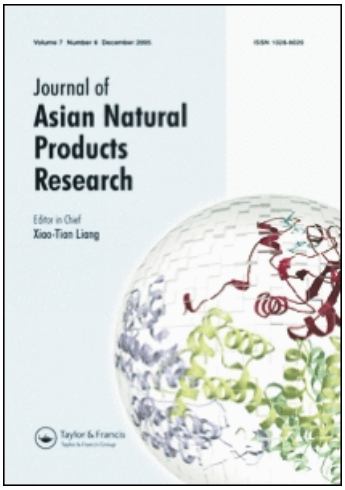

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Total synthesis of (−)-talaumidin and (−)-galbelgin

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(−)-Talaumidin (**1**) and (−)-galbelgin (**2**) have been synthesized via 4-pentenoic acid as a starting material with the overall yield of about 17.8 and 16.9%, respectively. The key steps include Evans asymmetry anti-aldol reaction, TBS protection, hydroboration, oxidation, Friedel–Crafts arylation, etc.

Keywords: (−)-talaumidin; (−)-galbelgin; total synthesis; anti-aldol reaction

1. Introduction

(−)-Talaumidin (**1**) and (−)-galbelgin (**2**) are naturally occurring lignans isolated from *Aristolochia arcuata* [1] and *Piper futokadsura* [2]. They belong to 2,5-diaryl-3,4-dimethyl-tetrahydrofuran lignans, an important subclass of lignans, which, recently, have stimulated substantial synthetic efforts due to their structural diversity and biological activity [3]. For example, (−)-talaumidin (**1**) has been proven to have significant neurotrophic property in the primary culture of rat cortical neurons, and could serve as a promising lead compound for treatment of neurodegenerative disorders, such as Alzheimer's and Parkinson's disease [4], while (−)-galbelgin (**2**) displays potent anti-HBV activity [5]. Although the synthesis of (−)-talaumidin (**1**) and (−)-galbelgin (**2**) ([6], Figure 1) has been reported by others, we would like to report a new facile synthetic route. The key steps in our synthesis include $MgCl_2$/TMSCl-promoted Evans asymmetry anti-aldol reaction [7] and Friedel–Crafts arylation/epimerization [8].

2. Results and discussion

The route of synthesis of (−)-talaumidin (**1**) and (−)-galbelgin (**2**) are shown in Schemes 1 and 2. Our synthesis starts with the Evans asymmetry anti-aldol reaction [7]. Thus, the treatment of (*R*)-3-(pent-4-enoyl)-4-phenyl-1,3-oxazolidin-2-one (**3**) and 3-methoxyl-4-benzoxyl-phenylaldehyde in the presence of $MgCl_2$/TMSCl gives compound **4**, followed by TBS protection affords compound **5**. Hydroboration of **5** with $LiBH_4$ gives compound **6** in good yield [9]. Treatment with methanesulfonyl chloride [10] and subsequent reduction with $LiAlH_4$ at 0°C [11] gives olefin **7** in 86% yield. Oxidation of **7** with OsO_4 and 2,6-lutidine [12] affords compound **8**, the TBS group removed by tetrabutyl ammonium fluoride (TBAF) yields cyclic compound **9**. Oxidation of **9** with pyridinium chlorochromate (PCC) [13] affords γ-lactone **10**, which upon α-methylation under conventional conditions (LHMDS, MeI) [14] exclusively produces 3,4-dimethyl-5-aryldihydrofuran-2(3H)-one (**11**) in 92% yield. The lactone **11** was

