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 antioxidative 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.3d

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

Results and Discussion

The phenylacetate 4 was prepared from an acetophenone by Willgerordt-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.6a

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 1

Scheme 2

Scheme 3. Reagents, conditions, and yield: i) MeOMCl, i-Pr2EtN, 0 ºC, 91%; ii) Sulfur, Morpholine, 130 ºC, 64%; iii) NaOH, EtOH, reflux, 92%; Me2SO4, MeOH, NaHCO3, RT, 91%.
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 benzyl 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).

The olefinic structure 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 LiBH4 are identical.

The cynamate 8c was refluxed for 5 hours with excess LiBH4 (6 eq.) to give 2-(2',4'-dimethoxymethoxyphenyl)-dihydrocynamyl alcohol 9 in moderate yield. The mixture of saturated alcohol 9 and Ph3P 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 13C NMR (300 MHz in CDCl3), and MS. Selected spectro-
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 1H-NMR (CDCl3, 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).

A mixture of 2,4-dihydroxybenzaldehyde (3.59 g, 0.01 mol), pyridine (7.91 g, 0.10 mol) and MgSO4 (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 and pyridine was recovered. The resulting concentrate was partitioned using hexane and CH2CN more than 15 times. The combined hexane solution was concentrated and purified by recrystallization (Hexane and EtOAc) to afford pure 6-formyl-5-hydroxy-2,2-dimethyl-2H-1-benzopyran (8c) (slightly yellow solid, 29.81 g, 0.097 mol). 1H-NMR (CDCl3, 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-hydroxy-2,2-dimethyl-2H-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 MgSO4 (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 MgSO4. The filtrate was heated to 120 °C under vacuum using aspirator, 3-methylbutenal and pyridine was recovered. The resulting concentrate was partitioned using hexane and CH2CN more than 15 times. The combined hexane solution was concentrated and purified by recrystallization (Hexane and EtOAc) to afford pure 6-formyl-5-hydroxy-2,2-dimethyl-2H-1-benzopyran (6) (68.1 g, 0.172 mol). TLC, Rf = 0.25 (EtOAc:Hexane, 40:60). 1H-NMR (CDCl3, 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 (d, 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). 13C-NMR (CDCl3, 75.45 MHz) δ 169.03, 158.55, 155.97, 154.78, 153.81, 151.33, 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.

**Compounds 8t:** TLC, Rf = 0.65 (EtOAc:Hexane, 40:60). 1H-NMR (CDCl3, 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, 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), KBr (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 LiBH4-THF solution resulted. To the LiBH4 solution (0.766 mol) was added 2,3-diarylpropanol. For its identification, the crude 2,3-diarylpropanol was used as itself without a further purification. 1H-NMR (CDCl3, 300 MHz) δ 7.71 (s, 1H), 7.68 (d, 1H, Ar-H), 7.55 (m, 2H), 6.83 (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-2H-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 phenylacetal (4) (54.1 g, 0.20 mol) and stirred for 30 minutes, then, a THF solution (150 mL) of a benzoyl protected pyranosylaldehyde (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 CH2Cl2 (200 mL). The combined organic layer was dried over MgSO4 and concentrated. The product is a mixture of 8c and 8t (95−95). The concentrate was recrystallized using CHCl3 and EtOAc (5:95, 100 mL) to give pure 2,3-diaryl-acrylate (8c) (68.1 g, 0.172 mol). TLC, Rf = 0.25 (EtOAc:Hexane, 40:60). 1H-NMR (CDCl3, 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 (d, 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). 13C-NMR (CDCl3, 75.45 MHz) δ 169.03, 158.55, 155.97, 154.78, 153.81, 151.33, 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.

2,4-Dimethoxyethylglabridin (11). 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 H2O (50 mL) 20 times to get rid of triphenylphosphine 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. 1H-NMR (CDCl3, 300 MHz) δ 7.03 (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). 13C-NMR (CDCl3, 75.45 MHz) δ 157.05, 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, 50.6, 31.70, 30.61, 27.79, 27.55. Mass (ApCI) m/z 325 (M+1).

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### References and Notes


