Supporting Information to the Paper:

Catalytic Chain-Breaking Pyridinol Antioxidants

Sangit Kumar, Henrik Johansson, Takahiro Kanda, Lars Engman, Thomas Müller, Mats*

Jonsson, Gian Franco Pedulli, Silvia Petrucci and Luca Valgimigli.

General Experimental Details

For ^1H NMR analysis (CDCl_3), Varian 500, 400 and 300 MHz spectrometers were used. ^{13}C spectra were recorded at 125, 100 and 75 MHz. NMR chemical shifts are reported in ppm referenced to the solvent peak of CDCl_3 (7.26 ppm for ^1H and 77.16 ppm for ^{13}C , respectively). Mass spectra reported are for ions of ^{80}Se . ES-MS data were obtained with an Sciex API ISO EX Spectrometer using direct inlet of a dilute methanol solution of compound. Microwave reactions were carried out in a Biotage Initiator 60 EXP focused microwave reactor equipped with an IR sensor for continuous monitoring of the reaction temperature. Melting points, obtained using a Stuart Scientific melting point apparatus, are uncorrected. THF was dried by distillation over sodium/benzophenone.

6-Bromo-3-pyridinol. 3-Amino-6-bromopyridine (1.73 g, 10 mmol) was dissolved in HBF_4 (5 mL, 50 % aq.) and water (5 mL) was added. To the resulting brownish solution, cooled to 0°C in an ice-bath, NaNO_2 (759 mg, 11 mmol) in water (5 mL) was added dropwise. The resulting yellowish heterogenous reaction mixture was stirred for 1 h at this temperature. After addition of water (5 mL), the mixture was stirred in an oil-bath for 5 h at 100°C (gas evolution). The cooled reaction mixture was then neutralized by addition of NaHCO_3 (5 % aq.) and the product extracted with ethyl acetate (5 x 35 mL). After drying (Na_2SO_4) and evaporation in *vacuo*, the resulting brownish solid was purified by column chromatography (SiO_2) using pentane/ethyl acetate (9:1) to give 1.04 g (60 %) of the title compound, mp $137\text{--}138^\circ\text{C}$ (lit. $135.5\text{--}136.5^\circ\text{C}$; den Hertog *et al.*; *Rec. Trav. Chim. Pays-Bas* **1959**, 69, 1281).

5-Hydroxy-2-pyridyl *n*-Octyl Telluride (7a): To the solution of lithiated 6-bromo-3-pyridinol prepared as described below (compound **7c**), finely ground elemental tellurium (0.762 mg, 6 mmol) was added at -78°C . The cooling bath was then removed and stirring continued for an additional 4 h at room temperature. The reaction mixture was then poured onto crushed ice and kept in the open air overnight. After evaporation of the solvent in *vacuo*, the residue was washed with some pentane to remove any dialkyl ditelluride present and

dissolved in EtOH (10 mL). To the remaining stirred dark red solution of crude bis-(5-hydroxy-2-pyridyl)ditelluride under N₂, NaBH₄ (0.18 g, 5 mmol) was added in portions until the colour of the reaction mixture had permanently faded away. Octyl bromide (1.0 g, 5 mmol) was added and stirring continued for 1 h when the contents of the reaction flask was poured into brine and extracted with Et₂O (15 mL x 4). After drying over Na₂SO₄ and evaporation in *vacuo* the product was purified by column chromatography using pentane/ethyl acetate (86:14) as an eluent. The title compound was obtained as a colourless solid (0.442 g, 66 %), mp 56-57 °C. ¹H NMR δ 8.18 (d, J = 3.1, 1H), 7.52 (dm, J = 8.4, 1H), 7.04 (dd, J = 8.4, 3.0, 1H), 3.01 (t, J = 7.5, 2H), 1.81 (m, 2H), 1.35-1.19 (several peaks, 10H), 0.86 (t, J = 6.9, 3H). ¹³C NMR δ 153.2, 139.0, 134.6, 126.1, 124.9, 32.2, 32.0, 32.0, 29.3, 29.0, 22.8, 14.2, 10.0. Anal. calcd for C₁₃H₂₁NOTe: C 46.62; H 6.32. Found: C, 46.49; H, 6.25.

5-Hydroxy-2-pyridyl *n*-Octyl Selenide (7b) was prepared according to the procedure for sulphide **7c**, using di-*n*-octyl diselenide instead of di-*n*-octyl disulfide. Yield: 65 %, mp 44-45 °C ¹H NMR δ 8.13 (d, J = 3.0, 1H), 7.34 (dm, J = 8.6, 1H), 7.15 (dd, J = 3.0, 8.6, 1H), 3.02 (t, J = 7.6, 2H), 1.71 (m, 2H), 1.39-1.23 (several peaks, 10H), 0.86 (t, J = 7.1, 3H). ¹³C NMR δ 152.6, 143.5, 137.8, 128.5, 125.6, 31.9, 30.4, 30.0, 29.3, 29.2, 27.8, 22.8, 14.2. Anal. calcd for C₁₃H₂₁NOSe: C 54.56; H 7.39. Found: C, 54.87; H, 7.39.

5-Hydroxy-2-pyridyl *n*-Octyl Sulfide (7c): To 6-bromo-3-pyridinol (348 mg, 2 mmol) in THF (10 mL) under N₂ at -78 °C was added dropwise *t*-BuLi (3.5 mL 1.7 M solution in pentane; 6 mmol). Then, di-*n*-octyl disulfide (872 mg, 3 mmol, 6 eq.) was added at -78 °C and the reaction mixture stirred for 30 min at this temperature and an additional 3h at room temperature. After pouring the reaction mixture into NaHCO₃ (5 % aq.), extraction with Et₂O, drying over Na₂SO₄ and concentration in *vacuo*, the crude product was purified by column chromatography using pentane/ethyl acetate (88:12) as an eluent to yield the title compound as a colourless solid (403 mg, 84 %), mp 70-71 °C. ¹H NMR δ 8.12 (d, J = 2.7, 1H), 7.23 (dd, J = 8.6, 2.7, 1H), 7.17 (d, J = 8.6, 1H), 6.68 (bs, 1H), 3.02 (t, J = 7.3, 2H), 1.63 (m, 2H), 1.43-1.30 (several peaks, 10H), 0.86 (t, J = 7.1, 3H). ¹³C NMR δ 151.9, 148.8, 136.9, 125.9, 125.0, 32.7, 31.9, 29.4, 29.3, 29.3, 29.0, 22.8, 14.2.

