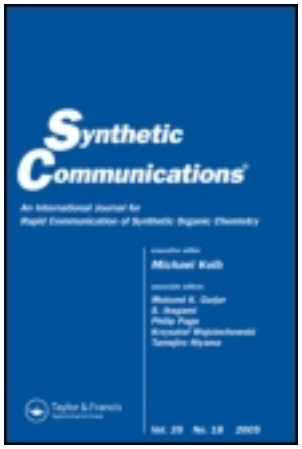

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DEVELOPMENT OF A KILOGRAM-SCALE SYNTHESIS OF SALIDROSIDE AND ITS ANALOGS

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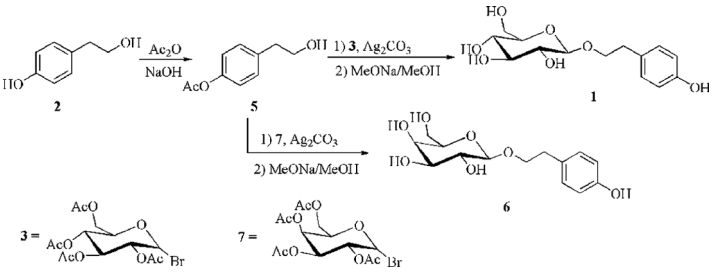
GRAPHICAL ABSTRACT



Abstract *An efficient, safe, and viable process has been developed for large-scale preparation of salidroside, a natural product. The process consists of two chemical steps, which produce the salidroside on a multikilogram scale with 72% overall yield and >98% purity. A series of novel salidroside analogs were prepared according to the same method.*

Keywords Kilogramscale; salidroside; synthesis; tyrosol glycoside

INTRODUCTION

Rhodiola sachalinensis, which belongs to the family Crassulaceae and the genus *Rhodiola*,[1] is a wild plant that can grow at the altitude of 1700–2500 m in the tundra zone in adverse circumstances and extreme weather conditions. It has been used as an adaptogen by Russian researchers because of its activity in increasing resistance to a variety of chemical, biological, and physical stressors.[2] In recent years, *Rhodiola sachalinensis* extract was supplied to astronauts, athletes, military personnel, and tourists in high-altitude areas to enhance their ability to survive in adverse

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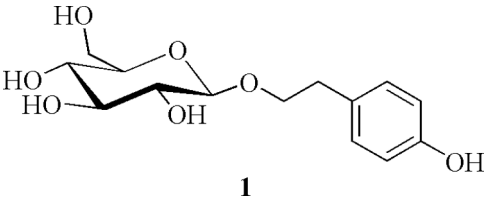


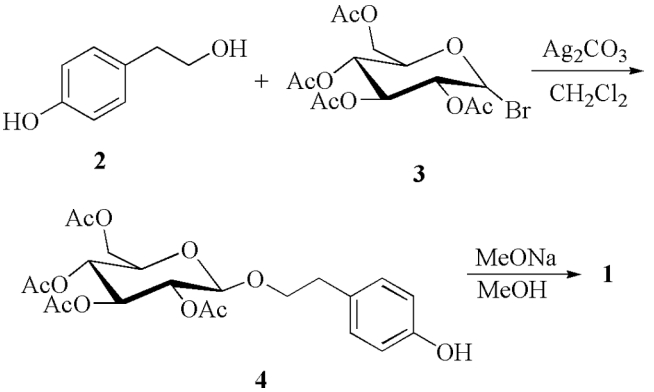
1

Figure 1. Structure of salidroside (**1**).

environments. Salidroside (**1**) has been identified as the most potent ingredient in *Rhodiola sachalinensis* (Fig. 1), and further studies have shown that **1** has many pharmacological functions including anticancer, antiaging, anti-inflammatory, oxygen-uptake enhancement, fatigue elimination, neuroprotective, hepatoprotective, and antioxidative effects.[3–6] Recently, more attention has been focused on the study of **1**. Our ultimate goal was to develop **1** as a new clinical drug.

