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Formal synthesis of semiaquilegin A

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ABSTRACT

A formal synthesis of semiaquilegin A is achieved starting from readily available oridonin in 19 linear steps. The absolute configuration of the natural product has been established. A variety of useful analogues were prepared through this synthetic route.

Semiaquilegin A (**1**) (Fig. 1) was isolated by Tu and co-workers from the roots of *Semiaquilegia adoxoides* (*DC.*) *Makino*., which has been used for treating inflammation, snakebite, bruises, and so on in Traditional Chinese Medicines (TCM).[1] The structure of semiaquilegin A is 16α-hydroxy-ent-kaurane-17,20-di-(3,4-dihydroxy-*E*-cinnamoyl) ester. It exhibits potent cytotoxic activity against many cancer cell lines, such as Bel-7402 (IC_{50} = 5.61 μM), BGC-803 (IC_{50} = 10.88 μM), Hela (IC_{50} = 4.36 μM), HL-60 (IC_{50} = 4.65 μM), and MCF-7 (IC_{50} = 6.38 μM).[2] The lack of availability from natural sources has severely hampered its further development. The complexity of its structure makes it difficult to provide a solution to this supply problem by total synthesis of this formidable target.[3] A semisynthesis of **1** from the readily available natural products is possibly the simplest approach since it can provide rapid access not only to **1** but also to other natural members of the ent-kaurane diterpenoids and a variety of natural product analogues.[4] In fact, there are numerous successful examples of this semisynthetic approach including taxanes,[5] camptothecins,[6] and ecteinascidins.[7]

Oridonin (**2**),[8] an ent-kaurane diterpenoid, would be an appropriate candidate, which has various pharmacological and physiological effects and has been used for the treatment of human cancers, especially for esophageal carcinoma.[9] The most relevant structural difference of the core of **1** with **2** is the presence of many hydroxy and ketone groups in **2** (Fig. 1). Thus, the conversion of **2** to **1** must involve appropriate deoxygenations at C-1, C-6, C-7, C-14, and C-15 of the ent-kaurane diterpenoid skeleton. Herein, we wish to report the formal synthesis of semiaquilegin A from oridonin.

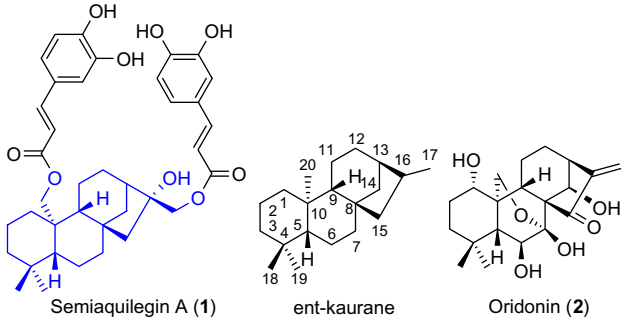

Figure 1. Structures of semiaquilegin A and oridonin.

The successful conversion of oridonin (**2**) to the semiaquilegin A (**1**) is outlined in Scheme 1. Protection of 7,14-dihydroxy in **2** with 2,2-dimethoxypropane in the presence of a catalytic amount of PTSA provided **3** in 91% yield.[10] The olefin of α,β-unsaturated ketone was first masked due to unsaturated ketone which resulted in a side reaction during Barton deoxygenation. Thus, epoxidation of **3** with 30% H_2O_2 and 6 N NaOH gave **4** in 88% yield (2:1 dr), which could be separated by careful flash column chromatography. However, the two diastereoisomers were not separated at this stage because there was no selectivity in the following radical epoxide-opening step. Reaction of **4** with NaH, CS_2, MeI, and imidazole in THF gave the thiocarbamate **5** in 88% yield.[11] Treatment of **5** with nBu$_3$SnH in the presence of AIBN under refluxing in toluene for 1 h gave **6a** and **6b** in 85% overall yield in a ratio of 2:1 with simultaneous deoxygenation and epoxide-opening.[12] The diastereomeric products could be separated and their relative

