論文の内容の要旨

論文題目　Synthetic Study of Highly Oxygenated Agarofuran Natural Products
(高酸化度アガロフラン系天然物の全合成研究)

氏名　石山　備凡

Introduction

More than 460 natural compounds possessing the dihydro-β-agarofuran (**1**) skeleton with a wide range of oxidation state has been isolated.[1] Although the poly-oxygenated natural compounds possess the same tricyclic core, they show different biological activities against different targets. For example, while hyponine B (**2**) shows highly selective anti-HIV activity against H9 lymphocytes,[2] and emarginatine B (**3**) possess cytotoxicity against human KB cells.[3] Meanwhile, the densely oxidized dihydro-β-agarofuran skeleton of **2** and **3**, characterized by 11 contiguous stereocenters 4 of which are tetrasubstituted and a 14-membered macrocycle, poses a formidable synthetic challenge. To develop an efficient synthetic route toward the highly oxygenated agarofuran natural products, **4** was set as the synthetic target because it possess all the pivotal structural features of highly oxygenated agarofuran compounds.

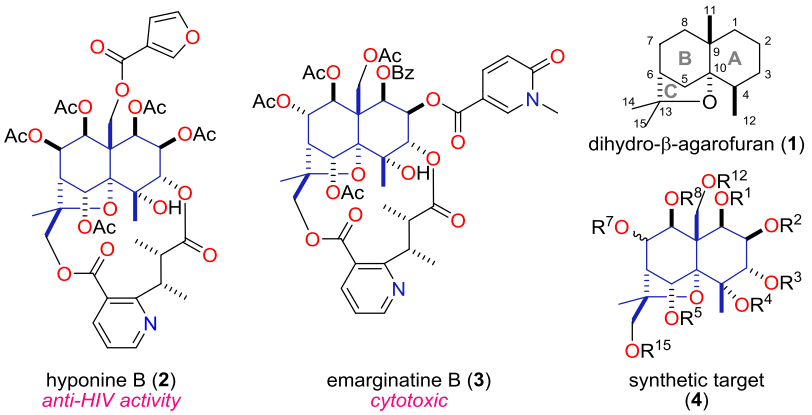
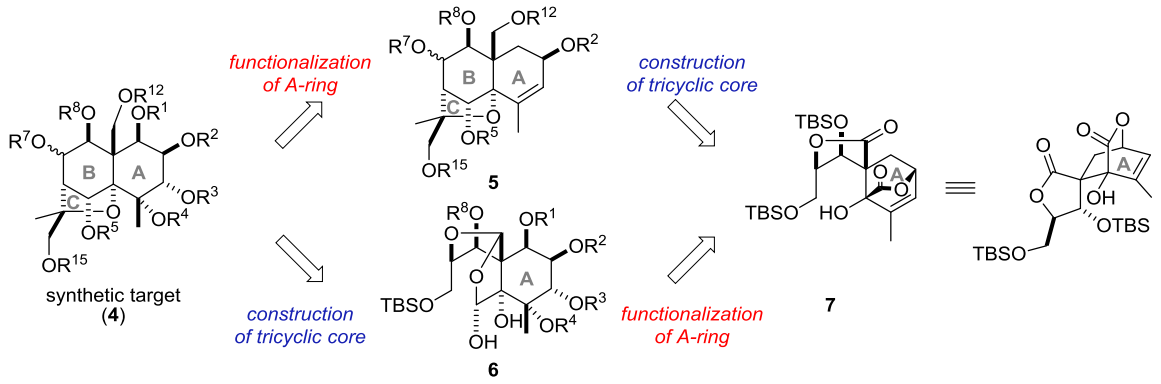


Figure 1. Agarofuran compounds.

The synthetic plan of **4** is shown in Scheme 1. Since the enantioselective synthesis of **7** had already been developed in my master's program, it was planned that the combination of two strategies, construction of the agarofuran tricyclic core and functionalization of the A-ring would establish flexible synthetic route to densly oxygenated agarofuran compounds. In this thesis, 1) reexamination of the Diels-Alder reaction, 2) synthesis of agarofuran tricyclic core, and 3) functionalization of A-ring is discussed.