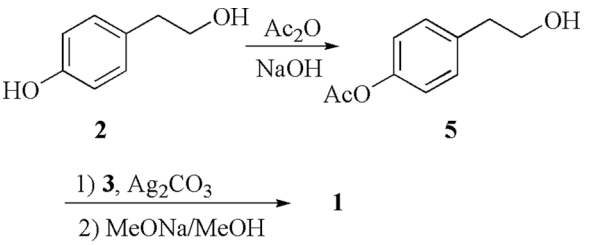
The most significant problem presented to us was the large-scale preparation of **1**. Because the content of **1** in *Rhodiola sachalinensis* is very low (<1.99%), and wild *Rhodiola sachalinensis* is on the edge of exhaustion because of overexploitation, a chemical synthetic route amenable to large-scale preparation is necessary to address initial pharmacological and toxicological requirements and fully develop the clinical applications of **1**. We report an efficient and safe preparation of **1** and its analogs on a multikilogram scale.

Compound **1** is (4-hydroxyphenethyl)-β-D-glucopyranoside, which can be synthesized by reaction of tyrosol (**2**) with 2,3,4,6-*O*-tetraacetyl-α-D-glucopyranosyl bromide (**3**) in the presence of Ag_2CO_3, followed by successive deacetylation (Scheme 1).[7] Unfortunately, the yield is very poor because of the competing reaction of the phenolic hydroxyl group of **2**. In 2004, Shi et al. improved the procedure by using nonproton solvent methylene chloride, which was still unfavorable because of the use of a chlorinated reaction solvent.[8] To improve the selectivity, several research groups tried to protect the phenolic hydroxyl group using benzyl or allylic



2 **3** **4**

Scheme 1. Reported synthetic scheme of **1**.



Scheme 2. Scalable preparation of **1**.

groups and managed to obtain the desired product in good yield.[9,10] However, these methods were deemed undesirable for scale-up owing to the multistep protecting and deprotecting reactions, high cost, and dangerous reagents (e.g., $LiAlH_4$, Grignard reagent, and ethylene oxide). Currently, there is no report of scalable synthesis of **1**.

Having already used an acetyl group as the protecting group for the hydroxyl group of **3**, we attempted to selectively protect the phenolic hydroxyl group of **2** with an acetyl group, which could then be removed together with the acetyl group of **3**. With this improvement, the preparation of **1** was condensed to a two-step synthesis. The route is shown in Scheme 2.

The first step was the selective acetylation of **2**, which already had been reported in some literature studies.[11–13] In our initial studies, we performed the acetylation reaction according to the literature.[11] Acetic anhydride was gradually added to the isopropanol solution of **2** containing saturated aqueous NaOH for 1 h with the pH maintained at 7–8. The phenol hydroxyl group could be ionized in the weak alkali reaction medium, but the alcohol hydroxyl could not. Hence, the 2-(4-acetoxyphenyl)ethanol (**5**) was obtained in 78% yield. However, the exothermic nature of this step presented a significant challenge to scale-up preparation. To avoid a sudden exotherm during the reaction, the addition rate of acetic anhydride was controlled, and the reaction temperature was lowered to 0 °C by a cooling bath. In practice, with the reaction proceeding, the solution has been observed to spontaneously form a thick slurry, making agitation difficult and resulting in an uncontrolled exotherm and formation of large amounts of tyrosol diacetate. We speculated that the formation of thick slurry was due to the NaOAc generated largely in the reaction. This problem could be solved by increasing the volume of water in the reaction system. Taking the exothermic effect into consideration, it was better to add ice instead of water. In fact, with the addition of ice, there was no thick slurry during the reaction, and the reaction temperature was well controlled. After further optimization, the reaction could proceed well in NaOH aqueous solution without isopropanol, which meant that the reaction was carried out in aqueous media. After completion of the reaction, the product was extracted into EtOAc. With the solvents evaporated, the desired product **5** was obtained as a colorless oil (3.24 kg, 90% yield) pure enough for the next step. The purity was determined by high-performance liquid chromatography (HPLC) area (>90%).

