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Total synthesis of leontopodioside A

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ABSTRACT

Leontopodioside A, isolated from the whole plants of *Leontopodium leontopodioides*, possesses significant α-glucosidase inhibitory activity. In this work, we studied the total synthesis of leontopodioside A by two strategies for the first time. The optimized strategy involved nine linear steps and has an overall yield of 16.1%. The key feature of the strategy is that glycosylation of chalcone acceptor first followed by the cyclization to construct the flavone scaffold, which has general applicability for the synthesis of flavonoid glycosides.

The exploration of natural products as a source of drug leads and candidates provides an opportunity for modern drug discovery [1]. As important natural polyphenolic compounds, flavonoids are abundant, widely distributed and diverse in structure [2]. It is believed that flavonoids have been implicated in a wide range of biological activities which are beneficial to humans, including antioxidative [3], antitumor [4], antiviral [5], antifungal [6], and anti-inflammatory [7] properties. Recently, with the development of separation-identification technology and the great advances on glycoscience, flavonoid glycosides, as another subgroup of flavonoids, have received increasing attention due to their unique properties as compared with their aglycones in pharmaceutical studies [8]. However, in contrast to an extensive investigation on flavonoids, flavonoid glycosides have not yet been thoroughly explored both on chemistry and biology.

Compositae plants of the genus *Leontopodium leontopodioides* (Willd.) are perennial herbs, mainly distributed in Asia, Europe and South America. There are about 41 species distributed in the northwest and northeast China, especially on the Tibetan plateau. Among them, there are 25 species are reported to be used as Chinese herbal medicine in folk [9]. *L. leontopodiodes* can be used to treat acute or chronic nephritis, urethritis, albuminuria, and hematuria, as well as wind fever cold, trauma bleeding and other diseases [10]. Previous studies revealed that the major active components isolated from *L. leontopodiode* are flavonoids, phenylpropanoids, sesquiterpenes, steroids, and volatile oils [11]. In 2016, a new acyl flavone glucoside, luteolin-4′-*O*-(6-*p*-hydroxybenzoyl)-β-D-glucopyranoside (leontopodioside A) was isolated from the whole plants of *Leontopodium leontopodioides* by Xie and co-workers [12]. It is reported [12] that leontopodioside A acted as an excellent α-glucosidase inhibitor *in vitro* with the IC_{50} values of 55.6 ± 1.9 μM in comparison with the positive reference, acarbose (IC_{50} = 626.3 ± 25.8 μM).

The significant α-glucosidase inhibitory activity of leontopodioside A attracted our attention. Besides, leontopodioside A has a unique structure as compares with those reported flavonoid glycosides, which rarely incorporated monoacyl group in the sugar part. It should be noted that although the natural flavonoid glycosides have been demonstrated to possess various clinically relevant properties, isolating large amounts of these compounds from plant sources needs complicated extraction, purification, and chromatography, which is a disadvantageous factor for the structure–activity relationship (SAR) study and their mechanistic evaluation of the *in vivo* activities. In our continuous interesting on the bioactive natural flavonoid glycosides [13], we decided to synthesize leontopodioside A. Here we would like to describe our synthetic efforts by using 3,4-dihydroxybenzaldehyde as the starting material.

According to the structure of leontopodioside A, the convergent synthetic strategy by connection of the aglycone with the sugar part together would be directly perceived through the senses.

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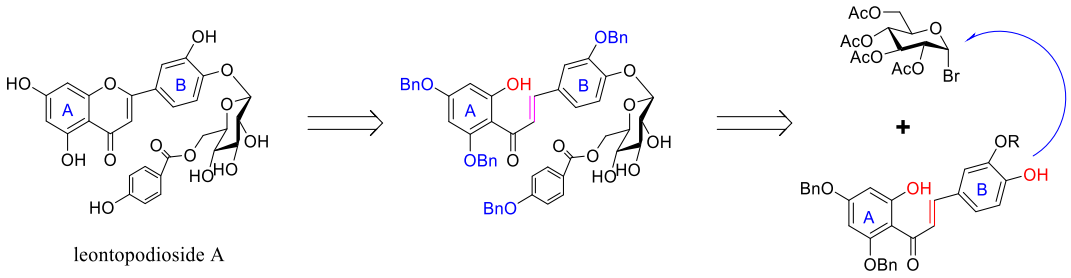


Scheme 1. Retrosynthetic analysis of leontopodioside A.

