博士論文（要約）

論文題目　　Synthetic Study of Daphnane Diterpenoids

（ダフナンジテルペン類の全合成研究）

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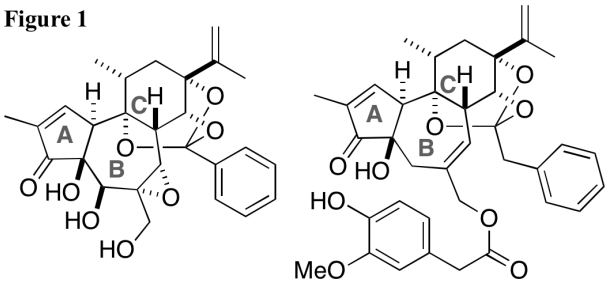
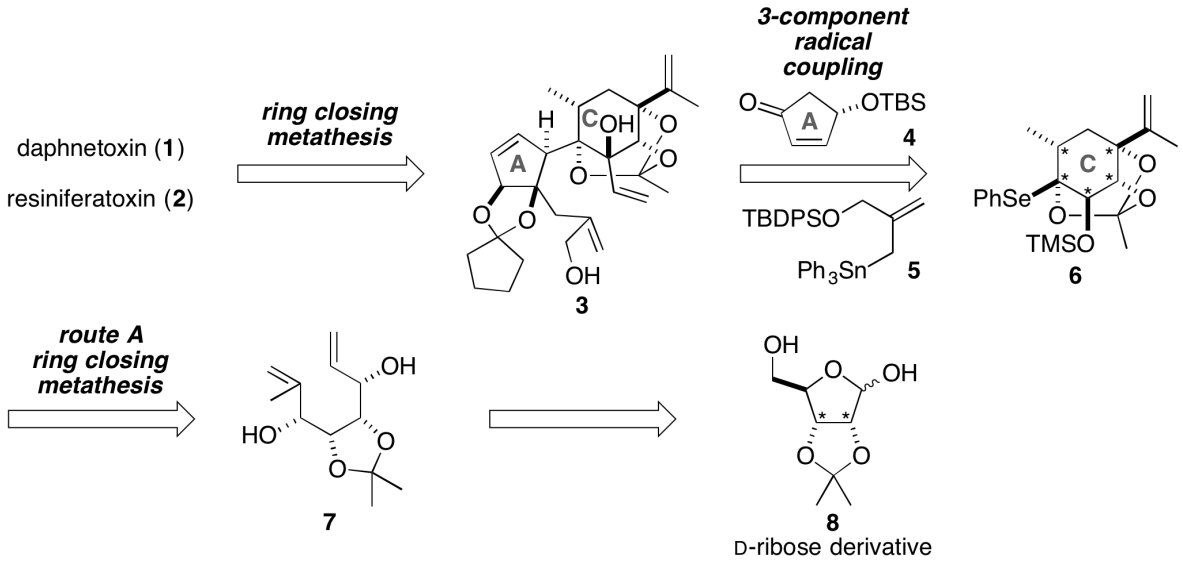
1. Introduction

There are over 120 daphnane diterpenes isolated from various *Thymelaeaceae spp.* and *Euphorbiaceae spp.* so far. While these natural compounds commonly have *trans*-fused 5/7/6 tricyclic carbonskeleton, they have wide range of biological activities. For example, daphnetoxin (**1**)[1] is a HIV inihibitor, and resiniferatoxin (**2**)[2] is an agonist of TRPV1, which is involved in pain transmission (Figure 1). In the light of these features, daphnane diterpenoids are expected to be seeds of drugs. However, total synthesis and preparation of artificial daphnane analogues have been hampered by their extremely complex structures. For example, they have many oxygen functionalities and many contiguous asymmetric centers on its 5/7/6 *trans*-fused tricyclic carbon skeleton. Not only to establish a unified method to synthesize daphnane diterpenoids, but also to develop artificial daphnane diterpene analogues, two synthetic plans that can afford various daphnane diterpenoids were set.