3-Hydroxy-2-pyridyl *n*-Octyl Telluride (8a) was prepared from 2-bromo-3-pyridinol by using the procedure for telluride **7a**. Yield: 62 %, mp 83-84 °C. ¹H NMR δ 8.14 (dd, J = 4.6, 1.6, 1H), 7.15 (dd, J = 8.2, 1.6, 1H), 7.08 (dd, J = 8.2, 4.6, 1H), 3.02 (t, J = 7.5, 2H), 1.79 (m, 2H), 1.37-1.23 (several peaks, 10H), 0.86 (t, J = 6.9, 3H). ¹³C NMR δ 155.3, 142.8, 130.7, 123.3, 119.9, 32.2, 31.9, 31.9, 29.3, 29.0, 22.8, 14.2, 9.6. Anal. calcd for C₁₃H₂₁NOTe: C 46.62; H 6.32. Found: C, 46.66; H, 6.40.

3-Hydroxy-2-pyridyl *n*-Octyl Selenide (8b) was prepared from 2-bromo-3-pyridinol by using the procedure for selenide **7b**. Yield: 50 %, mp 88-89 °C. ¹H NMR δ 8.15 (dd, J = 4.7, 1.5, 1H), 7.29 (dm, J = 8.1, 1H), 7.13 (dd, J = 8.1, 4.8, 1H), 5.30 (s, 1H), 3.10 (t, J = 7.5, 2H), 1.70 (m, 2H), 1.43-1.24 (several peaks, 10H), 0.86 (t, J = 7.1, 3H). ¹³C NMR δ 152.9, 142.2, 141.8, 123.0, 121.1, 31.9, 30.6, 30.0, 29.2, 29.1, 27.7, 22.7, 14.2. Anal. calcd for C₁₃H₂₁NOSe: C 54.54; H 7.39. Found: C, 54.39; H, 7.48.

3-Hydroxy-2-pyridyl *n*-Octyl Sulfide (8c) was prepared from 2-bromo-3-pyridinol according to the procedure for sulphide **7c**. Yield: 77 %, mp 101-103 °C. ¹H NMR δ 8.13 (dd, J = 4.8, 1.5, 1H), 7.22 (ddm, J = 8.1, 1.5, 1H), 7.06 (dd, J = 8.1, 4.8, 1H), 3.12 (t, J = 7.3, 2H), 1.63 (m, 2H), 1.41-1.24 (several peaks, 10H), 0.87 (t, J = 7.1, 3H). ¹³C NMR δ 151.9, 144.4,

141.6, 122.6, 121.7, 33.2, 31.9, 29.9, 29.3, 29.2, 28.9, 22.8, 14.2. Anal. calcd for C₁₃H₂₁NOS: C 65.23; H 8.84. Found: C, 65.17; H, 9.09.

3-Hydroxy-6-methyl-2-pyridyl *n*-Octyl Telluride (9a) was prepared from 2-iodo-6-methyl-3-pyridinol according to the procedure for telluride **7a**. Yield: 54 %. ¹H NMR δ 7.03 (d, *J* = 8.2, 1H), 6.90 (dm, *J* = 8.2, 1H), 2.97 (t, *J* = 7.4, 2H), 2.47 (s, 3H), 1.80 (m, 2H), 1.23-1.34 (several peaks, 10H), 0.86 (t, *J* = 7.1, 3H). ¹³C NMR δ 152.8, 151.9, 128.7, 123.3, 120.1, 32.1, 32.0, 31.9, 29.3, 29.0, 23.4, 22.8, 14.2, 10.2. Anal Calcd for C₁₄H₂₃NOTe: C, 48.19, H, 6.64. Found: C, 48.34; H, 6.73.

3-Hydroxy-6-methyl-2-pyridyl *n*-Octyl Selenide (9b) was prepared from 2-iodo-6-methyl-3-pyridinol according to the procedure for sulphide **9c**, using di-*n*-octyl diselenide instead of di-*n*-octyl disulfide. Yield: 60 %. ¹H NMR δ 7.09 (d, *J* = 8.2, 1H), 6.94 (dm, *J* = 8.2, 1H), 3.01 (t, *J* = 7.3, 2H), 2.47 (s, 3H), 1.68 (m, 2H), 1.38-1.24 (several peaks, 10 H), 0.87 (t, *J* = 6.9, 3H). ¹³C NMR δ 151.2, 150.7, 139.6, 123.4, 121.6, 31.9, 30.8, 29.9, 29.2, 29.1, 28.9, 23.5, 22.8, 14.2. Anal Calcd for C₁₄H₂₃NOSe: C, 56.02; H, 7.72. Found: C, 56.25; H, 7.86.

3-Hydroxy-6-methyl-2-pyridyl *n*-Octyl Sulfide (9c). 2-Iodo-6-methyl-3-pyridinol (235 mg, 1.0 mmol) and di-*n*-octyl disulfide (290 mg, 1.0 mmol) were added to a stirred mixture of CuI (3 mg, 0.015 mmol), Mg turnings (48 mg, 2.0 mmol) and 2,2'-bipyridyl (2.3 mg, 0.015 mmol) in DMF (5 mL). This mixture was heated to 200 °C in a sealed tube in a microwave reactor (300 W) for 6 h and then poured into water (15 mL). After extraction with Et₂O (20 mL x 4), the organic phase was washed with brine (50 mL), dried (MgSO₄), filtered, and evaporated in *vacuo*. Purification by flash chromatography using pentane/ethyl acetate (85:15) as eluent yielded 165 mg (65 %) of the title compound as an oil. ¹H NMR δ 7.09 (d, *J* = 8.2, 1H), 6.93 (d, *J* = 8.2, 1H), 5.93 (bs, 1H), 3.08 (t, *J* = 7.3, 2H), 2.48 (s, 3H), 1.62 (m, 2H), 1.42-1.27 (several peaks, 10H), 0.88 (t, 3H). ¹³C NMR δ 150.8, 150.0, 142.4, 122.5, 122.0, 33.5, 31.9, 30.0, 29.3, 29.2, 28.9, 23.5, 22.8, 14.2. Anal Calcd for C₁₄H₂₃NOS: C, 66.36; H, 9.15. Found: C, 66.14; H, 9.01.

