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Synthesis of (+)-anatoxin-*a* using enyne metathesis

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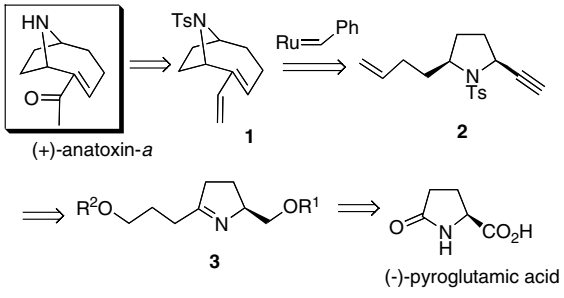
Abstract—Synthesis of *N*-tosylanatoxin-*a* was achieved by metathesis of enyne in *cis*-substituents on a pyrrolidine derivative. Metathesis reactions of enyne having terminal alkyne using various ruthenium-carbene complexes did not give a good results. However, when the terminal alkyne was protected with a TMS group, the reaction proceeded smoothly using a second-generation ruthenium-carbene complex to give the desired cyclized compound in high yield. Oxymercuration followed by Dess–Martin oxidation afforded *N*-tosylanatoxin-*a*.

Anatoxin-*a*, isolated from the blue-green freshwater alga *Anabaena flos aquae* is one of the most powerful agonists of the nicotinic acetylcholine receptor[1] 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.[2] 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 1.

(+)-Anatoxin-*a* should be synthesized from compound **1** having an azabicyclo[4.2.1]nonene ring system, which should be obtained by metathesis of enyne **2** in the *cis*-substituents on the pyrrolidine ring. To obtain this compound, hydrogenation of imine **3** should be suitable. This compound would be obtained from (−)-pyroglutamic acid. 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. In this retrosynthetic analysis, oxidation of diene is very important. Thus, the oxidation condition of the diene moiety was examined. As a model compound, azepine derivative **6** having a diene moiety was used. 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 **5**[3] and that compound **6** was obtained in good yield.[4e] Oxidation of **6** with $PdCl_2$ and CuCl in aqueous DMF was carried out under oxygen.[5] However, the solution changed to a yellow colour and the starting material was recovered in 79% yield after 24 h. Presumably, the diene moiety coordinated to the palladium complex and the oxidation did not proceed (Scheme 2).



Scheme 1. Retrosynthetic analysis of (+)-anatoxin-*a*.

Thus, oxymercuration of **6** followed by treatment with $NaBH_4$ was carried out and then the resultant alcohol was subjected to Dess–Martin oxidation[6] to give desired **7** in 67% yield from **6**.

Since conversion of diene **6** into α,β-unsaturated ketone **7** was achieved, the starting enyne **2a** was synthesized as shown in Scheme 3. Conversion of (−)-pyroglutamic acid into **8** by a known method[7] followed by treatment

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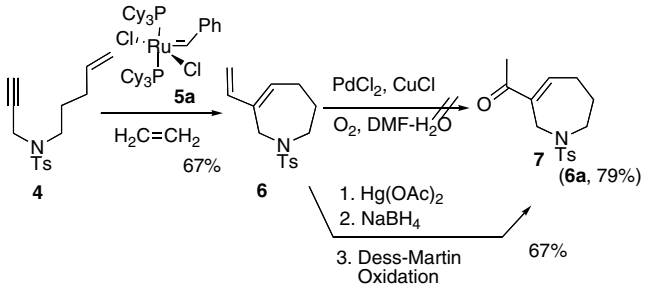
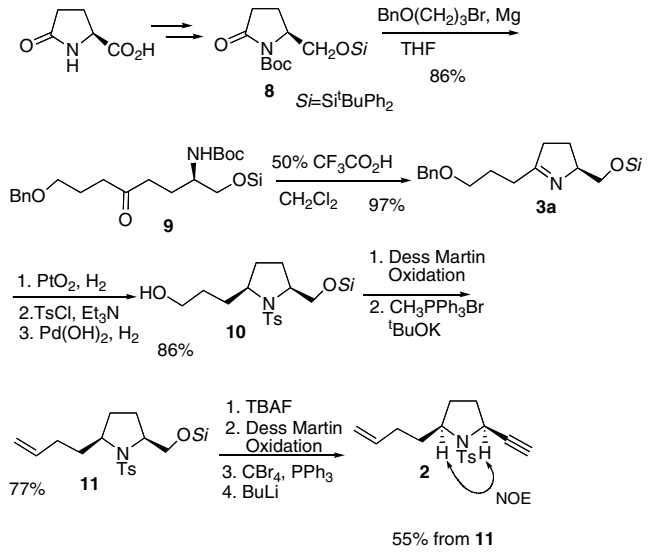


Scheme 2. Conversion of diene into α,β-unsaturated ketone.



