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Total synthesis of 14,21-diepi-squamocin-*K*

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ABSTRACT

A new method to prepare annonaceous acetogenins is described in the synthesis of the 14,21-diepimer (**14**) of *squamocin-K*. The synthesis utilized the controlled sequence of ring-closing metathesis (RCM) and cross metathesis (CM) reactions to incorporate the stereocenters and skeleton from (3*R*,4*R*)-1,5-hexadiene-3,4-diol and 10-chloro-1-decene. The lactone moiety was attached through nucleophilic substitution and achieved the desymmetrization. Inhibitory activities of **14** against human hormone-refractory prostate cancer cell line (PC-3) were also evaluated.

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1. Introduction

Annonaceous acetogenins are a large family of natural products, widely found in the tropical plant family of Annonaceae.[1] These compounds are potent inhibitors of mitochondrial complex I and have profound biological effects, such as cytotoxic, antitumor, antiparasitic, pesticidal, antimicrobial, and immunosuppressive activities.[2] Recent research also showed that they are toxic to cortical neurons and linked to some neurodegenerative disorders.[3]

The structure of annonaceous acetogenins is characterized by the long-chain (C32 or C34) fatty acids ending with an unsaturated γ-lactone and a hydrophilic central core constituted of cyclic ethers and hydroxyl groups. Based on the structure of their central core, these acetogenins are classified as mono-tetrahydrofuran (THF), adjacent bis-THF, and others.[2b] Most of the known annonaceous acetogenins belong to the subgroup of the adjacent bis-tetrahydrofurans, which in general, are also more potent in biological studies than the other two types.[4] The stereochemistry of the bis-THF core was reported to affect the anticancer activity of these compounds.[4h] Thus, many synthetic efforts for preparing or mimicking such acetogenins have been developed.[5–7]

Recently, we reported that the C_2 symmetrical (3*R*,4*R*)-1,5-hexadiene-3,4-diol (**1**)[8] could be the sole source for the key skeleton and stereocenters of the adjacent bis-THF core of annonaceous acetogenins, and the formal synthesis of asimicin.[9] Here, we report our progress in applying this strategy, which is exemplified in the total synthesis of 14,21-diepi-squamocin-*K* (Fig. 1).

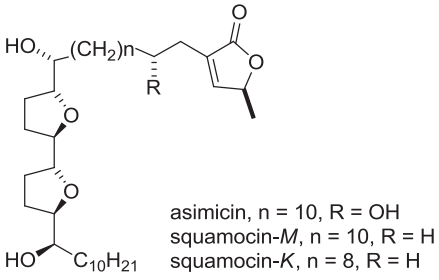

Fig. 1. Representative annonaceous acetogenins.

2. Results and discussion

The retrosynthetic analysis is shown in Scheme 1. We planned to assemble the molecular skeleton by controlled ring-closing metathesis (RCM) and cross metathesis (CM),[10] which extended the C_2 symmetry of diene-diol **1**. Desymmetrization and the incorporation of the lactone moiety were to be achieved by an S_N2 reaction.

Diene-diol **1** was converted to bis-methoxymethyl ether **2**, which was treated with boron trichloride followed by diisopropylethylamine (DIPEA) and two additional units of **1** to give diol **3** (Scheme 2). The remaining hydroxyl groups of **3** were protected by benzyl (Bn) or