3-Hydroxy-6-methyl-2-pyridyl Phenyl Telluride (10a), 3-Hydroxy-6-methyl-2-pyridyl Phenyl Selenide (10b) and 3-Hydroxy-6-methyl-2-pyridyl Phenyl Sulfide (10c) were prepared according to a literature procedure (Kumar, S.; Engman, L. *J. Org. Chem.* **2006**, *71*, 5400-5403).

2-Bromo-3-cyano-4,6-dimethylpyridine (12) was prepared according to the procedure for 2-bromo-3-cyano-5-methoxy-4,6-dimethylpyridine below, using 3-cyano-4,6-dimethyl-2-pyridinol as a starting material. Yield: 96 %, mp 116-117 °C. ¹H NMR δ 7.09 (m, 1H), 2.56 (d, *J*=0.58, 3H), 2.53 (d, *J*=0.73, 3H). ¹³C NMR δ 163.0, 154.3, 143.6, 123.6, 115.5, 111.8, 24.6, 20.9.

2-Bromo-3-cyano-5-methoxy-4,6-dimethylpyridine. Into a round-bottomed flask (200 mL) equipped with a refluxing condenser, 3-cyano-5-methoxy-4,6-dimethyl-2-pyridinol (1.90 g, 10.9 mmol), Bu₄NBr (4.80 g, 14.9 mmol), P₂O₅ (4.09 g, 28.8 mmol), toluene (110 mL) and a stirring bar were placed. The mixture was heated for 14 h under reflux. The toluene layer was decanted and washed with a saturated solution of NaHCO₃ (30 mL) and then with water (50 mL). To the oily residue left in the flask was added water (50 mL) and then powdered NaHCO₃ portionwise until there were no further evolution of gas. The mixture was extracted

with CH₂Cl₂ (ca. 250 mL), washed with brine (50 mL x 2) and then with water (30 mL). The toluene and CH₂Cl₂ solutions were combined and dried (MgSO₄). Removal of the solvent in *vacuo* and filtration of the product through a short pad of silica (Φ4 cm x 7 cm) eluting with pentane/CH₂Cl₂ (to remove any remaining tetrabutylammonium salts) afforded 2.23 g (84%) of the title compound as a white powder, mp 99-100 °C. ¹H NMR δ 3.76 (s, 3H), 2.54 (s, 3 H), 2.50 (s, 3 H). ¹³C NMR δ 158.0, 152.7, 147.1, 137.0, 115.2, 113.2, 60.7, 19.8, 15.3.

2-Bromo-4,6-dimethylpyridine-3-carboxylic acid amide (13) was prepared according to the procedure for 2-bromo-5-methoxy-4,6-dimethylpyridine-3-carboxylic acid amide below, using 2-bromo-3-cyano-4,6-dimethylpyridine as a starting material. Yield: 68 %, mp 179-180 °C. ¹H NMR δ 6.99 (s, 1H), 6.12 (bs, 1H), 5.78 (bs, 1H), 2.51 (s, 3H), 2.38 (s, 3H). ¹³C NMR δ 168.6, 160.2, 147.8, 137.5, 132.4, 124.4, 24.2, 19.5.

2-Bromo-5-methoxy-4,6-dimethylpyridine-3-carboxylic acid amide. To concentrated H₂SO₄ (2.16 mL 96%, 18 M; 39.0 mmol) in an Erlenmeyer flask (50 mL) heated at 90 °C in an oil bath, 2-bromo-3-cyano-5-methoxy-4,6-dimethylpyridine (2.70 g, 11.2 mmol) was added. The dark brown mixture was stirred at 100 °C for 3 h and then cooled to ca 90 °C. Water (7.0 mL) was added dropwise (**CAUTION!** Quick addition of water causes bumping) and the mixture quickly cooled down to 20 °C, and poured slowly into water (30 mL) in a beaker (250 mL). To this mixture, powdered NaHCO₃ was added in small portions until the evolution of CO₂ had ceased. After extraction with CH₂Cl₂ (120 mL x 3), washing with brine (40 mL x 2), and drying over MgSO₄ and evaporation of the solvent afforded 2.57 g (88%) of the title compound as colorless needles: ¹H NMR δ 6.07 (br s, 1 H), 5.82 (br s, 1 H), 3.73 (s, 3 H), 2.49 (s, 3 H), 2.34 (s, 3 H). ¹³C NMR δ 168.0, 154.4, 153.2, 140.6, 134.0, 130.7, 60.5, 19.3, 13.5.

3-Amino-2-bromo-4,6-dimethylpyridine (14) was prepared according to the procedure for 3-amino-2-bromo-5-methoxy-4,6-dimethylpyridine below, using 2-bromo-4,6-dimethylpyridine-3-carboxylic acid amide as a starting material. Yield: 84 %, mp 61-62 °C. ¹H NMR δ 6.82 (s, 1H), 4.01 (bs, 2H), 2.41 (s, 3H), 2.19 (s, 3H). ¹³C NMR δ 148.0, 137.5, 132.7, 128.6, 124.8, 22.9, 18.0.

3-Amino-2-bromo-5-methoxy-4,6-dimethylpyridine. To a solution of KOH (1.15 g, 20.6 mmol) in water (3 mL) in an Erlenmeyer flask (50 mL) at 0 °C, Br₂ (0.623 g, 0.200 mL, 3.9 mmol) was added dropwise by syringe. The resulting lemon-yellow solution was stirred for 5 min at this temperature and 2-bromo-5-methoxy-4,6-dimethylpyridine-3-carboxylic acid amide (0.777 g, 3.0 mmol) was added. After stirring for another 5 min, a mixture of water and THF (1 mL of each) was added slowly to the resulting yellow suspension and stirring continued for 10 min at 0 °C. The flask was then placed in an oil bath preheated to 70 °C and stirred for 0.5 h (the color of the solution turned to reddish orange). The temperature of the oil-bath was raised to 90 °C and stirring continued for another 3 h. The cooled brown residue was subjected to aqueous work-up. After extraction with CH₂Cl₂ (150 mL x 2), washing with brine (50 mL x 2), and drying over MgSO₄, removal of the solvent afforded the title compound (0.693 g, ~100%) as pale yellow needles, mp 96-97 °C ¹H NMR δ 3.91 (br s, 2H), 3.64 (s, 1H), 2.33 (s, 3H), 2.09 (s, 3H). ¹³C NMR δ 153.0, 141.6, 138.6, 125.4, 122.7, 60.5, 18.4, 10.9.