Figure 1



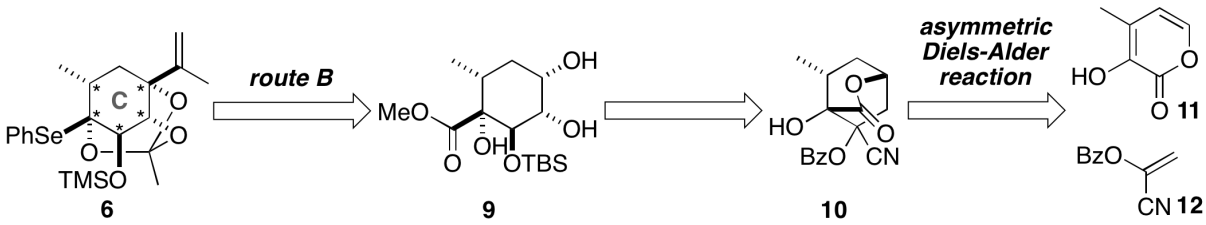
Scheme 1. Synthetic Plan of daphnetoxin (**1**) and resiniferatoxin (**2**)



2.Synthetic Plan

The synthetic plan is shown in Scheme 1. B-ring of **1** and **2** could be constructed by ring-closing metathesis of **3**. AC-ring compound **3** could be obtained by three-component radical coupling of **4**, **5** and **6**.[3] Bridgehead radical generated from **6** would attack cyclopentenone **4** and allyl stannane **5** successively. For the synthesis of **6**, two synthetic routes were planed. As "route A", diene **7**, which is a substrate of ring-closing metathesis was set and **7** could be transformed from D-ribose derivative **8**.[4] To shorten the synthetic route, another distinct route was examined as "route B" (Scheme 2). As a synthetic precursor of selenide **6**, methyl ester **9** was set. **9** would be synthesized from lactone **10**. **10** could be obtained through asymmetric Diels-Alder reaction of pyrone **11** and dienophile **12**.

