Supporting Information for

Intramolecular Base-Accelerated Radical-Scavenging Reaction of a Planar Catechin Derivative Bearing a Lysine Moiety

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General methods. The reagents and solvents used were of commercial origin (Wako Chemicals, Tokyo Chemical Industry, Sigma, Aldrich) and were employed without further purification. (+)-Catechin (Sigma) was dried under vacuum over 12hr. Melting points were measured on a Yanaco MP micromelting point apparatus and were not corrected. The ^{1}H NMR spectra and ^{13}C NMR spectra were recorded with a Varian AS 400 Mercury spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) and Varian 600MHz NMR system (600MHz for ^{1}H). Chemical shifts are expressed in ppm downfield shift from TMS or TSP (δ scale). Low resolution mass spectra were obtained with a Waters Micromass ZQ instrument under positive and negative ESI conditions. High resolution mass spectra were obtained on a JEOL MS700 mass spectrometer. The progress of all reactions was monitored by thin-layer chromatography on silica gel 60 F_{254} (0.25 mm, Merck). Column chromatography was performed on silica gel 60 (0.063-0.200 mm, Merck). The purity of all synthetic compounds was approximately > 98% (based on ^{1}H NMR spectra).

(6a*S*, 12a*R*)-3-(2,3,8,10-tetrahydroxy-5-methyl-5,6a,7,12a-tetrahydro-isochromeno [4,3-*b*] chromen-5-yl)-propionic acid ethyl ester (4)

To a solution of (+)-catechin (2.88 g, 10 mmol) and ethyl 4-oxovalerate (5.71 mL 40 mmol), in dry THF (150 mL) at –5°C, trimethylsilyl trifluoromethanesulfonate

(TMSOTf, 2.17mL, 1.20 mmol) was slowly added. After stirring for 30 min, the mixture was poured into water, extracted with diethyl ether (3 x 150 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered and the solvent was evaporated. The resultant solid was purified by column chromatography on silica gel (20:1 dichloromethane-methanol) to give 3.18 g (76.3%) of **4** a white solid; mp 171-173°C (dichloromethane-*n*-hexane); ^{1}H-NMR (DMSO-d_6) δ 1.11 (t, *J* = 7.2Hz 3H), 1.44 (s, 3H), 1.81 (t, *J* = 7.6Hz, 2H), 2.00 (t, *J* = 7.6Hz, 2H), 2.29 (m, 1H), 2.80 (m, 1H), 3.70 (m, 1H), 3.95 (q, *J* = 7.2Hz, 2H), 4.37 (d, *J* = 9.2Hz, 1H), 5.78 (d, *J* = 2.2Hz, 1H), 5.93 (d, *J* = 2.2Hz, 1H), 6.49 (s, 1H), 6.92 (s, 1H), 8.86 (s, 1H), 9.06 (s, 1H), 9.11 (s, 1H), 9.30 (s, 1H) ; $[M+H]^+$: 417; HR-MS(+EI) $[M]^+$ found 416.1473; $[M]^+$ calcd for $C_{22}H_{24}O_8$ 416.1471.

(6a*S*, 12a*R*)-3-(2,3,8,10-tetrabenzyloxy-5-methyl-5,6a,7,12a-tetrahydro-iso-chromeno [4,3-*b*]chromen-5-yl)-propionic acid ethyl ester (Bn$_4$-4)

To a solution of **4** (2.08 g, 5.0 mmol) and benzyl bromide (2.97 mL, 5 mmol) in dry DMF (50 mL), K_2CO_3 (3.26 g, 5.0 mmol) was added. After stirring overnight at rt, K_2CO_3 was filtered off. The filtrate was diluted with ethyl acetate (200 mL), washed with brine (3 x 200 mL), dried over Na_2SO_4, filtered and the solvent was evaporated. Purification by column chromatography on silica gel (20:1 dichloromethane-methanol) to give 3.48 g (76.3%) of **Bn$_4$-4** as a white solid; mp 158-160°C (ethyl acetate-*n*-hexane); ^{1}H-NMR (DMSO-d_6) δ 1.08 (t, *J* = 7.2Hz, 3H), 1.48 (s, 3H), 1.70 (m, 2H), 1.97 (m, 2H), 2.48 (m, 1H), 2.94 (m, 1H), 3.79 (m, 1H), 3.94 (q, *J* = 7.2Hz, 2H), 4.51 (d, *J* = 8.8Hz 1H), 5.07 (br s, 4H), 5.14 (br s, 4H), 6.27 (d, *J* = 2.2Hz, 1H), 6.40 (d, *J* = 2.2Hz, 1H), 6.90 (s, 1H), 7.20 (s, 1H), 7.25~7.52 (m, 20H); ^{13}C-NMR (DMSO-d_6) δ 14.1, 27.0, 28.7, 31.4, 38.0, 59.7, 69.3(2), 70.1, 70.3, 72.3, 76.6, 77.3, 93.9, 94.7, 102.3, 110.2, 111.6, 126.2, 127.2, 127.3, 127.6(2), 127.7(2), 127.8(4), 128.3(2), 128.4(2), 128.5(6), 132.6, 137.1, 137.2(2), 137.3, 147.3, 147.7, 154.9, 157.4, 158.3, 172.9; $[M+H]^+$: 777; HR-MS(+EI) $[M]^+$ found 776.3352; $[M]^+$ calcd for $C_{50}H_{48}O_8$ 776.3349.

