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The first total synthesis of glycyrol

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ABSTRACT

We report the first total synthesis of glycyrol. Glycyrol, isolated from Glycyrrhizae Radix, has a unique skeleton of a benzofuran coumarin. The key steps are Smiles rearrangement and selective introduction of prenyl and *O*-methyl groups. The first application of a novel precursor for Smiles rearrangement, 3-benzyloxy-substituted (diacetoxyiodo)benzene, showed the synthetic possibility for diverse precursors. The introduction of a benzyl protecting group was important because selective deprotection was hard due to the low solubility of intermediates.

Glycyrrhizae Radix is a traditional medicine in East Asia, and contains biologically active natural products such as glycyrrhizin, glycyrol, glycycoumarin, and liquoric acid.[1] Glycyrol has antibacterial activity against upper airway respiratory tract pathogens,[2] and down-regulates NF-κB and NF-κB dependent gene transcription.[3] Glycycoumarin has a similar structure to glycyrol and is a potent antispasmodic through inhibition of phosphodiesterase III[4] (Fig. 1). Glycycoumarin also relaxes abdominal convulsions induced by carbamylcholine (carbachol) in mice jejunum[5] and has more potent antimicrobial activity against MRSA than glycyrol.[6] Further in vivo testing of these compounds is difficult because of their limit quantities.[7] Therefore, we sought to develop a synthetic route for obtaining gram amounts of glycyrol and similar derivatives.

Glycyrol **1** was chemically studied in 1969 by Shibata and Saitoh,[8] and the revised structure of glycyrol was established in 1989 by Saitoh and co-workers.[9] The characteristic structural feature of glycyrol is a fusion of benzofuran and coumarin. Selective introduction of one methoxy group with two naked phenol groups and one prenyl group is a major challenge.

As shown in retrosynthetic analysis (Fig. 2), the key step is a Smiles-type rearrangement[10] followed by palladium-assisted ring closure[11] for construction of the benzofuran coumarin.

Synthesis of the (diacetoxyiodo)arene **5** containing the *O*-benzyl protecting group could allow for extensive application of the Smiles rearrangement. Normal (diacetoxyiodo)arenes usually contain methoxy, normal alkyl, or chloro groups that might be generally stable. However, selective deprotection of an *O*-methyl group is difficult when many are present, prompting us to look for alternative protecting groups. Furthermore, (diacetoxyiodo)arene

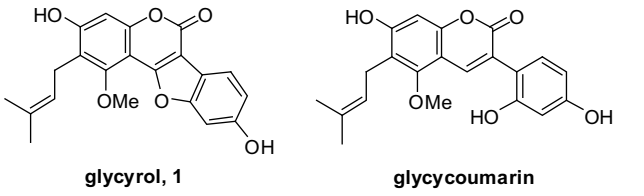

Figure 1. Structure of glycyrol **1** and glycycoumarin.

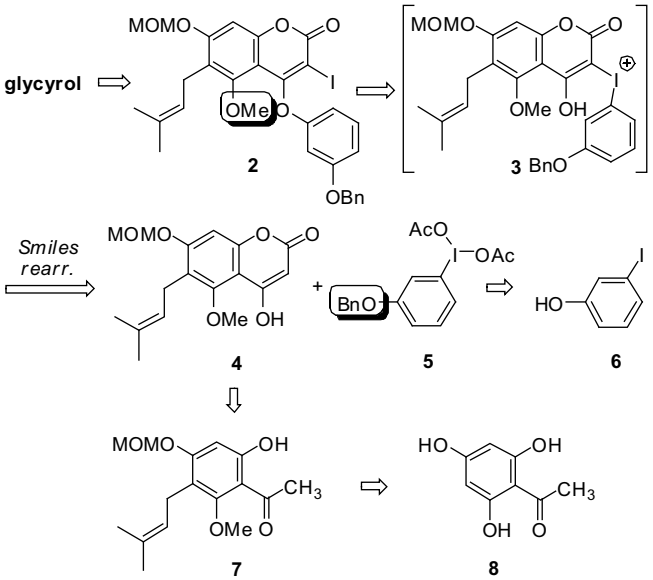

Figure 2. Retrosynthetic analysis of glycyrol **1**.

