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# Further studies on enantioselective synthesis of (+)-anatoxin-*a* using enyne metathesis: unexpected inversion of chirality via a skeletal rearrangement of 9-azabicyclo[4.2.1]nonene derivative

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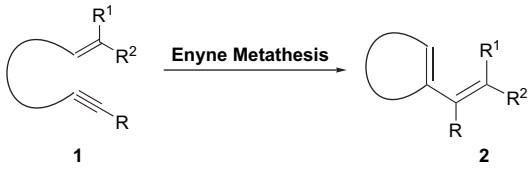
**Abstract**—The formal total synthesis of (+)-anatoxin-*a* was accomplished using enyne metathesis as a key step. It is very interesting that (+)-anatoxin-*a* was synthesized from (*S*)-pyroglutamic acid via an unusual inversion of chirality, which is rationalized in terms of a skeletal rearrangement of 9-azabicyclo[4.2.1]nonene derivative at the stage of oxymercuration of the diene.

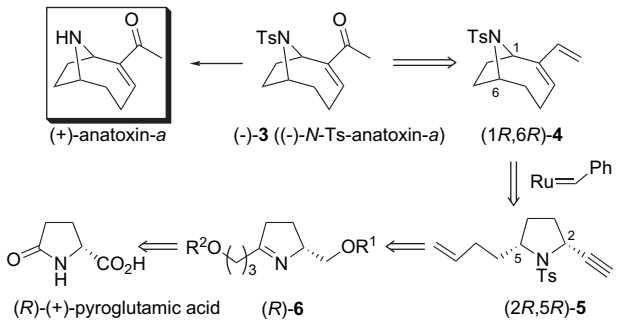

## 1. Introduction

Metathesis reaction is now one of the most promising strategies for the construction of various functionalized rings contained in natural products and biologically active substances.[1,2] Among the various types of metathesis reaction, enyne metathesis[3] has the following unique and useful properties for organic synthesis: (1) the terminal alkylidene moiety of alkene in the substrate **1** formally migrates on the alkyne carbon to produce the cyclized product **2** containing 1,3-diene, which should serve for further functionalization on the ring (Scheme 1) and (2) enyne metathesis is completely atom economical compared to the corresponding diene metathesis.




**Scheme 1**.

Recently, we have shown the efficiency of enyne metathesis for the construction of various ring-sized cyclic compounds and the synthesis of natural products and related compounds via ring-closing enyne metathesis and also for the synthesis of 1,3-diene derivatives from alkyne and ethylene via intermolecular enyne metathesis.[4] In that context, we had interest in the synthesis of anatoxin-*a*, which has a strained azabicyclo[4.2.1]nonene skeleton, via ring-closing enyne metathesis.[5] Anatoxin-*a*, which was isolated from the blue-green freshwater algae *Anabaena flos-aquae*, is one of the most powerful agonists of the nicotinic acetylcholine receptor[6] and has an azabicyclo[4.2.1]nonene skeleton bearing α,β-unsaturated ketone. Because of the unique structure and biological activity of anatoxin-*a*, many groups have synthesized anatoxin-*a* by various interesting methods.[7] The structure of anatoxin-*a* prompted us to attempt its synthesis using enyne metathesis as a key step. Our retrosynthetic analysis is shown in Scheme 2.




**Scheme 2**. Retrosynthetic analysis of (+)-anatoxin-*a*.

The synthesis of (+)-anatoxin-*a* from (−)-*N*-Ts-anatoxin-*a* ((−)-**3**) has been reported in the literature,[8] and (−)-**3** would be synthesized from (1*R*,6*R*)-**4** through oxidation of the 1,3-diene moiety. The compound (1*R*,6*R*)-**4** having a strained azabicyclo[4.2.1]nonene ring system would be constructed by metathesis of enyne (2*R*,5*R*)-**5** in the cis-substituents on the pyrrolidine ring. In the synthesis of

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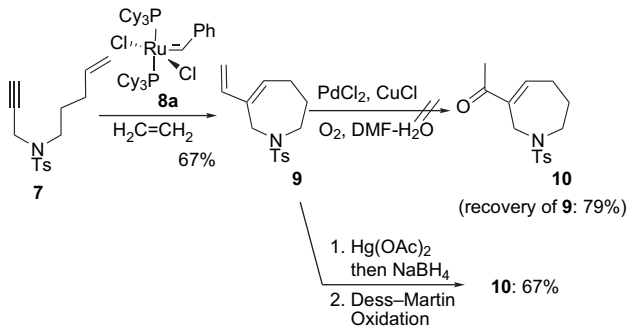
(2*R*,5*R*)-**5**, a *p*-toluenesulfonyl group as a protecting group on nitrogen was chosen because it was expected that $^{1}H$ and $^{13}C$ NMR spectral data in the case of an amide protecting group would be complicated because of the existence of rotation isomers of the amide carbonyl group. To synthesize the substrate (2*R*,5*R*)-**5** for enyne metathesis, hydrogenation of imine (*R*)-**6** should be suitable, and the compound (*R*)-**6** could be derived from (*R*)-(+)-pyroglutamic acid. We describe herein the synthesis of (+)-anatoxin-*a* using enyne metathesis as a key step.[9–11] Furthermore, during the course of our investigation, we encountered an unexpected inversion of chirality by a skeletal rearrangement of 9-azabicyclo[4.2.1]nonene derivative, which is also described.

## 2. Model study for conversion of 1,3-diene to α,β-unsaturated ketone

In the above-mentioned retrosynthetic analysis (Scheme 2), conversion of the 1,3-diene moiety in the cyclized product **4** is a very important process. Thus, the oxidation condition of the diene moiety was examined. As a model compound, azepine derivative **9** having a diene moiety was used (Scheme 3). We have already reported that metathesis of enyne having a terminal alkene and alkyne proceeded smoothly under ethylene gas using first-generation ruthenium–carbene complex **8a**[12] and that compound **9** was obtained from **7** in good yield.[4e]

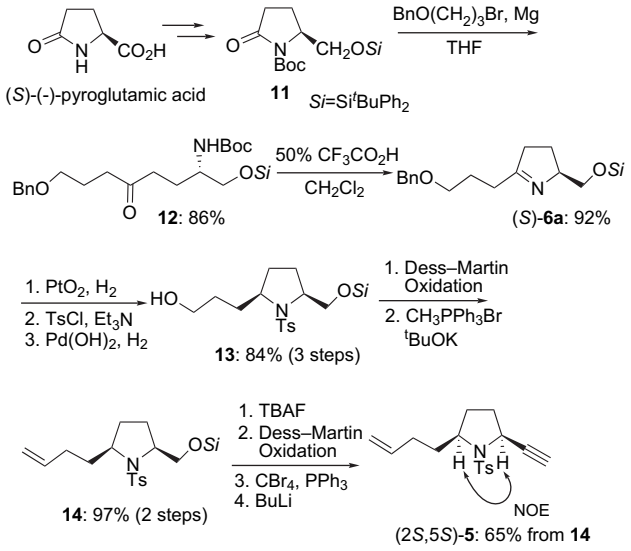



**Scheme 3**. Conversion of diene into α,β-unsaturated ketone.

First, oxidation of **9** with $PdCl_2$ and CuCl in aqueous DMF was carried out under oxygen.[13] However, the reaction mixture changed to yellow color and the starting material was recovered in 79% yield after 24 h, presumably indicating that the diene moiety in **9** strongly coordinated to the palladium complex and the oxidation of 1,3-diene moiety did not proceed. Next, oxymercuration of **9** followed by treatment with $NaBH_4$ was carried out and then the resultant alcohol was subjected to Dess–Martin oxidation[14] to give desired **10** in 67% yield from **9**.

## 3. Synthesis of anatoxin-*a* from (*S*)-(−)-pyroglutamic acid

Having achieved the conversion of diene **9** into α,β-unsaturated ketone **10**, we next investigated the synthesis of anatoxin-*a* as an optically active form. Initially, we chose (*S*)-(−)-pyroglutamic acid as the starting material because this material is readily available and is inexpensive compared to its enantiomer, (*R*)-(+)-pyroglutamic acid. In this case, (2*S*,5*S*)-**5** would be synthesized as the substrate for enyne metathesis, which should lead to the synthesis of (−)-anatoxin-*a*, the antipode of the naturally occurring form. The synthesis of (2*S*,5*S*)-**5** was carried out as shown in Scheme 4.