The coupling of **5** with **3** on a pilot scale was carried out under typical reaction conditions. Reaction of **5** and **3** occurred in the presence of Ag_2CO_3 and molecular sieve powder (4A) in CH_2Cl_2 for 16 h at ambient temperature. After filtration and

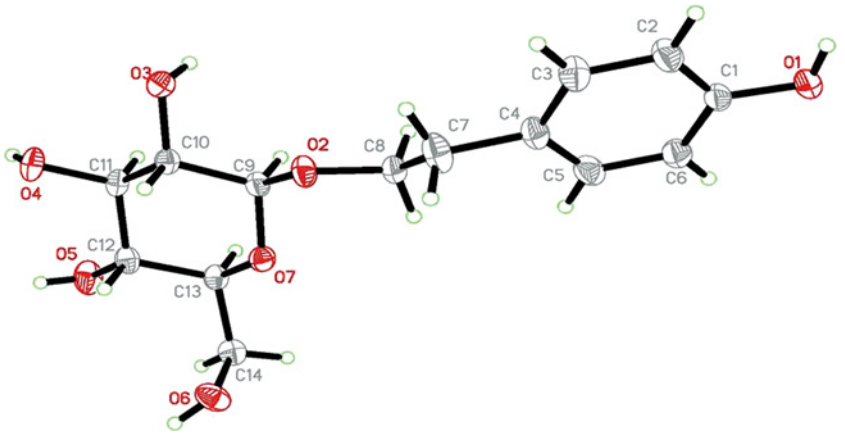
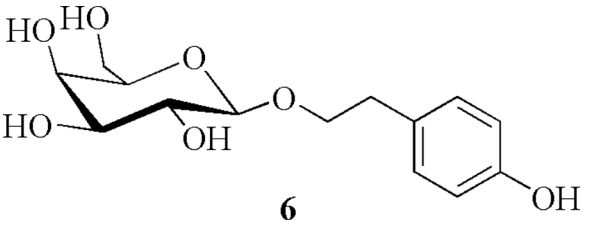


Figure 2. The X-ray crystal structure of **1**.

concentration, a syrupy residue was obtained. *n*-Hexane was slowly added to the syrupy residue under vigorous stirring. The precipitate obtained was collected by filtration and dried *in vacuo*, which was deprotected directly in the MeONa/MeOH. With extractive workup and recrystallization, **1** was isolated in 80% yield. The product was characterized by NMR, mass spectrometry (MS), and x-ray structure analysis (Fig. 2, Table 1), and the purity was determined by HPLC area (>98%). Tyrosol was the main by-product.

Table 1. Crystallographic data and refinement of **1**

Parameter	Value
Formula	$C_{14}H_{20}O_7$
Mr	300.30
T [K]	296(2)
Wavelength [Å]	0.71073
Crystal system	Orthorhombic
Space group	P 212121
Unit-cell dimensions [Å]	a = 6.0436(7), b = 7.7916(8), c = 30.070(3)
V (A^3)	1416.0(3)
Z	4
Density (calc.) (Mg/m^3)	1.409
Absorption coefficient (mm^{-1})	0.113
F(000)	640
Crystal sie (mm)	$0.33 \times 0.25 \times 0.14$
θ Range (°) for data collection	2.70–25.10
Reflections collected	7093
Independent reflections	2514
Data/restraints/parameters	2514/0/195
Goodness of fit on F^2	1.055
Final R indices [$I > 2\ \sigma(I)$]	R1 = 0.0304, wR2 = 0.0732
Final R indices (all data)	R1 = 0.0370, wR2 = 0.0757



6

Figure 3. Structure of tyrosol galactoside (**6**).

Next, a series of novel salidroside analogs were synthesized according to the same method. It was found that tyrosol galactoside (**6**) exhibited obvious antihypoxia, antifatigue, and antiradiation effects (Fig. 3). In particular, **6** showed excellent protective effect against liver injury. Compound **6** has been prepared on a multikilogram scale in our pilot plant according to a similar operation (70% of overall yield). Further study on **6** is currently in progress.

In summary, an efficient and safe large-scale preparation of tyrosol glycoside was developed. This procedure consisted of a two-step reaction starting from cheap and readily available starting materials. In addition, neither unsafe reagents nor complicated purification was required, and good yields were obtained. The preparations of **1** and **6** were scaled up successfully and reliably on a multikilogram scale in a pilot-plant facility. Good overall yields (70–72%) and purities (>98%) were obtained.

EXPERIMENTAL

All solvents and reagents were obtained from commercial suppliers and were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-300 spectrometer. HPLC analyses were performed on an Agilent 1100 liquid chromatograph equipped with an ultraviolet (UV) detector.

