

Study on the Synthesis of Dihydroflavonol Compounds

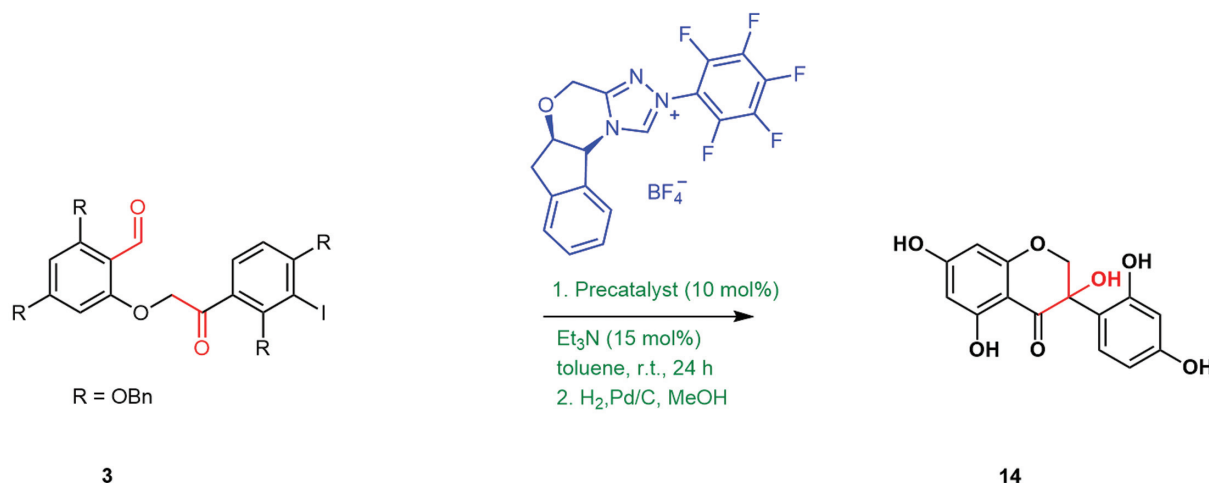
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Abstract

From the roots of *Campylotropis hirtella* (Franch.) Schindl., many natural dihydroflavonol compounds have been extracted, and they possess a structurally novel feature of chiral tertiary alcohol groups. However, the content of the compounds in the plant is extremely low. At this point, to satisfy the needs of further experimental research on these compounds, much effort has been invested in the chemical synthesis of the core structure of 3-hydroxy-3-phenylchroman-4-one. This study aimed to explore a novel method for the synthesis of dihydroflavonol (**3**), and its application in the production of a natural product (**14**). The method started with commercially available materials, and provided a foundation for total synthesis of natural compounds of dihydroflavonol.

Keywords

- ▶ natural compounds
- ▶ dihydroflavonol
- ▶ synthesis

Introduction

Campylotropis hirtella (Franch.) Schindl. is a valuable traditional Chinese medicinal plant found in subtropical areas of China. Their roots can be used to treat various diseases

including irregular menstruation, dysmenorrhea, bleeding, and gastric ulcer.^{1,2} Flavonoids are important active components of *C. hirtella* root, which have immunosuppressive effect and are a key source of tyrosinase inhibitors.^{3,4} Our previous study conducted systematic chemical studies on

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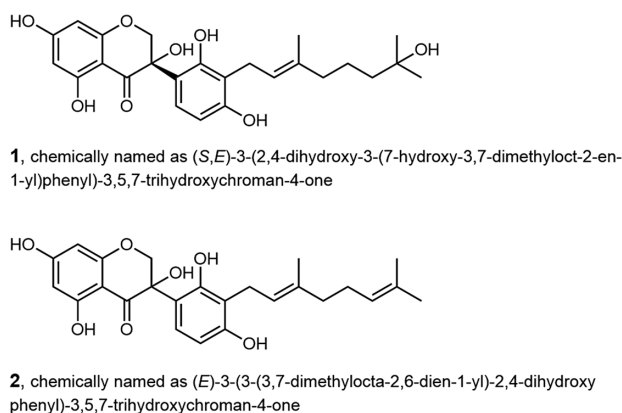


Fig. 1 Structures of natural compounds 1 and 2.