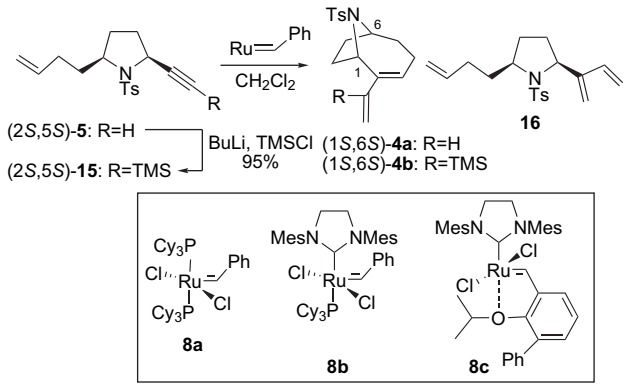



**Scheme 4**. Synthesis of a substrate.

Conversion of (−)-pyroglutamic acid into **11** by a known method[15] followed by treatment of **11** with Grignard reagent smoothly proceeded with opening of the pyrrolidine ring to give ketone **12**.[16] Deprotection of the *tert*-butoxycarbonyl group with $CF_3CO_2H$ gave cyclized imine (*S*)-**6a**.[16] Hydrogenation of (*S*)-**6a** using $PtO_2$ followed by protection of nitrogen with the tosyl group and then deprotection of the benzyl group gave pyrrolidine derivative **13**. Dess–Martin oxidation followed by Wittig reaction afforded alkene **14**, which was converted into enyne (2*S*,5*S*)-**5** by the usual method. The stereochemistry of the substituents on (2*S*,5*S*)-**5** was confirmed by an NOE experiment to be cis. Next, the construction of a 9-azabicyclo[4.2.1]nonene structure using enyne metathesis was investigated, and the results are summarized in Table 1.

We have already reported that the use of ethylene gas is effective for enyne metathesis of the substrate having a terminal alkyne.[4e,17] Thus, enyne metathesis of **5** was initially carried out using 5 mol % of **8a** in $CH_2Cl_2$ under ethylene gas, but the expected product **4a** was obtained in only 15% yield along with the starting material **5** and diene **16** in 25% and 13% yields, respectively (run 1). The diene **16** would be produced via an intermolecular metathesis reaction between the alkyne moiety in **5** and ethylene.[4c,4f,4m,4p,4t,18] Next, the second-generation Ru–carbene complex **8b**[19] was used and the reaction was carried out in $CH_2Cl_2$ upon heating under ethylene gas (run 2). However, the desired compound **4a** was obtained in only 7% yield along with **16** in 61% yield. When the reaction of **5** using **8c**[20] was carried out in $CH_2Cl_2$ at room temperature under ethylene gas, the yield of the desired product was slightly improved to 28%. However, no other identified product was obtained in this reaction (run 3). Next, we tried enyne metathesis of **15**, which was easily synthesized from **5** by protection of the terminal

**Table 1**. Enyne metathesis of (2*S*,5*S*)-**5** and (2*S*,5*S*)-**15**

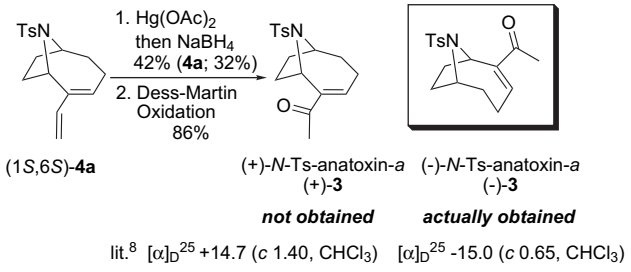



| Run[a] | Substrate | Ru catalyst[b] | Temp | Time (h) | Product (%) | | SM recov. (%) |
|---|---|---|---|---|---|---|---|
| | | | | | **4** | **16** | |
| 1 | (2*S*,5*S*)-**5** | **8a** | rt | 24.5 | 15 | 13 | 25 |
| 2 | | **8b** | Reflux | 2 | 7 | 61 | — |
| 3 | | **8c** | rt | 4 | 28 | — | — |
| 4 | (2*S*,5*S*)-**15** | **8b** | Reflux | 3.5 | 27 | — | 65 |
| 5 | | **8c** | rt | 3.5 | 27 | — | — |
| 6 | | **8b** | Reflux | 2.5 | 85 | — | — |

[a] Reactions for runs 1–3 were carried out under an atmosphere of ethylene, and reactions for runs 4–6 were carried out under an atmosphere of Ar.
[b] Run 1: 5 mol % of Ru–carbene complex was used; runs 2–5: 10 mol % of Ru–carbene complex was used; run 6: 20 mol % of Ru–carbene complex was used.

alkyne moiety with the silyl group.[4p] When enyne metathesis of **15** was carried out in $CH_2Cl_2$ using 10 mol % of **8b** under argon upon heating, the desilylated product **4a** instead of the expected product **4b** was obtained in 27% yield along with the starting material **15** in 65% yield (run 4). The reaction of **15** using Ru–carbene complex **8c** in $CH_2Cl_2$ at room temperature also gave the desilylated product **4a** in 27% yield, in which case, however, the starting material was completely consumed (run 5). Thus, enyne metathesis of **15** was carried out in $CH_2Cl_2$ using 20 mol % of **8b** under argon upon heating (run 6). As a result, the reaction was completed in 2.5 h and the cyclized product **4a** was obtained in 85% yield. In these reactions, desilylation occurred during the metathesis reaction,[21] although the reason is not clear.

Next, we investigated the final stage for the synthesis of anatoxin-*a* from the enyne metathesis product (1*S*,6*S*)-**4a** (Scheme 5).

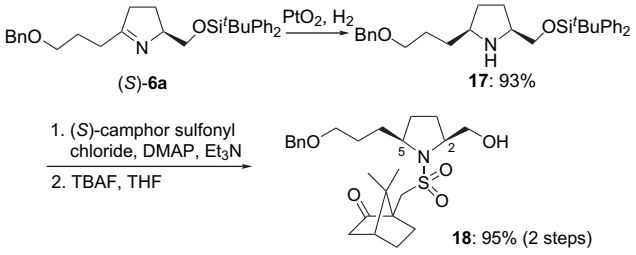



**Scheme 5**. Synthesis of *N*-tosylanatoxin-*a*.

Oxymercuration of (1*S*,6*S*)-**4a** followed by treatment with $NaBH_4$ afforded alcohol in 42% yield, and the starting material **4a** was recovered in 32% yield.[22] Dess–Martin oxidation of the alcohol afforded *N*-tosylanatoxin-*a*, whose spectral data unambiguously agreed with those reported in the literature.[8] However, we were surprised that *the* $[\alpha]_D$ *value of our synthetic N-tosylanatoxin-a showed a sign opposite to that of (+)-N-tosylanatoxin-a in the literature, although the absolute value was in agreement with that in the literature. This means that (−)-N-tosylanatoxin-a was synthesized from (S)-(−)-pyroglutamic acid along with an unexpected inversion of chirality during the synthesis.* Since conversion of (−)-*N*-tosylanatoxin-*a* to (+)-anatoxin-*a* had been already reported,[8] the formal total synthesis of (+)-anatoxin-*a* was achieved.[23]

## 4. Consideration of the inversion of chirality during the synthesis

We succeeded in the formal total synthesis of (+)-anatoxin-*a* from (*S*)-(−)-pyroglutamic acid using enyne metathesis as a key step. However, there remained the important question of when the inversion of chirality takes place during the synthesis. In order to answer this question, we first tried to confirm the absolute configuration of an intermediate before the metathesis reaction (Scheme 6). Hydrogenation of (*S*)-**6a**, which was derived from (*S*)-(−)-pyroglutamic acid as shown in Scheme 4, gave pyrrolidine derivative **17** in good yield. The compound **17** was successfully converted to the corresponding (*S*)-camphor sulfonamide **18**, which was easily crystallized.




**Scheme 6**. Confirmation of the absolute configuration of **6a**.

The absolute configuration of **18** was unequivocally determined by X-ray analysis as shown in Figure 1,[24] which means that the compound **17** maintained the chirality derived from (*S*)-(−)-pyroglutamic acid.

