Facile and Efficient Synthesis of (±)-Glabridin

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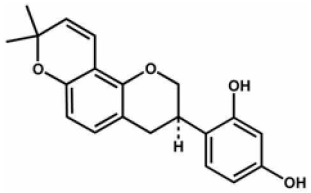
Glabridin (**1**) is an isoflavan isolated from a licorice of *Glycyrrhiza glabra*,[1] which has a history of consumption for the past 6000 years.[2] The licorice roots have long been used as flavoring and sweating agents, as well as demulcents and expectorants in western countries and in Asian countries to treat allergic inflammation. Numerous flavonoid compounds have been isolated from licorice and proved to show a variety of biological activity. Among them, glabridin (**1**) and its families have been verified to be responsible for the anti-oxidative effect and other activities shown in licorice.[3] Recently, glabridin has also been reported to inhibit efficiently the tyrosinase-dependent melanin biosynthesis, suggesting that it may serve as candidates for skin-lightening agents.[3f]

Our key strategy for the synthesis of glabridin, as shown in Scheme 2, is the aldol condensation between phenylacetate **4** and pyranosalicylaldehyde **6** to give 2-(2',4'-diprotected phenyl)cynamate **8**. And then, cynamate **8** is reduced to saturate dihydrocynamyl alcohol **9**, which is followed by the cyclization for the isoflavan structure.[4]



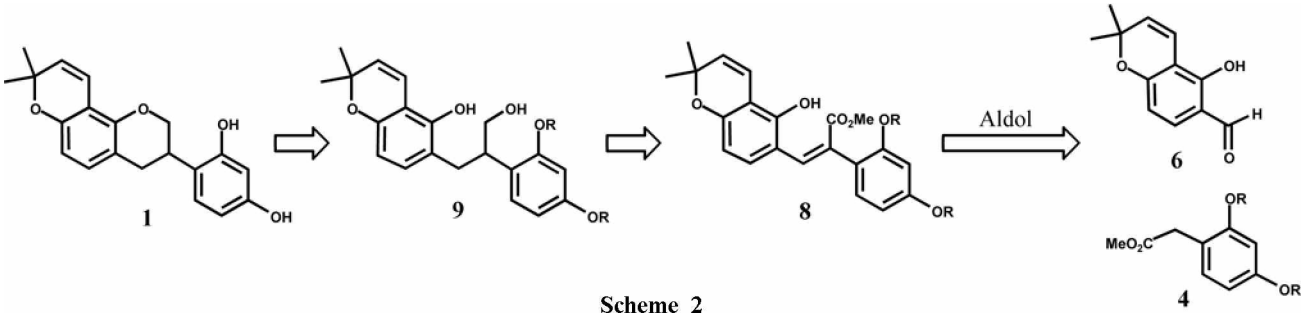
Glabridin (**1**)

Scheme 1

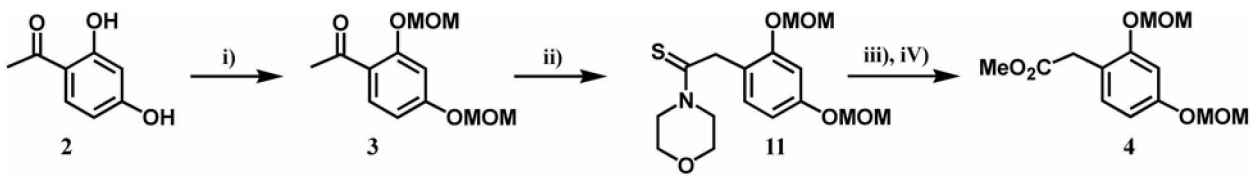
Results and Discussion

The phenylacetate **4** was prepared from an acetophenone by Willgerodt-Kindler reaction.[5] 2',4'-di(methoxymethoxy)-acetophenone **3**, which was prepared by the reaction of 2',4'-dihydroxy-acetophenone **2** with chloromethyl methyl ether (MOMCl) using diisopropylethylamine as base, was mixed with sulfur and morpholine and heated to give thiomorpholide **11**. The hydrolysis of thiomorpholide **11** gave a sodium phenylacetate, which was treated with dimethylsulfate to give methyl 2',4'-di(methoxymethoxy)phenylacetate **4**. (Scheme 3) Pyranosalicylaldehyde **6** was prepared by a thermal reaction using 2',4'-dihydroxybenzaldehyde **5**, 3-methylbuten-2-al, and pyridine, which is some modification of the reported method for 2',4'-dihydroxyacetophenone.[5(a)]