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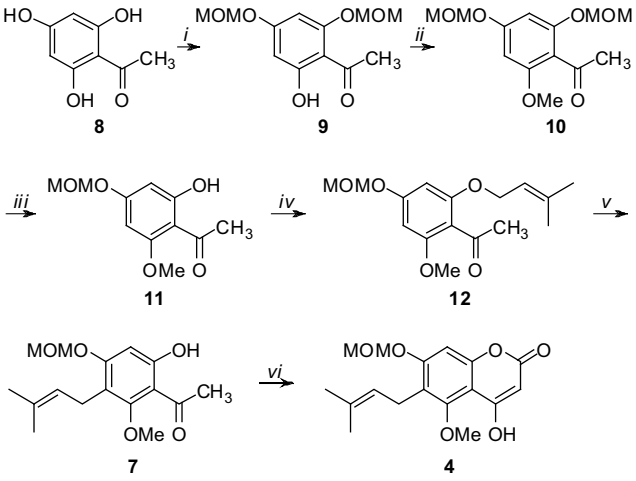
derivatives may have instability with substituents such as *O*-benzyl, a common protecting group of choice. Herein, we examined the stability of the 3-benzyloxy-(diacetoxyiodo)arene **5**. The substrate **4** for Smiles rearrangement might be synthesized from a simple, commercially available 2′,4′,6′-trihydroxyacetophenone **8** through four steps: (1) a selective MOM protection of ortho and para phenol groups,[12] (2) O-methylation of ortho phenol, (3) deprotection of one of two MOM groups followed by (4) tandem Claisen and Cope rearrangement of a prenyl group.

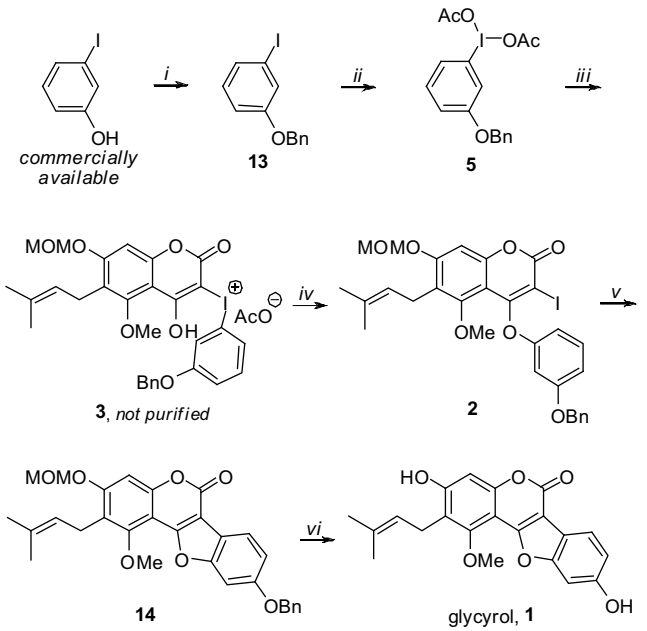
Our main innovation is the use of a new precursor of Smiles rearrangement, benzyloxy-substituted (diacetoxyiodo)arene. Modification and manipulation of the intermediates of benzofuran coumarin are generally difficult due to the very low solubility of the intermediates in organic solvents. Therefore, modifications and introduction of the necessary functional and protecting groups should be done before constructing the benzopyran coumarin.

The synthetic route for the formation of 4-hydroxycoumarin is shown in Scheme 1. The previous reported method initially indicated the direct introduction of the *meta*-prenyl group on 2′,4′,6′-trihydroxyacetophenone **8** at the start,[13] but this approach was not reproducible. In Scheme 1, the *ortho* and *para* phenol groups of 2′,4′,6′-trihydroxyacetophenone **8** were selectively protected to give **9** by treatment with 2 equiv of MOMCl in the presence of diisopropylethylamine. Since we predicted that selective O-methylation after benzofuran formation would be difficult due to low solubility, the *O*-methyl group in glycyrol **1** was introduced early. The ortho phenol group in **9** was methylated to afford *O*-methyl acetophenone **10** in two steps from **8**, with a 90% yield. The MOM group at *ortho*-position of *O*-methyl acetophenone **10** was deprotected with a catalytic amount of iodine in methanol,[12] which afforded **11** in 66% yield. The next steps were O-prenylation and tandem Claisen and Cope rearrangement. Although this synthetic procedure contained repeated protection and deprotection steps, it readily provided selective introduction of prenyl group and *O*-methyl group. The 2′-hydroxy group of **11** was treated with prenyl bromide and potassium carbonate in acetone at refluxing temperature to provide *O*-prenyl acetophenone **12**. *O*-Prenyl acetophenone **12** was converted to *meta*-prenyl acetophenone **7** in 68% yield through a tandem Claisen and Cope rearrangement by refluxing in *N*,*N*-diethylaniline. Using *N*,*N*-dimethylaniline instead of *N*,*N*-diethylaniline caused decomposition. Condensation of prenylated acetophenone **7** with diethyl carbonate in the presence of excess sodium hydride furnished 4-hydroxycoumarin **4**.

