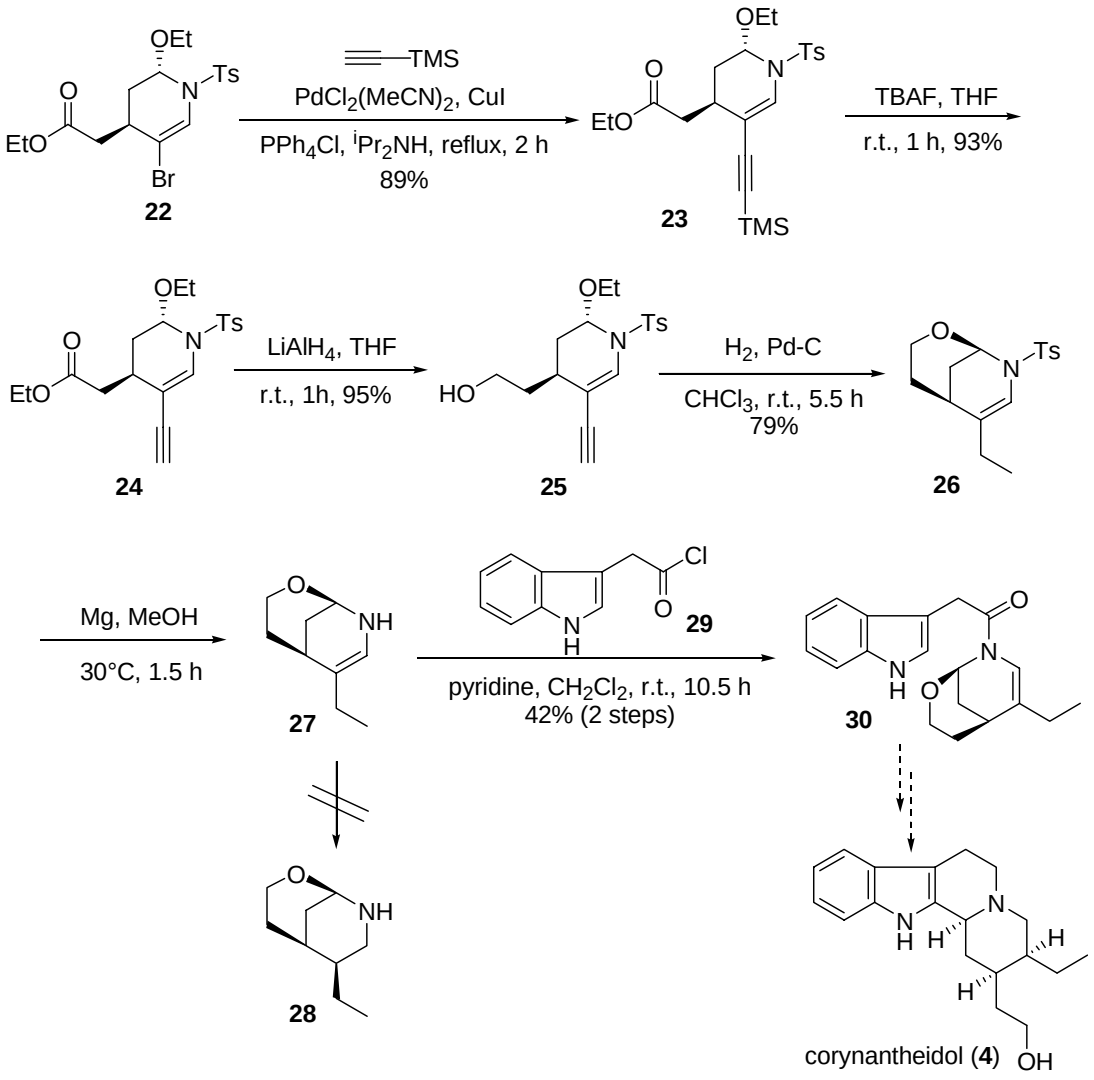
halide and acetylene. In order to introduce halogen atom at C5, **20** was reacted with NBS in THF–H_2O (2:1) to afford the desired bromohydrin **21**. The dehydration of **21** was successful using thionyl chloride and piperidine in DMF, giving the alkenyl bromide **22**, and setting the stage for the coupling reaction (Scheme 3).