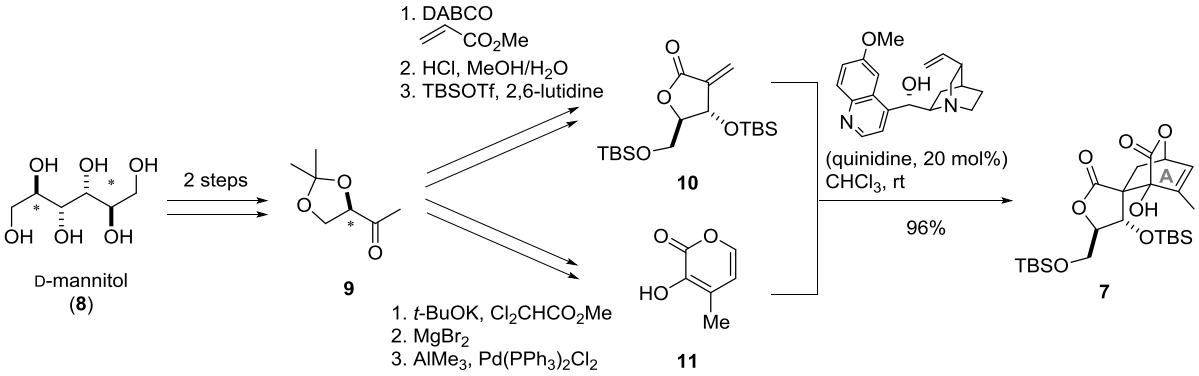
Scheme 1. Synthetic plan of **4**.



Diels-Alder reaction

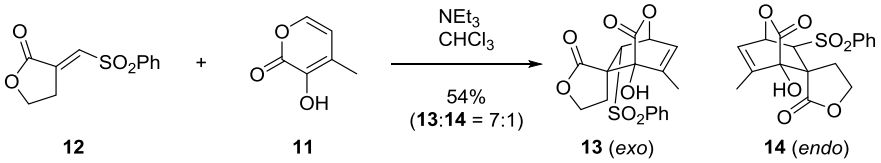
First, base-catalyzed Diels-Alder reaction was reexamined (Scheme 2). Enantio-pure dienophile **10** was synthesized from D-mannitol in 5 steps utilizing *anti*-selective Morita-Baylis-Hillman reaction. Meanwhile, diene **11** was also synthesized from D-mannitol (**8**) in 5 steps in a reproducible manner. The Diels-Alder reaction between **10** and **11** under quinidine catalyst proceeded to afford enantio-pure **7** in high selectivity.

Scheme 2. Diels-Alder reaction of diene **10** and **11**.



To expand the scope of the base-catalyzed Diels-Alder reaction, tri-substituted dienophile **12** was subjected to the Diels-Alder conditions with diene **11**. It was found that Diels-Alder adduct **13** can be obtained with high selectivity. In this reaction, the multiple functional groups and four contiguous stereocenters two of which are tetrasubstituted were introduced effectively.

Scheme 3. Diels-Alder reaction of trisubstituted olefin **12**.

