Supporting Information

**IMPACT OF GREEN TEA CATECHIN ECG AND ITS SYNTHESIZED FLUORINATED ANALOGUE ON PROSTATE CANCER CELLS AND INFLAMMATORY IMMUNOCOMPETENT CELLS**

Sven Stadlbauer¹, Carmen Steinborn¹, Amy Klemd¹, Fumihiko Hattori², Ken Ohmori², Keisuke Suzuki², Roman Huber¹, Philipp Wolf³, Carsten Gründermann¹

**Affiliations**

¹Center for Complementary Medicine, Institute for Infection Prevention and Hospital Epidemiology, Faculty of Medicine, University of Freiburg, Freiburg, Germany

²Department of Chemistry, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo, Japan

³Department of Urology, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

**Correspondence**

*PD Dr. Carsten Gründermann*

Center for Complementary Medicine

Institute for Infection Prevention and Hospital Epidemiology

Faculty of Medicine
University of Freiburg
Breisacher Str. 115B
79106 Freiburg
Germany
Phone: + 49 761 270 83170
Fax: + 49 761 270 83230
carsten.gruendemann@uniklinik-freiburg

Prof. Dr. Ken Ohmori
Department of Chemistry
Tokyo Institute of Technology
2-12-1 O-okayama, Meguro-ku
Tokyo 152-8551
Japan
Phone: + 81 3 5734 2761
Fax: + 81 3 5734 2788
kohmori@chem.titech.ac.jp

Dr. Sven Stadlbauer
Center for Complementary Medicine
Institute for Infection Prevention and Hospital Epidemiology
Faculty of Medicine
University of Freiburg
Breisacher Str. 115B
79106 Freiburg
Germany
Chemistry General Experimental Procedures

All manipulations of air and moisture sensitive reagents were performed in dried glassware and under an argon atmosphere. Tetrahydrofuran, diethyl ether, and toluene (anhydrous; Kanto Chemical Co., Inc.) were used as received. Dichloromethane was distilled successively from P₂O₅ and CaH₂ and stored over molecular sieve 4A. ASCA-2 (5% Pd(OH)₂/C) was obtained from N. E. Chemcat Co. For TLC analysis, Merck precoated plates (silica gel 60 F254, Art 5715, 0.25 mm) were used. Silica gel preparative TLC (PTLC) was performed on Merck Silica gel 60 PF254 (Art 7747). Melting point (m.p.) determinations were performed by using a Yanako MP-S3 or MP-500 instrument and are uncorrected. ¹H NMR and ¹³C NMR were measured on a JEOL JNM AL-300 (300 MHz) or a 400 MHz Bruker Avance DPX spectrometer. ¹⁹F NMR was measured on a 400 MHz Bruker Avance DPX. Chemical shifts are expressed in parts per million (ppm) downfield from the internal standard tetramethylsilane (0.00 ppm) for ¹H NMR and hexafluorobenzene (-162.2 ppm) for ¹⁹F NMR, and coupling constants are reported as hertz (Hz). Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. IR spectra were recorded on a Perkin Elmer 1600 FTIR, a Horiba FT-710, or a Perkin Elmer Spectrum 100 spectrometer. Attenuated Total Reflectance Fourier Transform Infrared (ATR-FTIR) spectra were recorded on a Perkin Elmer 1600 FTIR. Optical rotations ([α]₀) were measured on a JASCO DIP-1000 polarimeter or Schmidt + Haensch Polartronic H532 polarimeter at room temperature. The natural product ECG was synthesized as reported previously.