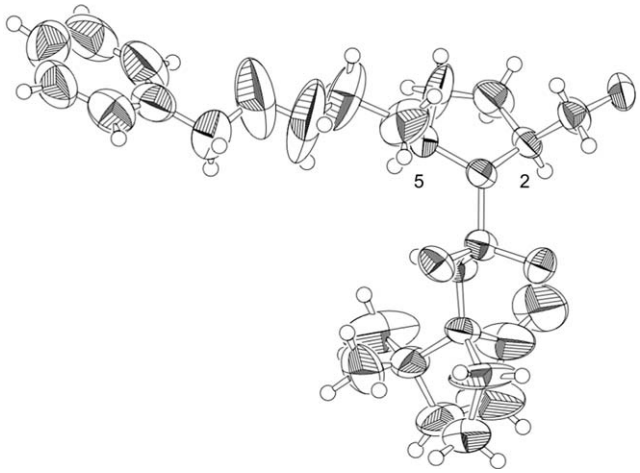
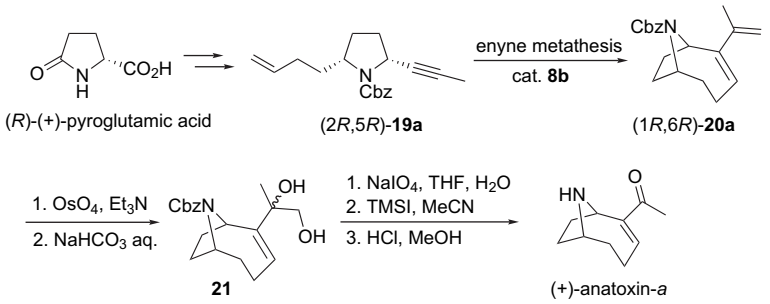



**Figure 1**. X-ray structure of compound **18**.

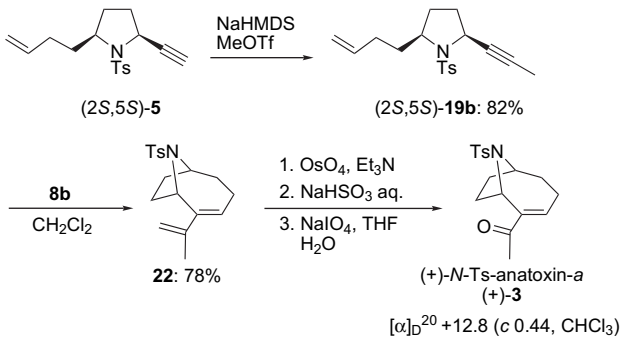



**Scheme 7**. Martin's total synthesis of (+)-anatoxin-*a*.

Since it is unlikely that the inversion of chirality with respect to both chiral centers at C2 and C5 positions takes place during the conversion of **17** to the metathesis substrate **5** (cf. Scheme 4), we presume that the compound **5** also maintains the chirality derived from (*S*)-(−)-pyroglutamic acid and that the inversion of chirality takes place at a later stage.

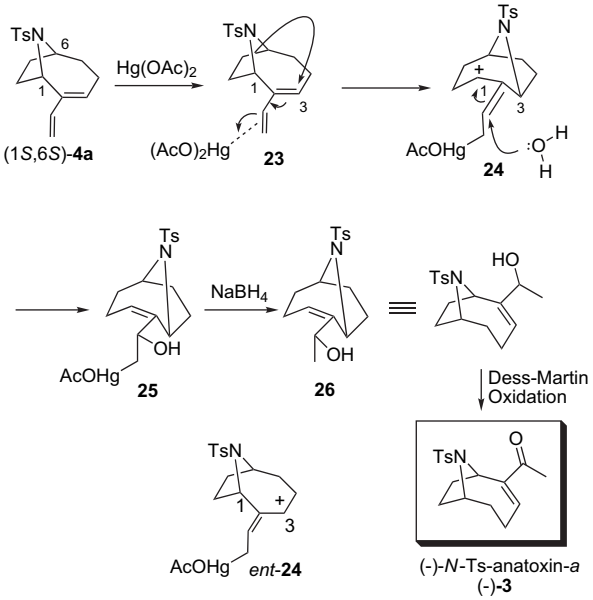
The total synthesis of (+)-anatoxin-*a* via enyne metathesis was reported by Martin at almost the same time as our report.[10] In Martin's synthesis, (1*R*,6*R*)-**20a** was constructed by enyne metathesis of (2*R*,5*R*)-**19a**, which was derived from (*R*)-(+)-pyroglutamic acid. Conversion of (1*R*,6*R*)-**20a** to (+)-anatoxin-*a* was achieved with the maintenance of chirality through osmylation of the alkene followed by cleavage of the corresponding diol (Scheme 7).

Martin's synthesis is very similar to our synthesis, although the substrate of enyne metathesis as well as the procedure for conversion of the diene moiety to α,β-unsaturated ketone is different. Thus, we investigated the conversion of (2*S*,5*S*)-**5** to *N*-Ts-anatoxin-*a* (**3**) according to Martin's procedure (Scheme 8).




**Scheme 8**. Conversion of (2*S*,5*S*)-**5** to *N*-Ts-anatoxin-*a* according to Martin's procedure.

As a result, (+)-*N*-Ts-anatoxin-*a* was obtained without the inversion of chirality originating from the substrate. This result strongly suggests that enyne metathesis proceeds with the maintenance of chirality regardless of the substrate and that the inversion of chirality in our synthesis takes place at the stage of conversion of the diene moiety to α,β-unsaturated ketone using oxymercuration reaction. One plausible mechanism for the inversion of chirality during the oxymercuration reaction is shown in Scheme 9.




**Scheme 9**. Plausible mechanism for inversion of chirality.

The diene moiety in (1*S*,6*S*)-**4a** would coordinate to $Hg(OAc)_2$ complex to produce olefin–Hg complex **23**. Migration of the nitrogen atom from the C1-position to the C3-position along with cleavage of the N–C1 bond would take place in the complex **23** to give **24**. Spontaneous nucleophilic attack of $H_2O$ on the allyl cation moiety in **24** would take place to give **25**, which was converted to the alcohol **26** by reduction with $NaBH_4$. It is noteworthy that the alcohol **26** has a (1*R*,6*R*)-configuration, which could be converted to (−)-*N*-Ts-anatoxin-*a* by Dess–Martin oxidation. If *ent*-**24** was produced along with **24** from the olefin–Hg complex **23**, or if **24** was in equilibrium with *ent*-**24**, racemization should occur in both cases to give **26** as a racemic mixture. The fact that (1*R*,6*R*)-**26** was obtained from (1*S*,6*S*)-**4a** with a high optical purity strongly suggests that the migration of the nitrogen atom from the C1-position to the C3-position in **23** took place in a stereospecific manner without the formation of *ent*-**24** and also that equilibrium between **24** and *ent*-**24** may not exist.

## 5. Conclusion

In summary, we have accomplished the formal total synthesis of (+)-anatoxin-*a* using enyne metathesis as a key step.

The remarkable features of our synthesis are as follows: (1) a highly strained azabicyclo[4.2.1]nonene skeleton was constructed by ring-closing enyne metathesis of a pyrrolidine derivative and (2) the synthesis of (+)-anatoxin-*a* was achieved from (*S*)-pyroglutamic acid via an unusual inversion of chirality, which is rationalized in terms of a skeletal rearrangement of 9-azabicyclo[4.2.1]nonene derivative at the stage of oxymercuration of the diene.

## 6. Experimental

### 6.1. General

All manipulations were carried out under an atmosphere of argon unless otherwise mentioned. Ethylene gas was purified by passage through the aqueous CuCl solution (2.0 g of CuCl in 180 mL of saturated $NH_4Cl$ aqueous solution) and concentrated $H_2SO_4$ and then KOH tubes. Ruthenium complexes **8a** and **8b** were purchased from Strem Chemicals, Inc. Ruthenium complex **8c** was prepared according to the literature procedure.[19] All other solvents and reagents were purified when necessary using standard procedure.