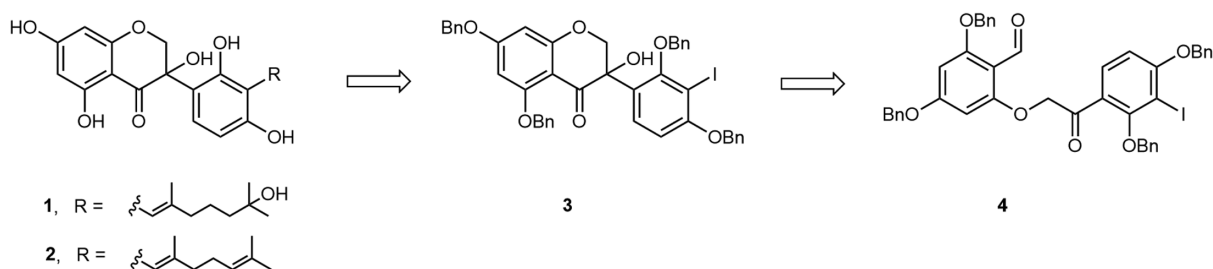
the extract of *C. hirtella* root, from which a dihydroflavonol compound with a chiral center of tertiary alcohol (**Fig. 1**, compound **1**) was isolated and identified, which was very similar to the structure of a substance discovered by Zhang et al in 2010 (**Fig. 1**, compound **2**).^{5,6} The core structure of the two compounds was 3-hydroxy-3-phenylchroman-4-one, and this inspires us to perform a case study to learn how to apply tools to the synthesis of dihydroflavonol derivatives.

A methanol extract of *Uraria crinita* afforded 3-(2,4-dihydroxyphenyl)-3,5,7-trihydroxychroman-4-one (**14**), which is a new 3-hydroxyisoflavanone, and exhibited weak or no cytotoxic activity against several human cancer cell lines (KB, HepG2, Lu, and MCF7).⁷ However, the natural source of **14** is very few and limited, and further pharmacological investigation of the compound remains with much challenges. To help the exploration of the compound and enrich the chemical library for biological activity, it is highly enviable to explore a novel synthesis route that utilizes the common structure, 3-hydroxy-3-phenylchroman-4-one, to achieve a series of dihydroflavonol compounds.

Results and Discussion

Synthesis of Key Intermediate and Core Structure

The core structures of compounds **1** and **2** are 3-hydroxy-benzopyranone as shown in **Scheme 1**, and the total synthesis route was designed as shown in **Scheme 2**, in which 2,4,6-trihydroxybenzaldehyde (**5**) and 1-(2,4-dihydroxyphenyl)ethan-1-one (**9**) are commercially available and used as the starting materials.



Scheme 1 Retrosynthetic analysis route.

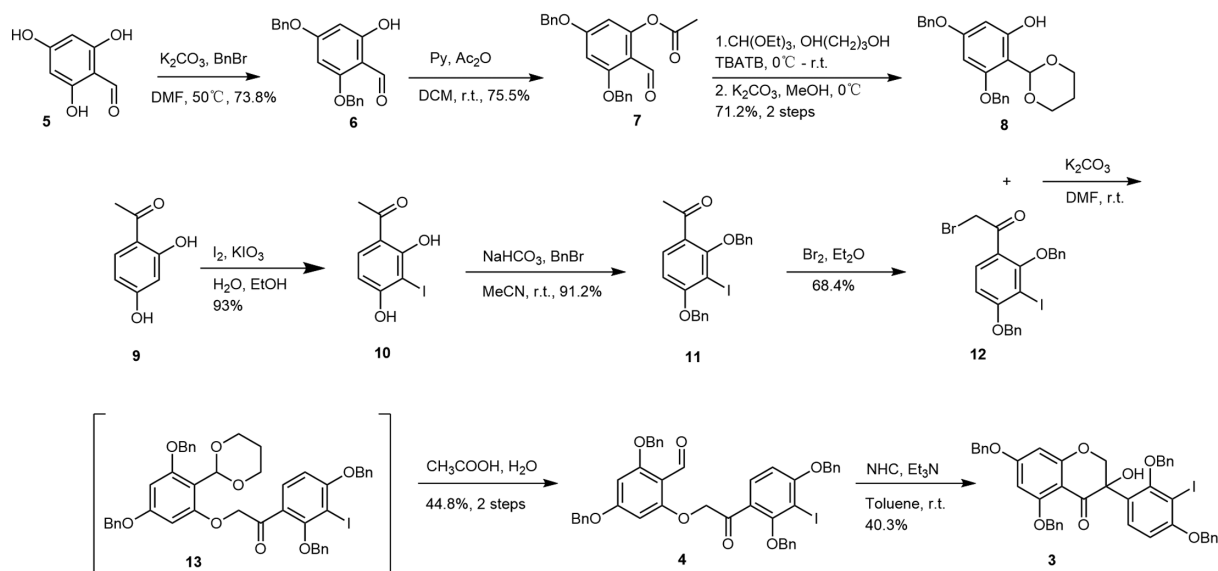
Compound **4** was a key intermediate. The key step of the synthesis of the compound is protecting its aldehyde group to avoid intramolecular aldol condensation reaction. Besides, as polyphenolic compounds, the phenol hydroxyl groups should also be protected, thus, the benzyl group was selected as a protecting group according to reported studies.^{8,9}