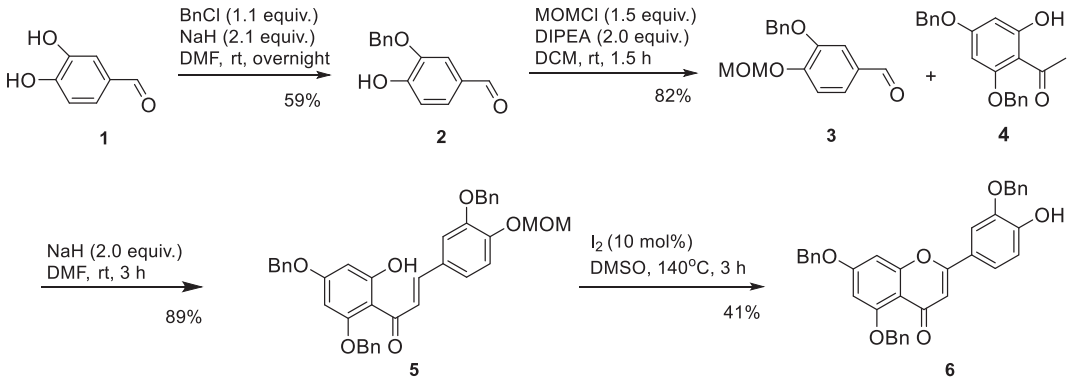
Retrosynthetic analysis of leontopodioside A was showed in Scheme 1.

The synthesis of key intermediate A was described in Scheme 2. As a commercially available starting material, 3,4-dihydroxybenzaldehyde **1** was treated with benzyl chloride and NaH to regioselectively produce the 3-*O*-benzyl product **2** in 59% yield according to literature procedures [14]. Then the left free phenolic OH was protected by a methoxymethyl (MOM) in the presence of the Hünig's base in dichloromethane, which is an indispensable step in the subsequent experiments. With 1-(2-hydroxy-4,6-diphenylmethoxyphenyl)ethanone **4** and compound **3** in hand, the flavone scaffold was constructed in two steps. The first step is the aldol condensation treated by NaH in DMF over 3 h to afford **5** in 89% yield. Compound **5** was easily recrystallized with ethanol. The second step is the ring-closure reaction, which is usually catalyzed by iodine [15] in dimethyl sulfoxide under high temperature. To our delight, treatment of compound **5** with iodine in dimethyl sulfoxide under 140 °C afforded the key intermediate **6** in 41% yield. It should be noted that under such conditions the cyclization take place followed by the removal of MOM group, which could be the reason of low yield of compound **6**.

€For the synthesis of flavonoid glycosides, the glycocidic linkage between the sugar chain and aglycone is often the most critical step. With the key intermediate **6** in hand, we turned our attention to select a suitable sugar donor for glycosylation. To our delight, the desired glycosylation product **8** could be obtained through coupling of the peracetylated glycosyl bromide **7** and flavonoid acceptor **6** by using 0.25 M K_2CO_3 as base [16] and tetrabutylazanium bromide (TBAB) as phase transfer catalyst. By contrast, when 1.0 M KOH was used as base, the phase transfer glycosylation system became complex. The deprotection of the acyl groups on compound **8** unexpectedly failed when the reaction was treated by the commonly used MeONa/MeOH system. Considering the instability of flavonoid ring in strong base [17], $(MeO)_2Mg$ was employed as base in DCM/MeOH (1:1) [18] instead. Whereas, it didn't work either. After carefully screened the consitions, the deprotecting reaction proceeded smoothly when 2.0 equiv. K_2CO_3 served as the base in MeOH/THF/H_2O (5:5:1) [19], which provided compound **9** in 89% yield finally. Then the desired compound **10** was prepared in 67% yield by a directly regioselective *O*-6 acylation of compound **9** in the presence of 1.5 equiv. of 4-(phenylmethoxy) benzoyl chloride **14** as acylating reagent assisted by Me_2SnCl_2. Finally, the target molecule was achieved in 74% yield after global deprotection of the benzyl group using hydrogen and 10% $Pd(OH)_2$/C. The structure of our total-synthesized leontopodioside A was confirmed by ^1H NMR, ^{13}C NMR, ^1H–^1H COSY, HMBC, and HSQC, and the data matched with those reported [12]. To the best of our knowledge, this is the first total synthesis of leontopodioside A so far (Scheme 3).