Synthesis of phenyl(2,4,6-trifluorophenyl)sulfane (4).
n-BuLi in hexane (1.59 M, 9.9 mL, 15.8 mmol) at -78°C was added to a solution of 1,3,5-trifluorobenzene (1.98 g, 15.0 mmol) in Et₂O (30 mL). After stirring for 2 h, S-phenyl benzenesulfonothioate (3.94 g, 15.8 mmol) in Et₂O (30 mL) was added and stirring was continued for 1.5 h. Then, the reaction was quenched with saturated aqueous NaHCO₃, and the mixture was extracted with EtOAc (x 3), and the combined organic extracts were washed with brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by distillation (130°C, 3.8 torr) to afford sulfide 4 (1.79 g, 50%) as a colorless oil.

4: Rf 0.59 (n-hexane/EtOAc = 10/1); m.p. 130°C (3.8 torr); ¹H NMR (300 MHz, CDCl₃) δ = 6.85 – 6.70 (m, 2H), 7.10 – 7.30 (m, 5H); ¹³C{¹H} NMR (75 MHz) δ = 100.5 – 101.0 (m, 2C), 163.5 (dt, J = 250, 14.8 Hz); IR (neat) 3050, 1620, 1600, 1460, 1430, 1120, 1020 cm⁻¹; Anal. calcd. for C₁₂H₇F₃S: C 59.99, H 2.94, S 13.35, Found: C 59.78, H 3.13, S 13.37.

Synthesis of compound 1,3,5-trifluoro-2-(phenylsulfinyl)benzene (5).

mCPBA (65%, 0.69 g, 2.6 mmol) at 0°C was added to a solution of 4 (0.61 g, 2.6 mmol) in dichloromethane (8.6 mL). After stirring for 4 h, the reaction mixture was quenched by 5% Na₂S₂O₃ solution, and the mixture was extracted with EtOAc (x 3), and the combined organic extracts were washed with brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 8/1) to afford sulfoxide (5) (0.65 g, 97%) as a white solid.

5: Rf 0.15 (hexane/EtOAc = 8/1); m.p. 61–63°C; ¹H NMR (300 MHz, CDCl₃) δ: 6.60 – 6.80 (m, 2H), 7.40 – 7.60 (m, 3H), 7.60 – 7.75 (m, 2H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ: 102.4 (dt, J = 103.0, 14.6 Hz), 124.5, 129.7, 131.5, 143.3, 160.3, 160.5, 160.6, 163.7, 163.9, 164.0, 164.1; IR (ATR): 3075, 3051, 2926, 2475, 2164, 1980, 1957, 1905, 1883, 1809, 1751, 1706, 1631, 1605, 1048, 1041, 1032, 1000, 915, 864, 853, 841, 747, 714, 696, 684 cm⁻¹; Anal. calcd. for C₁₂H₇F₃OS: C 56.25, H 2.75, S 12.51. Found: C 56.49, H 2.96, S 12.48.

Synthesis of diastereomeric mixture (2S)-2-(((1R)-(3,4-bis(benzyloxy)phenyl)(3,5-difluoro-2-(phenylsulfinyl)phenoxy)methyl)oxirane (7).
Sulfoxide (5) (3.32 mg, 12.9 mmol) at room temperature was added to a suspension of NaH (60% dispersion oil, washed with hexane, 0.61 g, 16.1 mmol) in toluene (6.0 mL). A solution of epoxyalcohol 6 (prepared according to Higuchi T, Ohmori K, Suzuki K: Chem Lett 2006; 35: 1006) in toluene (6.9 mL) was added at room temperature and stirring was continued for 60 h. The reaction was stopped by the addition of saturated aqueous NaHCO\(_3\), and the mixture was extracted with EtOAc (x 3). The combined organic extracts were washed with brine, dried (Na\(_2\)SO\(_4\)), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 8/1) to afford ether 7a (2.20 g, 34%) and 7b [2.88 g, 44%, mixture with para-substituted compound (ratio 25:1)] as an amorphous solid.