Intermediate **4** was synthesized from two fragments. Briefly, phenolic hydroxyl groups of **5** were selectively protected under alkaline conditions to give product **6** a yield of 73.8%. However, it is difficult to directly protect the aldehyde group of compound **6**, and this is because of the intramolecular hydrogen bonding between the aldehyde group and the *ortho*-phenolic hydroxyl group. Therefore, we mask the *ortho*-position of the phenolic hydroxyl group with acetyl protection to give compound **7**, followed by the protection of its aldehyde group to obtain compound **8**. Our initial study suggested that the benzyl groups of **7** were unstable under acidic conditions or high temperature, thus, a mild reaction condition was selected with tetrabutylammonium tribromide as catalyst to catalyze **7** and 1,3-propylene glycol to form an acetal that was hydrolyzed under alkaline conditions to obtain product **8**. Mechanically, alcohol may accelerate the formation of a hemiacetal, which is further facilitated by HBr generated in the media. On the other hand, HBr also protonates triethyl orthoformate to produce an oxonium species, which in turn reacts with an intermediate hemiacetal to give the desired acetal.¹⁰

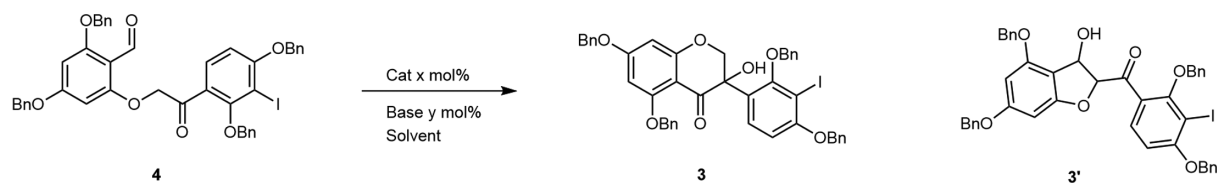
Another fragment focused on the formation of aryl iodide.¹¹ Compound **9** was used as a raw material to generate compound **12**. It is worth noting that introducing aryl iodide was innovative in the designed synthetic route, because it provides the possibility of adding side chains in the total synthesis of natural products. Then, K_2CO_3 -promoted addition of the phenolic hydroxyl group in compound **12** gives intermediate **4** with a two-step yield of 44.8%. Our data suggested that when the aldehyde group of **8** reacted with **12** under alkaline conditions, intramolecular aldol condensation could be avoided. However, aldol condensation could occur under both acidic and alkaline conditions. Hydrolyzing acetals under acidic conditions led to the formation of some aldol condensation products.

Intramolecular Benzoin Condensation and Synthesis of Compound 14

Compound **4** is involved in the most important step in the total synthesis, namely intramolecular cross-benzoin reaction, to



Scheme 2 The total synthesis route of the compounds and key intermediate **4**.