After the first preliminary total synthesis of leontopodioside A, we envisioned that there are some points need to be improved. For example, (1) the yield of key aglycone **6** was low; (2) intermediate **9** was quite difficult to be isolated from the reaction mixture; (3) the yield of *O*-6 acylated glucoside **10** was low. Therefore, a more efficient strategy was developed and which was depicted in Scheme 4. Based on the preliminary route, we decided to adjust the sequence of several steps in the process. Basically, the glycosylation reaction step was moved ahead of the cyclization step to block the 4-OH on ring B. A free 4-OH on ring B could disturb the cyclization reaction and which was protected by a MOM group previously. However, the MOM group is labile towards the cyclization coditions which although helped the cyclization but resulted in a low yield of **6** (Scheme 2).

The optimized synthetic route of leontopodioside A started from compound **5**. The deprotection of the MOM group on compound **5** with 3 M HCl in mathanol under reflux condition gave chalcone aglycone **11** in 91% yield in about 3 h. It is should be noted that if using THF as the solvent instead of methanol, the reaction can be done in a much shorter time (about 30 min). With the chalcone aglycone **11** in hand, the glycosylation reaction was carried out. Due to the presence of intramolecular hydrogen bond between the phenolic OH on ring A and the carbonyl group, phase-



Scheme 2. Synthesis of key aglycone 6.