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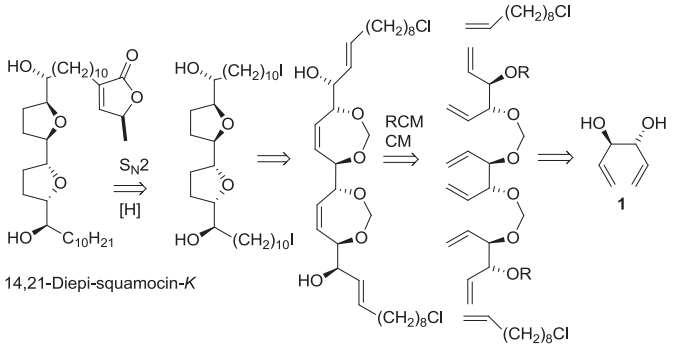
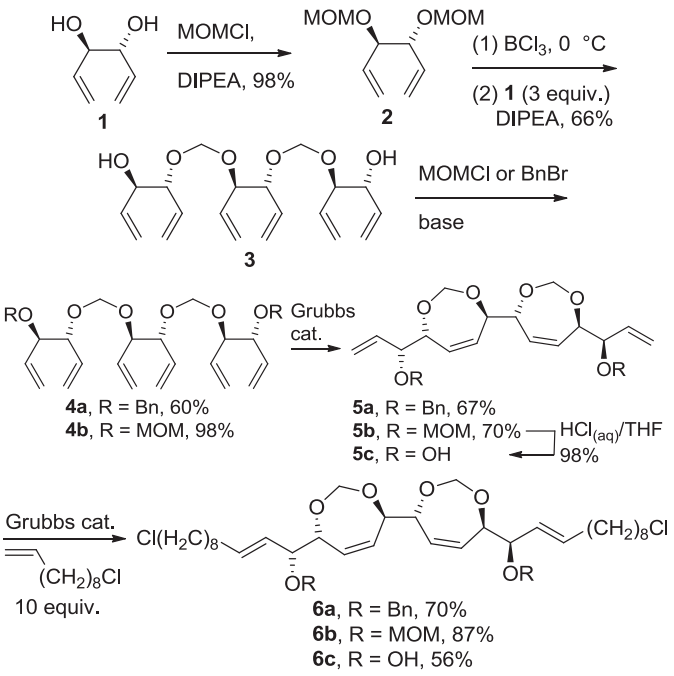


Scheme 1. Retrosynthetic analysis of 14,21-diepi-squamocin-*K*.



Scheme 2. Synthesis of 14,21-diepi-squamocin-*K*.

methoxymethyl (MOM) groups (**4a** and **4b**, respectively). Although the attempted RCM reaction of **3** with the second generation Grubbs catalyst gave the complicated mixture due to the competitive pathways between RCM and CM (Table 1, entry 1),[11] the RCM reactions of the protected **4a** and **4b** were successful to provide bis-4,7-dihydro-1,3-dioxepines **5a** and **5b** (Table 1, entries 2 and 3). Hydrolysis of **5b** afforded **5c**. Both MOM-protected **5b** and diol **5c** smoothly underwent intermolecular CM reactions with excess 10-chloro-1-decene to give **6b** and **6c**, respectively (entries 4, 5). In contrast, the CM reaction of Bn-protected **5a** was sluggish (entries 6 and 7). Fortunately, a satisfactory yield (70%) for the CM process of **5a** to **6a** was obtained in refluxing 1,2-dichloroethane (entry 8). The observed reactivity differences between **5a**–**c** in CM are explained by the differing affinities of the allylic substituents for the ruthenium catalyst (OH≈OMOM>OBn).[12] The development of practical RCM and CM conditions for the benzyl-protected substrates **4a** and **5a** was useful because the OBn group was stable to the strongly acidic conditions needed for the later hydrolysis of the methylene acetals (vide infra).[13] Consequently, compound **6a** was adopted for the synthesis of **14**.