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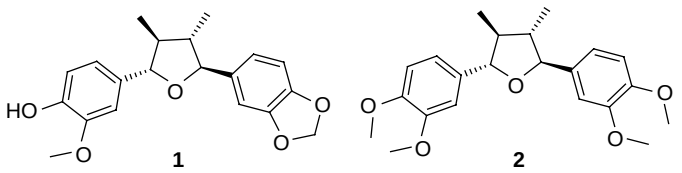
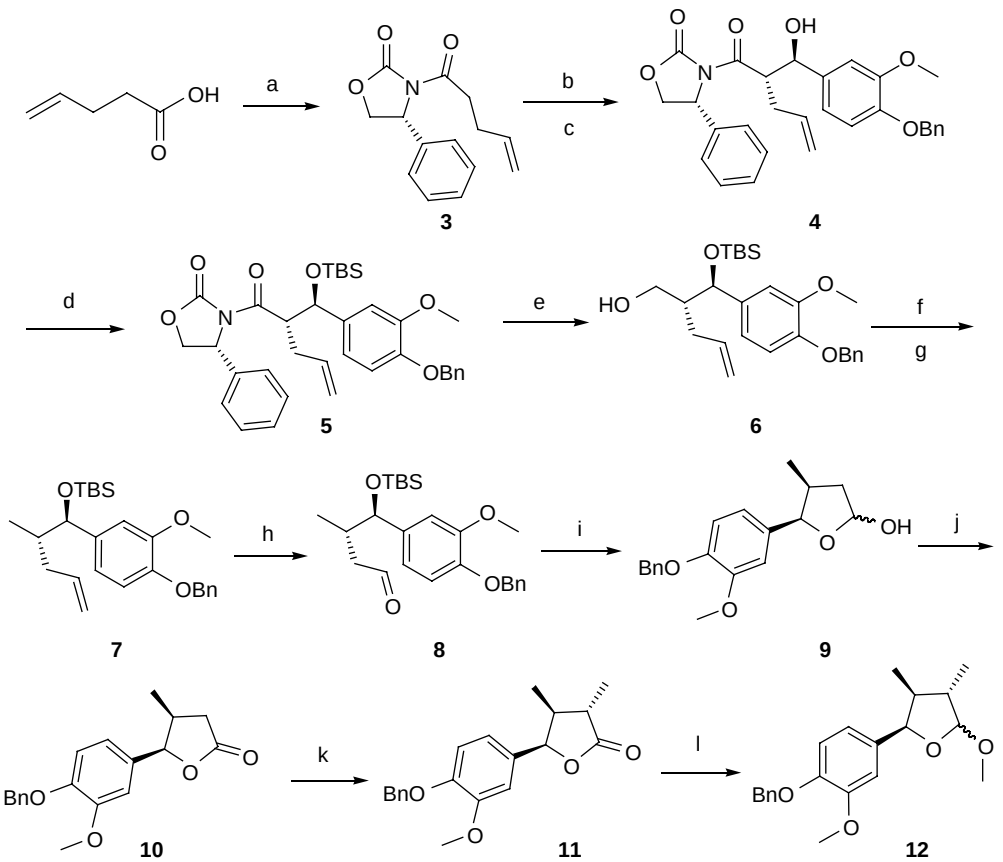


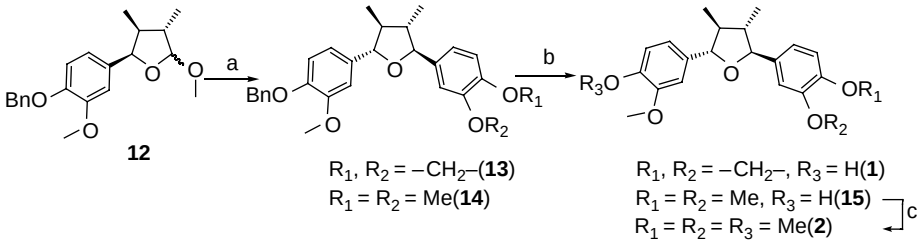
Figure 1. Structures of (−)-talaumidin (**1**) and (−)-galbelgin (**2**).

converted to the methyl acetal **12** through one-pot reduction with diisobutylaluminum (DIBAL-H) in CH_2Cl_2 at −78°C and acetalization in 85% yield.

