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Total synthesis of (±)-lysidicin A

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ABSTRACT

Lysidicin A, which has been isolated from *Lisidicie rhodostegia* possesses complicated structure. A total synthesis of lysidicin A has been achieved and is described herein. The key reaction is single and cascade Claisen rearrangements.

1. Introduction

Lisidicie rhodostegia Hance (Fabaceae) is a Chinese medicinal shrubbery plant, which has been used for the treatment of ache, fractures, and hemorrhage for a long time by local folks in China. Lysidicins A–C (**1**–**3**) have been isolated from the plant by Yu and co-workers in 2006[1] and the isolation of other lysidicins D–H have also been reported by the same group in 2007[2] and 2010.[3] Although lysidicin D–H showed stronger anti-oxidant activity than vitamin E,[2,3] the full details of biological activities of the other lysidicins have not been clarified yet. Meanwhile, among the lysidicin family, lysidicin A (**1**) has the most unique and complicated structure in which two acetals form spiro[furan-furofuran] ring system. Moreover, any other compounds possessing this unique structure have not been isolated. Interest in the construction of this novel structure and the additional contribution to bioassay prompted us to embark on the synthetic study of lysidicin A (**1**). Herein, we report a full detail of the efficient total synthesis of (±)-lysidicin A (**1**) (Fig. 1).

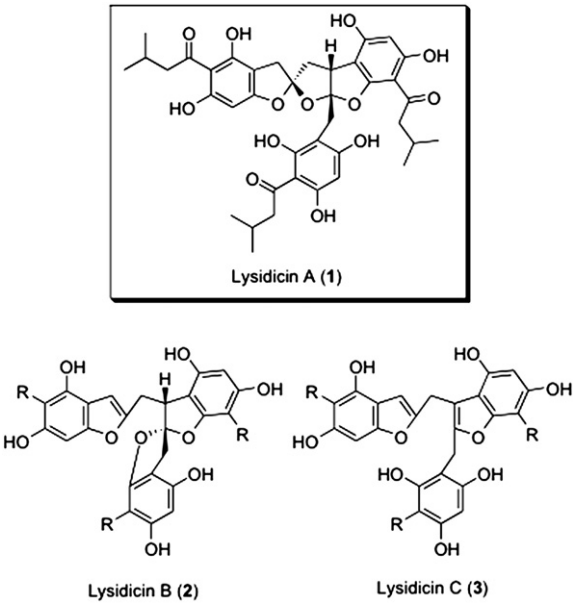

Fig. 1. Structures of lysidicin family: R=isovaleryl.

2. Results and discussion

Our synthetic strategy is shown in Scheme 1. Lysidicin A (**1**) would be synthesized from spiro[furan-furofuran] **4** by three Friedel–Crafts acylations. Spiro[furan-furofuran] **4** would be obtained from diene **5** by oxidative cleavage of two *exo*-olefins and subsequent intramolecular acetalization. The key step is the single and cascade Claisen rearrangements (**6**→**5**), which deliver the three aromatic rings to the correct positions, at the same time installing the two *exo*-methylenes as we have already reported the preliminary results recently.[4] Triether **6** would be readily obtained from phloroglucinol derivative **7** and triol **8**.

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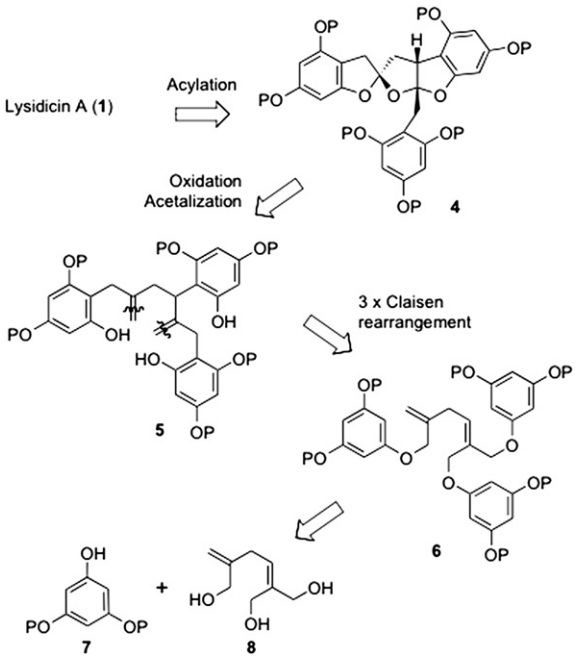
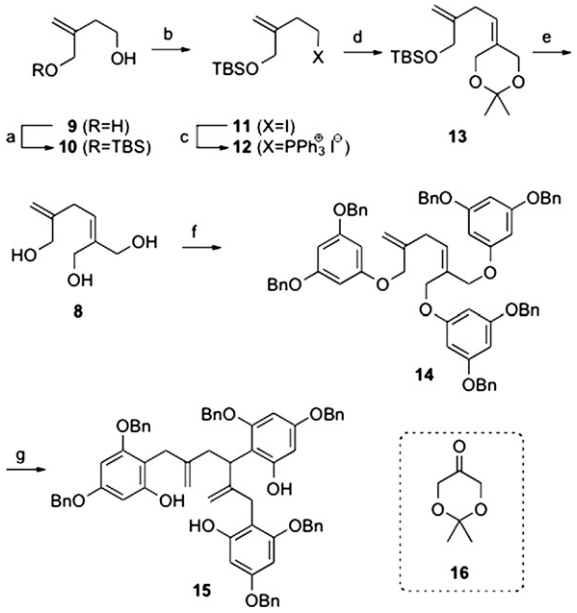