Scheme 3

Unfortunately, the typical reaction conditions for the Sonogashira coupling reaction[17] (trimethylsilyl)acetylene, $PdCl_2(Ph_3P)_2$, Et_3N, CuI), and also those using other palladium complexes [e.g., $Pd(OAc)_2$, $Pd_2(dba)_2$, $PdCl_2(MeCN)_2$] were found to be ineffective. However, when tetraphenylphosphonium chloride was added to the reaction mixture, the yield of **23** was greatly improved.[18] Finally, the best yield (89%) was recorded when $PdCl_2(MeCN)_2$, *N*,*N*-diisopropylamine, and tetraphenylphosphonium chloride were used as the catalyst, the base, and the additive, respectively, as shown in Scheme 4 (**22**→**23**). The trimethylsilyl group was removed by tetrabutylammonium fluoride in THF (93%), followed by reduction of the ester group with lithium aluminum hydride, to afford the alcohol **25** in a reasonable overall yield. Next, we planned the reduction of both the ethynyl group and internal enamine moiety at the same time. Thus, the alcohol **25** was subjected to catalytic hydrogenation (Pd-C in chloroform) to afford the bicyclic compound **26** in 79% yield. The production of the bicyclic compound **26** was rather convenient for us, because we expected that the reducing reagents would attack the enamine moiety from the convex (α–face) to afford the *cis* stereochemistry between C-4 and C-5 which corresponds to the D- ring system of corynantheidol **4**. Surprisingly, the internal olefin resisted catalytic hydrogenation using Pd-C, $Pd(OH)_2$, or PtO_2 as the catalyst, even when the hydrogen pressure was increased to 5 Kg/cm^2. Therefore, we changed the route with the removal of the tosyl group first, then reduction of the double bond or coupling with the indole part. The tosyl group of **26** was easily removed by stirring with magnesium in methanol at 30°C.[19] The

enamine **27** was found to be unstable, so it was subjected to catalytic hydrogenation or sodium borohydride reduction without purification. However, we also dropped this route due to only decomposition of the enamine was observed under these reaction conditions. Finally, the crude enamine **27** was reacted with 3-indoleacetyl chloride **29** [20] and pyridine to afford the key intermediate **30** for the corynantheidol synthesis. The total synthesis of corynantheidol and the chiral version of the Michael addition reaction are now in progress in our laboratory.



Scheme 4

Conclusions

The efficient method for functionalizing *N*-tosyl-2-pyridinone **1** was established by the reaction with *tert*-butyldimethylsilyl ketene acetal **2** catalyzed by several kinds of Lewis acids. Due to the

reactivities of the C-4 Michael adduct **3** or **7** were quite different from the usual enamines or silyl enol ethers, we could not perform direct syntheses from these compounds. However, the introduction of the C2 unit at the desired position was carried out by using a palladium catalyzed reaction. Although we have not finished our synthesis of corynantheidol **4**, we are now able to produce the key intermediate for total synthesis by 11 steps from **1**. The total synthesis of corynantheidol **4** and related natural products are now under way in our laboratory.

Experimental Section

General Procedures. All melting points were determined with Yazawa Micro Melting Point BY-2 and are uncorrected. ^{1}H NMR spectra (400 or 500 MHz) and ^{13}C-NMR spectra (100 or 125 MHz) were recorded on JEOL JMN AL-400 or JEOL GX-500 spectrometers, respectively. ^{1}H-NMR spectra (300 MHz) were measured with a Varian Gemini 2000. Chemical shifts (δ) are given from TMS (0 ppm) as internal standard for ^{1}H-NMR, and $^{13}CDCl_3$ (77.0 ppm) for ^{13}C-NMR. Mass spectra and high resolution mass spectra were measured on JEOL JMS-DX303 and MS-AX500 instruments, respectively. IR spectra were recorded on a Shimadzu FTIR-8400. "RT" denotes room temperature.

***N*-Tosyl-2-pyridinone (1).**[11,13] Under an Ar atmosphere, butyllithium (1.58 *M* hexane solution, 45 mL, 71 mmol) was added to a solution of 2-pyridinone (6.0 g, 63 mmol) in anhydrous THF (50 mL) at 0°C and stirred for 20 min at that temperature. A solution of *p*-toluenesulfonyl chloride (13.4 g, 69 mmol) in anhydrous THF (30 mL) was added and the stirring was continued for another 1 h. Water was added and the aqueous phase extracted with AcOEt. The combined organic solution was washed with sat. NaCl solution, dried over anhydrous $MgSO_4$, and evaporated. The crude product was chromatographed on silica gel [AcOEt–hexane (1:3)] to afford **1** as a colorless solid (12.7g, 80%), which was recrystallized from AcOEt to give colorless needles; mp 137–138°C (lit.[13] mp 128–130°C); IR (film, cm^{-1}) 1674, 1600, 1461, 1373, 1165; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (3H, s), 6.24 (1H, ddd, *J* = 7.2, 6.6, 1.5 Hz), 6.41 (1H, br. d, *J* = 9.3 Hz), 7.30 (1H, ddd, *J* = 9.3, 6.6, 2.0 Hz), 7.34 (2H, d, *J* = 8.2 Hz), 8.00 (2H, d, *J* = 8.2 Hz), 8.09 (1H, ddd, *J* = 7.2, 2.0, 0.7 Hz); ^{13}C NMR (100 MHz , $CDCl_3$) δ 21.7, 106.1, 123.3, 129.3, 129.7, 131.5, 133.2, 141.0, 146.0, 159.9; MS *m*/*z* : 249 (M^+, 0.25%), 91 (100.0%); HRMS Calcd. $C_{12}H_{11}NO_3S$: 249.0459, Found: 249.0419.