With the methyl acetal **12** in hand, we converted it into 2,5-diaryl-3,4-dimethyl-tetrahydrofuran through Friedel–Crafts type arylation conditions ($SnCl_4$, CH_2Cl_2, −78°C, 2 h) [8]. The Friedel–Crafts type arylation proceeds with the epimerization at the C2 position of **12** to provide 2,3-*trans*-3,4-*trans*-4,5-*trans*-tetrahydrofuran **13** and **14** as a



Scheme 1. Synthesis of compound (**12**). Reagents and conditions: (a) trimethylacetyl chloride, Et_3N, dry THF, −25°C; then LiCl, (*R*)-(−)-4-phenyl-2-oxazolidinone; (b) 3-methoxyl-4-benzoxyl-phenylaldehyde, $MgCl_2$, TMSCl, Et_3N, EtOAc; (c) TFA, CH_3OH; (d) imidazole, TBDMSCl, DMF; (e) $LiBH_4$, Et_2O/H_2O; (f) MsCl, Et_3N; (g) LAH, Et_2O, 0°C; (h) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane/H_2O; (i) TBAF, THF; (j) PCC, powdered molecular sieve, CH_2Cl_2; (k) LHMDS, CH_3I, THF, −78°C; (l) DIBAL-H, CH_2Cl_2, −78°C; then $(CH_3O)_3CH$, TsOH, H_2O/CH_3OH.



Scheme 2. Synthesis of (−)-talaumidin (**1**) and (−)-galbelgin (**2**). Reagents and conditions: (a) $SnCl_4$, 1,3-benzodioxole/1,2-dimethoxyl-benzene, CH_2Cl_2, −78°C, (b) H_2, Pd-C, EtOAc/EtOH, and (c) CH_3I, K_2CO_3, DMF.

single diastereomer. Finally, removal of Bn protecting group in **13** gives (−)-talaumidin (**1**) (90%).

The total synthesis of (−)-galbelgin (**2**) was also accomplished in two steps from the intermediate **14** as shown in Scheme 2 through Bn deprotection and *O*-methylation under conventional conditions (MeI, K_2CO_3, and DMF).

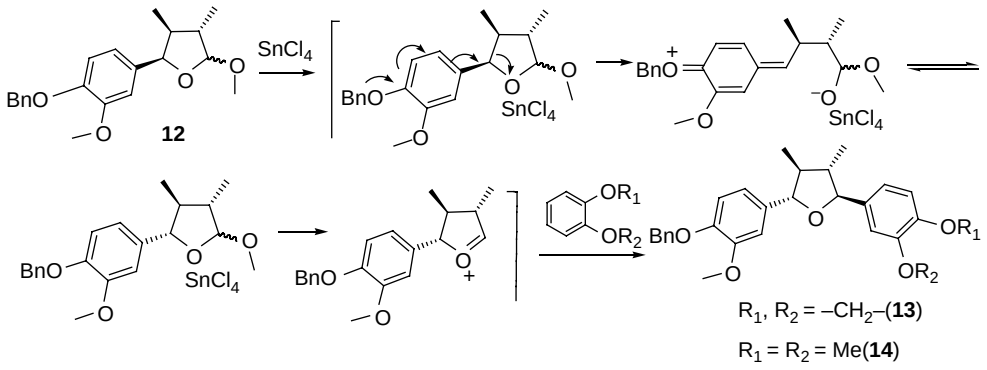
The observed epimerization of **13** and **14** have the 2,3-*trans*-3,4-*trans*-4,5-*trans*-configuration, which could be explained by the following mechanism as shown in Scheme 3. Lewis acid activation of the methyl acetal **12** by $SnCl_4$ combined with an inductive effect of the electron-donating Bn group and an steric effect of the *ortho*-methyl on the C2-aryl substituent effectively gives all *trans*-product.

In summary, the total synthesis of (−)-talaumidin (**1**) and (−)-galbelgin (**2**) was achieved in 17.8 and 16.9% overall yield, respectively. The synthesis was featured using Evans asymmetry anti-aldol reaction and Friedel–Crafts arylation and epimerization. These reactions could be run under mild conditions with high stereoselectivity. Application of this methodology to the synthesis of analogs of (−)-talaumidin (**1**) and (−)-galbelgin (**2**) is in progress.

3. Experimental

3.1 General experimental procedures

Melting points were determined with a Yanaco micrometer and are uncorrected. NMR spectra were taken on a Mercury-300 or INOVA-500 spectrometer with TMS as the internal reference. EI-MS was obtained on a ZAB-2F spectrometer. The optical rotations were recorded on a Perkin-Elmer 241 polarimeter. Column chromatography was performed on silica gel (160–200 mesh).



