Supporting Information

Total Synthesis of (±)-Glabridin

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3-(2,4-dimethoxyphenyl)-7-hydroxy-4H-chromen-4-one (**4**)

To a mixture of **3** (19.6 g, 0.1 mol) and resorcinol (11.0 g, 0.1 mol) was added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (30 mL). The reaction mixture was heated at 100 °C for 10 min and cooled to room temperature. Dry DMF (135 mL) was added, and the reaction mixture was heated at 55 °C for 20 min. MeSO_2Cl (80.0 g) was added, and the reaction mixture was heated at 80 °C for 3 h. The mixture was cooled to room temperature, and cold water (800 mL) was added. The precipitate was filtered using a Büchner funnel and washed with ice-cold EtOAc to yield 19.4 g (65%) of **4** as a nearly colorless solid. Mp: 265-267 °C. Rf 0.49 (1:1 hex : EtOAc). ^1H NMR ($\text{DMSO}-d_6$, 600 MHz): δ 10.76 (s, 1H), 8.12 (s, 1H), 7.91 (d, 1H, $J = 9.0$ Hz), 7.13 (d, 1H, $J = 7.8$ Hz), 6.92 (d, 1H, $J = 9.0$ Hz), 6.86 (d, 1H, $J = 1.8$ Hz), 6.63 (s, 1H), 6.56 (dd, 1H, $J = 8.4$ and 1.8 Hz), 3.80 (s, 3H), 3.72 (s, 3H); ^{13}C NMR ($\text{DMSO}-d_6$, 125 MHz): δ 174.85, 162.88, 161.11, 158.86, 157.95, 154.34, 132.48, 127.63, 122.06, 116.99, 115.47, 113.94, 104.98, 102.58, 99.00, 55.96, 55.71; ESI-MS: m/z (%) = 321 (100) [$\text{M} + \text{Na}^+$].

3-(2,4-dimethoxyphenyl)chroman-7-ol (**5**)

To a solution of **4** (14.9 g, 0.05 mol) in AcOH–EtOH (1 : 9, 500 mL) was added 5% Pd/C (containing about 50% water, 0.75 g). The reaction mixture was stirred at room temperature for 12 h under a hydrogen atmosphere. The mixture was filtrated, and the filtrate was concentrated in vacuo. The residue was recrystallized from EtOH at -10

°C to give pure 5 (12.4 g, 87% yield). Mp: 171-173 °C. Rf 0.39 (5:1 hex : EtOAc). ¹H NMR (DMSO- *d*₆, 600 MHz): δ 9.15 (s, 1H), 7.07 (d, 1H, *J* = 8.4 Hz), 6.86 (d, 1H, *J* = 8.4 Hz), 6.57 (d, 1H, *J* = 3.0 Hz), 6.48 (dd, 1H, *J* = 8.4 and 2.4 Hz), 6.28 (dd, 1H, *J* = 8.4 and 2.4 Hz), 6.18 (d, 1H, *J* = 2.4 Hz), 4.12 (dt, 1H, *J* = 10.2 and 2.4 Hz), 3.91 (t, 1H, *J* = 10.2 Hz), 3.79 (s, 3H), 3.74 (s, 3H), 3.33-3.35 (m, 1H), 2.87 (dd, 1H, *J* = 15.6 and 11.4 Hz), 2.72 (dd, 1H, *J* = 15.6 and 3.6 Hz); ¹³C NMR (DMSO- *d*₆, 125 MHz): δ 159.74, 158.21, 156.94, 154.97, 130.50, 127.94, 121.64, 113.07, 108.42, 105.13, 102.96, 98.92, 69.67, 55.91, 55.55, 31.33, 30.34; ESI-MS: *m/z* (%) = 309 (100) [M+Na⁺].

Data Collected on:
 Inova600-Inova600
 Archive directory:
 /report/home/sj/vnmrsys/data
 Sample directory:
 File: sw-h-dmso-jlwenhua-20121031
 Pulse Sequence: s2pu1
 Solvent: DMSO
 Solvent: DMSO
 Ambient temperature
 Filter: sw-h-dmso-jlwenhua-20121031
 INOVA-600 "Inova600"
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.592 sec
 Width 19001.8 Hz
 32 repetitions
 OBSERVE H1, 599.7757263 MHz
 DATA PROCESSING
 FT size 131072
 Total time 1 min, 32 sec