Scheme 3 Intramolecular benzoin reaction.

construct the core structure of dihydroflavonol and the chiral center with tertiary alcohol (**Scheme 3**). The catalyst and base of the reaction were screened. Unfortunately, no target product was observed when the catalysts *N*-heterocyclic carbenes **A–D** were chosen (**Fig. 2**)^{12,13} and the bases, such as Et₃N, DBU, Cs₂CO₃, and K₂CO₃ were selected

(entries 1–7, 10, 12; **Table 1**). Under these conditions, the intramolecular aldol condensation reaction was the main competitive reaction, and catalyst **C** and **D** were very effective at inducing intramolecular cross-benzoin reactions, producing the required core nucleus in an ideal yield. The reasons behind may be deduced as follows. First, the existence of the electron-withdrawing aryl substituent in triazole catalysts **C** and **D** can form nucleophilic intermediates only under weak basic conditions. Second, triazole catalysts have inherent basicity that can also catalyze aldol condensation reactions. The amount of base can be precisely controlled by using a weaker base than the catalyst, which helps to reduce the side reaction of aldol condensation.¹⁴ Catalyst **C** (15 mol%), Et₃N (10 mol%), and the solvent toluene were selected as the optimal conditions (**Table 1**, entry 9) with the maximum yield of compound **3** being 40%.

Under a H₂ atmosphere, Pd/C-catalytic hydrogenation of **3** afforded the target compound **14**. In the process, **3** was deprotected and aryl iodine was also removed (**Scheme 4**). Our data confirmed the structure of compound **14** as a dihydroflavonol compound, which was consistent with a reported study.⁷ Compound **14** had an optical rotation value of -10.498 , and an enantiomeric excess (*ee*) value of 46%. The (*S*)-enantiomers were predominant.¹⁵ Compound **14** contains four exposed phenolic hydroxyl groups, but it is stable at room temperature. However, in other methods of de-protection, we found that the tertiary alcohol structure would dehydrate under strong acidic conditions.

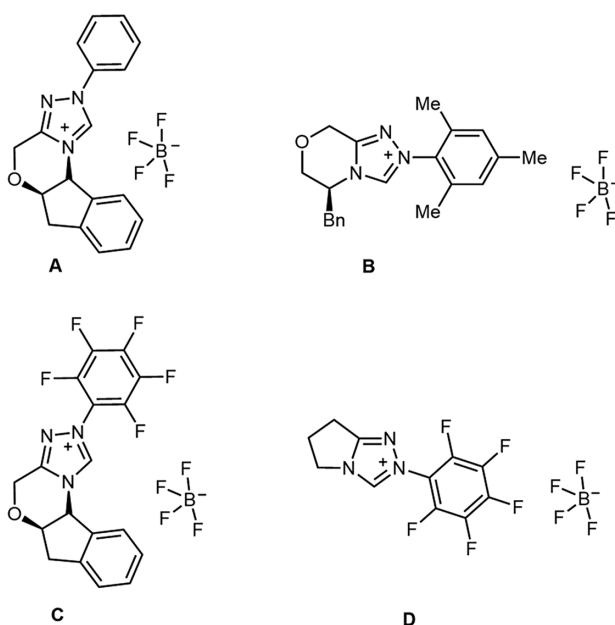
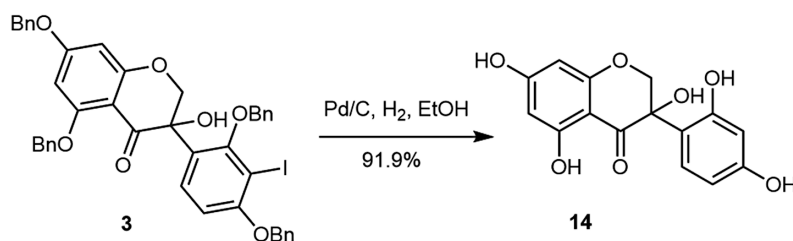


Fig. 2 Structures of *N*-heterocyclic carbene catalysts (A), (B), (C) and (D).