7a: R\(_f\) 0.44 (hexane/EtOAc = 8/1); m.p. 32–34°C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.51 (dd, \(J = 4.5\) Hz, 1H), 2.70 (dd, \(J = 4.5, 3.9\) Hz), 3.15 (ddd, \(J = 6.0, 3.9, 2.6\) Hz, 1H), 4.68 (d, \(J = 6.0\) Hz, 1H), 5.00 – 5.25 (m, 4H), 6.90 (d, \(J = 8.3\) Hz, 1H), 7.11 (d, \(J = 1.8\) Hz, 1H), 7.20 – 7.50 (m, 13H), 7.64 – 7.68 (m, 2H); \(^{13}\)C\{\(^1\)H\} NMR (75 MHz, CDCl\(_3\)) \(\delta\) 44.6, 54.2, 71.1, 82.8, 98.0 (d, \(J = 105.4\) Hz), 99.1 (d, \(J = 105.4\) Hz), 113.3, 114.8, 119.7, 127.2, 127.4, 127.8, 127.9, 128.0, 128.3, 128.5, 128.8, 130.1, 137.0, 143.8, 149.6 (d, \(J = 112.8\) Hz); IR (neat): 3060, 3030, 3000, 2930, 2880, 2250, 1950, 1880, 1810, 1640, 1610, 1580, 1515, 1455, 1430, 1380, 1355, 1340, 1270, 1220, 1200, 1170, 1130, 1090, 1050, 1020, 1005, 920, 870, 830, 820, 750, 740, 700, 650, 620 cm\(^{-1}\); Anal. calcd. for C\(_{35}\)H\(_{28}\)F\(_2\)O\(_5\)S: C, 70.22; H, 4.71; S, 5.36. Found: C, 70.10; H, 4.71; S, 5.44.

7b: R\(_f\) 0.35 (hexane/EtOAc = 8/1); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.75-2.85 (m, 2H), 3.30 – 3.45 (m, 1H), 4.76 (d, \(J = 5.8\) Hz, 1H), 5.00 – 5.20 (m, 4H), 6.35 – 6.50 (m, 1H), 6.60 (dd, \(J = 8.2, 2.0\) Hz, 1H), 6.72 (d, \(J = 2.0\) Hz, 1H), 6.80 – 6.90 (m, 1H), 7.25 – 7.55 (m, 13H), 7.70 – 7.80 (m, 2H).

Synthesis of diastereomer 8a of (\(1R,2S\))-1-(3,4-bis(benzyloxy)phenyl)-3-bromo-1-(3,5-difluoro-2-(phenylsulfinyl)phenoxy)propan-2-ol.

A solution of Li$_2$NiBr$_4$ (0.87 mL, ca. 0.4 M in THF, 348 µmol) was added to a solution of ether 7a (109.3 mg, 183 µmol) in THF (0.24 mL) at 0°C. After stirring for 7 h, the reaction was quenched by adding pH 7 phosphate buffer, and the resulting mixture was extracted with EtOAc (x 3). The combined organic extracts were washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by PTLC (hexane/EtOAc = 2/1) to afford bromohydrin 8a (115.2 mg; 94%).

8a: Rf 0.46 (hexane/EtOAc = 2/1); m.p. 38–45°C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 2.90–3.10 (m, 2H), 3.10 (d, $J = 6.3$ Hz), 3.66–3.80 (m, 1H), 5.10–5.30 (m, 5H), 6.10–6.20 (m, 1H), 6.40–6.50 (m, 1H), 6.86 (d, $J = 8.3$ Hz, 1H), 6.91 (dd, $J = 8.3$, 1.8 Hz, 1H), 7.09 (d, $J = 1.8$ Hz, 1H), 7.20–7.70 (m, 15 H); $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$) $\delta$: 33.4, 70.7, 71.1, 74.2, 81.1, 97.4, 113.3, 114.7, 120.1, 124.0, 127.2, 127.3, 127.7, 127.8, 128.3, 128.5, 129.3, 130.4, 137.0 (d, $J = 30$ Hz), 144.2, 148.9, 149.3; IR (neat): 3400, 3080, 3060, 3040, 2900, 2610, 1590, 1510, 1430, 1380, 1360, 1340, 1270, 1220, 1190, 1170, 1130, 1090, 1050, 1020, 1010, 910, 830, 750, 740, 700, 640 cm$^{-1}$; $[\alpha]_D^{27}$ 75.7 (c 0.63, CHCl$_3$); Anal. calcd. for C$_{35}$H$_{29}$BrF$_2$O$_5$S: C, 61.86; H, 4.30; S, 4.72. Found: C, 62.02; H 4.46; S, 5.02.