2-Bromo-4,6-dimethyl-3-pyridinol (15) was prepared according to the procedure for 6-bromo-3-pyridinol, using 3-amino-2-bromo-4,6-dimethylpyridine as a starting material. Yield: 43 %, mp 106-107 °C. ¹H NMR δ 6.84 (s, 1H), 5.78 (br s, 1H), 2.39 (s, 3H), 2.24 (s, 3H). ¹³C NMR 150.6, 146.1, 135.4, 129.6, 125.8, 23.1, 16.5.

2-Bromo-5-methoxy-4,6-dimethyl-3-pyridinol was prepared according to the procedure for 6-bromo-3-pyridinol, using 3-amino-2-bromo-5-methoxy-4,6-dimethylpyridine as a starting material. Yield: 54 %, mp 103-104 °C. ¹H NMR δ 5.79 (s, 1H), 3.69 (s, 3H), 2.38 (s, 3H), 2.21 (s, 3H). ¹³C NMR δ 153.7, 146.7, 144.5, 128.6, 123.4, 60.4, 18.5, 10.2.

3-Hydroxy-4,6-dimethyl-2-pyridyl *n*-Octyl Telluride (16a) was prepared according to the procedure for pyridinol **7a**, using 2-bromo-4,6-dimethyl-3-pyridinol as a starting material. Yield: 44 %. ¹H NMR δ 6.80 (s, 1H), 6.15 (bs, 1H), 2.93 (t, J = 7.7, 2H), 2.43 (s, 3H), 2.22 (s, 3H), 1.76 (m, 2H), 1.35-1.23 (several peaks, 10H), 0.86 (t, J = 7.2, 3H). ¹³C NMR δ 151.9, 151.6, 131.1, 127.8, 125.5, 32.0, 32.0, 31.9, 29.3, 29.0, 23.4, 22.8, 16.7, 14.2, 10.6. Anal. calcd for C₁₅H₂₅NOTe: C 49.64; H 7.02. Found: C, 49.46; H, 6.94.

3-Hydroxy-4,6-dimethyl-2-pyridyl *n*-Octyl Selenide (16b) was prepared according to the procedure for pyridinol **7b**, using 2-bromo-4,6-dimethyl-3-pyridinol as a starting material. Yield: 60 %. ¹H NMR δ 6.84 (s, 1H), 6.10 (bs, 1H), 3.08 (t, J = 7.2, 2H), 2.53 (s, 3H), 2.29 (s, 3H), 1.68 (m, 2H), 1.37-1.23 (several peaks, 10H), 0.86 (t, J = 7.0, 3H). ¹³C NMR δ 150.6, 149.9, 138.1, 133.0, 125.6, 31.9, 30.8, 29.9, 29.5, 29.3, 29.1, 23.4, 22.8, 16.3, 14.2. Anal. calcd for C₁₅H₂₅NOSe: C 57.32; H 8.02. N 4.46 Found: C, 57.37; H, 8.03 N 4.48.

3-Hydroxy-4,6-dimethyl-2-pyridyl *n*-Octyl Sulfide (16c) was prepared according to the procedure for pyridinol **7c**, using 2-bromo-4,6-dimethyl-3-pyridinol as a starting material. Yield: 35 %, ¹H NMR δ 6.80 (s, 1H), 5.91 (s, 1H), 3.03 (t, J = 7.4, 2H), 2.42 (s, 3H), 2.23 (s, 3H), 1.61 (m, 2H), 1.41-1.20 (several peaks, 10H), 0.87 (t, J = 7.1, 3H). ¹³C NMR δ 150.3, 149.0, 140.7, 132.8, 124.8, 34.4, 31.9, 30.2, 29.3, 29.2, 28.9, 23.6, 22.8, 15.9, 14.22. EI-MS: 267.8 [M+H]⁺, 290.0 [M+Na]⁺, 266.0 [M-H]⁻. Anal. calcd for C₁₅H₂₅NOS: C 67.37; H 9.42; N 5.24. Found: C, 66.99; H, 9.21 N 4.92.

3-Hydroxy-4,6-dimethyl-2-pyridyl Ethyl Telluride (17) was prepared according to the procedure for pyridinol **16a** using ethyl bromide instead of *n*-octyl bromide. Yield 43 %. ¹H NMR δ 6.81 (s, 1H), 5.99 (bs, 1H), 2.91 (q, J = 7.7, 2H), 2.43 (s, 3H), 2.23 (s, 3H), 1.63 (t, J = 7.7, 3H). ¹³C NMR δ 151.9, 151.7, 131.1, 127.7, 125.7, 23.5, 17.6, 16.7, 2.52. Anal. calcd for C₉H₁₃NOTe: C 38.77; H 4.70; N 5.02. Found: C, 39.01; H, 4.65; N 4.71.

3-Hydroxy-5-methoxy-4,6-dimethyl-2-pyridyl *n*-Octyl Telluride (18a) was prepared according to the procedure for pyridinol **7a**, using 2-bromo-5-methoxy-4,6-dimethyl-3-pyridinol as a starting material. Yield: 54 %. ¹H NMR δ 5.98 (s, 1H), 3.73 (s, 3H), 2.87 (t, J = 7.6, 2H), 2.44 (s, 3H), 2.23 (s, 3H), 1.77 (m, 2H), 1.32-1.22 (several peaks, 10H), 0.86 (t, J = 7.2, 3H). ¹³C NMR (CDCl₃) δ 154.3, 152.7, 146.1, 124.2, 121.4, 60.5, 32.0, 31.9, 29.3, 29.0, 22.8, 22.5, 19.1, 14.2, 10.7, 10.2.

