論文の内容の要旨

論文題目：A Study Towards Total Synthesis of Ryanodine

（リアノジンの全合成研究）

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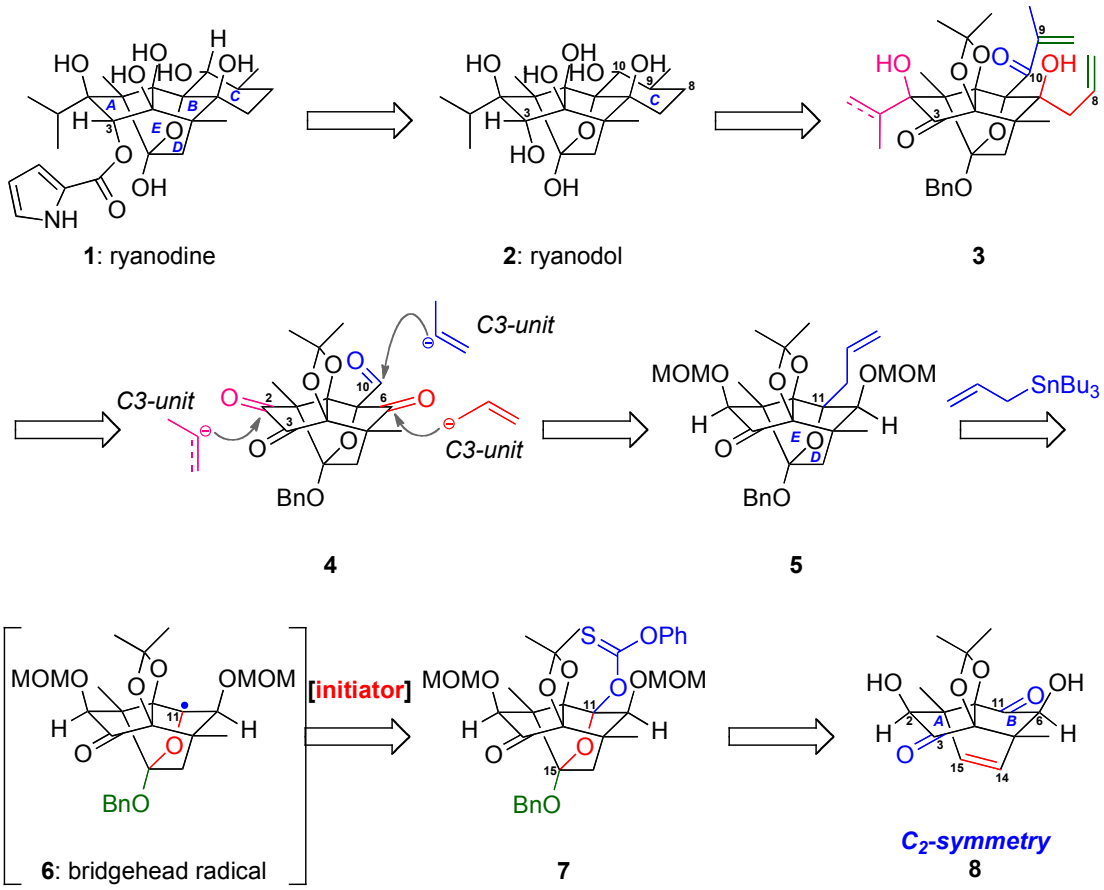
Abstract

Ryanodine (**1**, Scheme 1) was first isolated from stem and root material of *Ryania speciosa* Vahl by Folkers and colleagues at Merck in 1948.[1] Compound **1** is a potent modulator of intracellular calcium channels, designated as ryanodine receptors.[2] The complex molecular architecture of **1** including the fused five rings and the contiguous eleven stereogenic centers poses a unique synthetic challenge.[3] Herein efforts towards the total synthesis of **1** are described.

