論文の内容の要旨

論文題目：**Synthetic Study of Batrachotoxin**
(バトラコトキシンの全合成研究**)**

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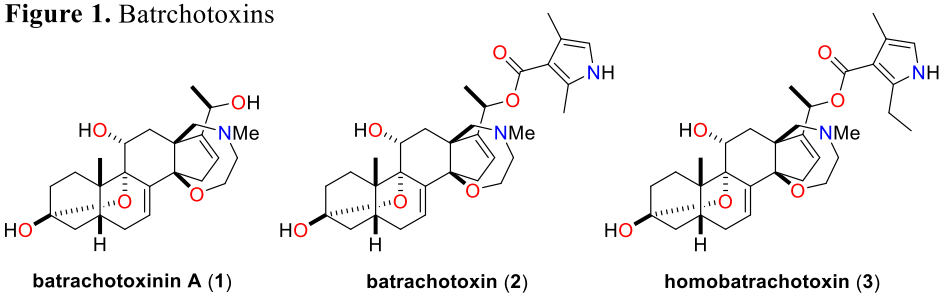
1. Synthetic Study of Batrachotoxin

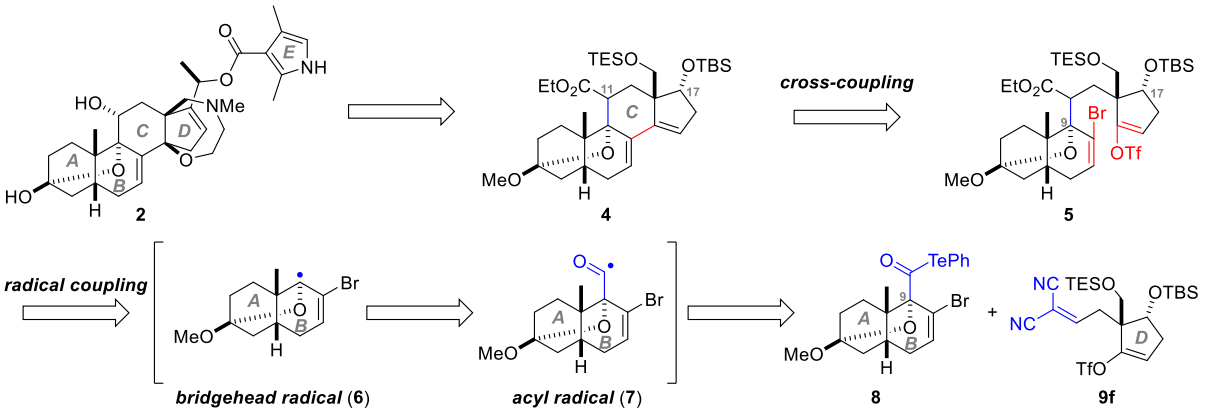
Batrachotoxins were isolated from Columbian poison frogs, *Phillobates* (Figure 1).[1] After the structure of batrachotoxin A (**1**) was determined by X-ray diffraction analysis, a partial synthesis from **1** revealed the structure of batrachotoxin (**2**).[2] Homobatrachotoxin (**3**) was also isolated from a bird, *Pitohui*.[3] Batrachotoxin (**2**) shows a potent neurotoxicity by activating a voltage gated sodium ion channel.[4] Its structure features a densely functionalized steroid-based hexacyclic skeleton. The AB- and CD-rings are *cis*-fused in its steroidal framework. Moreover, batrachotoxin (**2**) has five the tetrasubstituted carbons, the unique hemiacetal and the seven-membered oxazepane ring. Its highly oxidized structure poses a formidable synthetic challenge. So far, only three successful syntheses of batrachotoxins have been reported.[5] This dissertation disclosed a convergent synthetic approach towards a total synthesis of **2**.

