TOTAL SYNTHESIS OF (±)-GLABRIDIN

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GRAPHICAL ABSTRACT

Abstract An efficient formal synthesis of (±)-glabridin was accomplished in 10 steps from resorcinol using Raney Ni to reduce carbon–carbon double bonds in α,β-unsaturated carbonyl compound as the key step.

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Keywords Chemoselective reduction; glabridin; resorcinol; total synthesis

INTRODUCTION

In 1970s, glabridin was first isolated as an isoflavan from the root of a Glycyrrhiza glabra licorice.[1] The extract of the root of licorice is a Chinese herbal medicine that is used as demulcents and expectorants to treat allergic inflammation. Glabridin has been identified as responsible for the antioxidative effect and other activities shown in licorice.[2] Additionally, further research showed that glabridin could be used to efficiently inhibit the tyrosinase-dependent melanin biosynthesis, suggesting that it may serve as candidates for skin-lightening agents.[2e]

Although it has attracted considerable attention, only two total syntheses of (±)-glabridin have been reported, and Nahm by Yoo[3] and by Kenichi and Shingo[4]. In this article, we report our synthetic studies toward (±)-glabridin using...
the chemoselective reduction of conjugated olefins in \(\alpha,\beta\)-unsaturated carbonyl compound as the key step. The retrosynthetic sequence is represented in Scheme 1.

**RESULTS AND DISCUSSION**

At first, we obtained 2,4-dimethoxyphenylacetic acid (3) from resorcinol (2) through a four-step reaction as described in the literature.[5–7] In the next step, the preparation of the isoflavone 4 was easily achieved on the basis of the reported using \(\text{BF}_3\cdot\text{Et}_2\text{O}\) as the catalyst and solvent.[8] (Scheme 2).

With available isoflavone 4 in hand, our next task was to reduce both carbonyl group and carbon–carbon double bonds in 4. Initially, isoflavane 5 could be easily obtained in a single step according to Goto et al.’s method[8] in 87% yield. However, when isoflavane 5 was treated with 3-methyl-2-butenal through methods as described in the literature,[3,9] the major product 7 along with a trace amount of the target product 6 was isolated (Scheme 3).

Therefore, a stepwise reduction of 4 had to be conducted. The chemoselective reduction of conjugated olefins in \(\alpha,\beta\)-unsaturated carbonyl compounds have been reported.[10] After screening several reducing reagents (e.g., \(\text{Pd/C}\), \(\text{Raney Ni}\), \(\text{InCl}_3/\text{NaBH}_4\), \(\text{Na}_2\text{S}_2\text{O}_4\)), Raney Ni in dimethylformamide (DMF) was found to be a good choice for reducing reagent to produce 8 in a 91% yield (Table 1). Compound 8 was then reacted with 3-methyl-2-butenal in the presence of phenylboronic acid to afford 9 and 10 with a 84% yield and a 15:1 ratio. The isomers 9 and 10 could be isolated by column chromatography (Scheme 3).

Unfortunately, the methods to reduce the carbonyl group in 9 using \(\text{Zn(Hg)}/\text{HCl}\)[11] and \(\text{NH}_2\text{NH}_2/\text{NaOH}\)[12] were met with failure because the carbon–carbon

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**Scheme 1.** Retrosynthetic approach of (+)-glabridin.

**Scheme 2.** Reagents and conditions: (a) \(\text{Me}_2\text{SO}_4, \text{NaOH}/\text{H}_2\text{O}, \text{0 }^\circ\text{C to 70 }^\circ\text{C, 3 h, 85%}; (b) \(\text{CH}_2\text{COCl, AlCl}_3/\text{CH}_2\text{Cl}_2, 0\text{ }^\circ\text{C to rt, 1 h, 88%}; (c) sulfur, morpholine, 130\text{ }^\circ\text{C, 12 h}; (d) \text{NaOH, H}_2\text{O, reflux,12 h, 62% over two steps}; (e) resorcinol, \text{BF}_3\cdot\text{Et}_2\text{O, 100 }^\circ\text{C, 10 min}; (f) (1) DMF, 20\text{ }^\circ\text{C to 55\text{ }^\circ\text{C, 20 min}; (2) \text{MeSO}_2\text{Cl, 80 }^\circ\text{C, 3 h, 65% over two steps.}
double bonds could not be tolerated under the high-temperature condition. Then we examined other reducing reagents (LiAlH₄,[13] LiAlH₄=AlCl₃,[14] NaBH₄=AlCl₃,[15] NaBH₄=TFA[16]) and the reduction was accomplished in acceptable yield using LiAlH₄ (10eq) in THF (Table 2). Removal of both methyl ether groups[17] led to (±)-glabridin (1) in 84% yield (Scheme 3). Finally, we tried to separate racemic