Scheme 3. Mechanism of the Friedel–Crafts arylation and epimerization.

CH_2Cl_2 was distilled from P_2O_5; THF was distilled from sodium benzophenone ketyl.

*3.1.1 The synthesis of compound **6** from compound **3** has been reported in the literature [15]*

*3.1.2 (4S,5R)-5-(4-benzyloxy-3-methoxy-phenyl)-5-(tert-butyldimethylsilanyloxy)-4-methyl-1-pentene (**7**)*

To a cooled (0°C) solution of alcohol **6** (7.2 g, 16 mmol) in CH_2Cl_2 (50 ml), triethylamine (5.8 ml, 57 mmol) and MsCl (2.5 ml, 32 mmol) were added. After being stirred at 0°C for 2 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and diluted with CH_2Cl_2 (100 ml). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 ml). The combined organic layers were washed with 5% NaOH solution, water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. This crude mesylate was carried to the next step without further purification. To a solution of the above mesylate (7.82 g) in THF (150 ml), $LiAlH_4$ (1.82 g, 48 mmol) was added slowly at 0°C. After the mixture was stirred at room temperature for 3 h, the reaction was quenched with saturated aqueous NH_4Cl solution at 0°C, filtered through a pad of Celite, and the filter was washed by EtOAc (200 ml). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 60 ml). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, PE/EtOAc, 10/1) to afford alkene **7** as a colorless oil (5.52 g, 86%). $[\alpha]_D^{20}+29.0$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.29 (m, 5H, ArH), 6.83 (m, 3H, ArH), 5.76 (m, 1H, 2-H), 5.12 (s, 2H, $PhCH_2O$), 4.97 (complex, 2H, 1-H), 4.42 (d, $J = 4.8$ Hz, 1H, 5-H), 3.87 (s, 3H, OCH_3), 2.15 (m, 1H, 4-H), 1.75 (m, 2H, 3-H), 0.90 (s, 9H, $C(CH_3)_3$), 0.85 (d, $J = 6.4$ Hz, 3H, 4-CH_3), 0.06 (s, 3H, $SiCH_3$), and 0.21 (s, 3H, $SiCH_3$).

*3.1.3 (3S,4R)-4-(4-benzyloxy-3-methoxy-phenyl)-4-(tert-butyldimethyl-silanyloxy)-3-methylbutyraldehyde (**8**)*

To a solution of alkene **7** (6.3 g, 15 mmol) in dioxane/H_2O (3/1, total 135 ml), 2,6-lutidine (3.2 ml, 27.5 mmol), $NaIO_4$ (10.2 g, 50 mmol), and 4% OsO_4 solution (1 ml, 3 mmol) were added. After being stirred at room temperature for 3 h, H_2O (100 ml) and CH_2Cl_2 (200 ml) were added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 ml). The combined organic layers were washed with saturated aqueous sodium hydrogen sulfite, saturated aqueous sodium carbonate, water, and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, PE/EtOAc, 5/1) to afford aldehyde **8** as a colorless oil (5.4 g, 80%). $[\alpha]_D^{20}+20$ ($c = 1.4$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.68 (s, 1H, CHO), 7.55–7.29 (m, 5H, ArH), 6.83 (m, 3H, ArH), 5.12 (s, 2H, $PhCH_2O$), 4.30 (d, $J = 4.8$ Hz, 1H, 4-H), 3.87 (s, 3H, CH_3O), 2.92–3.01 (m, 1H, 2-H), 2.32–2.44 (m, 1H, 2-H), 2.12 (m, 1H, 3-H), 0.86 (s, 9H, $(CH_3)_3CSi$), 0.85 (d, $J = 4.8$ Hz, 3H, CH_3), 0.02 (s, 3H, $SiCH_3$), −0.22 (s, 3H, $SiCH_3$); ESI-MS *m/z* (%): 443 $[M + K]^+$, 313, 91 (100).