General procedure for the reaction of *N*-tosyl-2-pyridinone (1) and the *tert*-butyldimethylsilyl ketene acetal (2) in the presence of Lewis acid

Under Ar atmosphere, Lewis acid was added to a solution of *N*-tosyl-2-pyridinone **2** in 1,2-dichloroethane or dichloromethane at the temperature listed in Table 1. After stirring for 15 min, *tert*-butyldimethylsilyl ketene acetal was added and the mixture was stirred at the temperatures listed in Table 1. Buffer solution (phosphate, pH 6.86) was added and the stirring continued for

another 1 h. The aqueous solution was extracted with AcOEt, the combined organic solution washed with sat. NaCl solution, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography [AcOEt–hexane (1:9)].

Table 1, entry 2. According to the general procedure, *N*-tosyl-2-pyridinone **1** (124.5 mg, 0.50 mmol), $AlCl_3$ (6.8 mg, 51.0 μmol), and *tert*-butyldimethylsilyl ketene acetal **2** (0.3 mL, 1.20 mmol) in 1,2-dichloroethane (1.5 mL) were reacted at -40–0°C for 72 h. After purification, **3** (36.9 mg, 22%) was obtained and some **1** (20.0 mg, 16%) was recovered.

Table 1, entry 3. According to the general procedure, *N*-tosyl-2-pyridinone **1** (124.6 mg, 0.50 mmol), Et_2AlCl (0.98 *M* solution in hexane, 0.05 mL, 49.0 μmol), and *tert*-butyldimethylsilyl ketene acetal **2** (0.3 mL, 1.20 mmol) in 1,2-dichloroethane (1.5 mL) were reacted at -40°C for 24 h. After purification, **3** (121.1 mg, 72%) was obtained.

Table 1, entry 4. According to the general procedure, *N*-tosyl-2-pyridinone **1** (125.0 mg, 0.50 mmol), Me_3Al (0.98 *M* solution in hexane, 0.05 mL, 51.0 μmol), *tert*-butyldimethylsilyl ketene acetal **2** (0.3 mL, 1.20 mmol) in 1,2-dichloroethane (1.0 mL) was reacted at -40°C for 16 h. After purification, **3** (136.9 mg, 83%) and 4 (5.4 mg, 4%) were obtained.

Table 1, entry 5. According to the general procedure, *N*-tosyl-2-pyridinone **1** (3.0 g, 12 mmol), TBSOTf (0.32 g, 1.2 mmol), and *tert*-butyldimethylsilyl ketene acetal **2** (6.0 mL, 24 mmol) in dichloromethane (30 mL) were reacted at -78– -20°C for 24 h. After purification, **3** (3.61 g, 89%) was obtained.

Ethyl 2-[1-(4-methylphenyl)sulfonyl-2-oxo-1,2,3,4-tetrahydro-4-pyridinyl]acetate (3). Colorless prisms (recrystallized from Et_2O–hexane), mp 63–64°C; *Anal*. Calcd. $C_{16}H_{19}NO_5S$: C, 56.96; H, 5.68; N, 4.15. Found: C, 56.90; H, 5.69; N, 4.05. IR ($CHCl_3$, cm^{-1}) 1725, 1654; ^1H NMR (500 MHz, $CDCl_3$) δ 1.21 (3H, t, *J* = 6.7 Hz), 2.24 (1H, dd, *J* = 16.0, 7.3 Hz), 2.29 (1H, dd, *J* = 16.0, 7.3 Hz), 2.36 (1H, dd, *J* = 15.9, 8.5 Hz), 2.41 (3H, s), 2.62 (1H, dd, *J* = 15.9, 6.7 Hz), 2.90–2.91 (1H, m), 4.07 (2H, q, *J* = 6.7 Hz), 5.30 (1H, dd, *J* = 8.2, 3.7 Hz), 6.97 (1H, dd, *J* = 8.2, 1.2 Hz), 7.30 (2H, d, *J* = 8.2 Hz), 7.86 (2H, d, *J* = 8.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 21.6, 28.4, 38.49, 38.51, 60.8, 111.8, 124.4, 128.6, 129.5, 135.2, 145.3, 167.5, 170.8; MS *m/z*: 337 (M^+, 0.94%), 91 (100%); HRMS Calcd. $C_{16}H_{19}NO_5S$: 337.0984. Found: 337.0984.

8-*tert*-Butyldimethylsilyloxy-8-ethoxy-2-(4-methylphenyl)sulfonyl-2-azabicyclo[2.2.2]oct-5-en-3-one (5). Colorless prisms (recrystallized from Et_2O–hexane), mp 109–114°C. IR (KBr, cm^{-1}) 1720; ^1H NMR (500 MHz $CDCl_3$) δ 0.05 (6H, s), 0.78 (9H, s), 0.83 (3H, t, *J* = 7.3 Hz), 1.82 (1H, dd, *J* = 12.8, 1.8 Hz), 2.25 (1H, dd, *J* = 12.8, 3.7 Hz), 2.38 (3H, s), 3.40 (1H, dq, *J* = 8.0, 7.3 Hz), 3.47 (1H, dq, *J* = 8.0, 7.3 Hz), 3.65 (1H, dd, *J* = 6.7, 1.2 Hz), 5.31–5.33 (1H, m), 6.23 (1H, ddd, *J* = 7.0, 6.7, 1.8 Hz), 6.54 (1H, ddd, *J* = 7.0, 6.7, 1.2 Hz), 7.25 (2H, d, *J* = 8.2 Hz), 7.82 (2H, d, *J* = 8.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ -3.2, 14.6, 18.0, 21.5, 25.6, 43.5, 53.8, 56.6, 56.7, 101.0, 128.0, 129.2, 130.3, 133.3, 135.8, 144.6, 168.7; FAB-MS *m/z*: 452 (M^++1); HRMS Calcd. $C_{15}H_{26}NO_3Si$ (M^+-$C_7H_7SO_2$): 296.1682. Found: 296.1670.