Synthesis of diastereomer 8b of (1R,2S)-1-(3,4-bis(benzyloxy)phenyl)-3-bromo-1-(3,5-difluoro-2-(phenylsulfinyl)phenoxy)propan-2-ol.

To a solution of a 5:1 mixture of 7b and the para-substituted compound (72.6 mg) in THF (0.16 mL), a solution of Li$_2$NiBr$_4$ (0.58 mL, ca. 0.4 M in THF, 230 µmol) was added at 0°C. After stirring for 25 h, the reaction was quenched by adding pH 7 phosphate buffer, and the resulting mixture was extracted with EtOAc (x 3). The combined organic extracts were washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by PTLC (hexane/EtOAc = 2/1) to afford bromohydrin 8b (56.7 mg; 83%) as an amorphous solid.

8b: Rf 0.46 (hexane/EtOAc = 2/1); m.p. 48–52°C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 2.88–3.00 (m, 2H), 3.45 (dd, $J = 15.0$, 3.0 Hz, 1H), 3.78–3.90 (m, 1H), 4.75–5.00 (m, 3H), 5.09 (s,
2H), 6.10 – 6.17 (m, 2H), 6.40 (d, J = 1.8 Hz, 1H), 6.49 (dd, J = 8.3, 2.1 Hz, 1H), 6.52 (ddd, J = 9.0, 8.3, 2.1 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 7.20 – 7.60 (m, 12H), 7.60 – 7.70 (m, 2H); 
\[^{13}\text{C}\]NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 33.8, 71.1, 71.2, 73.5, 86.6, 97.2 (t, \(J = 103.0\) Hz), 99.7 (dd, \(J = 103.0, 14.6\) Hz), 112.6, 114.9, 116.0, 119.4, 124.2, 127.1, 127.5, 127.9, 128.0, 128.2, 128.5, 128.9, 130.1, 136.4, 136.8, 143.5, 149.0, 149.7, 159.5-160.5 (m, 1C), 164.1 (dd, \(J = 219.3, 66.1\) Hz), 168.0; IR (neat): 3060, 2990, 2910, 2875, 1950, 1865, 1910, 1740, 1610, 1590, 1510, 1455, 1445, 1430, 1370, 1340, 1270, 1235, 1200, 1185, 1130, 1090, 1055, 1010, 980, 950, 910, 860, 830, 810, 790, 740, 700 cm\(^{-1}\); \([\alpha]_{D}^{27}\) 112.9 (c 0.91, CHCl\textsubscript{3}); Anal. calcd. for C\textsubscript{35}H\textsubscript{29}BrF\textsubscript{2}O\textsubscript{5}S: C, 61.86; H, 4.30; S, 4.72. Found: C, 62.09; H 4.07; S, 5.02.

**Synthesis of** (((I\textsubscript{R},2S)-1-(3,4-bis(benzyloxy)phenyl)-3-bromo-1-(3,5-difluoro-2-(phenylsulfinyl)phenoxy)propan-2-yl)oxy)triethylsilane (9).