Table 1. Reduction of 4

| Entry | Conditions | Isolated yield (%) |
|-------|------------|--------------------|
| 1     | H₂, 5% (w/w) 10% Pt/C, AcOH, 100 °C, 12 h | 77 21 — |
| 2     | H₂, 5% (w/w) 5% Pt/C, AcOH, 100 °C, 12 h | 65 33 — |
| 3     | Na₂S₂O₄, PTK, NaHCO₃, toluene/H₂O, 110 °C, 4 h | — 42 Trace |
| 4     | 0.5 equiv InCl₃, 1 equiv NaBH₄, MeOH, 22 °C, 5 h | — 57 — |
| 5     | H₂, 200% (w/w) Raney Ni, DMF, 22 °C, 30 min | — 91 — |
| 6     | Li-NH₃, −30 °C, 2 h | — 75 — |
| 7     | 1 equiv NaBH₄, MeOH, 22 °C, 10 h | — Messy — |

Scheme 3. Reagents and conditions: (a) H₂, Raney nickel, 1 atm, rt, 30 min, 91% (b) H₂, 5% Pd/C (containing about 50% water), AcOH–EtOH(1:9), rt, 12 h, 87%; (c) (CH₃)₂C=CHCHO (1.5eq), phenylboronic acid (1.2eq), toluene/HOAc, reflux, 12 h, 87%; (d) LiAlH₄ (10eq), THF, rt ro reflux, 6 h, 75%; (e) BBr₃(5eq), CH₂Cl₂, −78 °C to rt, 2 h, 84%.
mixtures (i.e., compound 8 or 1) by the Chiralpak OD-H chiral column (250 mm × 4.6 mm × 5 μm) from Japan. Racemic mixtures were performed with a mobile phase consisted of n-hexane: isopropanol (80:20, v:v), at flow rate of 1.0 mL min⁻¹, and the UV detector wavelength was set at 282 nm. Unfortunately we failed.

In conclusion, we have synthesized (±)-glabridin from the easily available resorcinol in 10 steps with a 14% overall yield. This procedure provide a practical synthesis of (±)-glabridin. Efforts to complete an asymmetric synthesis of Glabridin are in progress.

**EXPERIMENTAL**

NMR spectra were in CDCl₃ or CD₃SOCD₃ (¹H at 600 MHz and ¹³C at 125 MHz). Column chromatography was performed on silica gel (300–400 mesh). All chemicals were purchased from Sigma Aldrich. Unless otherwise noted, all reagents were obtained commercially and used without further purification. DMF was dried by CaH₂. Compounds 4 and 5 were prepared as per reported procedures.[5–8]

**Synthesis of 7, 9, and 10: General Procedure**

A solution of 5 or 8 (0.02 mol), aldehyde (0.03 mol), phenylboronic acid (0.024 mol), and glacial HOAc (130 mL) in anhydrous toluene (100 mL) was refluxed for 12 h under N₂ in an apparatus fitted with a Dean–Stark trap. The mixture was cooled and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to give the major product 7 or 9 and 10.

**Compound 7**

Yield: 87%. Mp: 143–144°C. Rf 0.35 (20:1 hex–EtOAc). ¹H NMR (CDCl₃, 600 MHz): δ 7.06 (d, 1H, J = 8.4 Hz), 6.77 (s, 1H), 6.57 (s, 1H), 6.51 (d, 1H, J = 8.4 Hz), 6.33 (d, 1H, J = 10.2 Hz), 6.19 (s, 1H), 5.54 (d, 1H, J = 9.6 Hz), 4.16
(d, 1H, J = 10.2 Hz), 3.94 (t, 1H, J = 10.2 Hz), 3.81 (s, 6H), 3.51–3.60 (m, 1H), 2.89 (dd, 1H, J = 11.4 and 15.0 Hz), 2.76 (dd, 1H, J = 15.6 and 3.6 Hz), 1.39 (s, 6H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 159.64, 158.24, 155.01, 152.29, 128.30, 127.51, 126.92, 121.92, 121.85, 114.79, 114.56, 114.18, 104.06, 98.66, 75.99, 70.11, 55.34, 31.55, 30.34, 27.91; ESI-MS: \(m/z\) (%) = 353 (100) \([M + H]^+\]. Anal. calcd. for C\(_{22}\)H\(_{24}\)O\(_4\): C, 74.98; H, 6.86. Found: C, 74.88; H, 6.92.