Scheme 2. Revised synthetic plan of C-ring fragment **6**

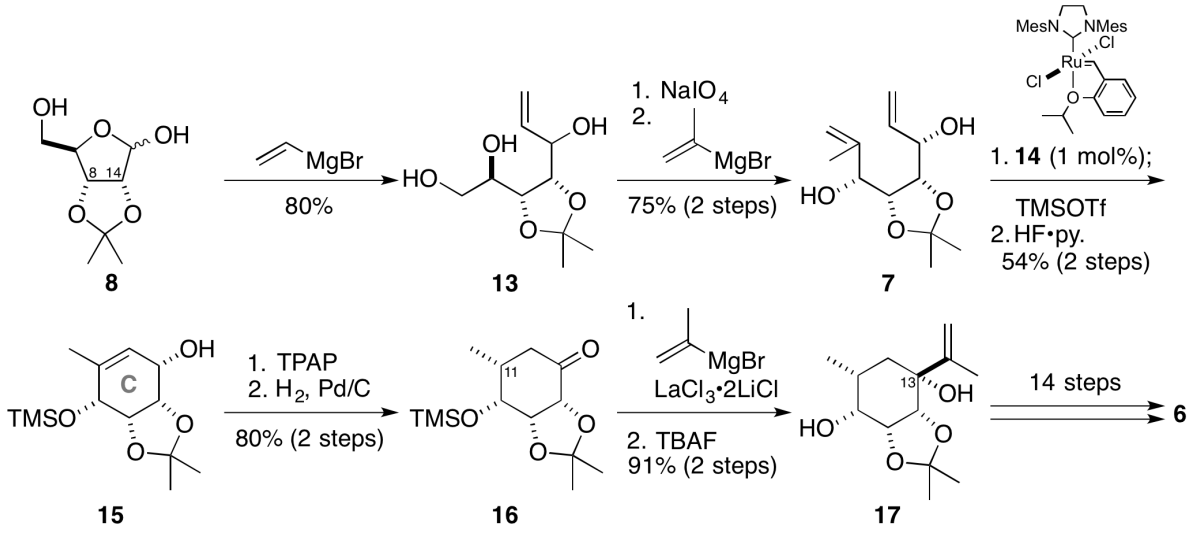


3. Methods and Results

3.1 Synthesis of A-ring fragment 6

O,Se-acetal **6** was synthesized (Scheme 3). Introduction of vinyl group to D-ribose derivative **8**[4] gave **13**. Oxidative cleavage of diol moiety and introduction of isopropenyl group gave diene **7**. These nucleophilic additions proceeded in high yield in the presence of free hydroxy groups to substantially simplify the synthesis of **7**. Ring-closing metathesis using Hoveyda-Grubbs 2nd catalyst (**14**) constructed C-ring. After protection of two hydroxy groups as bis-TMS ether, the less hindered TMS group was selectively removed to afford **15**. Oxidation of the hydroxy group and following hydrogenation of the double bond gave ketone **16**. Addition of isopropenyl group and removal of the TMS group derived **17**. Protection of the *cis*-diol moiety as acetonide enabled convex-face-selective hydrogenation and nucleophilic addition to introduce the desired stereocenters at C11 and C13 position to give known compound **17**. Reported 14-step sequence[3] gave radical donor **6**. The author has established the synthetic route for **6** in his master course. This synthetic route short cut the preparation of **6** from 26

Scheme 3. Synthesis of **6** (route A)

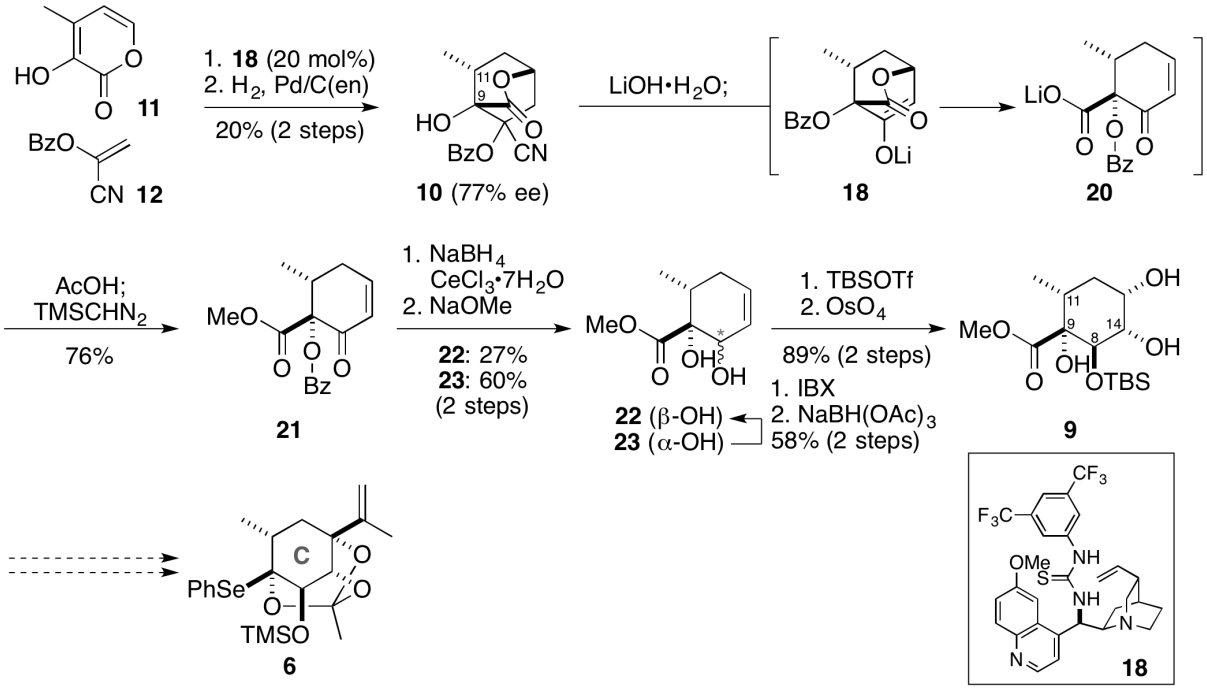


steps to 23 steps to make large-scale synthesis easier.