![Chemical structure of 9a](image)

TESOTf (48.0 mg, 362.2 µmol) in dichloromethane (0.5 mL) was added to a solution of bromohydrin 8a (36.6 mg, 54.3 µmol) and 2,6-lutidine (38.8 mg, 362.2 µmol) in dichloromethane (1.5 mL) at 0°C. After stirring for 15 min, the reaction was quenched by adding saturated NaHCO\textsubscript{3}, and the resulting mixture was extracted with EtOAc (x 3). The combined organic extracts were washed with 5% aqueous citric acid solution and brine, dried over Na\textsubscript{2}SO\textsubscript{4}, and concentrated in vacuo. The residue was purified by PTLC (hexane/EtOAc = 8/1) to afford silyl ether 14a (45.7 mg; quantitative) as a colorless oil.

\textbf{9a}: \(R_f\) 0.72 (hexane/EtOAc = 2/1); \(^1\text{H}\) NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 0.40 – 0.58 (m, 6H), 0.88 (t, \(J = 7.7\) Hz, 9H), 2.88 (dd, \(J = 10.3, 6.0\) Hz, 1H), 3.46 (dd, \(J = 10.3, 5.7\) Hz, 1H), 3.76 – 3.90 (m, 1H), 5.00 – 5.20 (m, 5H), 6.10 – 6.20 (m, 1H), 6.33 – 6.48 (m, 1H), 6.81 (dd, \(J = 8.3, 1.8\) Hz, 1H), 6.87 (d, \(J = 8.3\) Hz, 1H), 6.94 (d, \(J = 1.8\) Hz, 1H), 7.20 – 7.55 (m, 13H), 7.68 – 7.70 (m, 2H); \(^{13}\text{C}\)\(^{1}\text{H}\) NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 4.8, 6.8, 34.1, 70.9, 71.2, 75.0, 81.8, 99.0, 100.6, 113.8, 114.8, 120.0, 124.2, 127.2, 127.3, 127.8, 127.9, 128.1, 128.3, 128.5, 129.0, 130.1, 136.8, 137.0, 144.4, 148.7, 149.1; IR (neat): 3060, 2990, 2910, 2880, 1950, 1880, 1810, 1610, 1590, 1510, 1460, 1450, 1440, 1430, 1380, 1350, 1270, 1220, 1200, 1170, 1130,
1090, 1050, 1010, 980, 910, 830, 740, 700, 620 cm\(^{-1}\); \([\alpha]_D^{27}\) 23.6 (c 1.44, CHCl\(_3\)); Anal. calcd. for C\(_{41}\)H\(_{43}\)BrF\(_2\)O\(_5\)SSi: C, 62.03; H, 5.46; S, 4.04. Found: C, 62.33; H 5.70; S, 4.13.

**Synthesis of compound 9b**

TESOTf (662 mg, 2.5 mmol) in dichloromethane (2.0 mL) was added to a solution of bromohydrin 8b (506 mg, 0.75 mmol) and 2,6-lutidine (536 mg, 5.00 mmol) in dichloromethane (6.2 mL) at 0°C. After stirring for 25 min, the reaction was quenched by adding saturated NaHCO\(_3\), and the resulting mixture was extracted with EtOAc (x 3). The combined organic extracts were washed with 5% aqueous citric acid solution and brine, dried over Na\(_2\)SO\(_4\), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 4/1) to afford silyl ether 9b (556 mg, 93%) as a colorless oil.