Preparation of 2-(4-Acetoxyphenyl)ethanol 5

Ice (15 kg) was added to a stirred solution of **2** (2.76 kg, 20 mol) in 6 M NaOH aqueous solution (5 L). After the temperature was decreased to 0 °C, acetic anhydride (2.45 kg, 24 mol) was added slowly over 40 min under vigorous stirring with the pH maintained at 7–8. The addition was exothermic, and the temperature was no more than 10 °C. The reaction mixture was stirred at this temperature for 1 h until thin-layer chromatography (TLC), *n*-hexane/EtOAc 3:1) indicated that **2** had disappeared. The solution was extracted three times with EtOAc (3 × 20 L), and the combined organic solutions were washed with brine (5 L), dried over Na_2SO_4, and then concentrated *in vacuo* to give a colorless oil 3.24 kg at 90% yield, which is pure enough for the next step. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.24 (s, 3H), 2.75 (t, $J = 6.6$ Hz, 2H), 2.83 (s, 1H), 3.69 (t, $J = 6.6$ Hz, 2H), 6.98 (d, $J = 8.1$ Hz, 2H), 7.15 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 38.5, 63.3, 121.5, 130.0, 136.5, 149.1, 169.8.

Preparation of Salidroside 1

Ag_2CO_3 (4.11 kg, 15 mol) and molecular sieve powder (4A) (2.50 kg) were added to a stirred solution of **5** (2.70 kg, 15 mol) in CH_2Cl_2 (18 L). The resulting mixture was stirred for 15 min at ambient temperature, and a solution of 2,3,4,6-*O*-tetraacetyl-α -D-glucopyranosyl bromide **3** (6.60 kg, 15 mol) in CH_2Cl_2 (22 L) was added slowly over 40 min under vigorous stirring. The mixture was stirred for 16 h at room temperature. The reaction mixture was filtered, and the filtrate was washed with saturated $NaHCO_3$ (5 L) and brine (5 L), dried over Na_2SO_4, and then concentrated to afford a syrup. *n*-Hexane (3.5 L) was slowly added to the syrupy residue under vigorous stirring. The precipitate formed was collected by filtration and dried *in vacuo*. The solid was dissolved in MeOH (30 L), and MeONa (1.23 kg, 22.5 mol) was added. The mixture was stirred at ambient temperature for about 24 h until TLC (*n*-hexane/MeOH 3/1) indicated that the material had disappeared. Concentrated HCl was added slowly to adjust the pH to 6–7. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was recrystallized twice from *n*-hexane/MeOH (5/1), giving 3.83 kg of white powder **1** (80% yield). The purity was determined by HPLC area (>98%) (column, Inertsil ODS-3 150 × 4.6 mm, 5 μm; mobile phase, CH_3CN/H_2O 10/90; flow rate, 1.0 mL min^{-1}; detection, UV 275 nm). Mp 158–159 °C; ^{1}H NMR (300 MHz, MeOD): δ 2.85(m, 2H), 3.19–3.38 (m, 4H), 3.72 (d, $J = 5.4$ Hz, 2H), 3.87 (d, $J = 11$ Hz, 1H), 4.06 (d, $J = 7.5$ Hz, 1H), 4.32 (d, $J = 6.1$ Hz, 1H), 4.85 (s, 5H), 6.73 (d, $J = 6.5$ Hz, 2H), 7.08 (d, $J = 6.5$ Hz, 2H); ^{13}C NMR (75 MHz, MeOD): δ 35.0, 61.4, 70.3, 70.7, 73.7, 76.5, 76.7, 103.0, 114.8, 129.4, 129.6, 155.4; MS (ESI) m/z 323.1098 $[M + Na]^+$.