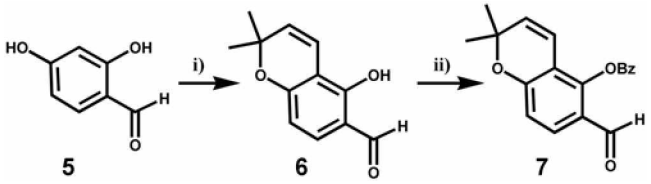
Aldol condensation between phenylacetate **4** and pyranosalicylaldehyde **6** were unsuccessful. When pyranosalicylaldehyde **6** was treated with an excess (> 2.0 eq) of an enolate from phenylacetate **4**, the condensation product was not isolated at all. The problem was overcome by a protec-



Scheme 2



Scheme 3. *Reagents, conditions, and yield*: i) MeOMCl, *i*-Pr_2EtN, 0 °C, 91%; ii) Sulfur, Morpholine, 130 °C, 64%; iii) NaOH, EtOH, reflux, 92%; Me_2SO_4, MeOH, $NaHCO_3$, RT, 91%.

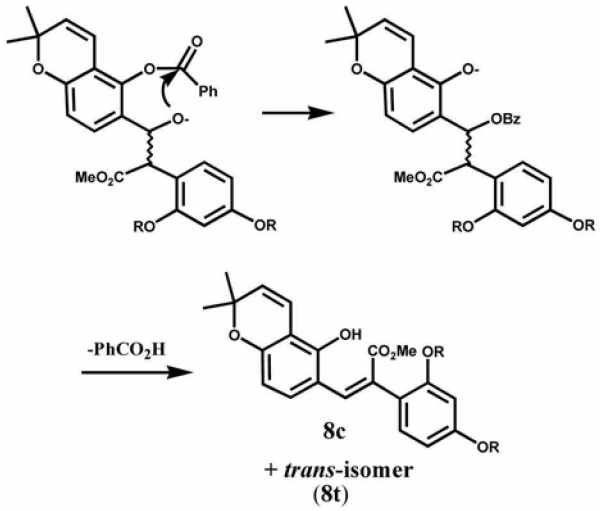


Scheme 4. *Reagents, conditions, and yield*: i) $(CH_3)_2C=CHCHO$, $MgSO_4$/py, 47%; (ii) $BzCl/CH_2Cl_2$, TEA, 0 °C, 97%.

tion of a phenol group in pyranosalicylaldehyde **6**. The protection of the phenol group seems to be able to remove the tight hydrogen-bonding between the phenol group and a neighboring formyl group, and also to increase the electrophilicity of the formyl group. Therefore, pyranosalicylaldehyde **6** was treated with benzoyl chloride and TEA to give a benzoate **7** in good yield. Phenylacetate **4** was treated with slightly excess (1.2 eq.) of LDA to give its enolate, which was reacted with the benzoate **7** of pyranosalicylaldehyde at −78 °C, then the reaction mixture was warmed to room temperature and stirred for additional 1 hour to give mainly 2-(2',4'-dimethoxymethoxyphenyl)cynamate **8c** in good yield. During the condensation, the protecting benzoate was released. It is assumed that when the benzoyl group attached to phenol is exposed to the attack of alkoxide resulted from aldol condensation, the benzoyl group would move to alkoxide and the rearranged benzoyl group seems to be easily eliminated to give the mixture of cynamates **8c** and **8t** (~95:5) (Scheme 5).[7]

The olefinic stucture of the cynamates is not certain, but the H-NMR spectra of the isomers are very similar except those of the vinyl protons, where **8c** gives a singlet at 7.82 ppm and the proton of **8t** is observed as a singlet at 7.93 ppm. In spite of the difference in their olefin structure, the reduction products from both isomers **8c** and **8t** using $LiBH_4$ are identical.