Ethyl[2-*tert*-butyldimethylsilyloxy-1-(4-methylphenylsulfonyl)-1,4-dihydro-4-pyridinyl]acetate (7). Under Ar atmosphere, *tert*-butyldimethylsilyl ketene acetal **2** (0.20 mL, 0.80 mmol) and TBSOTf (11 mg, 0.04 mmol) was added to a stirred solution of *N*-tosyl-2-pyridinone **1** (0.100 g,

0.40 mmol) in anhydrous CH_2Cl_2 at -78°C and gradually warmed to -20°C. After stirring for 24 h at the same temperature, the solvent and the excess reagent was evaporated to afford the crude product, which was dissolved in $CDCl_3$ and the ^{1}H-NMR measured. ^{1}H NMR (300 MHz $CDCl_3$) δ 0.17 (6H, s), 0.88 (9H, s), 1.20 (3H, t, *J* = 7.1 Hz), 1.87 (1H, dd, *J* = 16.4, 7.7 Hz), 2.02 (1H, dd, *J* = 16.4, 6.7 Hz), 2.39 (3H, s), 3.18–3.23 (1H, m), 4.06 (2H, q, *J* = 7.1 Hz), 4.10 (1H, dd, *J* = 4.2, 1.7 Hz), 5.01 (1H, ddd, *J* = 8.2, 4.0, 1.7 Hz), 6.64 (1H, dd, *J* = 8.2, 0.8 Hz), 7.27 (2H, d, *J* = 8.2 Hz), 7.66 (2H, d, *J* = 8.2 Hz).

Ethyl 2-[1-(4-methylphenylsulfonyl)-2-oxo-4-piperidinyl]acetate (8). A mixture of **3** (30 mg, 0.089 mmol) and catalytic Pd–C in AcOEt (2.0 mL) was stirred under hydrogen atmosphere for 13 h. The Pd–C was removed (Celite) and the filtrate concentrated *in vacuo*. The crude product was purified by silica gel chromatography eluted with AcOEt–hexane (1:2) to afford **8** (29 mg, 96%) as a colorless solid which was recrystallized from Et_2O–hexane to give colorless needles; mp 71–72°C; *Anal*. Calcd. $C_{16}H_{21}NO_5S$: C, 56.62; H, 6.24; N, 4.13; S, 9.45. Found: C, 56.56; H, 6.11; N, 4.12; 9.45; IR (KBr, cm^{-1}) 1733, 1690; ^{1}H-NMR (500 MHz $CDCl_3$) δ 1.22 (3H, t, *J* = 8.2 Hz), 1.53–1.61 (1H, m), 2.11 (2H, d, *J* = 10.4 Hz), 2.26 (2H, s), 2.41 (3H, s), 2.53–2.58 (2H, m), 3.64 (1H, td, *J* = 12.2, 4.3 Hz), 4.10 (2H, q, *J* = 6.7 Hz), 5.63 (1H, dt, *J* = 12.2, 4.3 Hz), 7.30 (2H, d, *J* = 8.2 Hz), 7.88 (2H, d, *J* = 8.2 Hz); MS *m/z* : 340 (M^++1); HRMS Calcd. $C_{16}H_{22}NO_5S$: 340.1249. Found: 340.1252.

2- (4-Methylphenylsulfonyl)-2-azabicyclo[2.2.2]oct-7-en-3,5-dione (9). A solution of **5** (0.171 g, 0.70 mmol) in HF–MeCN (1:19, 4.0 mL) was stirred at RT for 1.5 h. Saturated $NaHCO_3$ solution was added to the mixture, shaken, and extracted with AcOEt. The combined organic solution was washed with sat. NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The crude product was chromatographed on silica gel [AcOEt–hexane (1:1)] to afford **9** (0.103 g, 93%) as a colorless solid; IR (KBr, cm^{-1}) 1750, 1711; ^{1}H NMR (500 MHz $CDCl_3$) δ 2.41 (3H, s), 2.43 (2H, dd, *J* = 6.7, 2.4 Hz), 4.00 (1H, dd, *J* = 6.4, 1.2 Hz), 5.66–5.68 (1H, m), 6.40 (1H, ddd, *J* = 7.6. 6.4, 1.8 Hz), 6.72 (1H, ddd, *J* = 7.6, 5.8, 1.2 Hz), 7.30 (2H, d, *J* = 8.2 Hz), 7.84 (2H, d, *J* = 8.2 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 21.7, 38.3, 53.5, 65.4, 127.9, 128.1, 129.7, 134.2, 135.0, 145.7, 164.7, 198.1; MS *m/z*: 292 (M^++1); HRMS Calcd. $C_{14}H_{13}NO_4S$: 291.0565. Found: 291.0521.