STANDARD CARBON PARAMETERS

Data Collected on:
 Inova600-Inova600
 Archive directory:
 /report/home/sj/vnmrsys/data
 Sample directory:
 File: sw-c-dmso-jlwenhua-20120607
 Pulse Sequence: s2pu1
 Solvent: DMSO
 Solvent: DMSO
 Ambient temperature
 User: i-14-67
 Filter: sw-c-dmso-jlwenhua-20120607
 INOVA-600 "Inova600"
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.380 sec
 Width 37700.3 Hz
 818 repetitions
 OBSERVE C13, 150.8137312 MHz
 DECOUPLE H1, 599.7762447 MHz
 Power 46 dB
 Continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Gauss apodization 0.086 sec
 FT size 131072
 Total time 1 hr, 55 min, 28 sec

Chemical structure of compound **5**: 2-(4,6-dimethoxyphenyl)-2H-chromene.

¹H NMR spectrum (CDCl₃) of compound **5**. The spectrum shows peaks from 0 to 10 ppm. The chemical shifts (ppm) are listed on the right, and the integration values are shown below the baseline.

Chemical shifts (ppm): 9.161, 7.073, 7.051, 6.881, 6.852, 6.852, 6.571, 6.567, 6.481, 6.481, 6.481, 6.471, 6.471, 6.293, 6.277, 6.272, 6.272, 6.191, 6.191, 4.131, 4.111, 4.111, 4.111, 4.114, 4.103, 3.895, 3.895, 3.812, 3.812, 3.805, 3.762, 3.762, 3.553, 3.541, 3.541, 2.871, 2.871, 2.865, 2.865, 2.727, 2.727, 2.708, 2.708, 2.595, 2.595, 2.582, 2.582, 2.489, 2.489, 1.393.

Integration values: 1.01, 0.991, 0.991, 1.02, 1.06, 0.91, 1.02, 1.0, 1.0, 1.02, 1.0, 1.08, 1.56.

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Data Collected on
  Inova690-inova690
  Inova690 directory
  /export/home/csl/vmn/rsj/data
  Sample directory:
  File: su-c-dmso-j1wnhuwa-2012619
  Pulse Sequence: sz2pul
  Solvent: DMSO
  Ambient Temperature
  User: 1-14-97
  File: su-c-dmso-j1wnhuwa-2012619
  Inova690-inova690
  Relax. delay 2.000 sec
  Pulse delay 0.050 sec
  Acq. time 1:300 sec
  Width 3.000 MHz
  688 repetitions
  OBSERVE H1, 339.773732 MHz
  DECOUPLE H1, 539.774647 MHz
  Power 16 db
  Continuous by on
  WALTZ-16 modulated
  2D 1D PROCESSED
  Line broadening 0.5 Hz
  FT
  Total time 2 hr, 45 min, 26 sec
  153.749
  153.749