Our research group has already synthesized the C_2-symmetric intermediate (**8**, Scheme 1) by applying pairwise symmetrical functionalizations.[4] However, the previous studies in our group revealed that formation of the C10–C11 bond by nucleophilic addition to the C11-ketone of **8** was practically impossible, due to the extreme steric congestion around the C11-ketone. Therefore, a novel strategy towards construction of C11-tetrasubstituted

carbon center was necessitated. Accordingly, the author planned a new radical based strategy towards a total synthesis of **1** (Scheme 1). Targeted **1** would be converted from ryanodol **2**, which was to be synthesized through construction of the C-ring by ring-closing metathesis of acyclic enone **3**. Compound **3** in turn would be prepared by stepwise regio- and stereoselective introduction of three different C3-units to the C2-, C6-, and C10-carbonyl groups of **4**. Compound **4** would be generated from acetal **5**, which contains the fused ABDE-ring system. To construct the C11-tetrasubstituted carbon center, the author planned the α-alkoxybridgehead radical mediated reaction.[5] Specifically, thiocarbonate **7** would produce a highly reactive α-alkoxybridgehead radical, which would react with allylstannane to construct the tetrasubstituted carbon center. The precursor **7** could be synthesized from **8** through oxidative desymmetrization of the C14–C15 double bond and subsequent double acetalization at the C11- and C15-ketones.