The cynamate **8c** was refluxed for 5 hours with excess $LiBH_4$ (6 eq.) to give 2-(2',4'-dimethoxymethoxyphenyl)-



Scheme 5. Proposed mechanism for the condensation.

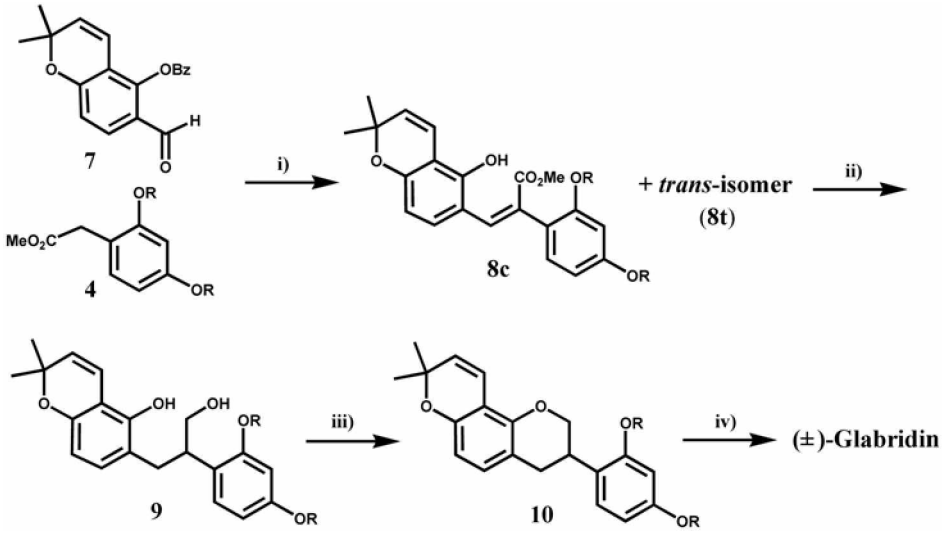
dihydrocynamyl alcohol **9** in moderate yield. The mixture of saturated alcohol **9** and Ph_3P was treated with DEAD under the reflux of THF to give the 2',4'-dimethoxymethyl protected glabridin **10** in good yield.

The MOM-protected glabridin **10** was labile to strong acids and successfully deprotected with TsOH in refluxing *i*-PrOH to afford (±)-glabridin **1** in 85% yield.

Our synthetic method is efficient and can make many derivatives of glabridin from various benzaldehydes and phenylacetates. We are now performing the synthesis for the derivatives of glabridin and will find the optimized derivatives that have improved inhibitory activity to tyrosinases and a better skin-whitening effect.

Experimental Section

All new compounds were fully characterized by ^1H and ^{13}C NMR (300 MHz in $CDCl_3$), and MS. Selected spectro-



Scheme 6. *Reagents, conditions, and yield*: i) LDA, THF, −78 °C, 87%; ii) $LiBH_4$, THF, reflux, 46%; iii) PPh_3, DEAD, THF, reflux, 86% Where, R in MOM; iv) TsOH, *i*-PrOH, reflux, 85%.

scopic data for compounds **1**, **4**, **6**, **7**, **8c**, **8t**, **9**, **10** are given. Proton NMR data for **1** are identical with NMR data from the natural product in reference 1.

Methyl 2,4-(dimethoxymethoxy)phenylacetate (4). This compound (4) was synthesized from acetophenone by known Willgerodt-Kindler reaction.[4] ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.09 (d, 1H, Ar-H), 6.80 (d, 1H, Ar-H, J = 2.4 Hz), 6.67 (dd, 1H, Ar-H), 5.17 (s, 2H), 5.15 (s, 2H), 3.68 (s, 3H), 3.59 (s, 2H), 3.47 (s, 3H), 3.45 (s, 3H).