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Data Collected on:
  inova600-inova600
Archive directory:
  /export/home/kai/vnmrsys/date
Sample directory:
  File: sw-c-cdc13-jiwenhua-20121123
Pulse Sequence: s2pul
Solvent: CDC13
Solvent: CDC13
Ambient temperature
User: i-14-87
File: sw-c-cdc13-jiwenhua-20121123
INOVA-600 "inova600"
```

150.641
156.287
151.821
144.781

123.169
126.851
127.535
121.855

116.561
114.552
110.804
108.268
104.877

98.672

77.227
77.227
76.804
76.804

Data Collected on:
 Inova600-inova600
 Archive directory:
 /export/home/sq/vnmrsys/data
 Sample directory:
 File: sw-h-dmsc-jvh-20120711-fu
 Pulse Sequence: s2pul
 Solvent: DMSO
 Solvent: DMSO
 Ambient Temperature
 File: sw-h-dmsc-jvh-20120711-fu
 INOVA-600 "inova600"
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 10001.8 Hz
 32 repetitions
 OBSERVE H1, 500.137252 MHz
 DATA PROCESSING
 FT size 131072
 Total time 1 min, 32 sec

STANDARD CARBON PARAMETERS

Data Collected on:
 Inova600-inova600
 Archive directory:
 /export/home/sq/vnmrsys/data
 Sample directory:
 File: sw-c-dmsc-jvh-20120711-fu
 Pulse Sequence: s2pul
 Solvent: DMSO
 Solvent: DMSO
 Ambient Temperature
 User: 1-14-97
 File: sw-c-dmsc-jvh-20120711-fu
 INOVA-600 "inova600"
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.380 sec
 Width 27700.3 Hz
 400 repetitions
 OBSERVE C13, 150.8137312 MHz
 DECOUPLE H1, 500.137252 MHz
 Power 46 dB
 Continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening 0.5 Hz
 FT size 131072
 Total time 1 hr, 16 min, 58 sec

Data Collected on:
 Inova600-inova600
 Archive directory:
 /export/home/csl/vnmrsw/data
 Sample directory:
 File: sw-h-cdc13-jlwenhua-20120813 -1
 Pulse Sequence: s2pul
 Solvent: CDCl3
 Solvent: CDCl3
 Ambient temperature
 File: sw-h-cdc13-jlwenhua-20120813
 INOVA-600 "Inova600"
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.832 sec
 Width 18901.8 Hz
 32 repetitions
 OBSERVE H1 501.7726536 MHz
 DATA PROCESSING
 FT size 131072
 Total time 1 min, 32 sec

STANDARD CARBON PARAMETERS

Data Collected on:
 Inova600-inova600
 Archive directory:
 /export/home/csl/vnmrsw/data
 Sample directory:
 File: sw-c-cdc13-jlwenhua-20120813 -1
 Pulse Sequence: s2pul
 Solvent: CDCl3
 Solvent: CDCl3
 Ambient temperature
 User: 1-10-87
 File: sw-c-cdc13-jlwenhua-20120813
 INOVA-600 "Inova600"
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.395 sec
 Width 37700.3 Hz
 384 repetitions
 OBSERVE C13 150.8130148 MHz
 DECOUPLE H1 501.7726537 MHz
 Power 46 dB
 continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening 0.5 Hz
 FT size 131072
 Total time 1 hr, 55 min, 28 sec

data
0120013-2

7.004
6.993
6.406
6.395
6.382
6.347
6.340
6.330
5.518
5.502
4.553
4.551
4.533
4.530
4.517
4.512
4.445
4.443
4.224
4.224
3.787
3.785

1.645
1.432

0.001

10

9 8 7 6 5 4 3 2 1 ppm

0.09
1.00
2.16
1.76
0.95
1.04
1.00
1.40
6.27
6.15

```
Data Collected on:
  inovat600-inova600
Archive directory:
  export/home/sd/1wmer/sys/data
Sample directory:

File: sw-c-cdc13-1jvwnhuc-20120813-2
Pulse Sequence: s2pul
Solvent: CDC13
Solvent: CDC13
Solvent temperature
  user: 13-14-67
File: sw-c-cdc13-1jvwnhuc-20120813-2
IMDA-600      "inova600"

Relax. delay 1.000 sec
Pulse width 0.9 degrees
Acq. time 1.300 sec
Fid 357790.3 Hz
272
OBSERVE C13, 150.631040 MHz
DECOUPLE H1, 593.750957 MHz
Waltz16
Continue on
  INVTZ-16 modulated
DATA PROCESSING
  Line broadening 0.5 Hz
  Gain 1.000000
Total time 1 hr, 55 min, 28 sec
```

Data Collected on: inovas60-inova600
 Archive directory: /export/home/sq/vnmrsvs/data
 Sample directory:
 File: sv-h-dmsc-jlwenhua-20121130
 Pulse Sequence: s2pul
 Solvent: DMSO
 Solvent: DMSO
 Ambient temperature
 File: sv-h-dmsc-jlwenhua-20121130
 INOVA-600 "inova600"
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.892 sec
 Width 15000.0 Hz
 OBSERVE H1: 500.137258 MHz
 32 repetitions
 DATA PROCESSING
 FT size 65536
 Total time 1 min, 32 sec

STANDARD CARBON PARAMETERS

Data Collected on: inovas60-inova600
 Archive directory: /export/home/sq/vnmrsvs/data
 Sample directory:
 File: sv-c-dmsc-jlwenhua-20121130
 Pulse Sequence: s2pul
 Solvent: DMSO
 Solvent: DMSO
 Ambient temperature
 User: 1-14-97
 File: sv-c-dmsc-jlwenhua-20121130
 INOVA-600 "inova600"
 Relax. delay 2.000 sec
 Pulse 45.0 degrees
 Acq. time 1.300 sec
 Width 27700.0 Hz
 1552 repetitions
 OBSERVE C13: 150.8137312 MHz
 DECOUPLE H1: 500.137258 MHz
 Power 48 dB
 continuous ly on
 WALTZ-16 modulated
 Gauss apodization 0.033 sec
 FT size 131072
 Total time 2 hr, 45 min, 28 sec