Ethyl 2-[2-hydroxy-1-(4-methylphenylsulfonyl)-1,2,3,4-tetrahydro-4-pyridinyl]acetate (18). To a solution of **3** (0.340 g, 1.0 mmol) in EtOH (14 ml) was added cerous chloride heptahydrate (0.560 g, 1.5 mmol) and sodium borohydride (59 mg, 1.6 mmol) at -78°C and the mixture was gradually warmed to -20°C. After stirring for 3 h, acetone was added to the mixture, and then filtered through a Celite pad. H_2O was added to the filtrate and extracted with AcOEt. The combined organic solution was washed with sat. NaCl solution, dried over anhydrous $MgSO_4$, and evaporated. The crude product was chromatographed on silica gel [AcOEt–hexane (1:3)] to provide **18** (inseparable diastereomeric mixture, 0.300 g, 89 %,) as a colorless oil; IR (neat, cm^{-1}) 3500, 1730, 1650, 1600; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (1H, br. t, *J* = 12.4 Hz), 1.23 (3H, t, *J* = 7.1 Hz), 2.03 (1H, ddd, *J* = 12.4, 4.5, 2.4 Hz), 2.24 (1H, dd, *J* = 15.1, 7.3 Hz), 2.29 (1H, dd, *J* = 15.1, 7.3 Hz), 2.43 (2.70H, s), 2.60 (0.30H, s), 2.81–2.86 (1H, m), 2.98 (0.86H, s), 3.12

(0.14H, br. s), 4.11 (2H, q, *J* = 7.1 Hz), 4.92 (0.84H, dt, *J* = 8.3, 2.0 Hz), 5.13 (0.16H, m), 5.48 (1H, s), 6.58 (1H, m), 7.30 (2H, d, *J* = 8.2 Hz), 7.68 (2H, d, *J* = 8.2 Hz); MS *m*/*z*: 339 (M^+, 0.7 %), 91 (100.0 %); HRMS Calcd $C_{16}H_{21}NO_5S$: 339.1156. Found: 339.1119.

(2R*,4R*)-Ethyl 2-[2-ethoxy-1-(4-methylphenylsulfonyl)-1,2,3,4-tetrahydro-4-pyridinyl]acetate (19) and (2S*,4R*)-ethyl 2-[2-ethoxy-1-(4-methylphenylsulfonyl)-1,2,3,4-tetrahydro-4-pyridinyl]-acetate (20). A solution of triethyl orthoformate (1.80 g, 12.15 mmol), pyridinium *p*-toluenesulfonate (0.15 g, 0.59 mmol), and **18** (2.00 g, 5.90 mmol) in anhydrous ethanol (44 mL) was stirred at RT for 38 h. The solvent and the excess reagent were evaporated. Water was added to the residue and the aqueous phase extracted with AcOEt. The combined organic solution was washed with sat. NaCl solution, dried ($MgSO_4$), and the solvent evaporated. The residue was chromatographed on silica gel [AcOEt–hexane (1:6)] to yield **19** (0.29 g, 14%) as a colorless solid and **20** (1.50 g, 70%) as a colorless oil.

19. Colorless needles from Et_2O–hexane, mp 67–68°C; *Anal*. Calcd. $C_{18}H_{25}NO_5S$: C, 58.53; H, 6.86; N, 3.81. Found: C, 58.65; H, 6.91; N, 3.53; IR (KBr, cm^{-1}) 1730, 1653, 1352, 1170; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.16 (3H, t, *J* = 7.3 Hz), 1.20 (1H, m), 1.23 (3H, t, *J* = 7.3 Hz), 1.89 (1H, d, *J* = 14.0 Hz), 2.42 (3H, s), 2.44 (1H, m), 2.54 (2H, d, *J* = 7.3 Hz), 3.53 (1H, dq, *J* = 9.6, 7.3 Hz), 3.76 (1H, dq, *J* = 9.6, 7.3 Hz), 4.11 (2H, q, *J* = 7.3 Hz), 5.18 (1H, ddd, *J* = 8.6, 4.8, 1.2 Hz), 5.22 (1H, s), 6.52 (1H, dt, *J* = 8.6, 1.2 Hz), 7.29 (2H, d, *J* = 8.3 Hz), 7.64 (2H, d, *J* = 8.3 Hz); ^{13}C-NMR (100 MHz , $CDCl_3$) δ 14.3, 15.0, 21.6, 25.8, 30.4, 39.7, 60.2, 63.3, 81.7, 113.4, 121.9, 126.6, 129.6, 136.1, 143.6, 172.6; MS *m*/*z*: 367 (M^+, 2.8%), 234 (100.0%); HRMS Calcd $C_{18}H_{25}NO_5S$: 367.1452. Found: 367.1452.

