論文の内容の要旨

論文題目：Study Towards the Total Synthesis of Resiniferatoxin

（レジニフェラトキシンの全合成研究）

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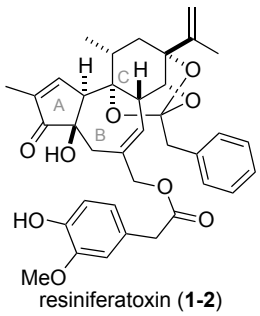
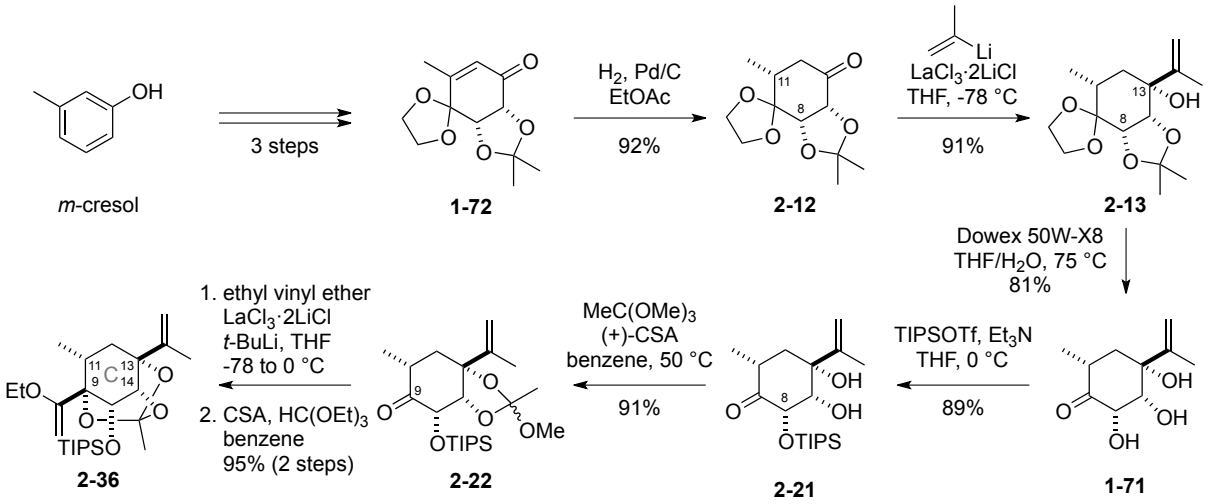


resiniferatoxin (**1-2**)

Resiniferatoxin (**1-2**), a daphnane diterpene isolated from the latex of spurge, *Euphorbia resinifera*, is an extremely potent activator of ion channel TRPV1 in the plasma membrane of sensory neurons. The fused tricyclic daphnane skeleton consisting of the densely functionalized five-, six-, and seven-membered rings (ABC-ring system) renders a great synthetic challenge. The present dissertation discloses the novel radical-mediated approach to the daphnane ABC-ring skeleton.

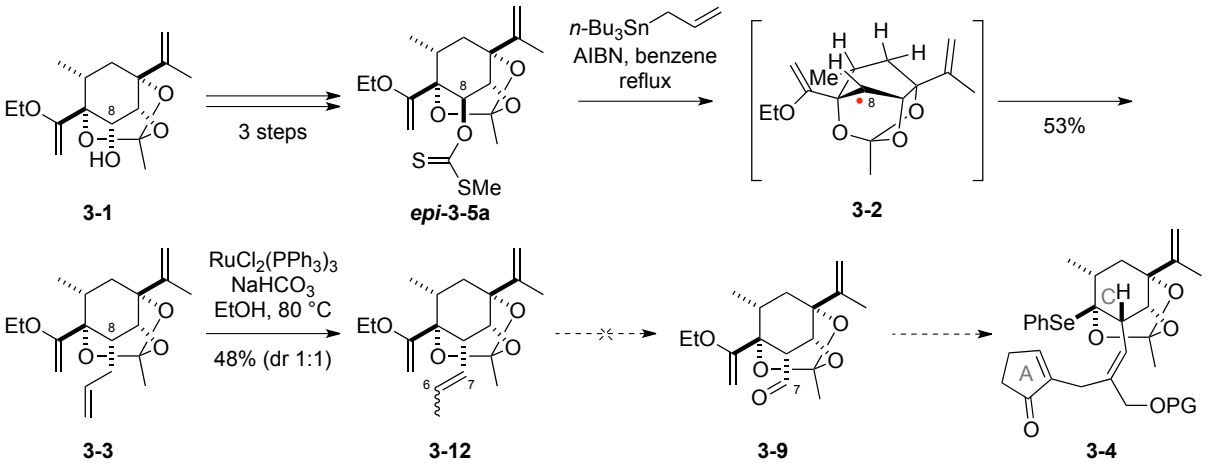
The first part of the synthesis deals with the concise approach to the highly functionalized C-ring component with the required stereochemistries and functionalities at the C9, 11, 13, and 14 positions (Scheme 1). The bicyclic scaffold **1-72** was accessed from *m*-cresol in 3 steps. The inherent facial bias predisposed by such a scaffold induced the stereoselective reactions to afford **2-12** and **2-13**. Deprotection of acetals of **2-13**, followed by regioselective protections of triol **1-71** resulted in **2-21**. The concavity on the molecule (**2-22**) was again exploited to stereoselectively install a carbon unit at the C9 position to enable the orthoester formation, leading to **2-36**.