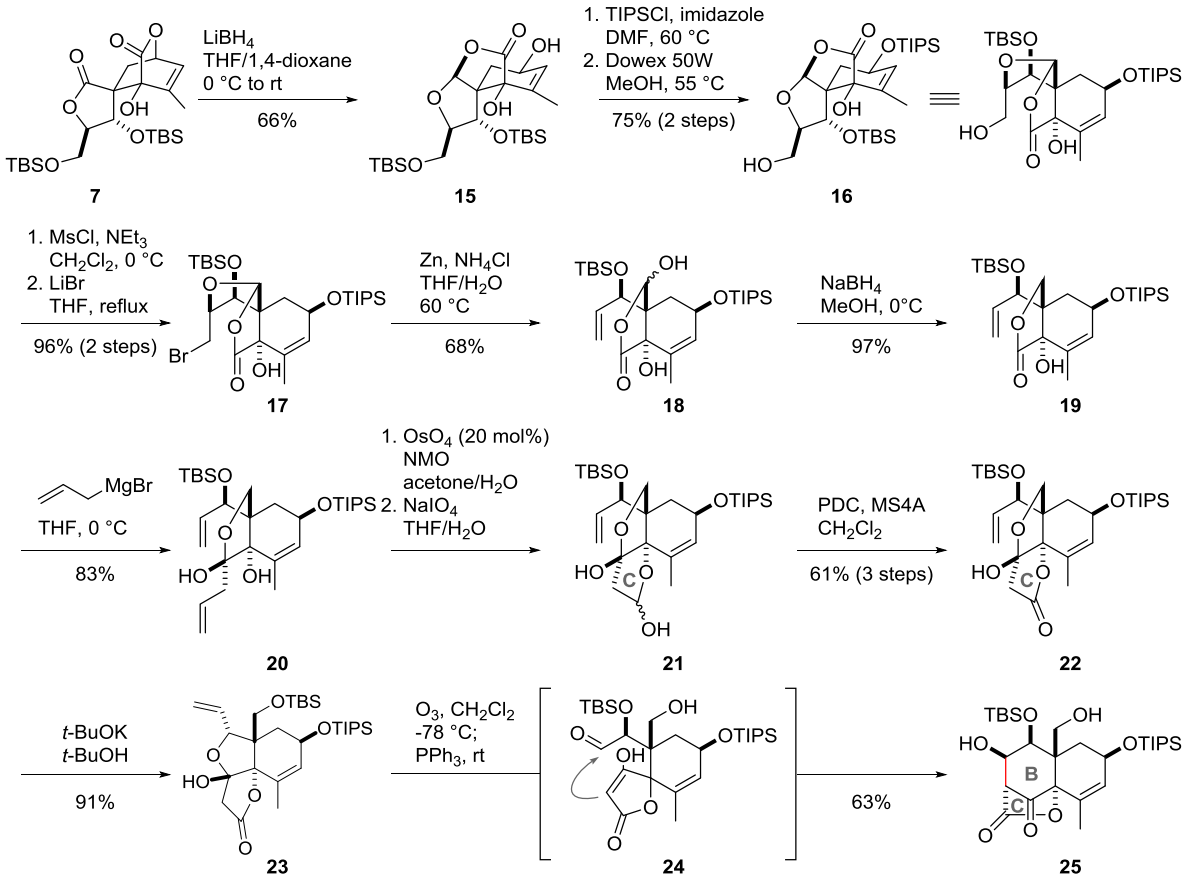


Construction of agarofuran tricyclic core

Next, agarofuran tricyclic core was successfully constructed from Diels-Alder adduct **7** by an ozonolysis/intramolecular aldol reaction strategy (Scheme 4). The conversion includes 1) reductive removal of bromide and ether ring-opening reaction (Booard elimination, **17** → **18**), 2) construction of reactive β-keto lactone utilizing the internal hydroxy group for tentative protection, and 3) one-pot ozonolysis/intramolecular aldol reaction to construct B ring (**23** → **25**).

Thus, highly functionalized compound **25** with agarofuran tricyclic core, possessing five stereocenters two of which are tetrasubstituted, was successfully synthesized in 6.6% yield over 13 steps from the Diels-Alder adduct **7**.

Scheme 4. Synthesis of agarofuran tricyclic core.