**6.1.1. 3-Acetyl-2,5,6,7-tetrahydro-1-*p*-toluenesulfonyl-1*H*-azepine (10).** To a solution of **9** (20 mg, 74 mmol) in $H_2O$/THF (1/1, 0.9 mL) was added $Hg(OAc)_2$ (36 mg, 112 mmol) at 0 °C, and the mixture was stirred at room temperature for 1.5 h. To the mixture were added MeOH (0.9 mL), 3 M NaOH aq (0.5 mL), and $NaBH_4$ (19 mg, 0.50 mmol), and the mixture was stirred at room temperature for 16 h. The mixture was extracted with $Et_2O$, and the organic layer was washed with brine, dried over $Na_2SO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 2:1) to give the alcohol (15 mg, 71%) as a colorless oil. IR (neat) $\nu$ 3482, 2925, 2853 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.70 (d, $J$=8.1 Hz, 2H), 7.30 (d, $J$=8.1 Hz, 2H), 5.79 (dd, $J$=5.5, 5.7 Hz, 1H), 4.29 (dd, $J$=12.9, 12.9 Hz, 1H), 3.91 (d, $J$=16.4 Hz, 1H), 3.76 (d, $J$=16.4 Hz, 1H), 3.51 (dd, $J$=12.7, 12.7 Hz, 1H), 3.33 (dd, $J$=11.7, 12.7 Hz, 1H), 2.42 (s, 3H), 2.23 (m, 2H), 1.94 (br, 1H), 1.81 (m, 2H), 1.26 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 143.0 (C), 142.1 (C), 136.1 (C), 129.5 (CH×2), 127.7 (CH×2), 127.0 (CH), 71.9 (CH), 50.4 ($CH_2$), 45.2 ($CH_2$), 26.8 ($CH_2$), 26.4 ($CH_2$), 21.9 ($CH_3$), 21.5 ($CH_3$); LRMS (EI) $m/z$ 295 ($M^+$), 277, 250, 224, 184, 155, 122, 91; HRMS (EI) calcd for $C_{15}H_{21}NSO_3$ ($M^+$) 295.1244, found 295.1242.

To a solution of the alcohol (11 mg, 0.037 mmol) in $CH_2Cl_2$ (1 mL) was added Dess–Martin periodinane (47 mg, 0.11 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. To the mixture were added satd $NaHCO_3$ aq and satd $Na_2S_2O_3$ aq, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine and dried over $Na_2SO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 1:1) to give **10** (10 mg, 95%) as a colorless oil. IR (neat) $\nu$ 3204, 2925, 1665, 1340, 1228, 1159, 1093 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.68 (d, $J$=8.1 Hz, 2H), 7.29 (d, $J$=8.1 Hz, 2H), 6.95 (dd, $J$=5.5, 5.9 Hz, 1H), 4.12 (s, 2H), 3.44 (t, $J$=6.3 Hz, 2H), 2.47 (dt, $J$=5.5, 5.9 Hz, 2H), 2.42 (s, 3H), 2.28 (s, 3H), 1.84–1.94 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.0 (C), 144.8 (CH), 142.9 (C), 140.9 (C), 136.1 (C), 129.4 (CH×2), 127.0 (CH×2), 49.5 ($CH_2$), 43.9 ($CH_2$), 27.1 ($CH_2$), 25.8 ($CH_2$), 25.6 ($CH_2$), 21.8 ($CH_3$); LRMS (EI) $m/z$ 293 ($M^+$), 155, 138, 109, 96; HRMS (EI) calcd for $C_{15}H_{19}O_3NS$ ($M^+$) 293.1083, found 293.1085.

**6.1.2. (2*S*)-8-Benzyloxy-1-(*tert*-butyldiphenylsilyloxy)-2-(*tert*-butyloxycarbonyl)-amino-octan-5-one (12).** A solution of 1-benzyloxy-3-bromo-propane (1.90 g, 8.3 mmol) in THF (7 mL) was added dropwise to a suspension of Mg (229 mg, 9.94 mmol) in THF (5 mL), and the mixture was stirred at room temperature for 30 min. To a THF solution of the Grignard reagent was added a solution of **11**[15] (2.25 g, 4.5 mmol) in THF (16 mL) at 0 °C, and the mixture was stirred at room temperature for 1.7 h. The reaction mixture was quenched by adding satd $NH_4Cl$ aq at 0 °C, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine and dried over $Na_2SO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3:1) to give **12** (2.77 g, 86%) as a colorless oil. IR (neat) $\nu$ 3364, 1714, 739, 701 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.62–7.65 (m, 4H), 7.29–7.43 (m, 11H), 4.64 (d, $J$=8.9 Hz, 1H), 4.47 (s, 2H), 3.55–3.64 (m, 3H), 3.44–3.49 (m, 2H), 2.40–2.52 (m, 4H), 1.86–1.92 (m, 2H), 1.76–1.83 (m, 2H), 1.43 (s, 9H), 1.07 (s, 9H); LRMS (EI) $m/z$ 603 ($M^+$+1), 546, 306, 278, 91; HRMS (EI) calcd for $C_{36}H_{50}O_5NSi$ ($M^+$+H) 604.3459, found 604.3450. $[\alpha]_D^{21}$ −13.0 ($c$ 1.03, $CHCl_3$).

**6.1.3. (*S*)-5-(3-(Benzyloxy)propyl)-2-(*tert*-butyldiphenylsilyloxymethyl)-3,4-dihydro-2*H*-pyrrole ((*S*)-6a).** To a solution of **12** (51 mg, 0.08 mmol) in $CH_2Cl_2$ (0.2 mL) was added trifluoroacetic acid (0.2 mL), and the mixture was stirred at room temperature for 2.5 h. To the mixture was added 3 M NaOH aq, and the aqueous layer was extracted with $Et_2O$. The organic layer was washed with brine and dried over $Na_2SO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 1:1) to give (*S*)-**6a** (38 mg, 92%) as a colorless oil. IR (neat) $\nu$ 1646, 1112, 737, 701 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.22–7.69 (m, 15H), 4.47 (s, 2H), 4.15 (m, 1H), 3.87 (dd, $J$=3.5, 10.0 Hz, 1H), 3.73 (dd, $J$=5.1, 10.0 Hz, 1H), 3.52 (t, $J$=6.2 Hz, 2H), 2.40–2.64 (m, 4H), 1.79–1.97 (m, 4H), 1.03 (s, 9H); LRMS (EI) $m/z$ 485 ($M^+$), 394, 336, 278; HRMS (EI) calcd for $C_{31}H_{39}O_2NSi$ ($M^+$) 604.3459, found 604.3450. $[\alpha]_D^{22}$ +41.5 ($c$ 1.01, $CHCl_3$).

**6.1.4. 3-((2*S*,5*R*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-1-*p*-toluenesulfonylpyrrolidin-5-yl)-propan-1-ol (13).** A solution of (*S*)-**6a** (118 mg, 0.24 mmol) and $PtO_2$ (6 mg, 0.02 mmol) in EtOH (1 mL) was stirred at room temperature under an atmosphere of hydrogen (1 atm) for 1 h. The mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (AcOEt only) to give the corresponding pyrrolidine (i.e., the compound **17** in Scheme 6) (109 mg, 92%) as a colorless oil. IR (neat) $\nu$ 3346, 1472, 739, 701 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.26–7.67 (m, 15H), 4.50 (s, 2H), 3.71 (dd, $J$=4.6, 10.0 Hz, 1H), 3.61 (dd, $J$=4.9, 10.0 Hz, 1H), 3.49 (t, $J$=5.4 Hz, 2H), 3.07–3.12 (m, 2H), 2.93 (br, 1H), 1.32–1.95 (m, 8H), 1.06

(s, 9H); LRMS (EI) *m/z* 603 ($M^+$), 546, 306, 278, 91; HRMS (EI) calcd for $C_{31}H_{42}O_2NSi$ ($M^+-1$) 488.2985, found 488.3009. $[\alpha]_D^{23}$ +2.0 (*c* 1.00, $CHCl_3$).

To a solution of the pyrrolidine (2.25 g, 4.5 mmol) in $CH_2Cl_2$ (9 mL) were added $Et_3N$ (2.0 mL, 15 mmol), *p*-toluenesulfonyl chloride (940 mg, 4.9 mmol), and DMAP (16 mg, 0.13 mmol), and the mixture was stirred at room temperature for 14 h. To the mixture was added 10% HCl aq, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine and dried over $Na_2SO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 4:1) to give the tosylamide (2.76 g, 96%) as a colorless oil. IR (neat) $\nu$ 2931, 2857, 2360, 1738, 1598, 1347, 1162, 1112 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.64–7.68 (m, 4H), 7.58 (d, *J*=7.9 Hz, 2H), 7.22–7.44 (m, 13H), 4.47 (s, 2H), 3.94 (d, *J*=5.9 Hz, 1H), 3.39–3.62 (m, 5H), 2.41 (s, 3H), 1.82–1.91 (m, 2H), 1.42–1.65 (m, 6H), 1.06 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 142.8 (C), 138.3 (C), 135.3 (CH×2), 134.4 (C), 133.2 (C), 133.0 (C), 129.4 (CH×4), 129.2 (CH×4), 127.9 (CH×2), 127.4 (CH×2), 127.2 (CH×2), 127.1 (CH×3), 72.5 ($CH_2$), 69.9 ($CH_2$), 66.3 ($CH_2$), 61.8 (CH), 61.5 (CH), 60.0 ($CH_2$), 33.0 ($CH_2$), 29.3 ($CH_2$), 26.7 ($CH_3$), 26.2 ($CH_2$), 21.2 ($CH_3$×2), 19.0 (C), 14.0 ($CH_3$); LRMS (EI) *m/z* 584 ($M^+-t$-Bu), 486, 372, 280, 155, 91; HRMS (EI) calcd for $C_{34}H_{38}O_4NSSi$ ($M^+-t$-Bu) 584.2296, found 584.2291. $[\alpha]_D^{27}$ −15.3 (*c* 0.96, $CHCl_3$).