6-Formyl-5-hydroxy-2,2-dimethyl-2*H*-1-benzopyran (6). A mixture of 2,4-dihydroxybenzaldehyde (**5**) (13.8 g, 0.10 mol), 3-methylbutenal (8.41 g, 0.10 mol), pyridine (7.91 g, 0.10 mol) and $MgSO_4$ (12.0 g, 0.10 mol) was vigorously stirred and heated at 130 °C. After stirring and heating was continued for 18 hr, to the mixture was added 3-methylbutenal (1.68 g, 0.020 mol) once more. And then, stirring and heating was continued for a further 10 hr. The reaction mixture was cooled to ambient temperature and then filtered to remove an insoluble solid including $MgSO_4$. The filterate was heated to 120 °C under vacuum using aspirator, 3-methylbutenal and pyridine was recovered. The resulting concentrate was partitioned using hexane and CH_3CN more than 15 times. The combined hexane solution was concentrated and purified by recrystallization (Hexane and EtOAc) to afford pure pyranosalicylaldehyde (**6**) (slightly yellow solid, 9.65 g, 0.047 mol). Spectral properties were in agreement with those reported.[6b,c] ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 11.64 (s, 1H), 9.66 (s, 1H), 7.29 (d, 1H, Ar-H, J = 8.6 Hz), 6.68 (d, 1H, J = 10.1 Hz), 6.42 (d, 1H, Ar-H), 5.61 (d, 1H, J = 10.1 Hz), 1.46 (s, 6H).

6-Formyl-5-benzoyloxy-2,2-dimethyl-2*H*-1-benzopyran (7). To a solution of 6-formyl-5-hydroxy-2,2-dimethyl-2H-1-benzopyran (**6**) (20.42 g, 0.10 mol) and benzoylchloride (14.06 g, 0.10 mol) in CH_2Cl_2 (500 mL) was added triethylamine (10.12 g, 0.10 mol) at 0 °C and then the resulting solution was stirred vigorously for 2 hr. The solution was treated with brine (300 mL) and then organic layer was separated. The organic layer was dried over $MgSO_4$, filtered and concentrated to give crude benzoate (**7**). The crude product was recrystallized with EtOAc to afford pure benzoate (**7**) (slightly yellow solid, 29.81 g, 0.097 mol). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.92 (s, 1H), 8.25 (m, 2H, Ar-H), 7.71 (d, 1H, Ar-H, J = 8.6 Hz), 7.68 (d, 1H, Ar-H), 7.55 (m, 2H), 6.83 (d, 1H, Ar-H, J = 8.6 Hz), 6.38 (d, 1H, J = 10.1 Hz), 5.69 (d, 1H, J = 10.1 Hz), 1.49 (s, 6H).

Methyl 2-(2,4-dimethoxymethoxyphenyl)-3-(5-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-yl) acrylate (8c). To a THF solution (250 mL) of LDA (1.0 M, 250 mL) at −78 °C was slowly added a THF solution (150 mL) of phenylacetate (**4**) (54.1 g, 0.20 mol) and stirred for 30 minutes, then, a THF solution (150 mL) of a benzoyl protected pyranosalicylaldehyde (**7**) (61.7 g, 0.20 mol) was slowly added maintaining below −70 °C. The resulting solution was stirred vigorously for 1 hr, warmed to ambient temperature and stirred for a further 1 hr. Brine (200 mL) was added to the solution and stirred for a further 30 min. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (200 mL). The combined organic layer was dried over $MgSO_4$ and concentrated. The product is a mixture of **8c** and **8t** (~95:5). The concentrate was recrystallized using $CHCl_3$ and EtOAc (5:95, 100 mL) to give pure 2,3-diarylacrylate (**8c**) (68.1 g, 0.172 mol). TLC, rf = 0.25 (EtOAc:Hexane, 40:60). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.82(s, 1H), 6.90 (d, 1H, Ar-H, J = 8.4 Hz), 6.86 (d, 1H, Ar-H, J = 2.2 Hz), 6.71 (d, 1H, Ar-H, J = 8.6 Hz), 6.61 (dd, 1H, Ar-H), 6.53 (d, 1H, J = 9.9 Hz), 6.22 (d, 1H, Ar-H), 5.53 (d, 1H, J = 9.9 Hz), 5.16 (s, 2H), 5.08 (s, 2H), 3.76 (s, 3H), 3.49 (s, 3H), 3.38 (s, 3H), 1.39 (s, 6H). ^{13}C-NMR ($CDCl_3$, 75.45 MHz) δ 169.03, 158.55, 155.97, 154.78, 150.49, 135.81, 131.53, 130.12, 128.80, 128.03, 119.21, 116.40, 114.91, 109.46 109.39, 109.07, 104.00, 94.89, 94.52, 76.10, 56.15, 56.01, 52.26, 27.82. Mass (ApCI) m/z 457 (M+1), 425, 393.