9b: \(R = 0.66\) (hexane/EtOAc = 2/1); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 0.35 – 0.55 (m, 6H), 0.85 (t, \(J = 7.7\) Hz, 9H), 3.18 (dd, \(J = 8.5, 3.4\) Hz, 1H), 3.95 – 4.10 (m, 2H), 4.92 (d, \(J = 11.6\) Hz, 1H), 5.04 (d, \(J = 11.6\) Hz, 1H), 5.11 (s, 2H), 5.33 (d, \(J = 3.4\) Hz, 1H), 6.17 – 6.22 (m, 1H), 6.36 – 6.45 (m, 1H), 6.50 – 6.65 (m, 2H), 6.82 – 6.84 (m, 1H), 7.20 – 7.55 (m, 13H), 7.70 – 7.80 (m, 2H); \(^{13}\)C\(^{\{1\}H}\) NMR (75 MHz, CDCl\(_3\)) \(\delta\) 4.7, 6.7, 33.7, 71.2, 71.3, 75.5, 82.0, 97.8, 98.2, 98.8, 99.3 (m, 1C), 113.6, 115.1, 119.7, 124.6, 124.6, 127.2, 127.4, 127.8, 128.4, 128.5, 128.8, 129.0, 130.1, 136.8, 137.0, 144.1, 148.9, 149.1; IR (neat): 3080, 3060, 2950, 2910, 2875, 1960, 1880, 1810, 1650, 1590, 1515, 1460, 1440, 1425, 1375, 1340, 1270, 1235, 1200, 1150, 1130, 1090, 1055, 1010, 980, 950, 900, 860, 810, 790, 750, 700, 670, 620 cm\(^{-1}\); \([\alpha]_D^{27}\) 102.2 (c 2.29, CHCl\(_3\)); Anal. calcd. for C\(_{41}\)H\(_{43}\)BrF\(_2\)O\(_5\)SSi: C, 62.03; H, 5.46; S, 4.04. Found: C, 62.33; H 5.70; S, 4.13.

**Synthesis of (((2R,3R)-2-(3,4-bis(benzyloxy)phenyl)-5,7-difluorochroman-3-yl)oxy)triethylsilane (10).**

- **Starting from 9a:**
Silyl ether 9a (1.16 g, 1.46 mmol) in THF (70 mL) was added to a solution of PhLi (4.19 mL, 1.04 M cyclohexane-ether solution, 4.38 mmol) in THF (52 mL) at -78°C. After stirring for 15 min, the reaction was quenched by adding water and extracted with EtOAc (x 3). The combined organic extracts were washed with saturated NaHCO$_3$ solution and brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 4/1) to afford flavan 10 (774 mg; 90%) as a colorless oil.

Starting from 9b:

Silyl ether 9b (100.4 mg, 127 µmol) in THF (6 mL) was added to a solution of PhLi (0.37 mL, 1.04 M cyclohexane-ether solution, 380 µmol) in THF (4.5 mL) at -78°C. After stirring for 15 min, the reaction was quenched by adding water and extracted with EtOAc (x 3). The combined organic extracts were washed with saturated NaHCO$_3$ solution and brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 4/1) to afford flavan 10 (67.8 mg; 91%) as a colorless oil.

10: R$_f$ 0.66 (hexane/EtOAc = 4/1); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 0.40 – 0.58 (m, 6H), 0.74 (t, $J = 7.8$ Hz, 9H), 2.80 (dd, $J = 36.1$, 3.2 Hz, 1H), 2.85 (dd, $J = 36.1$, 3.6 Hz, 1H), 4.15 – 4.25 (m, 1H), 4.90 – 4.96 (m, 1H), 5.10 – 5.20 (m, 4H), 6.35 – 6.50 (m, 2H), 6.85 – 6.95 (m, 2H), 7.05 – 7.10 (m, 1H), 7.25 – 7.50 (m, 10H); $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$) $\delta$: 4.6, 6.5, 27.6 (d, $J = 12.2$ Hz), 66.1, 71.3, 71.4, 79.4, 95.8 (t, $J = 102.9$ Hz), 99.5 (dd, $J = 99.3$, 14.7 Hz), 159.9 (dd, $J = 77.2$, 61.3 Hz), 163.1 (dd, $J = 73.5$, 61.3 Hz); IR (neat): 3100, 3060, 3040, 2950, 2910, 2880, 2740, 1870, 1810, 1720, 1620, 1600, 1510, 1470, 1430, 1380, 1340, 1270, 1200, 1150, 1120, 1070, 1040, 1010, 905, 840, 822, 810, 790, 740, 700 cm$^{-1}$; [$\alpha$]$_D^{27}$ -3.97 (c 1.46, CHCl$_3$); Anal. calcd. for C$_{35}$H$_{38}$F$_2$O$_4$Si: C, 71.40; H, 6.51. Found: C, 71.51; H 6.56.