20. IR (KBr, cm^{-1}) 1732, 1342, 1168, 1170; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.73 (1H, td, *J* = 12.8, 2.4 Hz), 1.17 (3H, t, *J* = 7.3 Hz), 1.21 (3H, t, *J* = 7.3 Hz), 1.95 (1H, m), 2.15 (2H, d, *J* = 7.3 Hz), 2.42 (3H, s), 2.80 (1H, m), 3.62 (1H, dq, *J* = 9.8, 7.3 Hz), 3.79 (1H, dq, *J* = 9.8, 7.3 Hz), 4.08 (2H, q, *J* = 7.3 Hz), 4.98 (1H, d, *J* = 7.9 Hz), 5.18 (1H, s), 6.50 (1H, ddd, *J* = 8.3, 2.4, 1.3 Hz), 7.29 (2H, d, *J* = 8.3 Hz), 7.64 (2H, d, *J* = 8.3 Hz); ^{13}C NMR (100 MHz , $CDCl_3$) δ 14.2, 14.9, 21.6, 24.9, 32.1, 39.1, 60.4, 63.1, 81.5, 113.0, 122.3, 126.7, 129.6, 136.0, 143.6, 171.6; MS *m*/*z*: 367 (M^+, 1.9%), 234 (100.0%); HRMS Calcd $C_{18}H_{25}NO_5S$: 367.1452. Found: 367.1466.

Ethyl 2-[5-bromo-2-ethoxy-6-hydroxy-1-(4-methylphenylsulfonyl)-4-piperidinyl]acetate (21). *N*-Bromosuccinimide (48.0 mg, 0.27 mmol) was added to a solution of **20** (100.0 mg, 0.27 mmol) in THF (1.0 mL) and H_2O (1.0 mL) at 0°C and stirred at the same temperature for 30 min. Saturated $NaHCO_3$ solution was added, and the mixture extracted with Et_2O. The combined organic solution was washed with H_2O then sat. NaCl solution, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with AcOEt–hexane (1:3) to afford **21** (110.0 mg, 89%) as a colorless solid, which was recrystallized from Et_2O–hexane to afford colorless needles; mp 70–72°C; *Anal*. Calcd. $C_{18}H_{26}BrNO_6S$: C, 45.56; H, 5.64; N, 3.02; Br, 17.21. Found: C, 46.47; H, 5.64; N, 2.98, Br; 17.09; IR (KBr, cm^{-1}) 3500, 1714, 1163.^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.05 (3H, t, *J* = 6.9 Hz), 1.27 (3H, t, *J* = 7.1 Hz), 1.75 (1H, td, *J* = 13.3, 2.9 Hz), 1.90 (1H, br. d, *J* = 13.3 Hz), 2.33 (1H, dd, *J* = 16.6, 7.6 Hz), 2.42 (3H, s), 2.43 (1H, dd, *J* = 16.6, 6.6 Hz), 2.78–2.87 (1H, m), 3.52 (1H,

q, *J* = 6.7 Hz), 3.54 (1H, q, *J* = 6.7 Hz), 4.08 (1H, d, *J* = 9.0 Hz), 4.14 (2H, q, *J* = 7.1 Hz), 4.35 (1H, s), 5.33 (1H, s), 5.52 (1H, d, *J* = 7.3 Hz), 7.28 (2H, d, *J* = 8.5 Hz), 7.79 (2H, d, *J* = 8.5 Hz); MS *m*/*z*: 465 (M^++ 2, 0.5%), 463 (M^+, 0.5%), 72 (100.0%); HRMS Calcd $C_{18}H_{26}NO_6S^{79}Br$: 463.0664. Found: 463.0670.

Ethyl 2-(5-bromo-2-ethoxy-1-[4-methylphenylsulfonyl]-1,2,3,4-tetrahydro-4-pyridinyl)acetate (22). Thionyl chloride (0.76 g, 6.38 mmol) and piperidine (0.18 g, 2.13 mmol) were added to a stirred solution of **21** (0.247 g, 0.53 mmol) in anhydrous DMF (25.0 ml) at 0°C. After stirring for 3 days at RT, H_2O was added, and the mixture extracted with Et_2O. The combined organic solution was washed with sat. NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated. The residue was chromatographed on silica gel [AcOEt–hexane (1:9)] to afford **22** (0.190 g, 80%) as a colorless solid, which was recrystallized from Et_2O to provide colorless prisms (mp 108–109°C); *Anal*. Calcd. $C_{18}H_{24}BrNO_5S$: C, 48.44; H, 5.42; N, 3.14; S, 7.18. Found: C, 48.52; H, 5.40; N, 3.23, S; 7.09; IR (KBr, cm^{-1}) 1737, 1169. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (1H, td, *J* = 13.2, 2.4 Hz), 1.17 (3H, t, *J* = 6.8 Hz), 1.21 (3H, t, *J* = 7.1 Hz), 2.00 (1H, dd, *J* = 16.0, 9.3 Hz), 2.12 (1H, ddd, *J* = 13.2, 5.7, 2.8 Hz), 2.44 (3H, s), 2.80 (1H, dd, *J* = 16.0, 4.1 Hz), 2.94–3.03 (1H, m), 3.59 (1H, dq, *J* = 9.6, 7.1 Hz), 3.78 (1H, dq, *J* = 9.5, 7.1 Hz), 4.03–4.10 (2H, m), 5.14 (1H, s), 6.87 (1H, s), 7.32 (2H, d, *J* = 8.3 Hz), 7.64 (2H, d, *J* = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 14.9, 21.7, 31.3, 33.4, 38.4, 60.6, 63.4, 81.2, 111.3, 123.5, 126.8, 129.9, 135.6, 144.1, 171.2; MS *m*/*z* : 447 (M^++ 2, 11.3%), 445 (M^+, 11.3%), 244 (100.0%); HRMS Calcd $C_{18}H_{24}NO_5S^{79}Br$: 445.0558. Found: 445.0518.