Compound **8t**: TLC, rf = 0.65 (EtOAc:Hexane, 40:60). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.93 (s, 1H), 6.92 (d, 1H, J = 8.4 Hz), 6.86 (d, 1H, J = 2.2 Hz), 6.71 (d, 1H, Ar-H), 6.62 (d, 1H, Ar-H), 6.60 (d, 1H, J = 10.1 Hz), 6.17 (d, 1H, J = 8.4 Hz), 5.53 (d, 1H, J = 10.1 Hz), 5.16 (s, 2H), 5.08 (s, 2H), 3.75 (s, 3H), 3.49 (s, 3H), 3.37 (s, 3H), 1.38 (s, 6H).

2-(2,4-Dimethoxymethoxyphenyl)-3-(5-hydroxy-2,2-dimethyl-2H-1-benzopyran-6-yl)propan-1-ol (9). A mixture of anhydrous THF (250 mL), KBH_4 (41.3 g, 0.766 mol) and LiCl (32.5 g, 0.766 mol) was refluxed for 5 hr with vigorous stirring and then cooled to ambient temperature. The mixture was filtered to remove KCl, and then a clear $LiBH_4$-THF solution resulted. To the $LiBH_4$ solution (0.766 mol) was added 2,3-diarylacrylate (**8c**) (50.0 g, 0.11 mmol) and the resulting solution was refluxed for 10 hr. After cooling to ambient temperature, brine (150 mL) was slowly added and the mixture was agitated for 1 hour. Organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 twice more (100 mL × 2). The combined organic layer was dried over $MgSO_4$ and concentrated to give a crude 2,3-diarylpropanol. For its identification, the crude 2,3-diarylpropanol (**9**) was purified by flash column chromatography to afford pure 2,3-diarylpropanol (**9**) (22.0 g, 0.0594 mol) and a minor side-product, 3-arylcoumarin. But, in the practical preparative process, crude 2,3-diarylpropanol (**9**) was used as itself without a further purification. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.66 (b, 1H), 7.17 (d, 1H, J = 8.4 Hz), 6.85 (d, 1H, J = 2.2 Hz), 6.77 (d, 1H, J = 9.9 Hz), 6.74 (d, 1H, J = 8.4 Hz), 6.70 (dd, 1H, Ar-H), 6.33 (d, 1H, J = 8.2 Hz), 5.58 (d, 1H, J = 9.9 Hz), 5.22 (s, 2H), 5.16 (s, 2H), 3.79 (b, 2H), 3.49 (s, 6H), 3.31 (m, 1H), 3.04 (dd, 1H, J = 14.1, 10.2 Hz), 2.70 (dd, 1H, J = 14.1, 4.0 Hz), 1.43 (s, 3H), 1.41 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75.45 MHz) δ 159.95, 155.22, 152.43, 150.84, 130.61, 128.78, 128.44, 124.94, 117.92, 117.46, 110.26, 108.82, 104.46, 103.58, 94.67, 94.51, 75.50, 63.43, 56.36, 56.04, 41.29, 30.81, 27.80, 27.57. Mass (ApCI) m/z 431 (M+1), 399, 381.