Preparation of *O*-benzyl-(diacetoxyiodo)arene **5** as a Smiles rearrangement precursor for the construction of benzofuran coumarin had unexpected difficulties (Scheme 2). Common substituents in commercially available or previously reported (diacetoxyiodo)arene were methoxy, methyl, or halo groups,[11] which are probably stable under harsh reaction conditions. We first coupled a commercially available 3-methoxy-1-(diacetoxyiodo)benzene with 4-hydroxycoumarin **4**. However, we were not able to distinguish the *O*-methyl groups in deprotection step, which was needed for correct synthesis. 1-Benzyloxy-3-iodobenzene could be selectively deprotected in the presence of a methoxy group. Benzylation of commercially available 2-iodophenol gave 1-(benzyloxy)-3-iodobenzene **13**, which was oxidized with sodium perborate tetrahydrate in glacial acetic acid at 40–45 °C to provide a crude 1-benzyloxy-3-(diacetoxyiodo)benzene **5**. However, 1-benzyloxy-3-(diacetoxyiodo)benzene **5** was more unstable than commercially available 3-methoxy-1-(diacetoxyiodo)benzene and decomposed within one day, even with refrigeration. It was guessed that the (diacetoxyiodo)benzene is likely to be an oxidizing agent and the benzylic position could be susceptible to this reagent, although the reactivity of (diacetoxyiodo)benzene is not so powerful as common oxidizing agents. Fortunately, a base-catalyzed condensation[11] of 4-hydroxycoumarin **4** with freshly prepared 1-benzyloxy-3-(diacetoxyiodo)benzene **5** successfully yielded an iodium acetate salt **3**, which was directly converted to 2-iodo-4-phenoxycoumarin **2** in 87% yield by refluxing in DMF. The whole Smiles rearrangement was simple due to a lack of purification steps. The palladium-mediated intramolecular coupling reaction of vinyl iodide with the phenyl group in **2** was readily achieved by using palladium(II) acetate and triethylamine in refluxing toluene to provide the crude benzofuran **14**. Finally, simultaneous deprotection of the MOM and benzyl groups with



Scheme 1. Construction of 4-hydroxycoumarin. Reagents and conditions: (i) MOMCl (2 equiv), DIPEA (3 equiv), DCM, 0 °C, 1 h; (ii) dimethyl sulfate (1 equiv), K_2CO_3 (2 equiv), acetone, 80 °C, 1 h, over two steps 90%; (iii) I_2 (cat.), CH_3OH, rt, 2 h, 66%; (iv) prenyl bromide (1.5 equiv), K_2CO_3 (2 equiv), acetone, 90 °C, 8 h, 66%; (v) *N*,*N*-diethylaniline, reflux, 1 h, 64%; (vi) NaH (6 equiv), diethyl carbonate, 130 °C, 1 h, 68%.



Scheme 2. The synthesis of glycyrol **1** using Smiles rearrangement and Pd-assisted coupling. Reagents and conditions: (i) BnBr (1.01 equiv), K_2CO_3 (2 equiv), acetone, rt, 6 h, 95%; (ii) sodium perborate tetrahydrate (10 equiv), acetic acid, 40–45 °C, 8 h; (iii) **4**, Na_2CO_3 (2 equiv), H_2O, rt, 2 h; (iv) DMF, 150 °C, 1 h, over three steps 87%; (v) $Pd(OAc)_2$ (0.2 equiv), TEA, toluene, reflux, 6 h; (vi) $AlCl_3$ (5 equiv), *N*,*N*-dimethylaniline, DCM, 50 °C, 30 min, over two steps 68%.

N,*N*-dimethylaniline and aluminum chloride in refluxing methylene chloride, followed by careful purification on a silica gel, furnished the desired target material glycyrol **1** in 68% yield in two steps. The structure of the synthetic glycyrol **1** was confirmed by comparing spectral data (proton NMR) to that of an authentic glycyrol sample and literature values.[1b]

In conclusion, glycyrol **1** was successfully synthesized in 10 steps in 10% overall yield from commercially available 2′,4′,6′-trihydroxyacetophenone. This novel synthetic process can be applied to gram-scale synthesis of glycyrol **1** for further biological characterization. We report the first success of applying 3-benzyloxy-(diacetoxyiodo)benzene to a Smiles rearrangement for synthesizing glycyrol derivatives.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.070.

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