3-Hydroxy-5-methoxy-4,6-dimethyl-2-pyridyl *n*-Octyl Selenide (18b) was prepared according to the procedure for pyridinol **7b**, using 2-bromo-5-methoxy-4,6-dimethyl-3-pyridinol as a starting material. Yield: 64 %. ¹H NMR δ 3.72 (s, 3H), 3.19 (t, J = 7.6, 2H), 2.44 (s, 3H), 2.20 (s, 3H), 1.72 (m, 2H), 1.44-1.26 (several peaks, 10H), 0.88 (t, 3H). ¹³C

NMR δ 154.1, 151.0, 144.9, 132.4, 126.1, 60.4, 31.9, 30.8, 29.9, 29.6, 29.2, 29.1, 22.7, 18.7, 14.1, 9.9. EI-MS; 346.4 $[M+H]^+$ (most abundant). Anal. calcd for $C_{16}H_{27}NO_2Se$: C 55.8; H 7.9; N 4.1. Found: C, 55.4; H, 7.7, N, 3.9

2-Bromo-5-methoxy-4,6-dimethylpyridine: 3-Amino-2-bromo-5-methoxy-4,6-dimethylpyridine (231 mg, 1.00 mmol) was dissolved in HBF_4 (0.5 mL, 50 % aq. solution), water (0.5 mL) was added and the resulting brownish solution cooled to $0^\circ C$. $NaNO_2$ (83 mg, 1.2 mmol) in water (0.5 mL) was added dropwise at $0^\circ C$. The resulting solution was stirred for 1 h at this temperature when hypophosphorous acid (0.491 mL 50% in H_2O , 4.74 mmol) was quickly added. The mixture was then heated under reflux for 15 min, cooled to ambient temperature and neutralized with $NaHCO_3$ (5 % aq.). After extraction with CH_2Cl_2 (3 x 25 mL), drying (Na_2SO_4) and concentration *in vacuo*, the brown residue was purified by column chromatography (SiO_2) eluting with CH_2Cl_2 to give the title compound (80 mg, 37 % yield) in the first fraction, 1H NMR δ 7.12 (s, 1H), 3.71 (s, 3 H), 2.46 (s, 3 H), 2.43 (s, 3 H). ^{13}C NMR δ 153.5, 153.2, 143.2, 134.8, 127.7, 60.2, 19.1, 15.7. and 2-bromo-5-methoxy-4,6-dimethyl-3-pyridinol (87 mg, 38 % yield) in the second fraction.

6-Bromo-2,4-dimethyl-3-pyridinol. To a solution of 2-bromo-5-methoxy-4,6-dimethylpyridine (216 mg, 1 mmol) in CH_2Cl_2 (10 mL), was added BBr_3 (2 mL 1.0 M solution in CH_2Cl_2 ; 2 mmol) at $-78^\circ C$ under N_2 . After stirring for 30 min at this temperature and then 16 h at ambient temperature, the reaction mixture was poured into cold water (10 mL) and $NaHCO_3$ (5 % aq.) was added. After extraction with CH_2Cl_2 (3 x 20 mL), drying over Na_2SO_4 and evaporation *in vacuo*, the resulting brownish solid was purified by column chromatography eluting with ethyl acetate/pentane (16:84), the title compound was obtained as a colourless solid (150 mg, 78 %), mp $105-106^\circ C$. 1H NMR δ 7.1 (s, 1 H), 6.42 (br s, 1H), 2.43 (s, 3 H), 2.23 (s, 3 H). ^{13}C NMR δ 149.4, 146.4, 137.0, 130.3, 127.6, 18.7, 15.9.

5-Hydroxy-4,6-dimethyl-2-pyridyl *n*-Octyl Telluride (19a) was prepared according to the procedure for pyridinol **7a**, using 6-bromo-2,4-dimethyl-3-pyridinol as a starting material. Yield: 47 %. 1H NMR δ 7.21(s, 1H), 3.04 (t, $J = 7.7$, 2H), 2.48 (s, 3H), 2.21 (s, 3H), 1.86 (m, 2H), 1.38-1.26 (several peaks, 10H), 0.87 (t, $J = 7.0$, 3H). ^{13}C NMR δ 148.2, 146.1, 132.9, 132.3, 127.4, 32.3, 32.2, 32.0, 29.3, 29.1, 22.8, 19.0, 15.2, 14.2, 9.7.

5-Hydroxy-4,6-dimethyl-3-pyridyl *n*-Octyl Selenide (19b): To the solution of dilithiated 6-bromo-2,4-dimethyl-3-pyridinol prepared as described below (compound **19c**), finely ground elemental selenium (0.32 g, 4.0 mmol) was added and stirring continued for 2h. The reaction mixture was then poured onto crushed ice and kept in the open air for 2h when a solution of saturated aqueous NH_4Cl was added. Extraction with Et_2O (3 x 50 mL), drying and evaporation afforded crude bis-(5-hydroxy-4,6-dimethyl-3-pyridyl) diselenide which was dissolved in $EtOH$ and cooled to $0^\circ C$ under N_2 . $NaBH_4$ (0.34 g, 10 mmol) was added in one portion and the reaction mixture was stirred for 30 min at room temperature, resulting in a faint yellowish solution. *n*-Octyl bromide (2.0 g, 10 mmol) was added by syringe and stirring continued for an additional 1 h when the reaction mixture was poured into water. Extraction with Et_2O (3 x 20 mL), drying over Na_2SO_4 , evaporation and purification by column chromatography eluting with pentane/ethyl acetate (90:10) afforded 0.185 g (54 %) of the title compound as a light yellow oil. 1H NMR δ 7.00 (s, 1H), 4.78 (br s, 1H), 3.06 (t, $J = 7.6$, 2H), 2.45 (s, 3H), 2.20 (s, 3H), 1.74 (m, 2H), 1.42-1.23 (several peaks, 10 H), 0.87 (t, $J = 7.0$, 3H). ^{13}C NMR δ 147.4, 145.2, 143.7, 133.1, 126.4, 32.0, 30.7, 30.2, 29.3, 29.3, 27.0, 22.8, 18.9, 15.4, 14.