Scheme 1 Synthesis of the functionalized C-ring



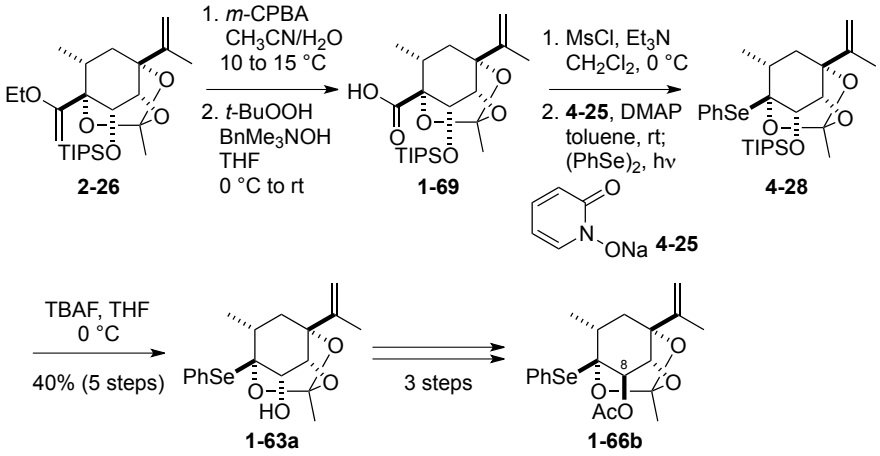
Conceptualization to assemble the daphnane ABC-ring skeleton led to the two markedly different approaches. The former involved in the carbon extension at the C8 position albeit encountered difficulties (Scheme 2). Alcohol **3-1** was converted to ***epi*-3-5a** and the subsequent Keck allylation successfully installed the carbon chain at the C8 position with the desired stereochemistry. Isomerization of the terminal olefin of **3-3** provided **3-12**. However, the cleavage of the C6-C7 olefin proved problematic and aldehyde **3-9** could not be attained. At this juncture, the approach to the AC-ring compound **3-4** was abandoned.

Scheme 2 The C8 carbon chain extension approach



Revised synthetic strategy ultimately culminated in the completion of the daphnane skeleton. To access the bridgehead radical precursor, **2-26** was first converted to carboxylic acid **1-69** (Scheme 3). Through radical-mediated processes from **1-69** installed the selenide group at the bridgehead position of **4-28**. After the removal of the TIPS protecting group, **1-63a** was revealed in 40% (5 steps) from **2-26**. This sequence successfully constructed otherwise inaccessible bridgehead O,Se-acetal in a very efficient manner. 3 steps from **1-63a** provided the crucial three-component radical precursor **1-66b**.

Scheme 3 Synthesis of O,Se-acetal



The construction of the daphnane ABC-ring skeleton required only four steps from O,Se-acetal **1-66b** (Scheme 4). Three-component radical coupling reaction of the C-ring component **1-66b**, the A-ring component **1-67b**, and the branched allyl stannane **1-68d** proceeded to give rise to the AC-ring compound **4-48bb** in a stereospecific manner. Conversion of **4-48bb** into corresponding xanthate provided another radical reaction precursor **1-64bb**. Heating **1-64bb** under microwave irradiation successfully triggered the 7-*endo* cyclization to forge the crucial C7-C8 linkage in a diastereoselective manner to generate the ABC-ring compound **4-51bb**. Removal of the TBDPS protecting group thus afforded **4-52bb**. Significantly, this radical cyclization secured the requisite C8 stereocenter. Overall, the two radical reactions established the three C-C- bonds, including the hindered tri- and

tetrasubstituted C9-C10 bond, and the four stereocenters. The present approach has attested the power and versatility of the radical reactions to realize the sterically congested C-C bond formations of the highly oxygenated substrates with many potentially reactive functionalities.

Scheme 4 Radical-mediated construction of the daphnane ABC-ring skeleton