**Compound 9**

Yield: 78%. Mp: 137–139°C. Rf 0.39 (6:1 hex–EtOAc). \(^1\)H NMR (CDCl\(_3\), 600 MHz): \(\delta\) 7.79 (d, 1H, J = 9.0 Hz), 7.00 (d, 1H, J = 8.4 Hz), 6.62 (d, 1H, J = 10.2 Hz), 6.45–6.49 (m, 3H), 5.59 (d, 1H, J = 10.2 Hz), 4.58 (t, 1H, J = 11.4 Hz), 4.52 (dd, 1H, J = 11.4 and 5.4 Hz), 4.24 (dd, 1H, J = 11.4 and 5.4 Hz), 3.83 (s, 3H), 3.77 (s, 3H), 1.47 (s, 3H), 1.44 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 191.55, 160.46, 159.13, 158.43, 157.95, 130.69, 128.74, 128.49, 116.02, 115.80, 115.46, 110.88, 109.18, 104.59, 99.09, 77.40, 71.24, 55.49, 55.36, 47.18, 28.37, 28.01; ESI-MS: \(m/z\) (%) = 367 (100) \([M + H]^+\].

**Compound 10**

Yield: 5.3%. Mp: 153–154°C. Rf 0.32 (6:1 hex–EtOAc). \(^1\)H NMR (CDCl\(_3\), 600 MHz): \(\delta\) 7.62 (s, 1H), 7.00 (d, 1H, J = 7.8 Hz), 6.49 (s, 1H), 6.46 (d, 1H, J = 7.8 Hz), 6.32–6.35 (m, 2H), 5.59 (d, 1H, J = 9.6 Hz), 4.55 (t, 1H, J = 10.8 Hz), 4.46 (dd, 1H, J = 10.8 and 4.8 Hz), 4.23 (dd, 1H, J = 10.8 and 4.8 Hz), 3.79 (s, 3H), 3.76 (s, 3H), 1.45 (s, 6H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 191.57, 163.49, 160.46, 159.86, 158.40, 130.66, 129.34, 125.41, 121.28, 116.06, 115.90, 114.54, 104.58, 104.07, 99.11, 77.79, 71.12, 55.48, 55.36, 47.34, 28.54, 28.52; ESI-MS: \(m/z\) (%) = 367 (100) \([M + H]^+\]; Anal. calcd. for C\(_{22}\)H\(_{22}\)O\(_5\): C, 72.12; H, 6.05. Found: C, 72.06; H, 6.14.

**3-(2,4-Dimethoxyphenyl)-7-hydroxycroman-4-one (8)**

Raney nickel (5.8 g, 0.1 mol) was added to a solution of 4 (2.98 g, 0.01 mol) in DMF (100 mL). The reaction mixture was further stirred at room temperature for 30 min under a hydrogen atmosphere. The mixture was filtrated, and the filtrate was concentrated in vacuo. The residue was recrystallized from EtOAc at –5°C to give pure 8 (2.73 g, 91% yield). Mp: 181–183°C. Rf 0.31 (2:1 hex–EtOAc). \(^1\)H NMR (DMSO-\(d_6\), 600 MHz): \(\delta\) 10.57 (s, 1H), 7.69 (d, 1H, J = 8.4 Hz), 6.69 (d, 1H, J = 8.4 Hz), 6.59 (d, 1H, J = 2.4 Hz), 6.53 (dt, 1H, J = 8.4 and 1.2 Hz), 6.48 (dd, 1H, J = 8.4 and 2.4 Hz), 6.35 (m, 1H), 4.53 (t, 1H, J = 10.8 Hz), 4.42 (dd, 1H, J = 10.8 and 5.4 Hz), 4.16 (dd, 1H, J = 10.8 and 5.4 Hz), 3.75 (s, 3H), 3.72 (s, 3H); \(^{13}\)C NMR (DMSO-\(d_6\), 125 MHz): \(\delta\) 190.8, 164.8, 163.7, 160.4, 158.6, 131.1, 129.4, 116.5, 114.5, 111.0, 105.3, 102.8, 99.2, 70.8, 56.0, 55.6, 47.1; ESI-MS: \(m/z\) (%) = 323 (100) \([M + Na]^+\].