Figure 1. Batrchotoxins



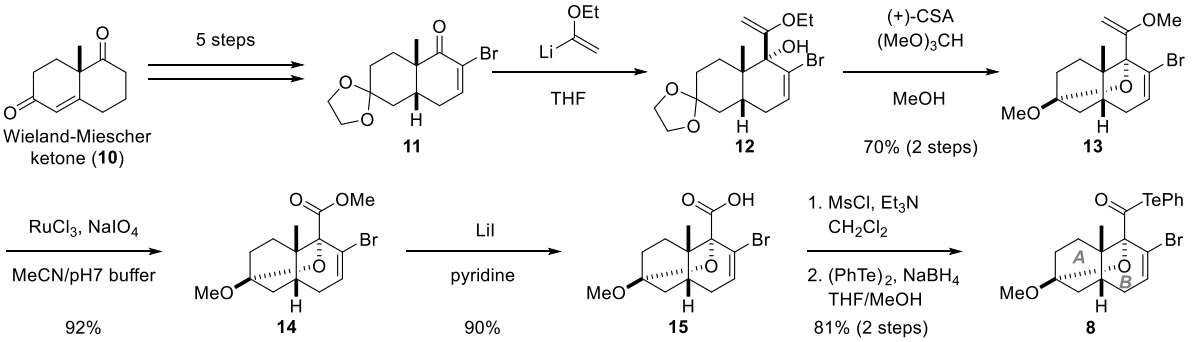
Synthetic plan of batrachotoxin (**2**) is shown in Scheme 1. Compound **4** was set as a key synthetic intermediate. Conversion of the ethoxycarbonyl group to the C11-α hydroxyl group, the seven-membered oxazepane ring formation and the carbon chain installation to the C17 position from **4** would lead to batrachotoxin (**2**). The C-ring of **4** would be constructed by a transition-metal mediated cross-coupling reaction of **5**. To efficiently synthesize the highly functionalized compound **5**, a bridgehead radical-based coupling reaction of AB-ring and D-ring would be applicable.[6] Bridgehead radical **6** would be generated via acyl radical **7** from acyl telluride **8**. Since bridgehead radical **6** is an electron rich radical, it would chemoselectively react with the electron deficient olefin of D-ring **9f**.

Scheme 1. Synthetic plan of batrachotoxin (**2**)



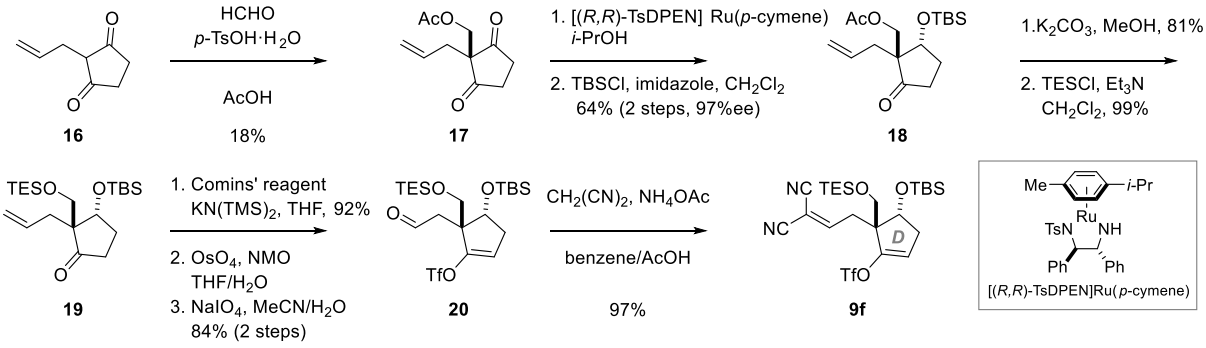
Synthesis of AB-ring **8** commenced with transformation of Wieland-Miescher ketone (**10**) to vinyl bromide **11** by 5 steps. Lithiated vinyl ether attacked to the ketone of **11** to give compound **12**. Treatment of **12** with (+)-CSA in methanol solution furnished a cyclic acetal structure. Compound **13** was then converted to ester **14** by chemoselective oxidative cleavage of the electron rich vinyl ether. After ester **14** was transformed to carboxylic acid **15**, acyl telluride **8** was finally accessed by two-step sequences, mesylation of the carboxylic acid and the following replacement by phenyl telluro group.