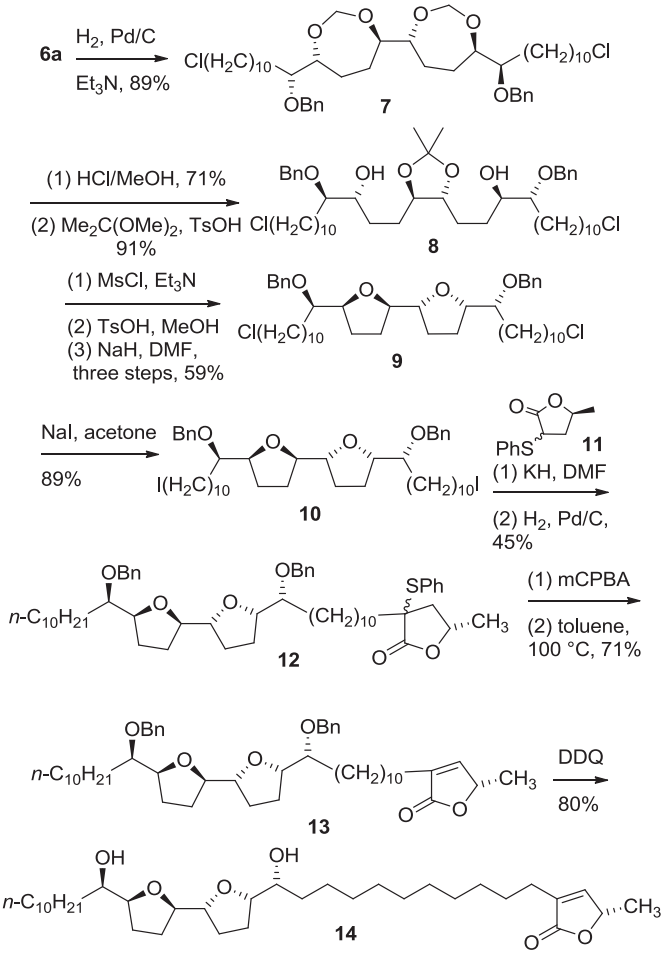
Tetraene **6a** was hydrogenated to **7**[14] and subsequent removal of the methylene acetal and formation of the acetonide gave diol **8**, in which the hydroxyl groups along the C_2 symmetrical axis are differentiated (Scheme 3). Mesylation, deprotection, and cyclization of

Table 1
Reaction conditions for the metathesis reactions of **3**–**5**

Entry	Reactant	Product	Solvent	Temp (°C)	Time (h)	Yield (%)
1[a]	**3**	**5c**	Toluene	70	3	0
2[a]	**4a**	**5a**	Toluene	75	3	67
3[a]	**4b**	**5b**	Toluene	70	3	70
4[b]	**5b**	**6b**	CH_2Cl_2	40	16	87
5[b]	**5c**	**6c**	CH_2Cl_2	40	16	56
6[b]	**5a**	**6a**	CH_2Cl_2	40	16	0
7[b]	**5a**	**6a**	Toluene	70	16	43
8[b]	**5a**	**6a**	$(CH_2Cl)_2$	84	16	70

[a] Ring-closing metathesis.
[b] Cross metathesis with 10-chloro-1-decene (10 equiv).

8 generated bis-THF derivative **9** with the stereochemistry *erythro*/*cis*/*threo*/*cis*/*erythro*. This was converted to the more reactive diiodide **10** for the subsequent nucleophilic substitution reaction. Although the reaction using lactone **11** as the nucleophile has been widely applied in related syntheses,[6] we found that nucleophilic substitution involving **10** and **11** was challenging as previously reported by Brown's and Tanaka's groups.[6j,15] After screening many reaction conditions, we found that the use of *N*,*N*-dimethylformamide (DMF) as the solvent and potassium hydride as the base yielded the mono-alkylation product **12** in a satisfactory yield (51%).[16] The remaining iodo group in **12** was reduced to give **13**, and the unsaturated lactone **14** was produced after the oxidation of phenyl sulfide and elimination of the corresponding sulfoxide. The 14,21-diepi-squamocin-*K* (**14**) was produced after removal of the benzyl groups by reaction with 2,3-dichloro-5,6-dicyano-*p*-



Scheme 3. Synthesis of 14,21-diepi-squamocin-*K* (continued).

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