**2',4'-Dimethylglabridin (6)**

A solution of 9 (3.66 g, 0.01 mol) in ether (40 mL) was added dropwise to a solution of LiAlH\(_4\) (3.8 g, 0.1 mol) in ether (150 mL) at 20°C and then the mixture was
boiled under reflux for 6 h. The solution was cooled. The 50 mL of EtOAc was added dropwise. The solid was removed, filtrate was concentrated, and residue was purified by flash chromatography on silica gel (EtOAc–hexane) to give \(6\) (2.64 g, 75% yield). Mp: 97–99 °C. Rf 0.39 (20:1 hex–EtOAc). \(^1\)H NMR (CDCl\(_3\), 600 MHz): \(\delta\) 7.02 (d, 1H, \(J = 8.4\) Hz), 6.82 (d, 1H, \(J = 8.4\) Hz), 6.64 (d, 1H, \(J = 9.6\) Hz), 6.45–6.48 (m, 2H), 6.36 (d, 1H, \(J = 7.8\) Hz), 5.55 (d, 1H, \(J = 9.6\) Hz), 4.34 (dd, 1H, \(J = 7.2\) and 1.8 Hz), 3.97 (t, 1H, \(J = 10.8\) Hz), 3.80 (s, 3H), 3.79 (s, 3H), 3.53–3.57 (m, 1H), 2.95 (dd, 1H, \(J = 15.6\) and 11.4 Hz), 2.82 (dd, 1H, \(J = 15.6\) and 3.0 Hz), 1.42 (s, 3H), 1.40 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 159.64, 158.29, 151.82, 149.78, 129.17, 128.51, 127.54, 121.86, 116.98, 114.53, 109.86, 108.57, 104.08, 98.67, 75.53, 70.20, 55.34, 55.32, 31.47, 30.58, 27.78, 27.49; ESI-MS: \(m/z (\%) = 353 (100) [M + H]^+\). 

(\(\pm\))-Glabridin (1)

A solution of boron tribromide (1.0 M in CH\(_2\)Cl\(_2\), 0.05 mol) was added to a stirred solution of \(6\) (3.52 g, 0.01 mol) in CH\(_2\)Cl\(_2\) (200 mL) at \(-78\) °C. The reaction mixture was further stirred at room temperature for 2 h. Then the mixture was poured into an aqueous solution of saturated NaHCO\(_3\) (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (100 mL) and dried (Na\(_2\)SO\(_4\)). Removal of the solvent in vacuo followed by purification on silica gel provided (\(\pm\))-glabridin (1) (2.72 g, 84%). Mp: 227–229 °C. Rf 0.41 (100:9 CH\(_2\)Cl\(_2\)-MeOH). \(^1\)H NMR (DMSO-\(d_6\), 600 MHz): \(\delta\) 9.39 (s, 1H), 9.11 (s, 1H), 6.86 (d, 1H, \(J = 7.8\) Hz), 6.83 (d, 1H, \(J = 8.4\) Hz), 6.54 (d, 1H, \(J = 9.6\) Hz), 6.33 (s, 1H), 6.29 (d, 1H, \(J = 8.4\) Hz), 6.19 (d, 1H, \(J = 8.4\) Hz), 5.64 (d, 1H, \(J = 10.2\) Hz), 4.23 (d, 1H, \(J = 10.2\) Hz), 3.93 (t, 1H, \(J = 10.2\) Hz), 3.29 (t, 1H, \(J = 10.2\) Hz), 2.89 (dd appeared t, 1H, \(J = 11.4\) Hz), 2.69 (dd, 1H, \(J = 16.2\) and 4.2 Hz), 1.76 (s, 6H); \(^{13}\)C NMR (DMSO-\(d_6\), 125 MHz): \(\delta\) 157.31, 156.28, 151.65, 149.67, 129.76, 129.62, 127.99, 117.85, 116.86, 115.17, 109.99, 108.53, 106.70, 102.92, 75.65, 70.17, 31.31, 30.41, 27.77, 27.66; ESI-MS: \(m/z (\%) = 347 (100) [M + Na]^+\). 

SUPPORTING INFORMATION

Full experimental detail and \(^1\)H and \(^{13}\)C NMR spectra can be found via the Supplementary Content section of this article’s Web page.

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