Scheme 2. Synthesis of AB-ring **8**



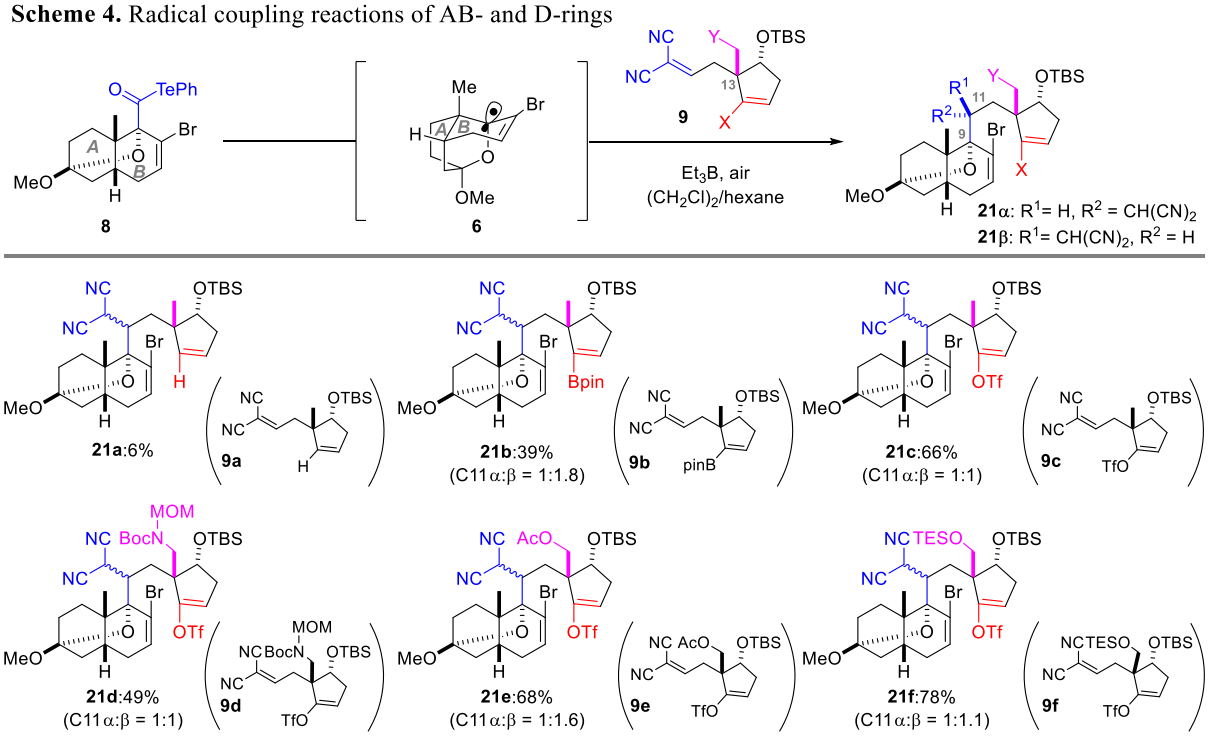
D-ring **9f** was then synthesized from diketone **16** (Scheme 3). Treatment of **16** with formaldehyde in acetic acid solution introduced the acetoxy methyl group to afford diketone **17**. TBS ether **18** was enantio and diastereoselectively obtained by Noyori asymmetric transfer hydrogenation and the following TBS protection of the resultant hydroxyl group. Acetyl group of the compound **18** was then converted to TES group by 2 steps. Vinyl triflation of ketone **19** and chemoselective oxidative cleavage of the terminal olefin gave aldehyde **20**. D-ring **9f** was obtained by condensation of aldehyde **20** with malononitrile.

Scheme 3. Synthesis of D-ring **9f**



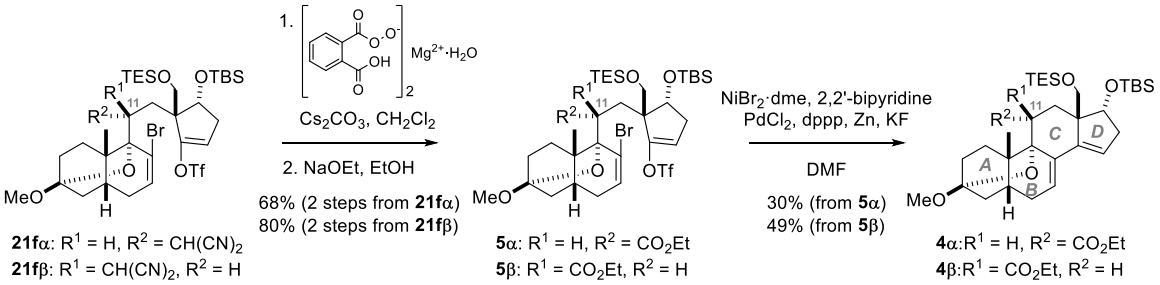
A key radical coupling reaction was investigated (Scheme 4). At first, three model substrates **9a-c**, which had the C13-methyl group, were used. When D-ring **9a** was used, the desired compound **21a** was obtained in only 6% yield. In this reaction, ethyl radical generated from Et_3B under air would react preferentially with the electron deficient olefin of **9a** rather than acyltelluride **8**. The reaction using D-ring **9b** improved the yield. This was because the sterically large pinacol boronate group would decrease the reactivity of **9b** compared to **9a** and ethyl radical would react with acyl telluride **8** to generate bridgehead radical **6**. Further improvement of the yield was realized when D-ring **9c** with triflate group was used. Based on the results of model study, D-rings **9d-f** were used for the radical coupling reactions. Although the yield was moderate when **9d** was used, the desired compound **21e** and **21f** were obtained in good yields. In this way, AB-ring **8** and D-ring **9** was connected in a convergent manner by utilizing the bridgehead radical-based coupling reaction. In addition, the C9-tetrasubstituted carbon was stereospecifically constructed because of the fixed bridgehead radical **6**.