A solution of the tosylamide (238 mg, 0.37 mmol) and $Pd(OH)_2/C$ (20 wt %, 55 mg, 0.08 mmol) in EtOH (4 mL) was stirred at room temperature under an atmosphere of hydrogen (1 atm) for 62 h. The mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (AcOEt only) to give **13** (195 mg, 95%) as a colorless oil. IR (neat) $\nu$ 3420, 2931, 2858, 1345, 1161 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.65–7.68 (m, 4H), 7.60 (d, *J*=8.4 Hz, 2H), 7.37–7.47 (m, 6H), 7.27 (d, *J*=8.4 Hz, 2H), 3.94 (d, *J*=5.9 Hz, 1H), 3.59–3.64 (m, 6H), 2.42 (s, 3H), 1.80–1.93 (m, 2H), 1.37–1.63 (m, 7H), 1.06 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 142.9 (C), 135.2 (CH×4), 135.1 (CH×4), 134.1 (C), 133.0 (C), 132.9 (C), 129.3 (CH), 129.2 (CH), 127.3 (CH), 127.2 (CH), 127.1 (CH), 127.0 (CH), 66.4 ($CH_2$), 62.3 ($CH_2$), 61.9 (CH), 61.6 (CH), 32.8 ($CH_2$), 29.5 ($CH_2$), 27.0 ($CH_2$), 26.9 ($CH_3$), 21.5 ($CH_3$), 21.4 ($CH_3$), 21.4 ($CH_3$), 21.3 ($CH_3$), 19.2 (C); LRMS (EI) *m/z* 550 ($M^+-1$), 494, 416, 338, 320, 155, 91; HRMS (EI) calcd for $C_{31}H_{40}O_4NSSi$ ($M^+-1$) 584.2296, found 584.2291. $[\alpha]_D^{27}$ −26.6 (*c* 1.42, $CHCl_3$).

**6.1.5. (2*S*,5*S*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-5-(but-3-enyl)-1-*p*-toluenesulfonylpyrrolidine (14).** To a solution of **13** (385 mg, 0.7 mmol) in $CH_2Cl_2$ (7 mL) was added Dess–Martin periodinane (442 mg, 1.0 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. To the mixture were added satd $NaHCO_3$ aq and satd $Na_2S_2O_3$ aq, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine and dried over $Na_2SO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 4:1) to give the aldehyde (380 mg, 99%) as a colorless oil. IR (neat) $\nu$ 2931, 2858, 1732, 1346, 1161; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 9.76 (s, 1H), 7.66–7.69 (m, 4H), 7.57 (d, *J*=8.4 Hz, 2H), 7.38–7.47 (m, 6H), 7.27 (d, *J*=8.4 Hz, 2H), 3.94 (dd, *J*=3.8, 10.0 Hz, 1H), 3.56–3.71 (m, 3H), 2.72–2.78 (m, 1H), 2.45–2.51 (m, 1H), 2.42 (s, 3H), 1.92–1.98 (m, 1H), 1.76–1.85 (m, 2H), 1.60–1.64 (m, 1H), 1.40–1.43 (m, 1H), 1.19–1.31 (m, 1H), 1.19 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 201.7 (C), 143.2 (C), 135.4 (CH×2), 134.1 (C), 133.2 (C), 133.1 (C), 129.5 (CH×4), 129.4 (CH×4), 127.5 (CH×2), 127.4 (CH×2), 66.6 ($CH_2$), 62.4 (CH), 60.7 (CH), 40.4 ($CH_2$), 30.2 ($CH_2$), 28.2 ($CH_2$), 27.1 ($CH_2$, $CH_3$), 21.7 ($CH_3$×3), 19.5 (C); LRMS (EI) *m/z* ($M^+-t$-Bu) 492, 414, 336, 280, 259, 155, 91; HRMS (EI) calcd for $C_{27}H_{30}O_4NSSi$ ($M^+-t$-Bu) 492.1654, found 492.1665. $[\alpha]_D^{27}$ −40.2 (*c* 0.97, $CHCl_3$).

To a solution of $Ph_3P^+CH_3Br^-$ (3.83 g, 10.7 mmol) in THF (27 mL) was added $^t$BuOK (1.09 g, 9.8 mmol) at 0 °C, and the mixture was stirred at room temperature for 20 min. To the solution was added a solution of the aldehyde (2.68 g, 4.9 mmol) in $CH_2Cl_2$ (22 mL) at −78 °C, and the mixture was allowed to warm to 0 °C and stirred at 0 °C for 14 h. To the mixture was added satd $NH_4Cl$ aq, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine and dried over $Na_2SO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3:1) to give **14** (2.61 g, 98%) as a colorless oil. IR (neat) $\nu$ 3070, 2958, 2930, 2857, 1736, 1639, 1598, 1348, 1162 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.67 (d, *J*=7.0 Hz, 4H), 7.60 (d, *J*=8.4 Hz, 2H), 7.38–7.46 (m, 6H), 7.26 (d, *J*=8.4 Hz, 2H), 5.78 (ddt, *J*=6.3, 10.2, 17.2 Hz, 1H), 5.00 (dd, *J*=0.9, 17.2 Hz, 1H), 4.94 (dd, *J*=0.9, 10.2 Hz, 1H), 3.94 (dd, *J*=2.4, 5.9 Hz, 1H), 3.49–3.67 (m, 3H), 2.42 (s, 3H), 1.87–2.08 (m, 4H), 1.18–1.51 (m, 4H), 1.07 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 142.9 (C), 137.7 (CH), 135.3 (CH×2), 134.5 (C), 133.3 (C), 133.1 (C), 129.4 (CH×2), 129.3 (CH×4), 127.5 (CH×4), 127.3 (CH×2), 114.5 ($CH_2$), 66.5 ($CH_3$), 62.0 (CH), 61.5 (CH), 35.8 ($CH_2$), 30.5 ($CH_2$), 29.6 ($CH_2$), 27.1 ($CH_2$), 27.0 ($CH_2$), 21.7 ($CH_3$×3), 19.4 (C); LRMS (EI) *m/z* 546 ($M^+$), 490, 414, 334, 292, 278, 252, 199, 155, 91; HRMS (EI) calcd for $C_{32}H_{41}O_3NSSi$ ($M^+$) 547.2569, found 547.2576. $[\alpha]_D^{23}$ −25.2 (*c* 1.07, $CHCl_3$).

**6.1.6. (2*S*,5*S*)-5-(But-3-enyl)-2-ethynyl-1-*p*-toluenesulfonylpyrrolidine ((2*S*,5*S*)-5).** To a solution of **14** (112 mg, 4.5 mmol) in THF (2 mL) was added TBAF (1.0 M THF solution, 0.3 mL, 0.3 mmol), and the mixture was stirred at room temperature for 1.5 h. To the mixture was added $H_2O$, and the aqueous layer was extracted with $Et_2O$. The organic layer was washed with brine and dried over $Na_2SO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 1:1) to give the alcohol (62 mg, 98%) as a colorless oil. IR (neat) $\nu$ 3510, 2954, 2874, 1736, 1640, 1598, 1343 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.72 (d, *J*=8.1 Hz, 2H), 7.33 (d, *J*=8.1 Hz, 2H), 5.84 (ddt, *J*=6.8, 10.3, 17.0 Hz, 1H), 5.06 (dd, *J*=1.8, 17.0 Hz, 1H), 4.99 (dd, *J*=1.8, 10.3 Hz, 1H), 3.60–3.71 (m, 4H), 2.86 (br, 1H), 2.44 (s, 3H), 2.10–2.16 (m, 2H), 1.91–1.98 (m, 1H), 1.49–1.70 (m, 4H), 1.34–1.42 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 143.4 (C), 137.5 (CH), 133.9 (C), 129.5 (CH×2), 127.3 (CH×2), 114.7 ($CH_2$), 66.0 ($CH_3$), 63.0 (CH), 62.1 (CH), 35.7 ($CH_2$), 30.5

($CH_2$), 29.4 ($CH_2$), 27.3 ($CH_2$), 21.7 ($CH_2$); LRMS (EI) *m/z* 309 ($M^+$), 278, 254, 224, 155, 122, 91; HRMS (EI) calcd for $C_{16}H_{23}O_3NS$ ($M^+$) 303.1396, found 309.1398. $[\alpha]_D^{21}$ +51.1 (*c* 1.33, $CHCl_3$).