(6a*S*, 12a*R*)-3-(2,3,8,10-tetrabenzyloxy-5-methyl-5,6a,7,12a-tetrahydro-iso-

chromeno[4,3-*b*]chromen-5-yl)-propan-1-ol (5)

A solution of **Bn$_4$-4** (1.55 g, 2.0 mmol) in dry THF (4 mL) was added dropwise to a suspension of $LiAlH_4$ (0.11 g, 3.0 mmol) in dry THF (40 mL) at 0°C and then stirred for 3hr. The mixture was cooled in ice and saturated Na_2SO_4 solution was added dropwise and then it was filtered and thoroughly washed with THF. The organic solution was washed with brine, dried over Na_2SO_4, filtered and the solvent was evaporated. The residue was purified by column chromatography on silica gel (20:20:1 dichloromethane-*n*-hexane-methanol) to give 1.35 g (92%) of **5** as a white solid; mp 199-203°C (dichloromethane-*n*-hexane); ^{1}H-NMR (DMSO-d_6) δ 1.41 (m, 2H), 1.45 (s, 3H), 1.70 (m, 2H), 2.43 (m, 1H), 2.96 (m, 1H), 3.23 (m, 2H), 3.80 (m, 1H), 4.49 (d, J = 9.1 Hz, 1H), 5.08 (br s, 4H), 5.13 (br s, 4H), 6.26 (d, J = 2.2 Hz, 1H), 6.39 (d, J = 2.2 Hz, 1H), 6.85 (s, 1H), 7.19 (s, 1H), 7.28 ~ 7.51 (m, 20H); $[M+H]^+$: 735; HR-MS(+EI) $[M]^+$ found 734.3251; $[M]^+$ calcd for $C_{48}H_{46}O_7$ 734.3243.

(6a*S*, 12a*R*)-6-benzyloxycarbonylamino-2-*tert*-butoxycarbonylamino-hexanoic acid 3-(2,3,8,10-tetrabenzyloxy-5-methyl-5,6a,7,12a-tetrahydro-isochromeno[4,3-*b*]chromen-5-yl)-propyl ester (6)

To a stirred solution of **5** (0.73 g, 1.0mmol) and N-α-(tert-Butoxycarbonyl)-N-ε-carbobenzoxy-L-lysine (0.46 g, 1.2 mmol) in dry dichloromethane (20 mL) at 0°C under argon, 4-dimethylaminopyridine (0.12g, 1.0mmol) and N, N'-dicyclohexylcarbodiimide (0.21 g, 1.0mmol) were added. The resulting solution was stirred at rt for 12 hr, and then filtered. After evaporation of the filtrate, the crude material was taken into ethyl acetate (100mL), washed with 0.2N HCl (50 mM), saturated $NaHCO_3$ (2 x 50 mL) and brine (2 x 50 mL) in this order. The organic phase was dried over Na_2SO_4, filtered and the solvent was evaporated. The residue was purified by column chromatography on silica gel (40:40:1 ethyl acetate-n-hexane-methanol) to give 0.68 g (62%) of **6** as a white solid; mp 143-145°C (methanol-diethyl ether); ^{1}H-NMR (DMSO-d_6) δ 1.27 (m, 1H), 1.32 (m, 1H), 1.32 (s, 9H, $C\underline{H}_3$x3), 1.45 (m, 2H), 1.46 (s, 3H), 1.57 (m, 2H), 2.45 (m, 1H), 2.93 (m, 3H), 3.82 (m, 1H), 3.86 (m, 1H), 4.01 (m, 2H), 4.49 (d, J = 9.1 Hz, 1H), 4.97 (s, 2H), 5.08 (s, 2H), 5.14 (br. s, 4H), 5.16 (s, 2H), 6.27 (d, J = 2.2 Hz, 1H), 6.40 (d, J = 2.2 Hz, 1H), 6.84 (s, 1H), 7.14 (d, *J* = 7.8 Hz,1H, amide), 7.19 (t, *J*=7.1 Hz, 1H, amide), 7.20 (s, 1H), 7.25~7.50 (25H, m); ^{13}C-NMR (DMSO) δ: 22.8, 24.9, 27.1, 28.0, 28.1(3), 28.9, 30.2, 38.8, 39.8, 53.6, 65.1(3), 69.2(2), 70.1, 70.4, 72.5, 77.5, 78.1, 93.8, 94.7, 102.3, 110.3, 111.6, 127.2, 127.5, 127.6, 127.7(8), 128.3(10), 128.4(6), 137.0, 137.1, 137.2(2), 137.3, 147.1, 147.7, 154.8, 155.5, 156.0, 157.3, 158.2, 172.6; $[M+H]^+$: 1097. $[M+H]^+$: 1097; HR-MS(FAB) $[M]^+$ found 1096.5095; $[M]^+$ calcd for $C_{67}H_{72}N_2O_{12}$ 1096.5085.