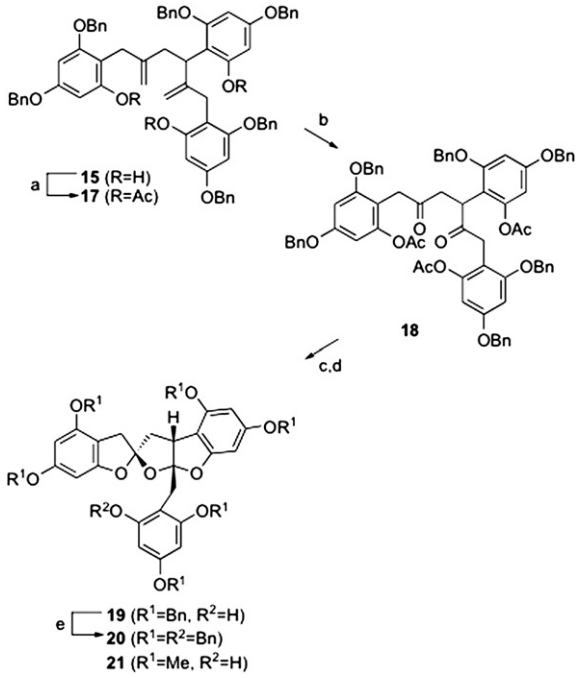
Scheme 1. Retrosynthetic analysis: P=protecting group.

The precursor **6** for the Claisen rearrangement was prepared from known **9**,[5] **16**[6,7] and phlorogulcinol dibenzyl ether [**7** (P=Bn)][8] in six steps almost in the same manner described previously by us except for the protecting groups in **7** (benzyl ethers instead of methyl ethers) as shown in Scheme 2.[4] In the Mitsunobu reaction (**8**–**14**), intramoleculary alkylated by-product, which was similar to the methyl protected compound described in our previous paper,[4] was also obtained (23%). The key step, single and cascade Claisen rearrangements, was then examined. As reported previously,[4] when the phenolic hydroxy groups of the substrate were protected as methyl ethers, the rearrangements were accelerated successfully only by aqueous Me_3Al[9] in refluxing CH_2Cl_2 and other thermal or Lewis acidic conditions resulted in failure. However, the same successful conditions were not fully applicable to benzylated precursor **14** due to the decomposition of the rearranged product, which decreased the yield to 35%. After several investigations, it was found that Me_3Al in the absence of water catalyzed the reaction more effectively even at room temperature and the product **15** was obtained in excellent yield (84%).

After the successful key step, the core framework of lysidicin A (**1**), spiro[furan-furofuran] ring system, was constructed (Scheme 3). Three phenolic hydroxy groups of **7** were temporarily acetylated, and the product **17** was submitted to ozonolysis to give desired diketone **18** in good yield. Removal of acetyl groups of **18** and subsequent acid treatment afforded the spiro[furan-furofuran] **19** successfully. ^{1}H NMR spectral data of the product **19** showed good accordance with those of our previously synthesized compound **21** whose stereostructure has been clarified unambiguously by X-ray crystallographic analysis.[4] The remaining phenolic hydroxy group of **19** was then protected to afford benzyl ether **20**.



Scheme 2. Preparation of **15**: reagents and conditions; (a) TBSCl, NaH, THF, −10 °C, 43%. (b) I_2, Imid., PPh_3, THF, rt. (c) PPh_3, CH_3CN, reflux. (d) *n*-BuLi, DME, then **16**, −78 to 0 °C, 83% in three steps. (e) AcOH/H_2O/THF=1:1:1, rt, 84%. (f) **7** (P=Bn), DEAD, PPh_3, THF, 0 °C to rt, 50%. (g) Me_3Al, CH_2Cl_2, 0 °C to rt, 84%.



Scheme 3. Preparation of spiro[furan-furofuran] **20**: reagents and conditions; (a) Ac_2O, NaH, THF, 0 °C, 92%. (b) O_3, CH_2Cl_2, −78 °C, then PPh_3, 83%. (c) K_2CO_3, MeOH, 0 °C. (d) TsOH, CH_2Cl_2, 0 °C to rt, 81% in two steps. (e) BnBr, NaH, DMF, 0 °C, 97%.

As described in the retrosynthetic analysis part, we planned to introduce the isovaleryl groups at the final stage of the synthesis. It should be noted that the acylation at the earlier stage gave the unsuccessful results as summarized in Scheme 4. When the model compound **22** with the isovaleryl group was subjected to Claisen rearrangement, the ketone reacted with Me_3Al and dehydrated products **23** and **24** were obtained. Friedel–Crafts acylation of **25** also caused an undesired benzofuran formation as well as the acylation to give **26** or **27** (regiochemistry was not determined). On the other hand, **28** with a partial substructure of **30** afforded the acylated product in good yield. However, **30** itself could not be triacylated probably due to the structural complexity.