To a solution of the alcohol (1.42 g, 4.6 mmol) in $CH_2Cl_2$ (46 mL) was added Dess–Martin periodinane (2.34 g, 5.5 mmol) at 0 °C, and the mixture was stirred at room temperature for 1.5 h. To the mixture were added satd $NaHCO_3$ aq and satd $Na_2S_2O_3$ aq, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine and dried over $Na_2SO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3:1) to give the aldehyde (1.20 g, 86%) as a colorless oil. IR (neat) $\nu$ 2924, 1734, 1639, 1598, 1348, 1161 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 9.63 (d, *J*=1.9 Hz, 1H), 7.71 (d, *J*=8.2 Hz, 2H), 7.34 (d, *J*=8.2 Hz, 2H), 5.83 (ddt, *J*=6.2, 10.2, 16.8 Hz, 1H), 5.06 (dd, *J*=1.7, 16.8 Hz, 1H), 5.01 (dd, *J*=1.7, 10.2 Hz, 1H), 3.87 (dd, *J*=1.9, 7.9 Hz, 1H), 3.67–3.71 (m, 1H), 2.44 (s, 3H), 1.97–2.17 (m, 4H), 1.69–1.75 (m, 1H), 1.52–1.62 (m, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 199.7 (C), 143.9 (C), 137.3 (C), 129.7 (CH×3), 127.5 (CH×2), 115.1 ($CH_2$), 67.8 (CH), 61.4 (CH), 35.4 ($CH_2$), 30.4 ($CH_2$), 30.1 ($CH_2$), 25.7 ($CH_2$), 21.8 ($CH_3$); LRMS (EI) *m/z* 307 ($M^+$), 278, 252, 224, 155, 91; HRMS (EI) calcd for $C_{16}H_{21}O_3NS$ ($M^+$) 307.1242, found 307.1242. $[\alpha]_D^{22}$ −50.6 (*c* 1.22, $CHCl_3$).

To a solution of $CBr_4$ (5.16 g, 16 mmol) in $CH_2Cl_2$ (19 mL) were added $PPh_3$ (8.16 g, 31 mmol) and a solution of the aldehyde (1.20 g, 3.9 mmol) in $CH_2Cl_2$ (59 mL) at 0 °C, and the mixture was stirred at the same temperature for 1.5 h. To the mixture was added $H_2O$, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine and dried over $Na_2SO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3:1) to give the corresponding dibromide (1.74 g, 96%) as a colorless oil. IR (neat) $\nu$ 2924, 1734, 1640, 1598, 1348, 1161 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.74 (d, *J*=8.2 Hz, 2H), 7.33 (d, *J*=8.2 Hz, 2H), 6.46 (d, *J*=7.9 Hz, 1H), 5.84 (ddt, *J*=6.7, 10.3, 17.0 Hz, 1H), 5.06 (dd, *J*=1.8, 17.0 Hz, 1H), 5.01 (dd, *J*=1.8, 10.3 Hz, 1H), 4.13 (dt, *J*=7.8, 7.8 Hz, 1H), 3.73–3.76 (m, 1H), 2.44 (s, 3H), 2.09–2.15 (m, 2H), 1.90–1.97 (m, 2H), 1.50–1.69 (m, 4H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 143.4 (C), 139.9 (CH), 137.4 (CH), 134.2 (C), 129.5 (CH×2), 127.5 (CH×2), 114.8 ($CH_2$), 89.3 (C), 62.9 (CH), 61.4 (CH), 35.8 ($CH_2$), 30.6 ($CH_2$), 30.2 ($CH_2$), 29.4 ($CH_2$), 21.7 ($CH_3$); LRMS (EI) *m/z* 463 ($M^+$), 408, 384, 308, 278, 252, 155, 91; HRMS (EI) calcd for $C_{17}H_{21}O_2NSBr_2$ ($M^+$) 460.9680, found 460.9659. $[\alpha]_D^{22}$ −76.6 (*c* 1.03, $CHCl_3$).

To a solution of the dibromide (129 mg, 0.3 mmol) in THF (3 mL) was added BuLi (1.55 M hexane solution, 0.6 mL, 0.9 mmol) at −78 °C, and the mixture was stirred at the same temperature for 1 h. To the mixture was added $H_2O$, and the aqueous layer was extracted with $Et_2O$. The organic layer was washed with brine and dried over $Na_2SO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3:1) to give (2*S*,5*S*)-**5** (68 mg, 80%) as a viscous oil. IR (neat) $\nu$ 3250, 2928, 1641, 1598, 1348, 1159 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.75 (d, *J*=8.2 Hz, 2H), 7.30 (d, *J*=8.2 Hz, 2H), 5.80 (ddt, *J*=6.5, 10.0, 17.0 Hz, 1H), 5.03 (dd, *J*=1.8, 17.0 Hz, 1H), 4.97 (dd, *J*=1.8, 10.0 Hz, 1H), 4.41–4.47 (m, 1H), 3.73–3.76 (m, 1H), 2.34 (s, 3H), 2.12 (d, *J*=2.4 Hz, 1H), 2.00–2.14 (m, 3H), 1.89–1.96 (m, 1H), 1.60–1.81 (m, 4H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 143.2 (C), 137.6 (CH), 135.4 (C), 129.4 (CH×2), 127.2 (CH×2), 114.7 ($CH_2$), 83.5 (CH), 71.5 (C), 61.1 (CH), 51.4 (CH), 35.5 ($CH_2$), 32.8 ($CH_2$), 30.5 ($CH_2$), 30.2 ($CH_2$), 21.7 ($CH_3$); LRMS (EI) *m/z* 303 ($M^+$), 274, 262, 248, 222, 155, 148, 91, 77, 65; HRMS (EI) calcd for $C_{17}H_{21}O_2NS$ ($M^+$) 303.1284, found 303.1293. $[\alpha]_D^{26}$ −41.9 (*c* 0.82, $CHCl_3$).

**6.1.7. (2*S*,5*S*)-5-(But-3-enyl)-2-(2-(trimethylsilyl)-ethynyl)-1-*p*-toluenesulfonylpyrrolidine ((2*S*,5*S*)-15).** To a solution of (2*S*,5*S*)-**5** (36 mg, 0.12 mmol) in THF (1 mL) was added BuLi (2.6 M hexane solution, 0.07 mL, 0.18 mmol) at −78 °C, and the mixture was stirred at the same temperature for 45 min. To the solution was added trimethylsilyl chloride (0.05 mL, 0.35 mmol) at −78 °C, and the mixture was stirred at the same temperature for 1 h. To the mixture was added $H_2O$, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine and dried over $Na_2SO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 5:1) to give (2*S*,5*S*)-**15** (42 mg, 95%) as a viscous oil. IR (neat) $\nu$ 2923, 1642, 1599, 1344, 1155 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.76 (d, *J*=7.6 Hz, 2H), 7.27 (d, *J*=7.6 Hz, 2H), 5.77 (ddt, *J*=6.5, 11.1, 17.2 Hz, 1H), 4.97 (dd, *J*=11.1, 17.2 Hz, 2H), 4.55 (dd, *J*=2.3, 7.3 Hz, 1H), 3.79–3.86 (m, 1H), 2.42 (s, 3H), 2.04–2.10 (m, 2H), 1.58–1.99 (m, 6H), 0.12 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 143.0 (C), 137.8 (CH), 136.5 (C), 129.3 (CH×2), 127.2 (CH×2), 114.5 ($CH_2$), 105.2 (C), 88.0 (C), 60.9 (CH), 52.1 (CH), 35.1 ($CH_2$), 33.2 ($CH_2$), 30.6 ($CH_2$), 30.1 ($CH_2$), 21.7 ($CH_3$), 0.1 ($CH_3$×3); LRMS (EI) *m/z* 375 ($M^+$), 360, 320, 220, 155, 91; HRMS (EI) calcd for $C_{20}H_{29}O_2NSSi$ ($M^+$) 375.1681, found 375.1688.

