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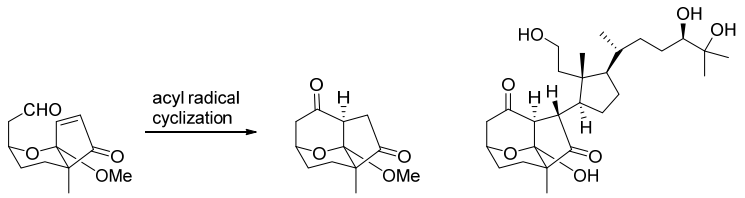

tricyclic core of aplysiasecosterol A

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Synthetic Studies toward Aplysiasecosterol A: Construction of the Novel Tricyclic Core

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ABSTRACT

Aplysiasecosterol A, a 9,11-secosterol compound, has a unique tricyclic γ-diketone skeleton including a hemiacetal. The novel tricyclic core of aplysiasecosterol A is constructed by using intramolecular radical cyclization as a key step.

Steroids are widely distributed in nature and have frequently been studied for their various interesting biological activities. In addition, numerous methods for synthesizing steroids have been reported. Secosteroids are a family of steroids that possess an opened ring. Synthetic and biological approaches for a number of well known secosteroids, including vitamin D groups, are available.[1] However, in the case of several more recently isolated secosteroids, no synthetic methods of have been developed. Aplysiasecosterol A (**1**),[2] a 9,11-secosterol compound, was isolated from *Aplysia kurodai* by our group in 2015 (Figure 1). This compound has a unique tricyclic γ-diketone skeleton including a hemiacetal, which is regarded as an interesting target of synthetic organic chemistry. Pinnigorgiol A (**2**) and its congeners,[3] which have the same tricyclic skeleton, were isolated in 2016. Although this unique skeleton is thought to be produced by a combination of α-ketol rearrangements of the AB ring of the steroid, no method for synthesizing either the tricyclic skeleton or aplysiasecosterol A (**1**) itself has been reported. Herein, we report the synthesis of this novel tricyclic skeleton by intramolecular radical cyclization as a key reaction.

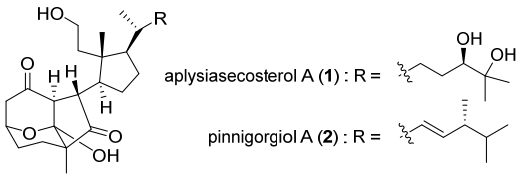
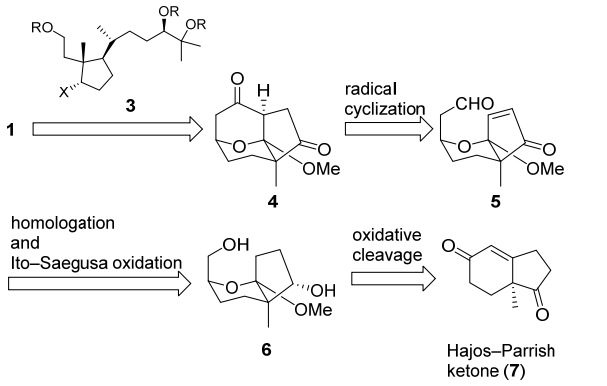


Figure 1. Structures of Aplysiasecosterol A and Pinnigorgiol A

The retrosynthetic pathway of aplysiasecosterol A (**1**) is shown in Scheme 1. We planned synthesis of **1** by coupling reaction of tricyclic ketone **4** and halide **3** with the side chain. The tricyclic ketone **4** could be constructed by intramolecular radical cyclization of aldehyde **5**. The aldehyde **5**, a cyclization precursor, was prepared from cyclic acetal **6** by oxidation of the cyclopentanol moiety and homologation. The cyclic acetal **6** could be synthesized from Hajos–Parrish ketone (**7**)[4] by oxidative cleavage of the double bond.



Scheme 1. Retrosynthetic Pathway of Aplysiasecosterol A

The starting point for this work was the construction of cyclic acetal **6** (Scheme 2). Stereoselective reduction of Hajos–Parrish

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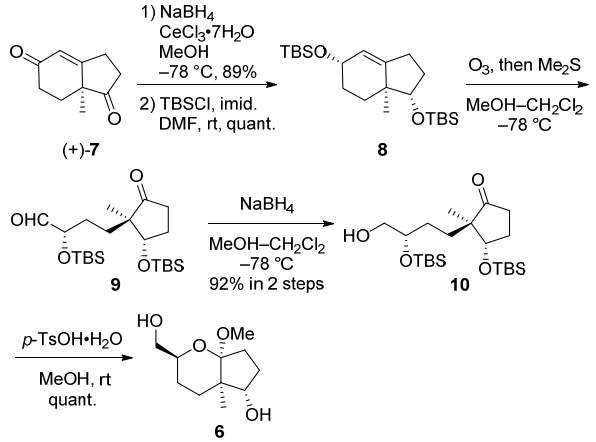
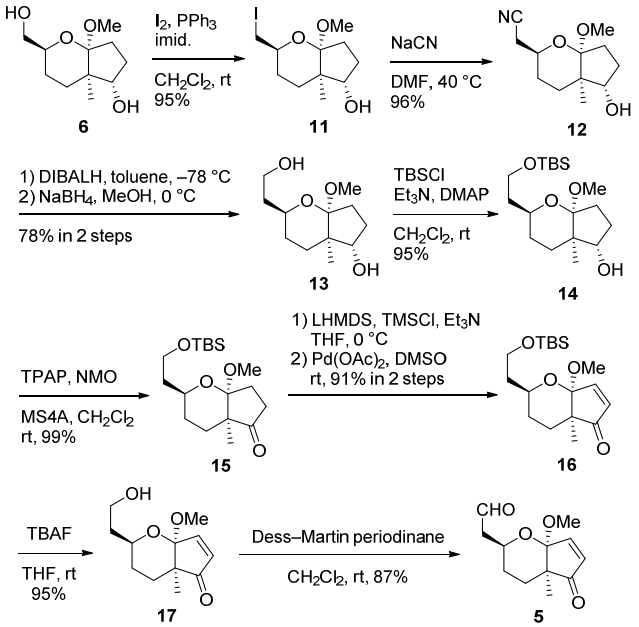
ketone (**7**) gave a diol,[5] and the resulting hydroxy groups were protected by TBS groups to provide di-TBS ether **8**. Ozonolysis of **8** afforded the keto-aldehyde **9**. Selective reduction[6] of the aldehyde group in **9** gave the alcohol **10** by $NaBH_4$ in CH_2Cl_2–MeOH. Under an acidic condition, removal of both TBS groups and methyl acetal formation were carried out to afford the cyclic acetal **6**. The stereochemistry of **6** was determined by NOE correlations (see SI).