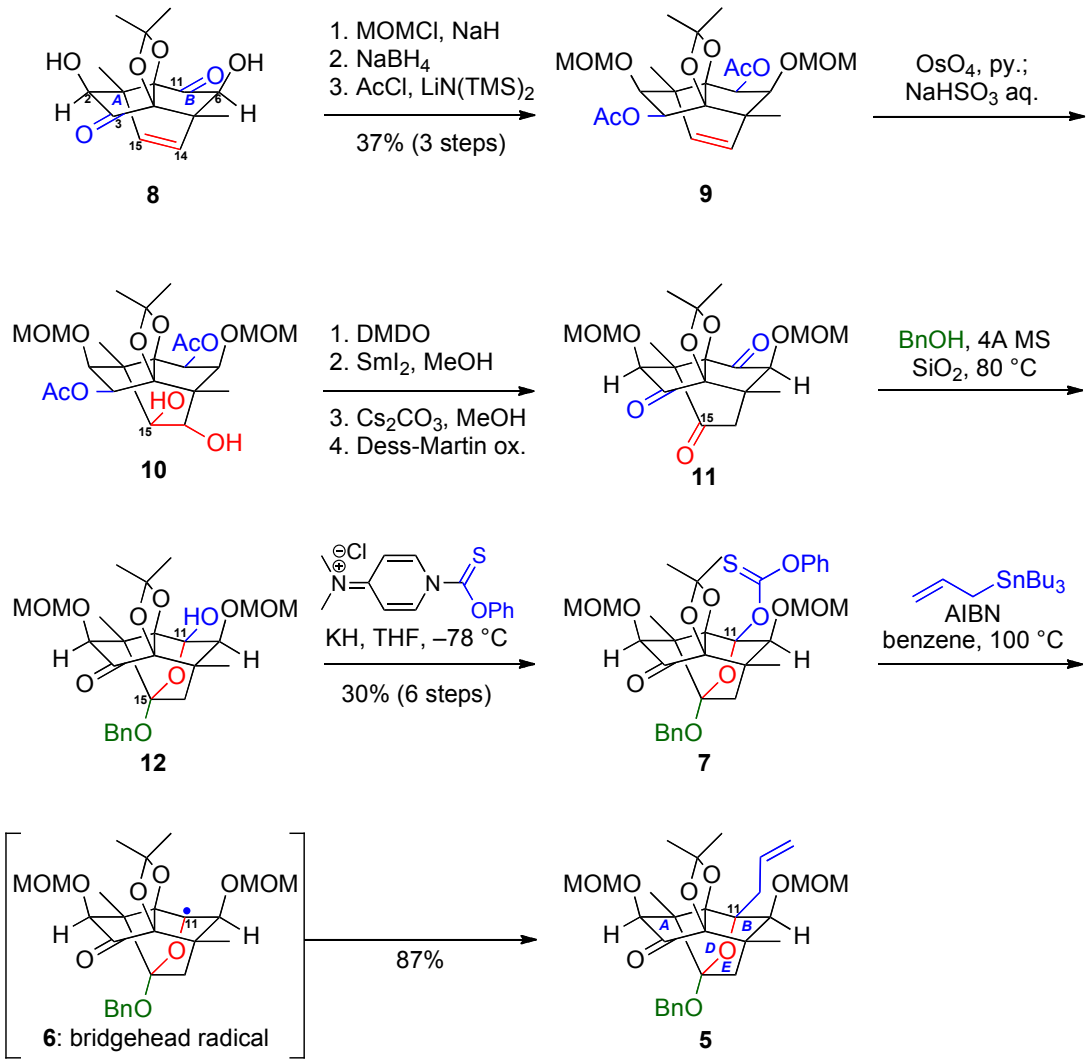


Scheme 1. Retrosynthetic analysis of **1** from **8**.

1. Construction of the ABDE-Ring System of Ryanodine

The intermediate **5**, containing tetracyclic fused ABDE-ring system, was synthesized from C_2-symmetric **8** (Scheme 2). C_2-symmetric diacetate **9** was prepared from **8** over 3 steps. The next reaction effectively desymmetrized C_2-symmetric **9**. Namely, dihydroxylation of the C14-C15 double bond gave desymmetrized acetal **10**. The following four steps smoothly converted **10** into triketone **11**. Then, treatment of **11** with benzyl alcohol in the presence of acidic SiO_2 at 80 °C produced tetracyclic hemiacetal **12**, which possesses the benzyl acetal at C15 position. The regioselective generation of **12** involved the intermolecular nucleophilic addition of benzyl alcohol to the C15-ketone and subsequent nucleophilic addition of the resultant hydroxy group of the hemiacetal to the C11-ketone. Conversion of **12** to thiocarbonate **7** was performed at –78 °C to produce the desired **7**. Remarkably, under the basic conditions, ejection of benzylalcohol and reformation of triketone were not observed.

With the radical precursor in hand, the author's efforts were turned to construction of the C11-tetrasubstituted carbon center. To our delight, treatment of **7** with allyltributyltin and AIBN in benzene at 100 °C gave rise to the tetracyclic ABDE-ring **5** in 90% yield. This result demonstrated the power of the α-alkoxybridgehead radical technology even for formation of the most sterically congested bonds.[5]