**6.1.8. Typical procedure for enyne metathesis of (2*S*,5*S*)-15 using Ru–carbene complex 8b (Table 1, run 6).** A solution of (2*S*,5*S*)-**15** (13 mg, 0.034 mmol) and Ru–carbene complex **8b** (6 mg, 0.007 mmol) in degassed $CH_2Cl_2$ (0.7 mL) was heated under reflux for 2.5 h. Upon cooling to room temperature, an excess amount of ethyl vinyl ether was added to the mixture in order to stop the metathesis reaction, and the mixture was stirred at room temperature for 1 h. After the mixture was concentrated, the residue was purified by column chromatography on silica gel (hexane/AcOEt=8:1) to give (1*S*,6*S*)-**4a** (9 mg, 85%) as a viscous oil.

IR (neat) $\nu$ 2925, 2852, 1732, 1633, 1598, 1337, 1161 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.73 (d, *J*=8.5 Hz, 2H), 7.27 (d, *J*=8.5 Hz, 2H), 6.21 (dd, *J*=10.9, 17.7 Hz, 1H), 5.67 (dd, *J*=5.8, 6.2 Hz, 1H), 5.14 (d, *J*=17.7 Hz, 1H), 4.98 (d, *J*=10.9 Hz, 1H), 4.90 (d, *J*=8.1 Hz, 1H), 4.41–4.44 (m, 1H), 2.42 (s, 3H), 2.16–2.29 (m, 2H), 2.00–2.08 (m, 2H), 1.72–1.85 (m, 2H), 1.56–1.69 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 143.2 (C), 142.8 (C), 138.1 (CH), 137.5 (C), 131.9 (CH), 129.4 (CH×2), 126.8 (CH×2), 111.0 ($CH_2$), 58.7 (CH), 57.6 (CH), 34.2 ($CH_2$), 31.8 ($CH_2$), 30.9 ($CH_2$), 29.9 ($CH_2$), 21.7 ($CH_3$); LRMS (EI) *m/z* 303 ($M^+$), 155, 148, 121, 91; HRMS (EI) calcd for

$C_{17}H_{21}O_2NS$ ($M^+$) 303.1294, found 303.1293. $[\alpha]_D^{22}$ −5.2 (*c* 1.03, $CHCl_3$).

**6.1.9. Spectral data of (2*S*,5*S*)-5-(but-3-enyl)-2-(1,3-butadien-2-yl)-1-*p*-toluenesulfonylpyrrolidine (16).** IR (neat) $\nu$ 2924, 2849, 1725, 1638, 1600, 1346, 1160 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.69 (d, *J*=8.1 Hz, 2H), 7.27 (d, *J*=8.1 Hz, 2H), 6.34 (dd, *J*=11.1, 17.8 Hz, 1H), 5.85 (ddt, *J*=6.3, 12.3, 16.6 Hz, 1H), 5.46 (s, 1H), 4.98–5.19 (m, 5H), 4.42–4.47 (m, 1H), 3.59–3.68 (m, 1H), 2.41 (s, 3H), 1.94 (m, 4H), 1.53 (m, 4H); LRMS (EI) *m*/*z* 331 ($M^+$), 276, 248, 176, 155, 91; HRMS (EI) calcd for $C_{19}H_{25}O_2NS$ ($M^+$) 331.1602, found 331.1606. $[\alpha]_D^{20}$ −16.9 (*c* 0.15, $CHCl_3$).

**6.1.10. Synthesis of (−)-*N*-Ts-anatoxin-*a* ((−)-3) from (1*S*,6*S*)-4a.** To a solution of $Hg(OAc)_2$ (12 mg, 38 mmol) in $H_2O$ (0.4 mL) was added a solution of (1*S*,6*S*)-**4a** (6 mg, 19 mmol) in THF (0.4 mL) at 0 °C, and the mixture was stirred at room temperature for 2.5 h. To the mixture was added MeOH (0.8 mL), 3 M NaOH aq (0.8 mL), and $NaBH_4$ (5 mg, 0.13 mmol) at 0 °C, and the mixture was stirred at room temperature for 37 h. To the mixture was added $H_2O$, and the aqueous layer was extracted with $Et_2O$. The organic layer was washed with brine and dried over $Na_2SO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 5:1) to give the alcohol (3 mg, 42%) as a colorless oil along with the starting (1*S*,6*S*)-**4a** (2 mg, 32%). IR (neat) $\nu$ 3511, 2966, 2928, 1735, 1598, 1338, 1160 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.75 (d, *J*=8.4 Hz, 2H), 7.28 (d, *J*=8.4 Hz, 2H), 5.62 (dd, *J*=5.7, 5.8 Hz, 1H), 4.53 (d, *J*=9.2 Hz, 1H), 4.44–4.45 (m, 1H), 4.30 (q, *J*=6.4 Hz, 1H), 2.42 (s, 3H), 2.25–2.31 (m, 1H), 1.86–1.95 (m, 3H), 1.49–1.75 (m, 4H), 1.35 (d, *J*=6.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 150.7 (C), 142.9 (C), 137.2 (C), 130.8 (C×2), 129.5 (CH×2), 126.9 (CH×2), 124.4 (CH), 72.2 (CH), 60.1 (CH), 57.6 (CH), 33.1 ($CH_2$×2), 28.9 ($CH_2$), 23.4 ($CH_2$), 22.1 ($CH_3$), 21.7 ($CH_3$); LRMS (EI) *m*/*z* 321 ($M^+$), 303, 166, 155, 91; HRMS (EI) calcd for $C_{17}H_{23}O_3NS$ ($M^+$) 321.1406, found 321.1398. $[\alpha]_D^{23}$ −39.0 (*c* 0.73, $CHCl_3$).

To a solution of the alcohol (7 mg, 0.02 mmol) in $CH_2Cl_2$ (0.5 mL) was added Dess–Martin periodinane (20 mg, 0.05 mmol) at 0 °C, and the mixture was stirred at room temperature for 1.5 h. To the mixture were added satd $NaHCO_3$ aq and satd $Na_2S_2O_3$ aq, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine and dried over $Na_2SO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 1:1) to give (−)-*N*-Ts-anatoxin-*a* ((−)-**3**) (6 mg, 86%) as a colorless solid, whose spectral data were identical with those previously reported.[8] $[\alpha]_D^{25}$ −15.0 (*c* 0.65, $CHCl_3$).

**6.1.11. (2*S*,5*R*)-5-(3-Benzyloxypropyl)-2-(hydroxymethyl)-1-((1*S*)-10-camphorsulfonyl)-pyrrolidine (18).** To a solution of **17** (323 mg, 0.66 mmol), which is an intermediate for the synthesis of **13** from (*S*)-**6a** (see, Section 6.1.4), in $CH_3CN$ (3 mL) were added $Et_3N$ (0.2 mL, 1.6 mmol), (1*S*)-10-camphorsulfonyl chloride (327 mg, 2.0 mmol), and DMAP (162 mg, 1.3 mmol), and the mixture was stirred at room temperature for 24 h. To the mixture was added 10% HCl aq, and the aqueous layer was extracted with AcOEt. The organic layer was washed with brine and dried over $Na_2SO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 4:1) to give the camphorsulfonamide (432 mg, 93%) as a colorless oil. IR (neat) $\nu$ 2957, 2859, 1745, 1345, 1150 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.63–7.68 (m, 4H), 7.23–7.43 (m, 6H), 4.45 (s, 2H), 3.82–3.73 (m, 1H), 3.58 (dd, *J*=7.3, 9.2 Hz, 1H), 3.41 (ddd, *J*=6.6, 9.2, 15.8 Hz, 2H), 3.23 (d, *J*=14.4 Hz, 1H), 2.61 (d, *J*=14.4 Hz, 1H), 2.48–2.59 (m, 1H), 2.37 (dt, *J*=4.0, 18.5 Hz, 1H), 1.79–2.10 (m, 7H), 1.26–1.69 (m, 6H), 1.13 (s, 3H), 1.06 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 215.0 (C), 138.3 (C), 135.3 (CH×4), 133.1 (C), 133.0 (C), 129.4 (CH×4), 128.1 (CH×2), 127.5 (CH×2), 127.4 (CH×2), 127.2 (CH), 72.8 ($CH_2$), 70.1 ($CH_2$), 66.3 ($CH_2$), 62.0 (CH), 61.7 (CH), 58.3 (C), 47.7 (C), 44.3 ($CH_2$), 43.0 (CH), 42.7 ($CH_2$), 33.4 ($CH_2$), 30.3 ($CH_2$), 27.3 ($CH_2$), 27.0 ($CH_2$, $CH_3$×3), 26.6 ($CH_2$), 25.5 ($CH_2$), 20.0 ($CH_3$×2), 19.4 (C); LRMS (EI) *m*/*z* 701 ($M^+$), 686, 644, 432, 218, 91; HRMS (EI) calcd for $C_{41}H_{55}O_5NSSi$ ($M^+$) 701.3556, found 701.3570. $[\alpha]_D^{20}$ +6.1 (*c* 1.34, $CHCl_3$).