For further simplification of the synthetic route of **6**, "route B" was examined (Scheme 4). Asymmetric Diels-Alder reaction of **11** and **12** and following hydrogenation gave **10**. Diels-Alder reaction using quinidine derivative as a catalyst afforded the desired tetra-substituted stereocenter at C9 (77% ee),[5] and facial selective hydrogenation gave the desired stereocenter at C11. The absolute stereochemistry and enantioexcess were determined by Mosher's method by transforming **21**, referred to

later, into (*R*) and (*S*)-MTPA esters. Conversion of the cyanohydrin moiety to ketone and methyl ester formation were conducted in a one pot. Treating of **10** with lithium hydroxide caused transposition of the benzoyl group to form **19**. **19** spontaneously opened the lactone to give enone **20**. Lithium carboxylate **20** was quenched with acetic acid and immediately treated with trimethyldiazomethane to afford methyl ester **21**. The enone moiety of **21** underwent 1,2-hydride reduction and debenzoylation to give a diastereomixture of **22** and **23** (dr = 1 : 2.6). The undesired isomer **23** was converged into **22** through oxidation and reduction. The secondary hydroxy group was selectively protected as TBS ether. Dihydroxylation proceeded from the opposite face of bulky TBS-oxy group to give **9** with the desired stereochemistry at C8, C9, C11 and C14.

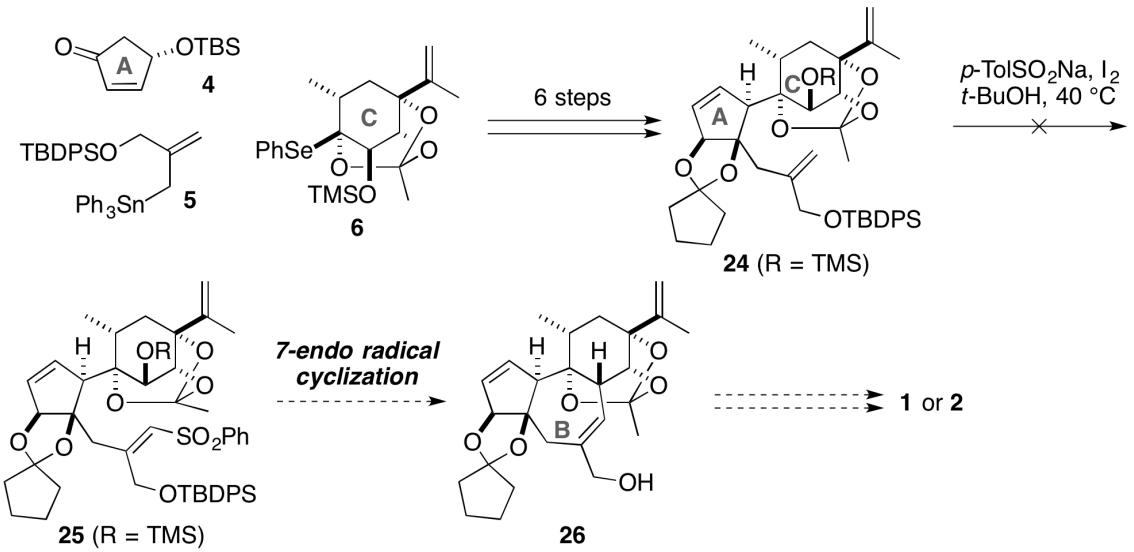
Scheme 4. Synthetic study of **6** (route B)