Scheme 4. Radical coupling reactions of AB- and D-rings



The steroid skeleton of batrachotoxin (**2**) was constructed by a cross-coupling reaction (Scheme 5). Esters **5α** and **5β** were synthesized from compounds **21fα** and **21fβ** by oxidation of the malononitrile moiety and the following ethanolysis of the resultant acyl cyanide. After screening of various reaction conditions, Ni,Pd-mediated cross-Ullmann coupling reactions[7] of **5α** and **5β** realized the C-ring construction to give key synthetic intermediates **4α** and **4β**.

Scheme 5. Construction of steroid skeleton of batrachotoxin (**2**)



2. Summary

In this dissertation, an efficient construction of the steroid skeleton of btarachotoxin (**2**) was presented. Two different types of reactions, a radical reaction and a transition-metal mediated cross-coupling reaction, have enabled the present synthesis. The present synthetic strategy was realized by the appropriate design of AB-ring and D-ring. The radical reaction connected AB-ring with D-ring through the chemoselective and stereospecific carbon-carbon bond formation in the presence of vinyl bromide and vinyl triflate groups. C-ring construction was achieved by the Ni,Pd-mediated cross-Ullmann coupling. To the author's best knowledge, this is the first example to apply a multimetallic mediated cross-Ullmann coupling to a synthetic study of highly oxygenated natural products. The complex core structure of batrachotoxin was furnished by 15 steps from Wieland-Miescher ketone (**10**). A total synthesis of batrachotoxin would be achieved after seven-membered oxazepane ring formation, carbon chain installation to the C17 position and introduction of C11α-hydroxy group.

3. References

(1) (a) Märki, F.; Witkop, B. *Experientia* **1963**, *19*, 329. (b) Daly, J. W.; Witkop, B.; Bommer, P.; Biemann, K. *J. Am. Chem. Soc.* **1965**, *87*, 124. (2) Tokuyama, T.; Daly, J.; Witkop, B.; Karle, I. L.; Karle, J. *J. Am. Chem. Soc.* **1968**, *90*, 1917. (3) Dumbacher, J. P.; Beehler, B. M.; Spande, T. F.; Garraffo, H. M.; Daly, J. W. *Science* **1992**, *258*, 799. (4) (a) Khodorov, B. I.; Revenko, S. V. *Neuroscience*, **1979**, *4*, 1315. (b) Khodorov, B. I. *Prog. Biophys. molec. Biol.* **1985**, *45*, 57. (5) (a) Imhof, R.; Gössinger, E.; Graf, W.; Berner-Fenz, L.; Berner, H.; Schaufelberger, R.; Wehrli, H. *Helv. Chim. Acta*, **1973**, *56*, 139. (b) Kurosu, M.; Marcin, L. R.; Grinsteiner, T. J.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 662. (c) Logan, M. M.; Toma, T.; Thomas-Tran, R.; Du Bois, J. *Science* **2016**, *354*, 865. (6) Nagatomo, M.; Kamimura, D.; Matsui, Y.; Masuda, K.; Inoue, M. *Chem. Sci.* **2015**, *6*, 2765. (7) Ackerman, L. K. G.; Lovell, M. M.; Weix, D. J. *Nature*, **2015**, *524*, 454.