Table 1 Screening intramolecular benzoin reaction conditions of **4**

Entry	Catalyst (mol%)	Base (mol%)	Solvent	Yield (% 3)	Yield (% 3')
1	A (15)	Et ₃ N (10)	THF	0	83
2	B (15)	Et ₃ N (10)	THF	0	<5
3	C (10)	Et ₃ N (20)	THF	0	50
4	C (1)	Cs ₂ CO ₃ (1)	THF	0	63
5	C (15)	Et ₃ N (15)	THF	0	65
6	C (15)	K ₂ CO ₃ (100)	THF	0	80
7	C (15)	K ₂ CO ₃ (10)	THF	<5	69
8	C (7.5)	Et ₃ N (7.5)	Toluene	35	60
9	C (15)	Et ₃ N (10)	Toluene	40	38
10	D (6)	DBU (5)	THF	0	75
11	D (7.5)	Et ₃ N (7.5)	Toluene	23	50
12 ^a	D (15)	K ₂ CO ₃ (100)	THF	0	83

^aReaction temperature is 23°C.



Scheme 4 Compound **14** was obtained via hydrogenation.

Conclusion

The total synthesis of natural compounds is one of the main driving forces for the development of organic chemistry, which has not only theoretical significance for the development of organic chemistry, but also important value for the development of natural medicine and clinical medicine. At the same time, pharmaceutical and organic chemists were attracted by high efficiency and low-toxic metabolites of flavonoids. In this study, starting from simple materials, we obtained the key structure of the three products by synthesis and designing experimental methods, which provided the basis for future total synthesis of natural compounds of dihydroflavonol.

In summary, we successfully synthesized a representative compound **14** and explored a new method to synthesize dihydroflavonol compounds, which provides a useful reference for future studies on the total synthesis of dihydroflavonol compounds.

Experimental Section

General

Unless otherwise noted, reagents were commercially available (obtained from Shanghai Titan Scientific Co., Ltd., Bide Pharmatech Ltd., Shanghai Suyuanchem Ltd., etc.) and are

analytically pure. NMR data were obtained using a Bruker ascend 400 instrument (Bruker BioSpin AG) at 400 MHz for ¹H and 101 Hz for ¹³C in CDCl₃ (Chloroform-*d*) or MeOD (Methanol-*d*). The chemical shifts are reported in δ ppm relative to tetramethylsilane. The molecular weight and purity of a compound were determined by Waters Corporation separations module LC/MS e2695.

Experimental Process

The synthesis steps of the key intermediate **4**, the core compound **3**, and the target product **14** are described as follows.

Preparation of Compound **4**

3,5-Bis(benzyloxy)-2-(1,3-dioxan-2-yl) phenol (**8**) (3.1 g, 7.8 mmol) and potassium carbonate (1.6 g, 11.7 mmol) were dissolved in dimethylformamide. The solution was stirred at room temperature for 30 minutes, then, 1-(2,4-bis(benzyloxy)-3-iodophenyl)-2-bromoethan-1-one (**12**, dissolved in acetone) was added, and the stirring was continued. The reaction was monitored by LC/MS (liquid chromatography/mass spectrometry). After 12 hours, the acetone was steamed. The residue was diluted with ethyl acetate (EA) and water three times for extraction. The organic layer was dried over sodium sulfate (Na₂SO₄), filtered, and concentrated under reduced pressure to give a crude

product, which was dissolved in methanol. Then, a mixture of acetic acid and water (4:1, 1 mL) was added. The solution was stirred for 1 hour. After the completion of the reaction, monitored by LC/MS, the methanol was evaporated. The residue was diluted with EA and saturated sodium chloride solution for extraction. The organic layer was dried over Na_2SO_4 , condensed, and purified by column chromatography (petroleum ether [PE]:dichloromethane = 1:4) followed by a silica gel column chromatography to obtain **4** (2.8 g, 44.8% yield) as a yellow solid.