2',4'-Di(methoxymethyl)glabridin (10). To a refluxing solution of crude 2,3-diarylpropanol (**9**) (50.0 g; estimated as about 50 mmol) and triphenylphosphine (12.8 g, 48.8 mmol) in THF (100 mL) was slowly added DEAD (40% in toluene, 20.0 g, 45.9 mmol) and then the reaction progress was

checked by TLC. If the reactant was detected on TLC, DEAD (40% in toluene, 2.0 g, 4.6 mmol) was added once more. And then, the reaction was checked again. A series of the above process was repeated until the reactant was not detected on TLC. If the reaction was completed, the solution was washed with dilute NaOCl (< 5%, 50 mL) to get rid of triphenylphosphine and thoroughly concentrated under vacuum to remove THF. The residue was partitioned with hexane (150 mL × 20), acetonitrile (80 mL) and H_2O (50 mL) 20 times to get rid of tirphenylphosphine oxide. The combined hexane layer was concentrated to give 2',4'-di(methoxymethyl)glabridin (15.3 g, 0.0435 mol), which could be easily purified by flash chromatography, if necessary. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.03 (d, 1H, J = 8.6 Hz), 6.84 (d, 1H, J = 2.5 Hz), 6.83 (d, 1H, J = 8.4 Hz), 6.69 (dd, 1H, J = 2.5, 8.6 Hz), 6.64 (d, 1H, J = 9.9 Hz), 6.36 (d, 1H, J = 8.4 Hz), 5.56 (d, 1H, J = 9.9 Hz), 5.20 (s, 2H), 5.16 (s, 2H), 4.36 (dq, 1H, J = 10.3 Hz), 4.00 (t, 1H, J = 10.3 Hz), 3.6 (m, 1H), 3.482 (s, 3H), 3.477 (s, 3H), 2.97 (dd, 1H, J = 15.0, 10.0 Hz), 2.84 (dd, 1H, J = 15.0, 5.1 Hz), 1.43 (s, 3H), 1.41 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75.45 MHz) δ 157.05, 155.83, 151.88, 149.71, 129.16, 128.94, 127.66, 123.54, 116.90, 114.39, 109.87, 108.86, 108.65, 103.46, 94.54, 94.46, 75.55, 70.19, 56.21, 56.06, 31.64, 30.76, 27.78, 27.49. Mass (ApCI) m/z 413 (M+1), 381.

Glabridin (1). To a solution of 2',4'-di(methoxymethyl)-glabridin (**10**) (4.12 g, 10.0 mmol) in isopropanol (100 mL) was added TsOH (2.85 g, 15 mmol) at ambient temperature and then the mixture was stirred at 40 °C for 6 hours. After half deprotected (mono-deprotected) intermediate 2'-(methoxymethyl) glabridin was disappreaed, the mixture was cooled to ambient temperature and the solvent was evaporated. The residue was dissolved in EtOAc and washed with water and dried with $MgSO_4$ then concentrated. The concentrate was recrystallized with chloroform and ethyl ether to afford glabridin (**1**) (2.76 g, 8.5 mmol). The ^{1}H-NMR data are identical to those reported previously.[1] ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.95 (d, 1H, J = 8.4 Hz), 6.82 (d, 1H, J = 8.3 Hz), 6.65 (d, 1H, J = 9.9 Hz), 6.38 (dd, 1H, J = 8.4 Hz), 6.37 (d, 1H, J = 8.3 Hz), 6.31 (d, 1H, J = 2.6 Hz), 5.56 (d, 1H, J = 9.9 Hz), 5.20 (b, 2H), 4.37 (m, 1H, J = 10.3 Hz), 4.02 (t, 1H, J = 10.1 Hz), 3.48 (m, 1H), 2.97 (dd, 1H, J = 9.9 Hz), 2.85 (m, 1H), 1.43 (s, 3H), 1.41 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75.45 MHz) δ 155.25, 154.44, 151.91, 149.75, 129.18, 128.95, 128.41, 120.01, 116.95, 114.32, 109.93, 108.73, 107.98, 103.11, 75.62, 70.00, 31.70, 30.61, 27.79, 27.55. Mass (ApCI) m/z 325 (M+1).

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