Preparation of Tyrosol Galactoside 6

Compound **6** was synthesized according to the preparation of **1**, using 2,3,4,6-*O*-tetraacetyl-α -galactopyranosyl bromide **7** in place of **3**. The desired compound was obtained as a white powder at 3.60 kg at 78% yield. The purity was determined by HPLC area (>98%) (column, Inertsil ODS-3 150 × 4.6 mm, 5 μm; mobile phase, CH_3CN/H_2O 7/93; flow rate, 1.2 mL min^{-1}; detection, UV 275 nm). Mp 161–162 °C; ^{1}H NMR (300 MHz, MeOD): δ 2.76 (m, 2H), 3.10–3.33 (m, 4H), 3.55 (m, 1H), 3.75 (d, $J = 12.0$ Hz, 2H), 3.96 (d, $J = 7.2$ Hz, 1H), 4.30 (d, $J = 6.1$ Hz, 1H), 6.72 (d, $J = 6.6$ Hz, 2H), 7.09 (d, $J = 6.6$ Hz, 2H); ^{13}C NMR (75 MHz, MeOD): 35.0, 61.1, 70.7, 71.2, 73.6, 75.1, 75.2, 103.3, 114.9, 129.5, 129.6, 155.3.

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REFERENCES

1. Jun, F. K.; Ohba, H. *Rhodiola sachalinensis. Flora China.* **2001**, *8*, 202.
2. Kelly, G. S. *Rhodiola rosea*: A possible plant adaptogen. *Altern Med. Rev.* **2001**, *6*, 29.

3. Linh, P. T.; Kim, Y. H.; Hong, S. P.; Jian, J. J.; Kang, J. S. Quantitative determination of salidroside and tyrosol from the underground part of *Rhodiola rosea* by high-performance liquid chromatography. *Arch. Pharm. Res.* **2000**, *23*, 349.
4. Lee, M. W. Y.; Lee, A.; Park, H. M.; Toh, S. H.; Lee, E. J.; Jang, H. D. Antioxidative phenolic compounds from the roots of *Rhodiola sachalinensis* A. Bor. *Arch. Pharm. Res.* **2000**, *23*, 455.
5. Darbinyan, V.; Kteyan, A.; Panossian, A.; Gabrielian, E.; Wikman, G.; Wagner, H. Rhodiola rosea in stress-induced fatigue—A double blind cross-over study of a standardized extract SHR-5 with a repeated lowdose regimen on the mental performance of healthy physicians during night duty. *Phytomedicine* **2000**, *7*, 365.
6. Agnieszka, M.; Hoser, G.; Furmanowa, M.; Urbanska, N.; Pietrosiuk, A.; Zobel, A.; Mieczyslaw, K. Antiproliferative and antimitotic effect, S phase accumulation and induction of apoptosis and necrosis after treatment of extract from *Rhodiola rosea* rhizomes on HL-60 cells. *J. Ethnopharmacol.* **2006**, *103*, 43.
7. Troshchenko, J. Synthesis of glycoside of 2-(p-hydroxy–phenyl)-ethanol(tyrosol). *Khim. Prir. Soedin* **1969**, *5*, 256.
8. Shi, L. F.; Cai, Z.; Yao, B. Preparation of salidroside derivatives as antioxidants. *Faming Zhuanli Shenqing Gongkai Shuomingshu*. 2004; CN Patent 1475492 A 20040218.
9. Li, G. Q.; Li, C. Synthesis of 2-(N-arylaminomethyl)-5-(E) pentylidene cyclopentanoe derivatives and studies on their anti-inflammatory activity. *Chin. J. Med. Chem.* **1996**, *2*, 136.
10. Zhang, S. Q.; Shang, G. W.; Li, Z. J.; Wang, A. B.; Cai, M. S. A new approach to synthesis of solidroside. *Chin. J. Med. Chem.* **1997**, *4*, 256.
11. Srivastava, V.; Tandon, A.; Ray, S. Convenient and selective acetylations of phenols, amines, and alcohols. *Synth. Commun.* **1992**, *18*, 2703.
12. Paradisi, M. P.; Zecchini, G. P.; Torrini, I. Selective acylations of aminophenols and hydroxyalkylphenols with 1-acetyl-*v*-triazolo/_4,-5-*b*/pyridine. *Tetrahedron Lett.* **1986**, *27*(41), 5029–5032.
13. Zhao, X. G.; Cammidge, A. N.; Horwell, D. C. Dendroid peptide structural mimetics of ω-conotoxin MVIIA based on a 2(1H)-quinolinone core. *Tetrahedron* **2000**, *56*, 5169–5175.