*3.1.4 (4S,5R)-5-(4-benzyloxy-3-methoxy phenyl)-4-methyltetrahydrofuran-2-ol (**9**)*

To a solution of aldehyde **8** (3.3 g, 7.8 mmol) in THF (50 ml), TBAF (3.2 g, 10 mmol) was added. After the mixture was stirred at the room temperature for 2 h, the reaction was quenched with saturated aqueous NH_4Cl solution at 0°C. The mixture was diluted with EtOAc (60 ml). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 60 ml). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, PE/EtOAc, 3/1) to afford alcohol **9** as a colorless oil (2.2 g, 90%). HR-EI-MS *m/z*:

337.1415 $[M + Na]^+$ (calcd for $C_{19}H_{22}O_4Na$, 337.1416).

3.1.5 (4S,5R)-5-(4-benzyloxy-3-methoxy phenyl)-4-methyl-tetrahydrofuran-2(3H)-one (**10**)

To a solution of alcohol **9** (5.0 g, 15.8 mmol) in CH_2Cl_2 (50 ml), powdered molecular sieve (1.0 g) and PCC (4.2 g, 19.5 mmol) were added. After the mixture was stirred at room temperature for 1 h, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, PE/EtOAc, 5/1) to afford 4,5-*cis*-γ-lactone **10** as a colorless oil (3.9 g, 79%). $[\alpha]_D^{20}+26.0$ ($c = 1.0$, $CHCl_3$) ([6], $[\alpha]_D^{20}+26.7$ ($c = 2.3$, $CHCl_3$)); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.28–7.45 (m, 5H, ArH), 6.89 (d, $J = 8.0$ Hz, 1H, ArH), 6.78 (d, $J = 2.0$ Hz, 1H, ArH), 6.70 (ddd, $J = 8.0$, 2.0, 0.8 Hz, 1H, ArH), 5.54 (d, $J = 5.6$ Hz, 1H, 5-H), 5.15 (s, 2H, $PhCH_2$), 3.89 (s, 3H, CH_3O), 2.78–2.86 (m, 2H, 3-H), 2.35 (m, 1H, 4-H), and 0.71 (d, $J = 7.2$ Hz, 3H, 4-CH_3); HR-EI-MS *m/z*: 313.1432 $[M + H]^+$ (calcd for $C_{19}H_{21}O_4$, 313.1440).

3.1.6 (3S,4S,5R)-3,4-dimethyl-5-(4-benzyl oxy-3-methoxyphenyl)-dihydrofuran-2(3H)-one (**11**)

To a cooled (−78°C) solution of lactone **10** (6 g, 19 mmol) in anhydrous THF (100 ml), LHMDS (27 ml, 1 M solution in THF, 27 mmol) was added dropwise. The resulting mixture was stirred for 30 min and MeI (3 ml, 74 mmol) was added. The reaction mixture was stirred at −78 to −20°C for 3 h, then quenched with saturated aqueous NH_4Cl solution and diluted with EtOAc (100 ml). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 50 ml). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; PE/EtOAc, 5/1) to afford compound **11** as a colorless oil (4.7 g, 75%). $[\alpha]_D^{20}-30.0$ ($c = 1.0$, $CHCl_3$) ([6], $[\alpha]_D^{20}-30.2$ ($c = 1.3$, $CHCl_3$)); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.27–7.43 (m, 5H, ArH), 6.86 (d, $J = 8.0$ Hz, 1H, ArH), 6.66 (d, $J = 2.0$ Hz, 1H, ArH), 6.63 (dd, $J = 8.0$, 2.4 Hz, 1H, ArH), 5.48 (d, $J = 7.6$ Hz, 1H, 5-H), 5.14 (s, 2H, $PhCH_2O$), 3.85 (s, 3H, CH_3), 2.44 (m, 1H, 3-H), 2.32 (m, 1H, 4-H), 1.26 (d, $J = 7.2$ Hz, 3H, 3-CH_3), and 0.74 (d, $J = 6.8$ Hz, 3H, 4-CH_3); HR-EI-MS *m/z*: 349.1421 $[M + Na]^+$ (calcd for $C_{20}H_{22}O_4Na$, 349.1410).