Scheme 2. Synthesis of Cyclic Acetal **6**

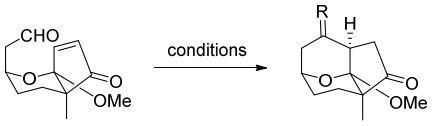
With the cyclic acetal **6** in hand, we next synthesized aldehyde **5**, a precursor of intramolecular radical cyclization (Scheme 3). Iodination of the hydroxy group of **6** under Appel conditions afforded iodide **11**, and the introduction of a cyano group for homologation gave cyanide **12**. Two-step reduction of the cyano group by DIBALH and $NaBH_4$ afforded diol **13**, the primary hydroxy group of which was protected as a TBS ether.[7] Next, we attempted transformation of the 5-membered ring in **14**. Oxidation of the hydroxy group in **14** under Ley–Griffith conditions[8] gave ketone **15**. Ketone **15** was oxidized to enone **16** by using Ito–Saegusa oxidation.[9] Finally, removal of the TBS group gave alcohol **17**, which was transformed by Dess–Martin oxidation into aldehyde **5**, a precursor of cyclization.



Scheme 3. Synthesis of Aldehyde **5**, a Precursor of Intramolecular Radical Cyclization

We next examined the crucial construction of the tricyclic core of aplysiasecosterol A (**1**) by intramolecular radical cyclization (Table 1). The radical cyclization of **5** with samarium diiodide did not give the tricyclic alcohol **18**. In this reaction, a dimer of **5** was obtained. We considered that this intramolecular cyclization may require high temperature in order to bring the two reaction sites close enough to contact each other. Therefore, we tried radical cyclization at high temperature. In entry 2, the treatment of **5** with tributyltin hydride and AIBN as a radical initiator gave the tricyclic ketone **18**, but the yield was low (ca. 10%). This reaction was accompanied with a complex mixture containing byproducts, including prodcuts from the reduction of the enone double-bond. We exchanged tributyltin hydride for tris(trimethylsilyl)silane[10] because this sterically bulky silane was not expected to affect the double bond. However, this condition did not give the target material (entry 3). In 2005, Tomioka *et al*. reported the thiol-catalyzed acyl radical cyclization of alkenals.[11] We next attempted to use their conditions. The reaction of **5** with *t*-dodecanthiol and V-40 in boiling toluene afforded the desired tricyclic ketone **4** in 74% yield (entry 4). The stereochemistry of tricyclic ketone **4** was determined by comparison of the spectral data with those of natural product (see SI) and X-ray crystallographic analysis (Figure 2).

Table 1. Study of Intramolecular Radical Cyclization



Entry	Conditions	Result
1	SmI_2, THF, 0 °C	dimer of **5**
2	Bu_3SnH, AIBN benzene, reflux	**18** : ca. 10%
3	TTMSS, AIBN toluene, reflux	complex mixture
4	*t*-dodecanthiol, V-40 toluene, reflux	**4** : 74%

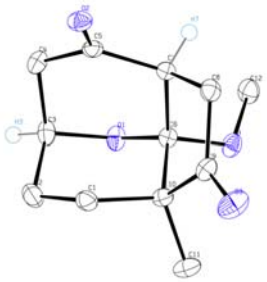


Figure. 2 X-ray Crystallographic Structure of **4** (CCDC 1552880)

In conclusion, we have achieved construction of the novel tricyclic skeleton of aplysiasecosterol A by using intramolecular

radical cyclization as a key step. Development of an approach toward the synthesis of aplysiasecosterol A itself is currently underway in our group.

Acknowledgments

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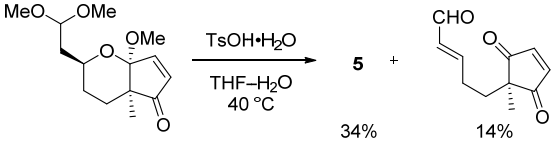
7. In the case that aldehyde was protected as a dimethyl acetal, the conversion of the dimethyl acetal to aldehyde **5** was a low-yield one.



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Supplementary Material

Supplementary data (^{1}H and ^{13}C spectra) associated with this article can be found, in the online version, at doi:XXX.