5-Hydroxy-4,6-dimethyl-2-pyridyl *n*-Octyl Sulfide (19c): To a solution of 6-bromo-2,4-dimethyl-3-pyridinol (0.202 g, 1.0 mmol) in THF (15 mL) was added dropwise *t*-BuLi (1.8 mL 1.7 M in pentane; 3 mmol) at -78 °C. The solution was stirred for 20 min at this temperature and 15 min at room temperature. The reaction mixture was again cooled to -78 °C and di-*n*-octyl disulfide (0.58 g, 2 mmol) was added dropwise and stirring was continued for 1 h at room temperature. A saturated solution of NH₄Cl was added and the mixture was extracted with ether (3 x 25 mL). Drying over Na₂SO₄, removal of the solvent *in vacuo* and purification of the crude product by column chromatography using ethylacetate/ pentane (13:87) as eluent afforded the title compound (0.17 g, 64 %). ¹H NMR δ 6.86 (s, 1H), 4.82 (bs, 1H), 3.04 (t, *J* = 7.6, 2H), 2.44 (s, 3H), 2.20 (s, 3H), 1.64 (m, 2 H), 1.41-1.26 (several peaks, 10H), 0.87 (t, *J* = 7.0, 3H). ¹³C NMR δ 148.4, 146.8, 144.8, 133.3, 123.0, 32.0, 31.8, 29.7, 29.3, 29.3, 29.0, 22.8, 19.0, 15.7, 14.3.

HPLC Peroxidation Assay

Inhibition times (*T*_{inh}) and inhibited rates of peroxidation (*R*_{inh}) were determined as previously described (Malmström, J.; Jonsson, M.; Cotgreave, I. A.; Hammarström, L.; Sjödin, M.; Engman, L. *J. Am. Chem. Soc.* **2001**, *123*, 3434-3440. Shanks, D.; Amorati, R.; Fumo, M. G.; Pedulli, G. F.; Valgimigli, L.; Engman, L. *J. Org. Chem.* **2006**, *71*, 1033-1038).

Kinetic Measurements in Homogenous Phase Autoxidations.

Kinetic measurements with peroxy radicals were performed by studying the inhibited autoxidation of 4.3 M styrene in chlorobenzene at 303 K, initiated by AIBN, in the presence of variable amounts (1-20 x 10⁻⁶M) of pyridinol **16a**, or α-tocopherol (α-TOH) or its synthetic analogue 2,2,5,7,8-pentamethyl-6-chromanol as reference antioxidants. The autoxidation was followed by monitoring the oxygen consumption in an oxygen uptake apparatus built in our laboratory and based on a Validyne DP15 differential pressure transducer, which have been previously described (Amorati, R.; Pedulli, G.F.; Valgimigli, L.; Attanasi, O.A.; Filippone, P.; Fiorucci, C.; Saladino, R. *J. Chem. Soc., Perkin Trans. 2* **2001**, 2142-2146). Overall the process can be described by reactions I-VI, where RH is the oxidizable substrate and ArOH is the antioxidant.

The rate of initiation *R*_i was measured in a preliminary set of experiments from the length of the inhibition period *T*_{inh}, using α-TOH as a reference antioxidant: *R*_i = 2[α-TOH] / *T*_{inh}. Integration of the oxygen consumption trace afforded the rate of reaction with peroxy radicals *k*_{inh}, according to equation VII.

$$\Delta[\text{O}_2]_t = -k_p/k_{inh} [\text{RH}] \ln(1-t/T_{inh}) \quad \text{(VII)}$$

In order to evaluate the co-antioxidant behaviour of thiols towards pyridinol **16a**, autoxidation studies were performed by adding 1-2 equivalents of *n*-dodecanthiol or *n*-octadecanethiol, or *N*-(*t*-

butoxycarbonyl)-cysteine methyl ester (LIPcys), a lipid soluble analogue of NAC, to the autoxidating mixture inhibited by **16a** (4.5×10^{-6} M).

Assay for Thiol Peroxidase Activity

Thiol peroxidase activity was determined spectrophotometrically as recently described. (Kumar, L. Engman, L. Valgimigli, R. Amorati, M. G. Fumo, G. F. Pedulli, *J. Org. Chem.* **2007**, 72, 6046-6055).

¹H NMR spectrum of **7a**.

^{13}C NMR spectrum of **7a**.

^1H NMR spectrum of **7b**.

^{13}C NMR spectrum of **7b**.

^1H NMR spectrum of **7c**.

¹³C NMR spectrum of **7c**.

¹H NMR spectrum of **8a**.

STANDARD 1H OBSERVE

Pulse Sequence: s2pul

Solvent: cdcl3

Temp. 25.0 C / 298.1 K

File: OrthoOHPyTeOctyl_1H

PULSE SEQUENCE: s2pul

Pulse 37.1 degrees

Acq. time 3.744 sec

Width 6000.6 Hz

8 repetitions

OBSERVE H1, 399.98 MHz

DATA PROCESSING

Line broadening 0.2 Hz

Ft size 65536

Total time 1 minute

^{13}C NMR spectrum of **8a**.

¹H NMR spectrum of **8b**.

Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp: 25.0 C / 298.1 K
 File: h1-thomas-fsawing_ortho_se_pyridinol_lh_4_sep_cdcl3_500
 INOVA-500 Unit500
 User henrik
 Date 2007
 PULSE SEQUENCE: s2pul
 Pulse 73.5 degrees
 Acq. time 3.000 sec
 Width 8000.0 Hz
 F2 repetitions
 F2 frequency 499.94 MHz
 DATA PROCESSING
 Line broadening 0.2 Hz
 FT size 6536
 Total time 1 minutes

¹³C NMR spectrum of **8b**.

¹H NMR spectrum of **8c**.

¹³C NMR spectrum of **8c**.

¹H NMR spectrum of **9a**.

¹³C NMR spectrum of **9a**.

¹H NMR spectrum of **9b**.

^{13}C NMR spectrum of **9b**.

¹H NMR spectrum of **9c**.

¹H Observe

Archive directory: /home/vnmr1/vnmrSYS/data
Sample directory:

Pulse Sequence: s2pul
Solvent: CDCl₃
Temp. 25.0 C / 298.1 K
File: PyOHSeOctyl¹H

PULSE SEQUENCE: s2pul
Pulse 43.2 degrees
Acq. time 3.700 sec
Width 4800.8 Hz
8 repetitions
OBSERVE H1, 300.03 MHz
DATA PROCESSING
Line broadening 0.2 Hz
Ft size 65536
Total time 1 minute

^{13}C NMR spectrum of **9c**.

^1H NMR spectrum of **12**.

^{13}C NMR spectrum of **12**.