3.1.7 (3S,4S,5R)-2-methoxy-3,4-dimethyl-5-(4-benzyloxy-3-methoxyphenyl)-tetra-hydrofuran (**12**)

To a solution of lactone **11** (0.84 g, 2.5 mmol) in anhydrous CH_2Cl_2 (8 ml), DIBAL-H (4 ml, 1 M solution in hexane, 4 mmol) was added dropwise at −78°C. After being stirred for 1 h, the reaction mixture was quenched with MeOH and allowed to warm to room temperature. To this mixture, MeOH (4 ml), trimethyl orthoacetate (0.39 g, 3.7 mmol), and PTSA (0.1 g, 0.5 mmol) were added. The resulting mixture was stirred for 2 h at room temperature, quenched with saturated aqueous $NaHCO_3$ solution, and diluted with EtOAc (60 ml). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 60 ml). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; PE/EtOAc, 10/1 to 4/1) to afford ca. 1:1 mixture of methyl acetal **12** as a colorless oil (0.76 g, 85%). HR-EI-MS *m/z*: 365.1732 $[M + Na]^+$ (calcd for $C_{21}H_{26}O_4Na$, 365.1723).

3.1.8 5-[(2S,3S,4S,5S)-5-(4-benzyloxy-3-methoxyphenyl)-3,4-dimethyl-tetrahydrofuran-2-yl]-benzo[1,3]-dioxole (**13**)

To a stirred solution of methyl acetal **12** (200 mg, 0.58 mmol) and 1,3-benzodioxole (500 mg, 4 mmol) in anhydrous CH_2Cl_2 (10 ml), $SnCl_4$ (0.07 ml, 0.58 mmol) was

added dropwise at −78°C. After being stirred at the same temperature for 2 h, the reaction mixture was quenched with NH_4Cl solution, and diluted with CH_2Cl_2 (50 ml). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 ml). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, PE/EtOAc, 10/1) to afford *O*-benzyl talaumidin **13** as a colorless oil (210 mg, 85%). $[\alpha]_D^{20} - 89$ ($c = 0.9$, $CHCl_3$) ([6], $[\alpha]_D^{20} - 49.5$ ($c = 0.57$, $CHCl_3$)); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.27–7.45 (m, 5H, ArH), 6.76–6.98 (m, 6H, ArH), 5.94 (s, 2H, $PhCH_2O$), 5.15 (s, 2H, CH_2), 4.61 (d, $J = 7.6$ Hz, 2H, 2-H, 5-H), 3.92 (s, 3H, CH_3O), 1.71–1.84 (m, 2H, 3,4-H), 1.04 (d, $J = 4.8$ Hz, 3H, CH_3), and 1.02 (d, $J = 4.8$ Hz, 3H, CH_3); HR-EI-MS *m/z*: 455.1822 $[M + Na]^+$ (calcd for $C_{27}H_{28}O_5Na$, 455.1834).

3.1.9 (−)-Talaumidin (*1*)

To a solution of **13** (100 mg, 0.29 mmol) in EtOAc/EtOH (3/1, 4 ml), 10% Pd/C (30 mg) was added at room temperature. After being stirred at the same temperature for 1 h, the reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, PE/EtOAc, 6/1 to 3/1) to afford (−)-talaumidin (**1**) as a colorless oil (70 mg, 90%). $[\alpha]_D^{20} - 80$ ($c = 0.4$, $CHCl_3$) ([6], $[\alpha]_D^{20} - 81.8$ ($c = 0.047$, $CHCl_3$)); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.94–6.78 (m, 6H, ArH), 5.95 (s, 2H, OCH_2O), 5.59 (s, 1H, OH), 4.61 (d, $J = 9.0$ Hz, 2H, 2-H, 5-H), 3.91 (s, 3H, CH_3O), 1.72–1.79 (m, 2H, 3-H, 4-H), 1.04 (d, $J = 4.6$ Hz, 3H, CH_3), and 1.02 (d, $J = 4.6$ Hz, 3H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) 147.7, 146.9, 146.6, 145.1, 136.5, 134.1, 119.6, 119.4, 114.0, 108.5, 107.9, 106.5, 100.9, 88.3, 88.1, 55.9, 51.1, 50.8, and 13.8. HR-EI-MS *m/z*: 343.1538 $[M + H]^+$ (calcd for $C_{20}H_{23}O_5$, 343.1545).