Synthesis of (2R,3R)-2-(3,4-bis(benzyloxy)phenyl)-5,7-difluorochroman-3-ol (11).

TBAF (0.15 mL, 1 M solution in THF, 153.6 µmol) was added to a solution of flavan 10 (67.0 mg, 113.8 µmol) in THF (2.3 mL) at 0°C. After stirring for 15 min at room temperature, the reaction was quenched by adding phosphate buffer (pH = 7) and the mixture was extracted with EtOAc (x 3). The combined organic extracts were washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 4/1) to afford flavan 10 (67.8 mg; 91%) as a colorless oil.
and concentrated in vacuo. The residue was purified by PTLC (hexane/EtOAc = 4/1) to afford flavan 11 (50.5 mg; 94%) as a colorless oil.

11: $R_f$ 0.65 (hexane/EtOAc = 1.5/1); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 1.65 (d, $J = 4.4$ Hz, 1H), 2.85 – 3.05 (m, 2H), 4.15 – 4.25 (m, 1H), 4.88 – 5.02 (m, 1H), 5.10 – 5.30 (m, 1H), 6.35 – 6.60 (m, 2H), 6.90 – 7.00 (m, 2H), 7.00 – 7.15 (m, 1H), 7.20 – 7.55 (m, 10H); $^{13}$C($^1$H) NMR (75 MHz, CDCl$_3$) $\delta$: 26.6 (d, $J = 12.3$ Hz), 65.3, 71.2, 71.3, 78.6, 96.6 (t, $J = 102.9$ Hz), 99.8 (dd, $J = 99.2$, 14.7 Hz), 103.4 (dd, $J = 88.2$, 14.7 Hz), 113.3, 115.0, 119.3, 127.2, 127.4, 127.8, 127.9, 128.4, 128.5, 130.4, 136.9, 137.0, 149.1 (d, $J = 7.4$ Hz), 155.4, 155.5, 155.6, 160.0, 163.3 (d, $J = 83.3$ Hz); IR (ATR): 3450, 3060, 3030, 2920, 2870, 1960, 1870, 1810, 1635, 1600, 1510, 1495, 1450, 1422, 1380, 1365, 1350, 1310, 1270, 1225, 1175, 1120, 1090, 1070, 1030, 1007, 950, 840, 790, 780, 740, 700, 670, 650, 610 cm$^{-1}$; $[\alpha]_D^{27}$ -4.95 (c 1.42, CHCl$_3$); Anal. calcd. for C$_{29}$H$_{24}$F$_2$O$_4$: C, 73.41; H, 5.10. Found: C, 73.24; H 5.16.

Synthesis of (2R,3R)-2-(3,4-bis(benzyloxy)phenyl)-5,7-difluorochroman-3-yl 3,4,5-tris(benzyloxy)benzoate (12).

DMAP (2.2 mg, 18 μmol), triethylamine (51 μL, 0.36 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl, 35 mg, 0.18 mmol) were added to a solution of flavan 11 (43.0 mg, 91 μmol) and 3,4,5-tris(benzyloxy)benzoic acid (60 mg, 136 μmol) in dichloromethane (1 mL) at 0°C. After stirring for 17 h at room temperature, the reaction was quenched by adding water at 0°C. The products were extracted with EtOAc (x 3) and the combined organic extracts were washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by PTLC (cyclohexane/EtOAc = 6/1) to afford ester 12 (55 mg, 68%) as an amorphous solid.