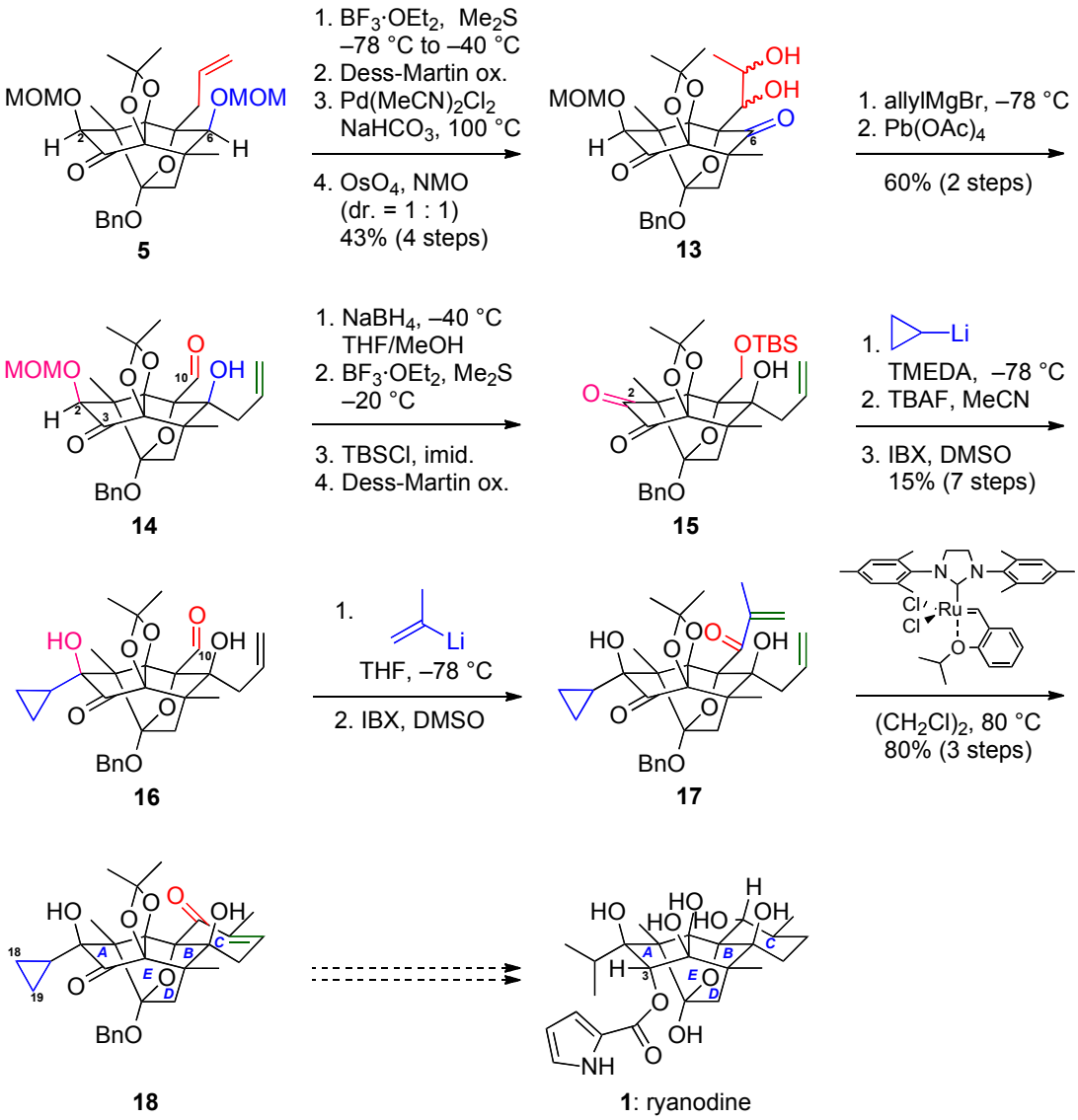


Scheme 2. Construction of the ABDE-ring system of **1** from **8**.

2. *Synthesis of Fully Functionalized Pentacyclic Skeleton*

Fully functionalized intermediate **18** was synthesized from intermediate **5** (Scheme 3). The MOM group at C6-OH of **5** was selectively removed by treatment with $BF_3 \cdot OEt_2$ and Me_2S at –40 °C. After oxidation of the resultant alcohol with Dess–Martin reagent, the terminal double bond was isomerized to the internal double bond using $PdCl_2(MeCN)_2$ at 100 °C. The internal double bond was then dihydroxylated with OsO_4 to provided diketo-diol **13** as a 1 : 1 diastereomixture. Subsequent nucleophilic addition of allylMgBr to **13** in THF at –78 °C proceeded regio- and stereoselectively at C6-ketone. Then, oxidative

cleavage of the 1,2-diol of **13** with $Pb(OAc)_4$ in benzene produced aldehyde **14**. After considerable experimentation, the author found that installation of the cyclopropyl group at C2 as an isopropyl equivalent was necessary before cyclization of the C-ring by RCM. The aldehyde of **14** was chemoselectively reduced by $NaBH_4$ to the primary alcohol and subsequent cleavage of the MOM ether using $BF_3 \cdot OEt_2$ and Me_2S at –20 °C afforded the triol. TBS protection of the obtained triol, followed by Dess–Martin oxidation, provided 1,2-diketone **15**. Addition of the cyclopropyl group to C2-ketone of **15** was successfully accomplished by using cyclopropyl lithium in the presence of TMEDA. Then, the TBS group was removed by treatment with TBAF in MeCN and the resultant alcohol was oxidized by IBX to aldehyde **16**. The addition of isopropenyl lithium to the aldehyde of **16** provided the diene as a single diastereomer. After oxidation of the resultant C10-hydroxy group with IBX, RCM of **17** with Hoveyda–Grubbs' 2nd generation catalyst smoothly constructed the pentacyclic skeleton of **18**, a fully functionalized intermediate of ryanodol **3** and ryanodine **1**. Efforts towards total synthesis of **1** from **18** are currently underway.



Scheme 3. Construction of fully functionalized pentacyclic skeleton of **1** from **5**.

References

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