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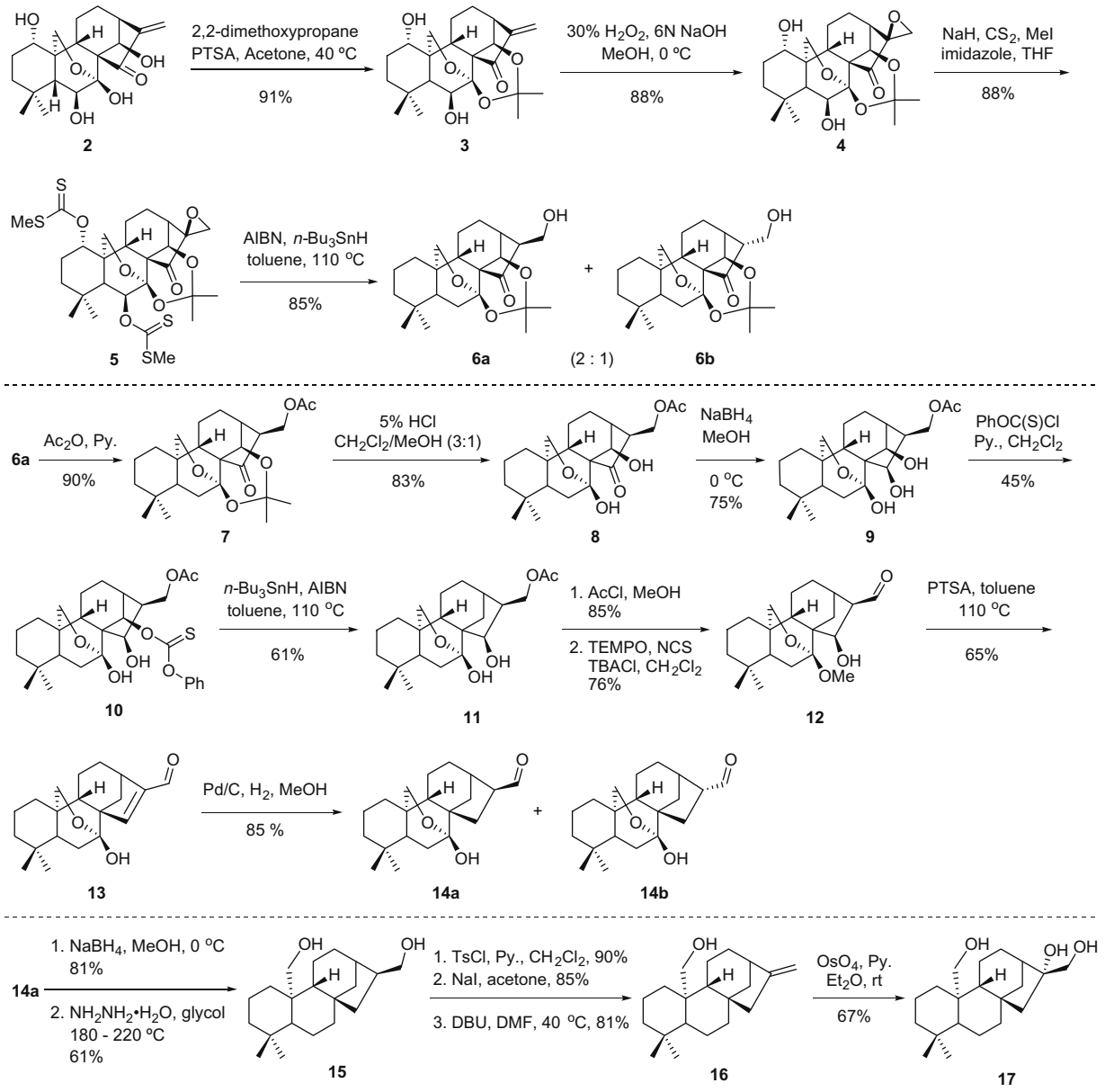