(6a*S*, 12a*R*)-6-amino-2-*tert*-butoxycarbonylamino-hexanoic acid 3-(2,3,8,10-tetrahydroxy-5-methyl-5,6a,7,12a-tetrahydro-isochromeno[4,3-*b*]chromen-5-yl)-propyl ester (3)

Solution of **6** (549 mg, 0.5 mmol) in THF (50 mL) was subjected to hydrogenolysis in the presence of 10% Pd/C (100 mg) for 22 hr. The catalyst was removed by filtration and the filtrate was purified by C-18 column (Varian Bond Elute) to give 244 mg (81%) of **3** as a white solid; mp 126-128°C; ^{1}H-NMR (D_2O) δ 1.15(m, 2H), 1.29(s, 9H), 1.33(m, 2H), 1.42(s, 3H), 1.46(m, 2H), 1.57(m, 2H), 1.78(m, 2H), 2.26(m, 1H), 2.32(m, 1H), 2.53(m, 2H), 2.77(m, 1H), 2.81(m, 1H), 3.71(m, 1H), 3.82(m, 1H), 4.00(m, 2H), 4.35(d, *J* = 8.8 Hz, 1H), 5.77(d, *J* = 2.4 Hz, 1H), 5.92(d, *J* = 2.4 Hz, 1H), 6.45(s, 1H), 6.89(s, 1H); ^{13}C-NMR (D_2O) δ 23.1, 27.8, 27.9, 28.6, 30.5, 31.5, 38.5, 41.1, 52.8, 65.5, 73.5, 80.3, 83.3, 83.5, 94.5, 98.3, 100.5, 113.3, 117.0, 126.5, 128.8, 142.5, 144.0, 156.2, 157.9, 158.1, 159.8, 170.4; $[M+H]^+$: 603; HR-MS(+EI) $[M]^+$ found 602.2846; $[M]^+$ calcd for $C_{31}H_{42}N_2O_{10}$ 602.2841.

Antioxidant activity measurements.

Since the phenoxyl radical of **3** generated in the reaction of **3** with radicals readily reacts with molecular oxygen (O_2), reactions were carried out under strictly de-aerated conditions. A continuous flow of Ar gas was bubbled through a MeCN solution (3.0 mL) containing galvinoxyl radical (GO•, 2.4 x 10^{-3}M) in a square quartz cuvette (10mm id) with a glass tube neck for 10min. Air was prevented from leaking into the neck of the cuvette with a rubber septum. Typically, an aliquot of **3** (2.0×10^{-2} M), which was also in de-aerated MeCN, was added to the cuvette with a microsyringe. This led to a reaction of **3** with GO•. UV-vis spectral changes associated with the reaction were monitored using an Agilent 8453 photodiode array spectrophotometer. The rates of the GO•-scavenging reactions of **3** were determined by monitoring the absorbance change at 428 nm due to GO• ($\varepsilon = 1.32 \times 10^5$ M^{-1} cm^{-1}) using a stopped-flow technique on a UNISOKU RSP-1000-02NM spectrophotometer. The pseudo-first-order rate constants (k_{obs}) were determined by a least-squares curve fit using an Apple Macintosh personal computer. The first-order plots of $\ln(A - A\infty)$ *vs.* time (A and $A\infty$ are denoted as the absorbance at the reaction time and the final absorbance, respectively) were linear until three or more half-lives with the correlation coefficient $q > 0.999$.

Theoretical Calculations.

The semiempirical calculations by the PM3 method were performed on a COMPAQ DS20E computer. Final geometries and energetics were obtained by optimizing the total molecular energy with respect to all structural variables. The geometries of the radicals were optimized using the unrestricted Hartree–Fock (UHF) formalism as implemented in the Gaussian 98 program. (1)

Density functional calculations were performed on a COMPAQ DS20E computer using the Amsterdam Density Functional (ADF) program version 1999.02 developed by Baerends et al (2, 3). The electronic configurations of the molecular systems were described by an uncontracted triple-z Slater-type orbital basis set (ADF basis set IV), with a single polarization function used for each atom. Core orbitals were frozen through 1s (C, O). The calculations were performed using the local exchange-correlation potential of Vosko et al (4) and the nonlocal gradient corrections of Becke (5) and Perdew (6,7) during the geometry optimizations. First-order scalar relativistic correlations were added to the total energy. Final geometries and energetics were optimized using the algorithm of Versluis and Ziegler (8) provided in the ADF package and were considered to be converged when the changes in bond lengths between subsequent iterations fell below 0.01 Å.

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