User: henrikj
 Date: Mar 9 2007
 PULSE SEQUENCE: zgpg30
 Relax. delay 1.500 sec
 Pulse 64.5 degrees
 Acq. time 1.199 sec
 Width 25000.0 Hz
 18000 repetitions
 OBSERVE C13, 100.58 MHz
 DECOUPLE H1, 399.98 MHz
 Power 48 dB
 Continuously on
 Multiscan 4
 Multiscan gated
 Single precision data
 DATA PROCESSING
 Line broadening 1.0 Hz
 FT size 65536
 Total time 13.5 hours

¹H NMR spectrum of 2-Bromo-3-cyano-5-methoxy-4,6-dimethylpyridine.

¹³C NMR spectrum of 2-Bromo-3-cyano-5-methoxy-4,6-dimethylpyridine.

^1H NMR spectrum of **13**.

¹³C NMR spectrum of **13**.

¹H NMR spectrum of 2-Bromo-5-methoxy-4,6-dimethylpyridine-3-carboxylic acid amide.

¹³C NMR spectrum of 2-Bromo-5-methoxy-4,6-dimethylpyridine-3-carboxylic acid amide.

^1H NMR spectrum of **14**.

^{13}C NMR spectrum of **14**.

^1H NMR spectrum of 3-amino-2-bromo-5-methoxy-4,6-dimethylpyridine.

¹³C NMR spectrum of 3-amino-2-bromo-5-methoxy-4,6-dimethylpyridine.

¹H NMR spectrum of **15**.

^{13}C NMR spectrum of **15**.

¹H NMR spectrum of 2-bromo-5-methoxy-4,6-dimethyl-3-pyridinol.

¹³C NMR spectrum of 2-bromo-5-methoxy-4,6-dimethyl-3-pyridinol.

^1H NMR spectrum of **16a**.

^{13}C NMR spectrum of **16a**.

¹H NMR spectrum of **16b**.

^{13}C NMR spectrum of **16b**.

¹H NMR spectrum of **16c**.

STANDARD PROTON PARAMETERS
Pulse Sequence: #2pul
Solvent: cdcl3
Temperature: 25.0 C / 298.1 K
File: b1-75_andra_kolonnuppreingen_1H_CDCL3
INOVA-500 "unity500"
User: henrikj
Date: Oct 16 2007
PULSE SEQUENCE: #2pul
Pulse: 73.5 degrees
Acq. time: 3.000 sec
Width: 8000.0 Hz
16 repetitions
OBSERVED F1: 499.94 MHz
NUC1: 13C
P1: 12.00
Line broadening: 0.2 Hz
FT size: 65536
Total time: 1 minute

¹³C NMR spectrum of **16c**.

¹H NMR spectrum of **17**.

¹³C NMR spectrum of **17**.

experiment 84 after vacuum
Pulse Sequence: s2pul
Solvent: CDCl3
Temp: 25.0 C / 298.1 K
User: 1-14-87
File: h3_84_after_vacuum_13c_cdc13_500
INOVA-500 "unity500"
User: henrikj
Date: Nov 21 2007
Pulse Sequence: s2pul
Pulse: 26.5 degrees
Pulse: 26.5 degrees
Acq. time 1.300 sec
Width 2996.3 Hz
10700 repetitions
SOLVENT CH1
DECOUPLE CH1
Power 33 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line 8
FT 84.131072
Total time 12.8 hours

¹H NMR spectrum of **18a**.

¹³C NMR spectrum of **18a**.

¹H NMR spectrum of **18b**.

¹³C NMR spectrum of **18b**.

¹H NMR spectrum of 2-bromo-5-methoxy-4,6-dimethylpyridine.

^{13}C NMR spectrum of 2-bromo-5-methoxy-4,6-dimethylpyridine.

```

NAME: 2-bromo-5-methoxy-4,6-dimethylpyridine
Pulse 125.8 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
96 repetitions
OBSERVE C13, 75.44 MHz
DECOUPLE H1, 300.03 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 7 minutes
  
```

¹H NMR spectrum of 6-bromo-2,4-dimethyl-3-pyridinol

¹³C NMR spectrum of 6-bromo-2,4-dimethyl-3-pyridinol

Pulse Sequence: s2pul
Solvent: CDCl₃
Temp. 25.0 C / 298.1 K
File: OH2MepYBr3_13C

PULSE SEQUENCE: s2pul
Relax. delay 3.000 sec
Pulse 64.5 degrees
Acq. time 1.199 sec
Width 25000.0 Hz
992 repetitions
OBSERVE C13, 100.58 MHz
DECOUPLE H1, 399.98 MHz
Power 48 dB
continuously on
WALTZ-16 modulated
Single precision data
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 69 minutes