Ethyl 2-[2-ethoxy-1-(4-methylphenylsulfonyl)-5-trimethylsilylethynyl-1,2,3,4-tetrahydro-4-pyridinyl]acetate (23). $PdCl_2(MeCN)_2$ (4.7 mg, 18.0 μmol), CuI (1.1 mg, 5.6 μmol), and Ph_4PCl (39.0 mg, 0.10 mmol) were added to a solution of **22** (50.0 mg, 0.11 mmol) in $_iPr_2NH$ (1.6 ml) at RT and the mixture was warmed at 84°C. Trimethylsilylacetylene (0.48 mL, 0.34 mmol) was added to the mixture and heated at reflux for 18 h. The precipitate was filtered off (Celite pad) and the filtrate extracted with Et_2O. The combined organic solution was washed with sat. NaCl solution, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with AcOEt–hexane (1:4) to afford **23** (46.0 mg, 89%) as a colorless oil; IR (neat, cm^{-1}) 2958, 2142, 1732, 1620, 1352, 1269, 1248; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.18 (9H, s), 0.82 (1H, td, *J* = 13.2, 2.5 Hz), 1.14 (3H, t, *J* = 7.1 Hz), 1.22 (3H, t, *J* = 7.1 Hz), 2.03–2.08 (2H, m), 2.43 (3H, s), 2.80–2.89 (2H, m), 3.58 (1H, dq, *J* = 9.4, 6.9 Hz), 3.73 (1H, dq, *J* = 9.5, 6.9 Hz), 4.06–4.12 (2H, m), 5.18 (1H, m), 6.97 (1H, br. t, *J* = 1.5 Hz), 7.30 (2H, d, *J* = 8.3 Hz), 7.65 (2H, d, *J* = 8.3 Hz); MS *m*/*z* : 463 (M^+, 16.3%), 262 (100.0%); HRMS Calcd $C_{23}H_{33}NO_5SiS$: 463.1850. Found: 463.1825.

Ethyl 2-[2-ethoxy-5-ethynyl- (4-methylphenylsulfonyl)-1,2,3,4-tetrahydro-4-pyridinyl]acetate (24). A solution of TBAF (70–75% solution in H_2O, 15.0 mg, 57 μmol) and **23** (27.0 mg, 57 μmol) in THF (0.43 mL) was stirred at RT for 1 h, then the mixture was extracted with Et_2O. The combined organic solution was washed with sat. NaCl solution, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel chromatography eluting with AcOEt–hexane (1:4) to afford **24** (21.0 mg, 93%) as a colorless oil; IR (neat, cm^{-1}) 3277, 2978, 2094,

1732, 1622, 1352, 1167; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.81 (1H, td, *J* = 12.6, 2.4 Hz), 1.16 (3H, t, *J* = 6.9 Hz), 1.21 (3H, t, *J* = 7.1 Hz), 2.02–2.10 (2H, m), 2.43 (3H, s), 2.80–2.89 (2H, m), 2.92 (1H, s), 3.60 (1H, dq, *J* = 9.5, 7.1 Hz), 3.74 (1H, dq, *J* = 9.5, 7.1 Hz), 4.08 (2H, m), 5.19 (1H, s), 7.00 (1H, s), 7.31 (2H, d, *J* = 8.3 Hz), 7.66 (2H, d, *J* = 8.3 Hz); ^{13}C-NMR (100 MHz , $CDCl_3$) δ 14.2, 14.9, 21.6, 26.7, 31.8, 3.4, 60.4, 63.4, 78.4, 81.15, 81.24, 105.5, 126.8, 129.8, 135.9, 144.1, 171.8; MS *m*/*z* : 391 (M^+, 14.0%), 91 (100.0%); HRMS Calcd $C_{20}H_{25}NO_5S$: 391.1452. Found: 391.1454.

2-Ethoxy-5-ethynyl-4-[2-(1-hydroxyethyl)]-1-[4-methylphenylsulfonyl]-1,2,3,4-tetrahydropyridine (25). A solution of **24** (0.435 g, 1.11 mmol) in anhydrous THF (6.0 ml) was added to a suspension of $LiAlH_4$ (53.0 mg, 1.11 mmol) in anhydrous THF (4.0 mL) at 0°C. After being stirred for 1 h at RT, aqueous ammonia solution was added. The inorganic precipitate was filtered off (Celite) and the filtrate extracted with AcOEt. The combined organic solution was washed with sat. NaCl solution, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with AcOEt–hexane (1:2) to provide **25** (0.370 g, 95%) as a colorless oil; IR (neat, cm^{-1}) 3427, 3286, 2927, 2094, 1620, 1352, 1165; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.74 (1H, td, *J* = 12.8, 2.4 Hz), 1.16 (3H, t, *J* = 7.1 Hz), 1.25 (1H, s), 1.37–1.46 (1H, m), 2.00 (1H, ddd, *J* = 13.4, 5.6, 2.9 Hz), 2.11 (1H, ddt, *J* = 7.1, 3.9, 3.9 Hz), 2.43 (3H, s), 2.46–2.55 (1H, m), 2.92 (1H, s), 3.51–3.66 (3H, m), 3.77 (1H, dq, *J* = 9.5, 7.1 Hz), 5.17 (1H, s), 6.98 (1H, s), 7.31 (2H, d, *J* = 8.3 Hz), 7.64 (2H, d, *J* = 8.3 Hz); ^{13}C-NMR (100 MHz , $CDCl_3$) δ 14.9, 21.7, 26.8, 31.8, 35.1, 60.5, 63.4, 78.0, 81.3, 81.8, 107.5, 126.8, 129.6, 129.8, 135.8, 144.1; MS *m*/*z*: 349 (M^+, 31.8%), 91 (100.0%); HRMS Calcd $C_{18}H_{23}NO_4S$: 349.1348. Found: 349.1378.