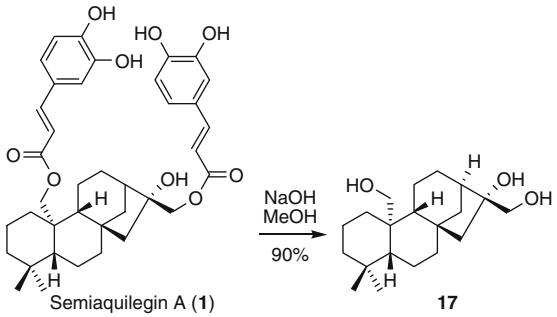
Scheme 1. Synthesis of the core moiety of semiaquilegin A.

configurations were deduced by the NOESY spectrum. It is noteworthy that the epoxide was opened without stereoselectivity in this case, and both diastereoisomers of **5** gave the same result.

Protection of 17-hydroxy in **6a** with Ac_2O in pyridine provided **7** in 90% yield. At this stage, initial attempt for reduction of the 15-carbonyl group in **7** with $NaBH_4$ failed possibly due to the steric hindrance of acetonide protecting group. Removal of acetonide group with 5% HCl gave **8** in 83% yield. An attempt to remove the 14-hydroxy of **8** was unsuccessful due to the competitive retro-aldol reaction under basic conditions. Thus, reduction of 15-carbonyl group of **8** with $NaBH_4$ gave **9** smoothly in 75% yield. Reaction of **9** with CS_2 and MeI in the presence of a strong base such as NaH in THF did not give the corresponding thiocarbamate, instead, it resulted in a complicated product. To our delight, treatment of **9** with PhOC(S)Cl and pyridine resulted in selective reaction of 14-hydroxy to give phenylthionocarbonate **10**, which was reacted with AIBN and nBu$_3$SnH to provide the desired product **11**.[13]

The removal of 15-hydroxy was the most difficult. After the failure of various direct strategies, we took another indirect tactic. Thus, treatment of **11** with acetyl chloride in MeOH followed by selective oxidation of the primary 17-hydroxy with TEMPO and NCS provided aldehyde **12**.[14] Elimination of 15-hydroxy with PTSA gave the α,β-unsaturated aldehyde **13** in 65% yield. Reduction of unsaturated aldehyde **13** (Pd/C, 1 atm H_2 balloon) gave **14a** and **14b** in a ratio of 2:1, which could be separated by flash column chromatography. Reduction of **14a** with $NaBH_4$ followed by Wolff–Kishner–Huang reaction with $NH_2NH_2{\cdot}H_2O$ gave **15** successfully in a one-pot manner. Selective protection of primary 17-hydroxy with TsCl, followed by a treatment with NaI, then elimination of 17-iodine with DBU in DMF smoothly afforded the exocyclic double bond product **16**. Finally, treatment of **16** with OsO_4/Py directly gave the desired product **17** in a single diastereoisomer through substrate control.[15,3]

Hydrolysis of natural semiaquilegin A with NaOH in MeOH provided **17** in 90% yield (Scheme 2). Spectroscopic data for the synthetic **17** matched that of degradation from natural product. Its optical rotation $\{[\alpha]_D^{25}$ −102 (c 0.98, $CHCl_3$)} was essentially identical to that of the degradative product $\{[\alpha]_D^{25}$ −105 (c 0.38, $CHCl_3$)}.



Scheme 2. Hydrolysis of semiaquilegin A.

In summary, we have achieved the formal synthesis of semiaquilegin A from a readily available oridonin. The present approach demonstrates that the feasibility of the synthesis was not only proved to rigorously define the full structures of a natural product but also to provide a variety of useful analogues. Preparations of analogues of **1** for detailed structure–activity relationship studies are currently in progress in our laboratory and will be reported in due course.

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Supplementary data

Supplementary data (detailed experimental procedures, compound characterization, and copies of spectral data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.118.

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