Compound **4**, chemically named “2,4-bis(benzyloxy)-6-(2-(2,4-bis(benzyloxy)-3-iodophenyl)-2-oxoethoxy) benzaldehyde”: ^1H NMR (400 MHz, CDCl_3) δ 10.48 (s, 1H), 7.86 (d, $J = 8.7$ Hz, 1H), 7.55 (dd, $J = 12.9, 7.3$ Hz, 4H), 7.50–7.42 (m, 4H), 7.37 (ddt, $J = 11.3, 7.4, 3.7$ Hz, 8H), 7.31 (dd, $J = 8.2, 2.1$ Hz, 4H), 6.81 (d, $J = 8.8$ Hz, 1H), 6.21 (d, $J = 1.6$ Hz, 1H), 5.82 (d, $J = 1.6$ Hz, 1H), 5.28 (s, 2H), 5.16 (d, $J = 13.7$ Hz, 4H), 5.07 (s, 2H), 4.86 (s, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 193.15, 187.51, 164.75, 162.81, 162.59, 162.37, 159.74, 136.17, 135.71, 135.65, 135.56, 132.46, 128.76, 128.73, 128.67, 128.42, 128.29, 128.25, 127.99, 127.68, 127.05, 126.92, 124.62, 109.79, 108.79, 93.50, 92.78, 85.93, 77.39, 77.08, 76.76, 73.46, 71.43, 70.62, 70.26; LC-MS (m/z): calcd. for $[\text{M} + \text{H}]^+$; found 790.84.

Preparation of Compound 3

Compound **4** (350 mg, 0.44 mmol) and catalyst (31 mg, 0.07 mmol) were dissolved in toluene. The mixture was stirred at room temperature under nitrogen protection for 30 minutes, then Et_3N (4.5 mg, 0.04 mmol) was added. After 24 hours, the reaction was quenched with water. The organic layer was dried over Na_2SO_4 , extracted with EA and saturated sodium chloride solution three times, condensed, and purified by column chromatography (PE:EA = 7:1) to give **3** (41 mg, 40.3% yield) as a light yellow solid.

Compound **3**, chemically named “5,7-bis(benzyloxy)-3-(2,4-bis(benzyloxy)-3-iodophenyl)-3-hydroxychroman-4-one”: ^1H NMR (400 MHz, CDCl_3) δ 7.58–7.52 (m, 2H), 7.42 (dd, $J = 15.1, 7.3$ Hz, 4H), 7.33–7.17 (m, 14H), 7.04 (d, $J = 8.7$ Hz, 1H), 6.45 (d, $J = 8.7$ Hz, 1H), 6.07 (d, $J = 2.2$ Hz, 1H), 5.94 (d, $J = 2.2$ Hz, 1H), 5.21 (d, $J = 11.3$ Hz, 1H), 5.14 (d, $J = 10.2$ Hz, 1H), 5.10–5.01 (m, 4H), 4.96 (d, $J = 12.5$ Hz, 1H), 4.88 (s, 2H), 4.51 (s, 1H), 4.10 (d, $J = 11.3$ Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 191.67, 165.51, 164.69, 160.77, 159.40, 159.03, 137.16, 136.29, 136.24, 135.61, 129.72, 128.76, 128.64, 128.62, 128.48, 128.42, 128.21, 127.98, 127.83, 127.77, 127.72, 126.98, 126.66, 126.62, 107.83, 104.65, 95.03, 94.50, 87.28, 75.62, 73.08, 72.97, 71.06, 70.43, 70.29; LC-MS (m/z): calcd. for $[\text{M} + \text{H}]^+$; found 790.69.

Preparation of Compound 14

Compound **3** (100 mg, 0.13 mmol) was dissolved in ethanol, and then an appropriate amount of catalyst Pd/C was added. The mixture was stirred at room temperature under a hydrogen atmosphere for 6 hours. The reaction was monitored by LC/MS and filtered after the reaction completed. The solid **14** (50.0 mg, 91.9%) was obtained after drying. High-performance liquid chromatography (HPLC) analysis showed an *ee* (%) value

of the compound to be 46%. Chiral HPLC analysis was performed via an IE-3 column (0.46×25 cm, $3 \mu\text{m}$) on a chiral stationary phase. The moving phase was *n*-hexane/isopropanol with a volume ratio (v/v) of 80/20. The detection wavelength was UV 214 nm. The flow rate was 0.7 mL/min).