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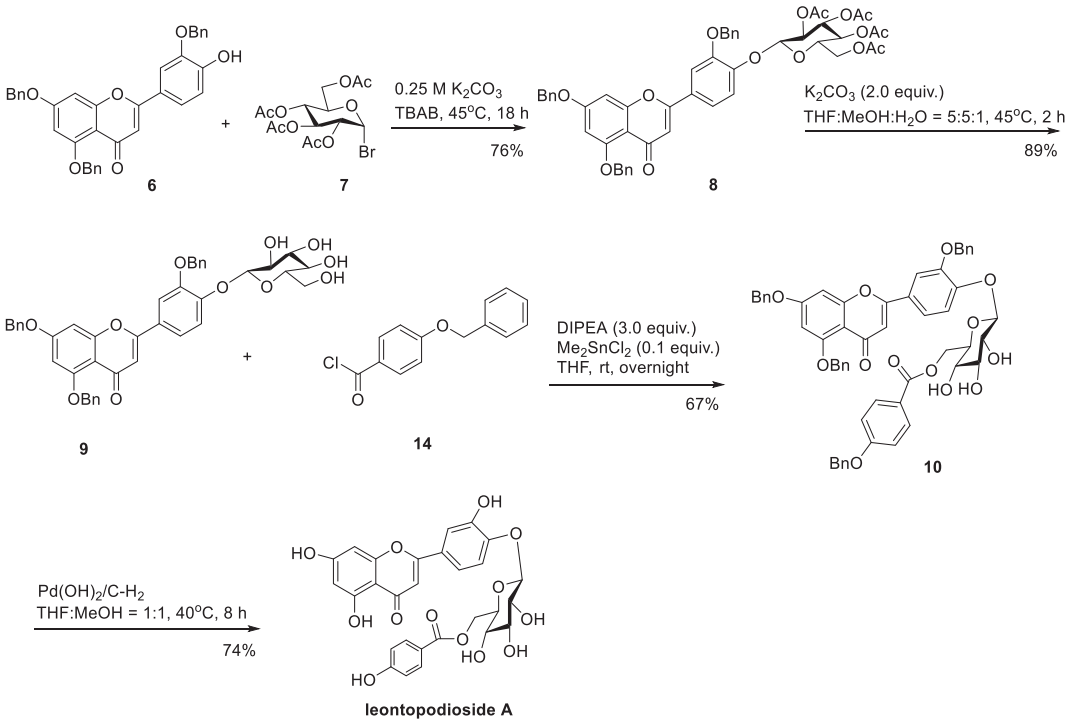
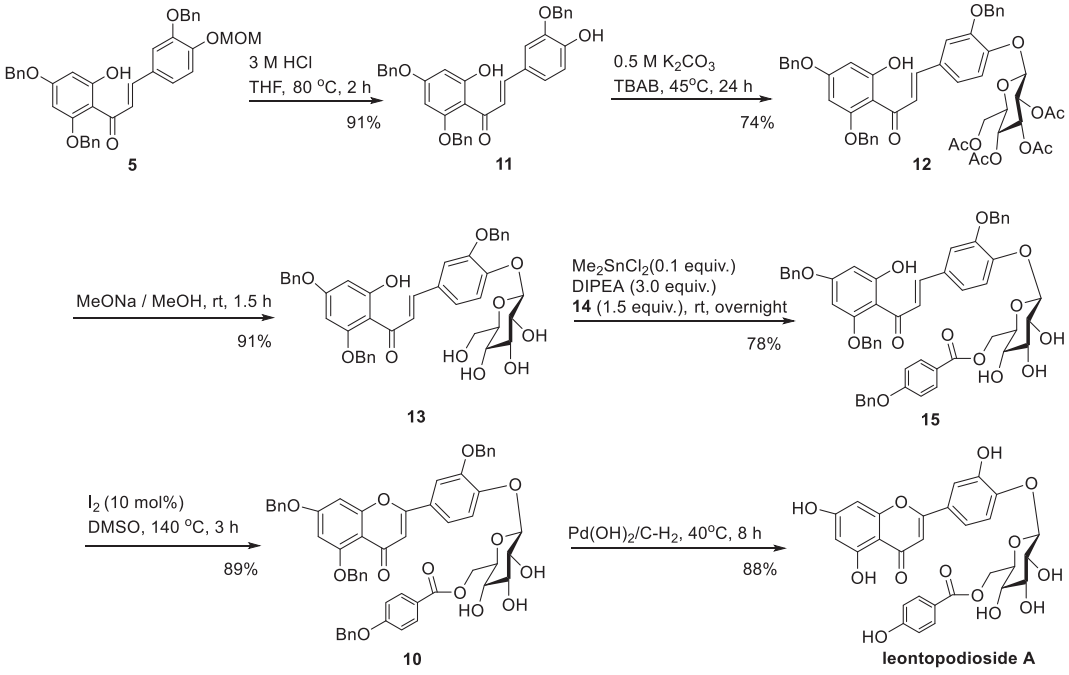


Scheme 3. Synthesis of leontopodioside A.



Scheme 4. Optimized synthesis of leontopodioside A.

transfer glycosylation reaction occurs only on the free 4-OH on ring B to afford the desired glycosylation compound **12**, by using 0.5 M K_2CO_3 as base in 74% yield. At this point, we could achieve the deprotection of the acyl groups easily using MeONa/MeOH system since chalcone aglycone **11** is stable in bases. And it is interesting that at this stage the yields of Me_2SnCl_2-assisted *O*-6 acylation of glucoside and the subsequent cyclization reaction were both increased (78% and 89%, respectively). The reaction conditions for these two steps are the same as those described in the previous section. Finally, deprotection of the benzyl groups of flavonoid glycoside **10** using hydrogen and $Pd(OH)_2/C$ gave the target molecule in 88% yield. The structure of the optimized-synthesis leontopodioside A was also confirmed by extensive NMR and MS spectra.

In summary, leontopodioside A was synthesized in nine linear steps using 3,4-dihydroxybenzaldehyde as starting material in 16.1% overall yield, for the first time. The structure of our total-synthesized leontopodioside A was confirmed by extensive NMR and Ms spectra, and the data matched with those reported [13]. The

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remarkable strategy in this synthesis involves the glycosylation of chalcone acceptor first followed by the cyclization, which has general applicability for the synthesis of flavonoid glycosides. Efficient synthesis and sufficient amounts accumulated of flavonoid glycosides will hopefully facilitate further structure–activity relationship studies of this class of compounds.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151886.

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