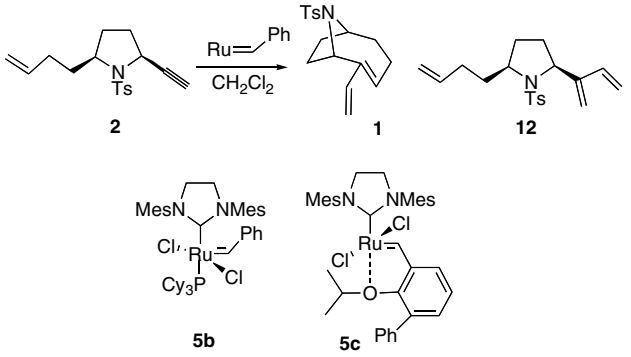
Scheme 3. Synthesis of a substrate.

of **8** with Grignard reagent smoothly proceeded to give ketone **9**.[8] Deprotection of the *tert*-butoxycarbonyl group with CF_3CO_2H gave cyclized imine **3a**.[8] Hydrogenation of **3a** using PtO_2 followed by protection of nitrogen with the tosyl group and then deprotection of the benzyl group gave pyrrolidine derivative **10**.

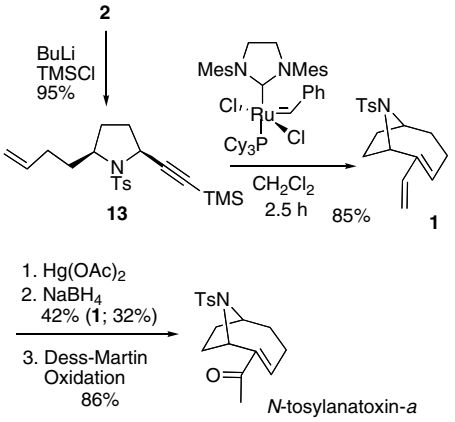
Dess–Martin oxidation followed by Wittig reaction afforded alkene **11**, which was converted into enyne **2** by the usual method. The stereochemistry of the substituents on **2** was confirmed by an NOE experiment to be *cis*.

Enyne metathesis of **2** was carried out using **5a** in CH_2Cl_2 under ethylene gas, but **1** was obtained in 15% yield along with the starting material **2** and diene **12**[9] in 25% and 13% yields, respectively. Next, the second-generation ruthenium-carbene complex **5b**[10] was used and the reaction was carried out in CH_2Cl_2 upon heating under ethylene gas. However, the desired compound **1** was obtained in only 7% yield along with **12** in 61% yield. Enyne metathesis was carried out under various conditions: in the presence or absence of ethylene and using **5a**, **5b** or **5c**[11] as a ruthenium catalyst. However, the results were not good (Scheme 4).

Thus, alkyne of **2** was protected with the silyl group[9d] and the enyne metathesis of **13** was carried out in



Scheme 4. Enyne metathesis of **2**.



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

CH_2Cl_2 using 20 mol % of **5b** under argon upon heating. After 2.5 h, the desired cyclized compound **1** was obtained in 85% yield. In this reaction, desilylation occurred during the reaction,[9] although the reason is not clear. Oxymercuration of **1** followed by treatment with $NaBH_4$ afforded alcohol in 42% yield (**1** was recovered in 32% yield). Dess–Martin oxidation afforded *N*-tosylanatoxin-*a*, whose spectral data and $[\alpha]_D$ value agreed ($[\alpha]_D$ −15.0, *c* 0.65) with those reported in the literature.[12] Since *N*-tosylanatoxin-*a* had been already converted into anatoxin-*a*[12] the total synthesis of (+)-anatoxin-*a* was achieved (Scheme 5).

Further studies are in progress.

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