Compound **14**, chemical named “3-(2,4-dihydroxyphenyl)-3,5,7-trihydroxychroman-4-one.” $[\alpha]^{20}_{\text{D}}$ 10.498 (c 0.15, MeOH). ^1H NMR (400 MHz, MeOD) δ 7.30 (d, $J = 8.5$ Hz, 1H), 6.33 (dd, $J = 8.5, 2.4$ Hz, 1H), 6.27 (d, $J = 2.3$ Hz, 1H), 5.90 (d, $J = 2.2$ Hz, 1H), 5.88 (d, $J = 2.2$ Hz, 1H), 4.79 (d, $J = 11.9$ Hz, 1H), 4.09 (d, $J = 11.9$ Hz, 1H). ^{13}C NMR (101 MHz, MeOD) δ 195.12, 166.78, 165.01, 162.97, 158.46, 155.08, 127.95, 115.70, 106.16, 102.65, 100.70, 95.84, 94.61, 73.88, 73.43; LC-MS (m/z): calcd. for $[\text{M} - \text{H}]^+$; found 302.97.

Supporting Information

Spectroscopic characterization processes (^1H NMR and ^{13}C NMR) for compound **4**, **3**, and **14**, as well as chiral HPLC results of compound **14**, are included in the Supporting Information (►Figs. S1–S7 [online only]).

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Conflict of Interest

The authors declare no conflict of interest.

References

- Li X, Xuan B, Shou Q, Shen Z. New flavonoids from *Campylotropis hirtella* with immunosuppressive activity. *Fitoterapia* 2014; 95:220–228
- Wang Z, Yang L, Yang X, Zhang X. Advances in the first total synthesis of natural flavonoids. *Synth Commun* 2013;43(23): 3093–3114
- Shou QY, Fu RZ, Tan Q, Shen ZW. Geranylated flavonoids from the roots of *Campylotropis hirtella* and their immunosuppressive activities. *J Agric Food Chem* 2009;57(15):6712–6719
- Tan X, Song YH, Park C, et al. Highly potent tyrosinase inhibitor, neorauflavane from *Campylotropis hirtella* and inhibitory mechanism with molecular docking. *Bioorg Med Chem* 2016;24(02): 153–159
- Xie YG, Li T, Wang GW, et al. Chemical constituents from *Campylotropis hirtella*. *Planta Med* 2016;82(08):734–741
- Zhang S, Tan Q, Shou Q, Qin G, Shen Z. Two new isoflavonones from radix *Campylotropis hirtella* [in Chinese]. *Acta Chim Sin* 2010;68(21):2227–2230
- Thien DD, Tai BH, Dai TD, et al. New phenolics from *Uraria crinita* (L.) DC. *Nat Prod Res* 2022;36(13):3381–3388
- Forsberg LK, Anyika M, You Z, et al. Development of noviomimetics that modulate molecular chaperones and manifest neuroprotective effects. *Eur J Med Chem* 2018;143:1428–1435
- Kommerer R, Bhimapaka CR. A simple and efficient approach for the preparation of dihydroxanthyletin, xanthyletin, decursinol and marmesin. *Synth Commun* 2020;50(21):3204–3211
- Gopinath R, Haque SJ, Patel BK. Tetrabutylammonium tribromide (TBATB) as an efficient generator of HBr for an efficient

- chemoselective reagent for acetalization of carbonyl compounds. *J Org Chem* 2002;67(16):5842–5845
- 11 Tian T, Zhu Z, Ding Y, Li G, Li N, Shen T. Synthesis and cytotoxic evaluation of sanjoseolide and representative analogues. *ACS Omega* 2020;5(51):33478–33483
 - 12 Ema T, Nanjo Y, Shiratori S, Terao Y, Kimura R. Solvent-free benzoin and stetter reactions with a small amount of NHC catalyst in the liquid or semisolid state. *Org Lett* 2016;18(21):5764–5767
 - 13 Takikawa H, Suzuki K. Modified chiral triazolium salts for enantioselective benzoin cyclization of enolizable keto-aldehydes: synthesis of (+)-sappanone B. *Org Lett* 2007;9(14):2713–2716
 - 14 Zhang G, Yang S, Zhang X, et al. Dynamic kinetic resolution enabled by intramolecular benzoin reaction: synthetic applications and mechanistic insights. *J Am Chem Soc* 2016;138(25):7932–7938
 - 15 Xie YG, Li T, Wang GW, et al. Chemical constituents from *Campyloptropis hirtella*. *Planta Med* 2016;82(08):734–741