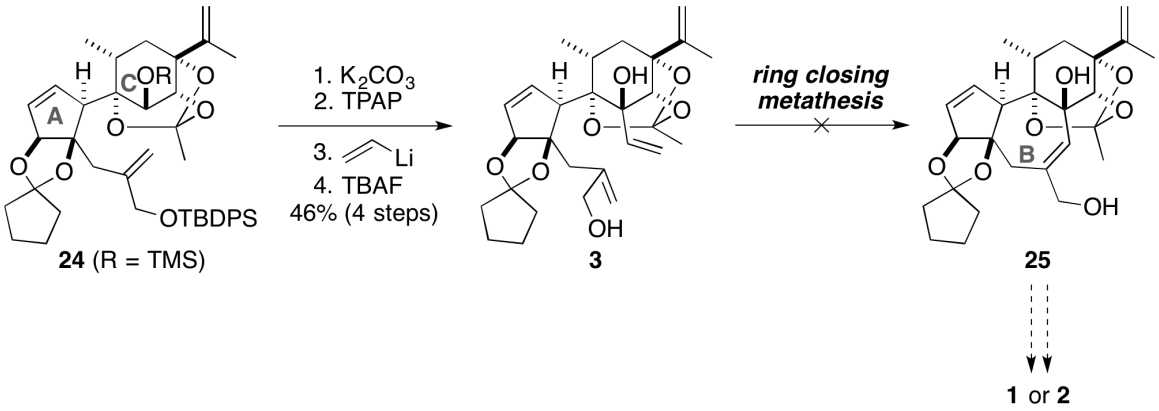
3.2. B-ring formation

Reported 6-step transformation including three-component radical coupling gave **24** (Scheme 5). First, B-ring formation using 7-endo radical cyclization (**25** to **26**) was planed. However, the substrate **25** was not obtained from **24**. Then, ring-closing metathesis to construct B-ring was planned (Scheme 6). 4-step sequence from **24** was conducted to prepare **3**, which was set as a precursor of ring-closing metathesis. However, ring-closing metathesis to give ABC-ring compound **26** did not proceed at all.

Scheme 5. Attempted synthesis of vinyl sulfone **25**



Scheme 6. Synthesis of tetraene **3** and attempted ring-closing metathesis



4. Conclusion

In this dissertation, the synthetic study of **1** and **2** was presented. The author accomplished short cut of the synthetic route of C-ring compound **6**, which has five stereocenters starting from D-ribose derivative **8** (route A). This achievement enabled large-scale synthesis of synthetic intermediate **6** to promote the synthetic study of daphnane diterpenes. The author also examined a distinct route, which could enable further short-cut synthesis of **6**. Asymmetric Diels-Alder reaction of **11** and **12** constructed C-ring and following 8-step transformations introduced the desired four stereocenters (route B) to give **9**. B-ring formation using 7-*endo* radical cyclization or ring-closing metathesis was also examined. While the preparation of the substrate for ring-closing metathesis was successful, the attempts for B-ring construction were not successful. These results suggested that excessively functionalized substrate would be unfavorable for ring-closing metathesis and prompted us to accomplish the total synthesis of daphnane diterpenes using 7-*endo* radical cyclization reported previously.

References: 1) Stout, G. H.; Balkenhol, W. G.; Poling, M.; Hickernell, G. L. *J. Am. Chem. Soc.* **1970**, *92*, 1070. 2) (a) Hergenhahn, M.; Adolf, W.; Hecker, E. *Tetrahedron Lett.* **1975**, *16*, 159. (b) Adolf, W.; Sorg, B.; Hergenhahn, M.; Hecker, E. *J. Nat. Chem.* **1982**, *45*, 347. 3) (a) Murai, K.; Katoh, S.; Urabe, D.; Inoue, M. *Chem. Sci.* **2013**, *4*, 2364. (b) Hashimoto, S. Master Thesis, The University of Tokyo, 2015. 4) Kotsuki, H.; Miyazaki, A.; Ochi, M. *Tetrahedron Lett.* **1991**, *32*, 4503. 5) Wang, Y.; Li, H.; Wang, Y.-Q.; Liu, Y.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 6364.