6-Ethyl-8-(4-methylphenylsulfonyl)-8-aza-2-oxobicyclo[3.2.1]oct-6-ene (26). A mixture of **25** (118.0 mg, 0.34 mmol) and a catalytic amount of Pd–C in $CHCl_3$ (3.0 mL) was stirred under hydrogen at RT for 24 h. The mixture was filtered, and the filtrate concentrated *in vacuo*. The residue was subjected to silica gel chromatography [AcOEt–hexane (1:6)] to yield **26** (83.0 mg, 79%) as a solid, which was recrystallized from Et_2O–hexane to give colorless needles (mp 69–70°C); IR ($CHCl_3$, cm^{-1}) 2960, 1660, 1596, 1352, 1161; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.02 (3H, t, *J* = 7.4 Hz), 1.19 (1H, br. d, *J* = 12.4 Hz), 1.47 (1H, br. d, *J* = 12.7 Hz), 1.76 (1H, m), 1.96–2.08 (3H, m), 2.32 (1H, br. s), 2.41 (3H, s), 2.81 (1H, td, *J* = 12.4, 3.2 Hz), 3.27 (1H, dd, *J* = 11.8, 5.2 Hz), 5.68 (1H, s), 6.65 (1H, s), 7.27 (2H, d, *J* = 8.3 Hz), 7.80 (2H, d, *J* = 8.3 Hz); ^{13}C-NMR (100 MHz , $CDCl_3$) δ 12.6, 21.6, 26.6, 27.4, 27.6, 30.7, 58.5, 77.2, 120.1, 122.7, 127.3, 129.3, 137.2, 143.3; MS *m*/*z*: 307 (M^+, 100.0%); HRMS Calcd $C_{16}H_{21}NO_3S$: 307.1242. Found: 307.1252.

6-Ethyl-8-[(*1H*)-indol-3-yl]-2-oxoethyl-8-aza-2-oxobicyclo[3.2.1]oct-6-ene (30). Under an Ar atmosphere, a mixture of magnesium (51.0 mg, 2.08 mmol) and **26** (32.0 mg, 0.21 mmol) in anhydrous methanol (2.0 mL) was stirred at RT for 1.5 h. The mixture was filtered through Celite and the filtrate extracted with AcOEt. The combined organic solution was washed with sat. NaCl solution, dried over anhydrous $MgSO_4$, and evaporated. The crude **27** was used to the next reaction without further purification.

To a stirred solution of the crude **27** and pyridine (41.0 mg, 0.52 mmol) in anhydrous CH_2Cl_2 (2.0 ml) was added 3-indoleacetyl chloride **29** (41.0 mg, 0.21 mmol) at 0°C and the mixture was stirred for 10.5 h at RT. H_2O was added to the mixture and extracted with AcOEt. The combined organic solution was washed with sat. NaCl solution, dried over anhydrous $MgSO_4$, and evaporated. The residue was chromatographed on silica gel [AcOEt–hexane (1:2)] to afford **30** (13.0 mg, 42%) as a colorless oil; IR (neat, cm^{-1}) 3319, 1651; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.04 (3H, t, *J* = 7.4 Hz), 1.39 (1H, d, *J* = 12.8 Hz), 1.92 (1H, ddt, *J* = 13.5, 5.5, 3.7 Hz), 2.03 (1H, dt, *J* = 12.8, 3.1 Hz), 2.04–2.13 (2H, m), 2.36 (1H, m), 3.65 (1H, dt, *J* = 12.8, 3.1 Hz), 3.70 (1H, dd, *J* = 12.8, 5.5 Hz), 3.87 (1H, d, *J* = 6.4 Hz), 4.09 (1H, d, *J* = 6.4 Hz), 5.56 (1H, s), 7.08 (1H, s), 7.17 (1H, t, *J* = 7.9 Hz), 7.32 (1H, d, *J* = 7.9 Hz), 7.36 (1H, s), 7.63 (1H, d, *J* = 7.9 Hz), 8.13 (1H, br.); MS *m*/*z*: 310 (M^+, 100.0%); HRMS Calcd $C_{19}H_{22}N_2O_3$: 310.1681. Found: 310.1670.

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