3.1.10 (2S,3S,4S,5S)-2-(4-benzyloxy-3-methoxyphenyl)-5-(3,4-dimethoxyphenyl)-3,4-dimethyl-tetrahydrofuran (*14*)

To a stirred solution of methyl acetal **12** (200 mg, 0.58 mmol) and 1,2-dimethoxylbenzene (570 mg, 4 mmol) in anhydrous CH_2Cl_2 (10 ml), $SnCl_4$ (0.07 ml, 0.58 mmol) was added dropwise at −78°C. After being stirred at the same temperature for 2 h, the reaction mixture was quenched with NH_4Cl solution, and diluted with CH_2Cl_2 (50 ml). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 ml). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, PE/EtOAc, 15/1) to afford *O*-benzyl galbelgin **14** as a colorless oil (210 mg, 80%). $[\alpha]_D^{20} - 79$ ($c = 0.6$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.28–7.45 (m, 5H, ArH), 6.83–6.98 (m, 6H, ArH), 5.15 (s, 2H, $PhCH_2O$), 4.64 (d, $J = 12$ Hz, 2H, 2-H, 5-H), 3.92 (s, 3H, CH_3O), 3.91 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 1.79 (s, 2H, 3,4-H), 1.05 (d, $J = 4.8$ Hz, 3H, CH_3), and 1.03 (d, $J = 4.8$ Hz, 3H, CH_3); HR-EI-MS *m/z*: 471.2148 $[M + Na]^+$ (calcd for $C_{28}H_{32}O_5Na$, 471.2147).

3.1.11 (2S,3S,4S,5S)-2-(3,4-dimethoxyphenyl)-5-(3-hydroxyl-4-benzyloxyphenyl)-3,4-dimethyl tetrahydrofuran (*15*)

To a solution of **14** (100 mg, 0.22 mmol) in EtOAc/EtOH (3/1, 4 ml), 10% Pd/C (30 mg) was added at room temperature. After being stirred at the same temperature for 1 h, the reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, PE/EtOAc, 10/1 to 8/1) to afford alcohol **15** as a colorless oil (75 mg, 90%). $[\alpha]_D^{20} - 100$ ($c = 0.45$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.83–6.96 (m, 6H, ArH), 5.57 (s, 1H, OH), 4.65 (d, $J = 12.0$ Hz, 2H, 2-H, 5-H), 3.92 (s, 3H, CH_3O), 3.91 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 1.78 (s, 2H, 3,4-H), 1.05 (d, $J = 6.0$ Hz, 3H, CH_3), and 1.03 (d,

$J = 6.0$ Hz, 3H, CH_3); HR-EI-MS *m/z*: 381.1669 $[M + Na]^+$ (calcd for $C_{21}H_{26}O_5Na$, 381.1678).

3.1.12 (−)-Galbelgin (**2**)

To a solution of the above alcohol **15** (75 g, 0.2 mmol) in DMF (3 ml), anhydrous K_2CO_3 (55.2 mg, 0.4 mmol) and MeI (50 μl, 0.8 mmol) were added. After being stirred for 12 h at room temperature, the mixture was diluted with EtOAc (20 ml). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 ml). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, PE/EtOAc, 10/1 to 8/1) to afford (−)-galbelgin (**2**) as a white solid (68 mg, 92%); mp 142–143°C, $[\alpha]_D^{20} - 98$ ($c = 0.5$, $CHCl_3$) ([6], $[\alpha]_D^{20} - 102$ ($c = 0.04$, $CHCl_3$)); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.97 (d, $J = 1.6$ Hz, 2H), 6.92 (dd, $J = 8.4$, 1.6 Hz, 2H), 6.85 (d, $J = 8.4$ Hz, 2H), 4.66 (d, $J = 9.2$ Hz, 2H), 3.91 (s, 6H), 3.88 (s, 6H), 1.78–1.81 (m, 2H), and 1.05 (d, $J = 5.6$ Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 149.0, 148.5, 134.9, 118.6, 110.8, 109.2, 88.3, 55.9 (two carbons are overlapped), 51.0, and 13.8; HR-EI-MS *m/z*: 395.1822 $[M + Na]^+$ (calcd for $C_{22}H_{28}O_5Na$, 395.1834).

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