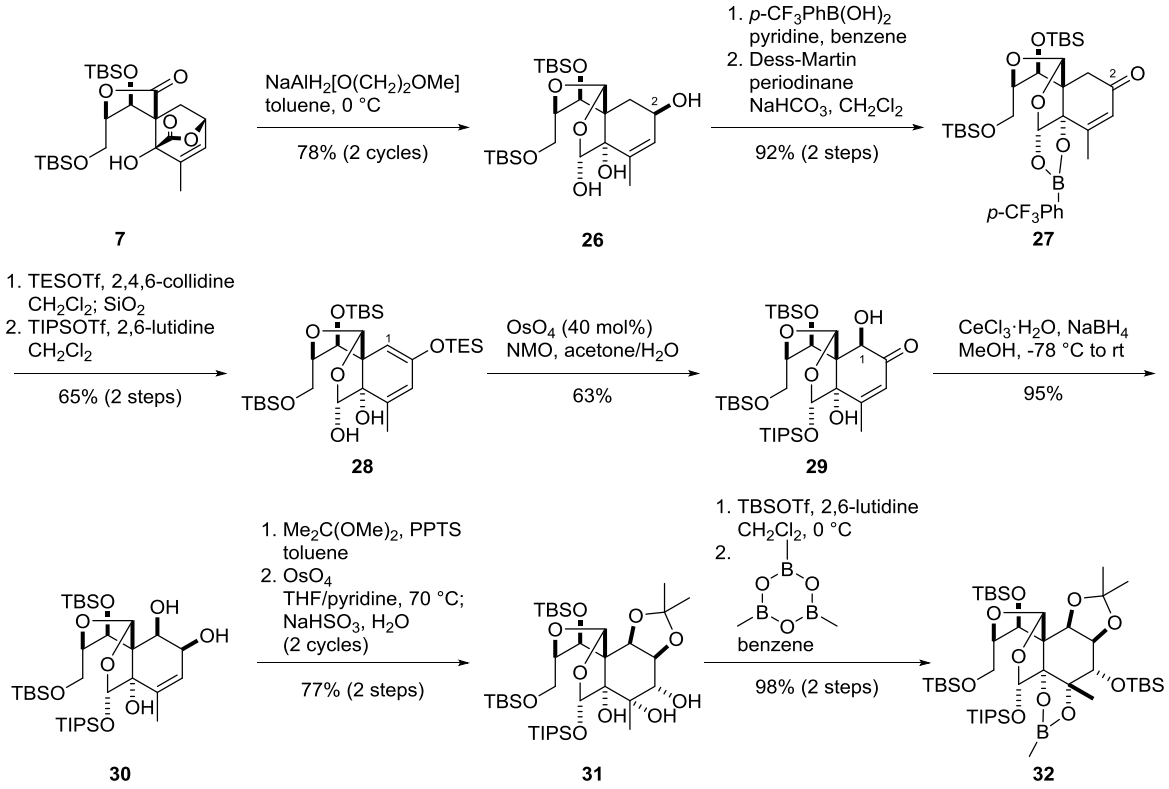


Functionalization of A-ring

On the other hand. full functionalization of A-ring was successfully achieved as shown in Scheme 5. The key factor for the success of stereoselective transformations was the precise control of electron density at the A-ring double bonds. Thus, introduction of silyl enol ether (**27** → **28**) enabled the stereoselective introduction of hydroxy group at the C1 position from the upper face (**28** → **29**). Another definitive strategy was the use of boronate as an easily detachable protecting group, enabling the selective reactions at the C2 functional groups (**26** → **28**).

Accordingly, compound **32**, A-ring fully functionalized with nine contiguous stereocenters three of which are tetrasubstituted, was synthesized from Diels-Alder adduct **7** in 21% yield over 11 steps.

Scheme 5. Full-functionalization of A-ring.



Summary

To summarize, three methods, Diels-Alder reaction (**8** → **10** and **11** → **7**), construction of tricyclic core (**7** → **25**), and functionalization of A-ring (**7** → **32**), have been established for the synthesis of highly oxygenated agarofuran compound **4**.

References: (1) (a) Spivey, A. C.; Wetson, M.; Woodhead, S. *Chem. Soc. Rev.* **2002**, *31*, 43. (b) Gao, J.-M.; We, W.-J.; Zhang, J.-W.; Konishi, Y. *Nat. Prod. Rep.* **2007**, *24*, 1153. (2) (a) Duan, H.; Kawazoe, K.; Takaishi, Y. *Phytochemistry* **1997**, *45*, 617. (b) Duan, H.; Takaishi, Y.; Imakura, Y.; Jia, Y.; Li, D.; Cosentino, M.; Lee, K.-H. *J. Nat. Prod.* **2000**, *63*, 357. (3) Kuo, Y.-H.; Chen, C.-H.; Kuo, L.-M. Y. *J. Nat. Prod.* **1990**, *53*, 422.