To a solution of the camphorsulfonamide (432 mg, 0.62 mmol) in THF (7 mL) was added TBAF (1.0 M THF solution, 1.0 mL, 1 mmol) at 0 °C, and the mixture was stirred at room temperature for 4 h. To the mixture was added $H_2O$, and the aqueous layer was extracted with $Et_2O$. The organic layer was washed with brine and dried over $Na_2SO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 4:1) to give **18** (271 mg, 95%) as a colorless solid, which was recrystallized from ether to give a colorless plate (mp 107–109 °C) for X-ray analysis.[24]

IR (neat) $\nu$ 3482, 2956, 2882, 1744, 1340, 1149 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.28–7.36 (m, 5H), 4.49 (s, 2H), 3.84–3.91 (m, 1H), 3.77–3.83 (m, 2H), 3.55–3.69 (m, 2H), 3.49 (dd, *J*=6.1, 6.5 Hz, 2H), 3.29 (d, *J*=4.2 Hz, 1H), 2.84 (d, *J*=4.2 Hz, 1H), 2.50–2.56 (m, 1H), 2.35–2.41 (m, 1H), 1.51–2.11 (m, 14H), 1.15 (s, 3H), 0.90 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 214.9 (C), 138.2 (C), 128.1 (CH×2), 127.4 (CH×2), 127.3 (CH), 72.9 ($CH_2$), 70.0 ($CH_2$), 66.2 ($CH_2$), 63.1 (CH), 62.2 (CH), 58.3 (C), 47.8 (C), 44.0 ($CH_2$), 43.0 (CH), 42.6 ($CH_2$), 33.3 ($CH_2$), 30.2 ($CH_2$), 27.5 ($CH_2$), 27.0 ($CH_2$), 26.6 ($CH_2$), 25.6 ($CH_2$), 20.3 ($CH_3$), 20.0 ($CH_3$); LRMS (EI) *m*/*z* 464 ($M^+$), 446, 432, 248, 218, 91; HRMS (EI) calcd for $C_{25}H_{37}O_5NS$ ($M^+$) 463.2404, found 463.2392. $[\alpha]_D^{20}$ +34.1 (*c* 0.73, $CHCl_3$).

**6.1.12. (2*S*,5*S*)-5-(But-3-enyl)-2-(prop-1-ynyl)-1-*p*-toluenesulfonylpyrrolidine ((2*S*,5*S*)-19b).** To a solution of (2*S*,5*S*)-**5** (101 mg, 0.33 mmol) in THF (1.6 mL) was added NaHMDS (1.0 M THF solution, 1.0 mL, 1 mmol) at −78 °C, and the mixture was stirred at the same temperature for 5 min. To the mixture was added methyl trifluoromethanesulfonate (0.2 mL, 1.7 mmol) at −78 °C, the mixture was stirred at the same temperature for 2 h. To the mixture was added satd $NaHCO_3$ aq, and the aqueous layer was extracted with $Et_2O$. The organic layer was washed with brine and dried over $Na_2SO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3:1) to give (2*S*,5*S*)-**19b** (87 mg, 82%)

as a colorless oil. IR (neat) $\nu$ 2925, 2852, 1732, 1633, 1598, 1337, 1161 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.73 (d, $J$=8.0 Hz, 2H), 7.29 (d, $J$=8.0 Hz, 2H), 5.82 (ddt, $J$=6.2, 10.3, 16.4 Hz, 1H), 5.03 (d, $J$=16.4 Hz, 1H), 4.97 (d, $J$=10.3 Hz, 1H), 4.41 (m, 1H), 3.66–3.77 (m, 1H), 2.41 (s, 3H), 2.00–2.12 (m, 3H), 1.55–1.94 (m, 1H). $[\alpha]_D^{21}$ −61.4 ($c$ 0.94, $CHCl_3$).

**6.1.13. (1*S*,6*S*)-2-(2-Propen-2-yl)-9-*p*-toluenesulfonyl-9-azabicyclo[4.2.1]nona-2ene (22).** A solution of (2*S*,5*S*)-**19b** (87 mg, 0.3 mmol) and Ru–carbene complex **8c** (23 mg, 0.03 mmol) in degassed $CH_2Cl_2$ (3 mL) was stirred at room temperature for 29 h. To the mixture was added DMSO (0.1 mL), and the mixture was stirred at room temperature for 23 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3:1) to give **22** (68 mg, 78%) as a colorless oil. $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.72 (d, $J$=8.3 Hz, 2H), 7.27 (d, $J$=8.3 Hz, 2H), 5.77 (dd, $J$=5.9, 6.6 Hz, 1H), 4.93–5.04 (m, 3H), 4.39–4.40 (m, 1H), 2.44–2.53 (m, 1H), 2.41 (s, 3H), 2.14–2.27 (m, 1H), 2.00–2.10 (m, 1H), 1.88 (s, 3H), 1.52–1.83 (m, 5H); LRMS $m/z$ 317 ($M^+$), 302, 261, 162, 155, 91; HRMS calcd for $C_{18}H_{23}O_2NS$ ($M^+$) 317.1452, found 317.1449. $[\alpha]_D^{21}$ −12.4 ($c$ 1.03, $CHCl_3$).

**6.1.14. (+)-*N*-Ts-anatoxin-*a* ((+)-3).** To a solution of $OsO_4$ (47 mg, 0.15 mmol) in THF (2 mL) was added $Et_3N$ (0.04 mL, 0.3 mmol), and the mixture was stirred at room temperature for 5 min. To the mixture was added a solution of **22** (47 mg, 0.15 mmol) in THF (1.2 mL) at −78 °C, the mixture was stirred at room temperature for 64 h. To the mixture was added satd $NaHSO_3$ aq (2.6 mL), and the mixture was heated under reflux for 2.5 h. The mixture was extracted with AcOEt, and the organic layer was washed with brine and dried over $Na_2SO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3:1) to give the diol (31 mg, 59%) as a colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.73 (d, $J$=8.2 Hz, 2H), 7.29 (d, $J$=8.2 Hz, 2H), 5.69 (dd, $J$=7.0, 7.0 Hz, 1H), 4.73 (d, $J$=9.4 Hz, 1H), 4.43 (dd, $J$=3.5, 3.8 Hz, 1H), 3.72 (d, $J$=11.1 Hz, 1H), 3.58 (d, $J$=11.1 Hz, 1H), 2.75 (br, 1H), 2.55 (br, 1H), 2.42 (s, 3H), 2.23–2.39 (m, 2H), 1.91–2.05 (m, 2H), 1.49–1.79 (m, 4H), 1.36 (s, 3H). $[\alpha]_D^{21}$ −62.8 ($c$ 1.23, $CHCl_3$).

To a solution of the diol (31 mg, 0.09 mmol) in $H_2O$/THF (1/1, 1.7 mL) was added $NaIO_4$ (58 mg, 0.27 mmol), and the mixture was stirred at room temperature for 1.5 h. To the mixture was added $H_2O$, and the aqueous layer was extracted with $Et_2O$. The organic layer was washed with brine and dried over $Na_2SO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexane/AcOEt = 3:1) to give *N*-Ts-anatoxin-*a* **3** (24 mg, 85%) as a colorless solid, whose spectral data were identical to those previously obtained. And the $[\alpha]_D$ value of the synthetic *N*-Ts-anatoxin-*a* ($[\alpha]_D^{20}$ +12.8 ($c$ 0.44, $CHCl_3$)) was identical to that previously reported.[7e]

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22. The optical purity of the recovered **4a** was completely same to that of the starting material **4a** of the oxymercuration reaction.
23. In our preliminary communication,[9] the structure of the synthetic (+)-*N*-Ts-anatoxin-*a* was incorrectly drawn as that of the antipode (i.e., (−)-*N*-Ts-anatoxin-*a*) because of the confusion arising from the unexpected inversion of chirality.
24. Crystallographic data for the structure of **18** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 295170. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].