12: $R_f$ 0.66 (hexane/EtOAc = 1.5/1); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 3.16 (m, 2H), 5.07 (m, 10 H), 5.15 (s, 1H), 5.72 (s, 1H), 6.61 (m, 1H), 6.63 (m, 1H), 6.88 (d, $J = 8$ Hz, 1H), 6.92 (d, $J = 8$ Hz, 1H), 7.05 (s, 2H), 7.27-7.42 (m, 25 H); $^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$) $\delta$: 25.0, 60.4, 67.2, 71.2, 71.2, 71.4, 75.1, 109.2, 113.6, 114.7, 124.6, 127.2, 127.4, 127.5, 127.8,
128.0, 128.1, 128.2, 128.4, 128.5, 128.6, 130.1, 136.5, 136.9, 137.1, 137.4, 142.9, 149.1, 149.2, 156.0, 160.9 (m), 163.0 (m), 164.8, 171.3; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ 112.7 (m), 114.7 (m); $[\alpha]_{D}^{25}$ -92.9 (c 2.19, THF); HR-MS (ESI+) calcd., 897.99126 found 897.32422–1.0 ppm.

Synthesis of (2R,3R)-2-(3,4-dihydroxyphenyl)-5,7-difluorochroman-3-yl 3,4,5-trihydroxybenzoate, (-)-5,7-difluoro-epicatechin-3-O-gallate (2).

A mixture of 12 (58.2mg, 49.3 μmol) and 5% Pd(OH)$_2$/C (12 mg) in THF (4.0 mL) and MeOH (4.0 mL) was stirred under an H$_2$ atmosphere for 2 h at room temperature. The mixture was filtered through a glass fiber filter under an Ar atmosphere, and half of the volume of the filtrate was evaporated. The mixture was filtered through a Celite pad under an argon atmosphere, and half of the volume of the filtrate was evaporated. Then, H$_2$O was added and the remaining MeOH evaporated. The water phase was lyophilized to afford (−)-5,7-difluoro-epicatechin 3-O-gallate (2) (18.9 mg, 84%) as a white powder. 2: R$_f$ 0.20 (CHCl$_3$/MeOH = 9/1); $^1$H NMR (400 MHz, MeOD$_4$) $\delta$ 2.89 (d, $J$ = 16 Hz, 1H), 3.09 (d, $J$ = 16 Hz, 1H), 5.10 (s, 1H), 5.48 (s, 1H), 6.40 – 6.50 (m, 2H), 6.61 (d, $J$ = 8 Hz), 6.72 (d, $J$ = 8 Hz), 6.81 (s, 2H), 6.83 (s, 1H); $^{13}$C{$^1$H} NMR (100 MHz, MeOD$_4$) $\delta$: 24.5, 25.1, 66.9, 67.5, 78.0, 95.5 (t, $J$ = 25 Hz), 99.3 (dd, $J$ = 25, 4 Hz), 103.5 (dd, $^2J_{CF}$ = 22 Hz, $^4J_{CF}$ = 4 Hz), 113.6, 114.7, 117.9, 119.7, 129.0, 138.6, 144.7, 144.9, 145.0, 156.5, 160.6 (m), 163.0 (m), 165.8; $^{19}$F NMR (376 MHz, MeOD$_4$) $\delta$: 114.9 (m), 116.9 (t); $[\alpha]_{D}^{25}$ –96.1 (c 1.13, MeOH); HR-MS (ESI+) calcd., 447.36626; found, 469.07075 – 0.4 ppm.
Determination of IC_{50} values

**Fig. S1** Determination of the IC_{50} value for ECG. 95% CI lower: 32.04, upper: 46.85 µM.

**Fig. S2** Determination of the IC_{50} value for ECG. 95% CI lower: 11.78, upper: 13.91 µM.
Analytical data

$^1$H NMR spectra for 12.

$^{13}$C\{$^1$H\} NMR spectra for 12.
HR-MS (ESI positive) spectra for 12.

\[ ^1H \text{ NMR spectra for 2.} \]
$^{13}\text{C} \{^1\text{H}\}$ NMR spectra for 2.

$^{19}\text{F}$ NMR spectra for 2.
HR-MS (ESI positive) spectra for 2.