¹H NMR spectrum of **19a**.

```

Pulse Sequence: sfgul
Solvent: CDCl3 298.1 K
Temp: 298.1 K
Sample: 1,1,1-trichloro-2,2,2-trifluoroethane-d5
P1: 0.001000 sec
P2: 0.001000 sec
P3: 0.001000 sec
P4: 0.001000 sec
P5: 0.001000 sec
P6: 0.001000 sec
P7: 0.001000 sec
P8: 0.001000 sec
P9: 0.001000 sec
P10: 0.001000 sec
P11: 0.001000 sec
P12: 0.001000 sec
P13: 0.001000 sec
P14: 0.001000 sec
P15: 0.001000 sec
P16: 0.001000 sec
P17: 0.001000 sec
P18: 0.001000 sec
P19: 0.001000 sec
P20: 0.001000 sec
P21: 0.001000 sec
P22: 0.001000 sec
P23: 0.001000 sec
P24: 0.001000 sec
P25: 0.001000 sec
P26: 0.001000 sec
P27: 0.001000 sec
P28: 0.001000 sec
P29: 0.001000 sec
P30: 0.001000 sec
P31: 0.001000 sec
P32: 0.001000 sec
P33: 0.001000 sec
P34: 0.001000 sec
P35: 0.001000 sec
P36: 0.001000 sec
P37: 0.001000 sec
P38: 0.001000 sec
P39: 0.001000 sec
P40: 0.001000 sec
P41: 0.001000 sec
P42: 0.001000 sec
P43: 0.001000 sec
P44: 0.001000 sec
P45: 0.001000 sec
P46: 0.001000 sec
P47: 0.001000 sec
P48: 0.001000 sec
P49: 0.001000 sec
P50: 0.001000 sec
P51: 0.001000 sec
P52: 0.001000 sec
P53: 0.001000 sec
P54: 0.001000 sec
P55: 0.001000 sec
P56: 0.001000 sec
P57: 0.001000 sec
P58: 0.001000 sec
P59: 0.001000 sec
P60: 0.001000 sec
P61: 0.001000 sec
P62: 0.001000 sec
P63: 0.001000 sec
P64: 0.001000 sec
P65: 0.001000 sec
P66: 0.001000 sec
P67: 0.001000 sec
P68: 0.001000 sec
P69: 0.001000 sec
P70: 0.001000 sec
P71: 0.001000 sec
P72: 0.001000 sec
P73: 0.001000 sec
P74: 0.001000 sec
P75: 0.001000 sec
P76: 0.001000 sec
P77: 0.001000 sec
P78: 0.001000 sec
P79: 0.001000 sec
P80: 0.001000 sec
P81: 0.001000 sec
P82: 0.001000 sec
P83: 0.001000 sec
P84: 0.001000 sec
P85: 0.001000 sec
P86: 0.001000 sec
P87: 0.001000 sec
P88: 0.001000 sec
P89: 0.001000 sec
P90: 0.001000 sec
P91: 0.001000 sec
P92: 0.001000 sec
P93: 0.001000 sec
P94: 0.001000 sec
P95: 0.001000 sec
P96: 0.001000 sec
P97: 0.001000 sec
P98: 0.001000 sec
P99: 0.001000 sec
P100: 0.001000 sec
P101: 0.001000 sec
P102: 0.001000 sec
P103: 0.001000 sec
P104: 0.001000 sec
P105: 0.001000 sec
P106: 0.001000 sec
P107: 0.001000 sec
P108: 0.001000 sec
P109: 0.001000 sec
P110: 0.001000 sec
P111: 0.001000 sec
P112: 0.001000 sec
P113: 0.001000 sec
P114: 0.001000 sec
P115: 0.001000 sec
P116: 0.001000 sec
P117: 0.001000 sec
P118: 0.001000 sec
P119: 0.001000 sec
P120: 0.001000 sec
P121: 0.001000 sec
P122: 0.001000 sec
P123: 0.001000 sec
P124: 0.001000 sec
P125: 0.001000 sec
P126: 0.001000 sec
P127: 0.001000 sec
P128: 0.001000 sec
P129: 0.001000 sec
P130: 0.001000 sec
P131: 0.001000 sec
P132: 0.001000 sec
P133: 0.001000 sec
P134: 0.001000 sec
P135: 0.001000 sec
P136: 0.001000 sec
P137: 0.001000 sec
P138: 0.001000 sec
P139: 0.001000 sec
P140: 0.001000 sec
P141: 0.001000 sec
P142: 0.001000 sec
P143: 0.001000 sec
P144: 0.001000 sec
P145: 0.001000 sec
P146: 0.001000 sec
P147: 0.001000 sec
P148: 0.001000 sec
P149: 0.001000 sec
P150: 0.001000 sec
P151: 0.001000 sec
P152: 0.001000 sec
P153: 0.001000 sec
P154: 0.001000 sec
P155: 0.001000 sec
P156: 0.001000 sec
P157: 0.001000 sec
P158: 0.001000 sec
P159: 0.001000 sec
P160: 0.001000 sec
P161: 0.001000 sec
P162: 0.001000 sec
P163: 0.001000 sec
P164: 0.001000 sec
P165: 0.001000 sec
P166: 0.001000 sec
P167: 0.001000 sec
P168: 0.001000 sec
P169: 0.001000 sec
P170: 0.001000 sec
P171: 0.001000 sec
P172: 0.001000 sec
P173: 0.001000 sec
P174: 0.001000 sec
P175: 0.001000 sec
P176: 0.001000 sec
P177: 0.001000 sec
P178: 0.001000 sec
P179: 0.001000 sec
P180: 0.001000 sec
P181: 0.001000 sec
P182: 0.001000 sec
P183: 0.001000 sec
P184: 0.001000 sec
P185: 0.001000 sec
P186: 0.001000 sec
P187: 0.001000 sec
P188: 0.001000 sec
P189: 0.001000 sec
P190: 0.001000 sec
P191: 0.001000 sec
P192: 0.001000 sec
P193: 0.001000 sec
P194: 0.001000 sec
P195: 0.001000 sec
P196: 0.001000 sec
P197: 0.001000 sec
P198: 0.001000 sec
P199: 0.001000 sec
P200: 0.001000 sec
P201: 0.001000 sec
P202: 0.001000 sec
P203: 0.001000 sec
P204: 0.001000 sec
P205: 0.001000 sec
P206: 0.001000 sec
P207: 0.001000 sec
P208: 0.001000 sec
P209: 0.001000 sec
P210: 0.001000 sec
P211: 0.001000 sec
P212: 0.001000 sec
P213: 0.001000 sec
P214: 0.001000 sec
P215: 0.001000 sec
P216: 0.001000 sec
P217: 0.001000 sec
P218: 0.001000 sec
P219: 0.001000 sec
P220: 0.001000 sec
P221: 0.001000 sec
P222: 0.001000 sec
P223: 0.001000 sec
P224: 0.001000 sec
P225: 0.001000 sec
P226: 0.001000 sec
P227: 0.001000 sec
P228: 0.001000 sec
P229: 0.001000 sec
P230: 0.001000 sec
P231: 0.001000 sec
P232: 0.001000 sec
P233: 0.001000 sec
P234: 0.001000 sec
P235: 0.001000 sec
P236: 0.001000 sec
P237: 0.001000 sec
P238: 0.001000 sec
P239: 0.001000 sec
P240: 0.001000 sec
P241: 0.001000 sec
P242: 0.001000 sec
P243: 0.001000 sec
P244: 0.001000 sec
P245: 0.001000 sec
P246: 0.001000 sec
P247: 0.001000 sec
P248: 0.001000 sec
P249: 0.001000 sec
P250: 0.001000 sec
P251: 0.001000 sec
P252: 0.001000 sec
P253: 0.001000 sec
P254: 0.001000 sec
P255: 0.001000 sec
P256: 0.001000 sec
P257: 0.001000 sec
P258: 0.001000 sec
P259: 0.001000
```

¹H NMR spectrum of **19b**.

^{13}C NMR spectrum of **19b**.

¹H NMR spectrum of **19c**.

¹³C NMR spectrum of **19c**.