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SYNTHESIS OF IDEBENONE; A SYNTHETIC ANALOG OF COENZYME $\ensuremath{\mathbb{Q}}$

Young-Sik Jung ^a , Bo-Young Joe ^a , Churl-Min Seong ^a & No-Sang Park ^a

^a Bioorganic Division, Korea Research Institute of Chemical Technology, P.O. Box 107, Yusong, Taejon, 305 606, Korea Published online: 15 Aug 2006.

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SYNTHESIS OF IDEBENONE; A SYNTHETIC ANALOG OF COENZYME Q

Young-Sik Jung,* Bo-Young Joe, Churl-Min Seong, and No-Sang Park*

Bioorganic Division, Korea Research Institute of Chemical Technology, P.O. Box 107, Yusong, Taejon 305 606, Korea

ABSTRACT

Idebenone, a synthetic analog of coenzyme Q, was prepared from the tetramethoxytoluene 2. Two main transformations in this procedure are Friedel–Crafts acylation of 2 to 4 and CAN assisted oxidation of 7 to the quinone 8.

Idebenone¹ (2,3-dimethoxy-5-methyl-6-(10-hydroxy)decyl-1,4-benzoquinone) is a synthetic analog of coenzyme Q^2 which is a lipid-soluble electron carrier that functions in a critical position in the mitochondria electron transport chain. Although the precise mechanism of action of idebenone is unknown, preclinical studies suggest that idebenone may exert cytoprotective properties by acting as a free radical scavenger.¹ In addition, it also appears to improve cerebral metabolism, correct neurotransmitter defects, and enhance memory and learning. The study of structurally

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^{*}Corresponding author.

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varied derivatives for biological testing led us to investigate idebenone synthesis. The first synthesis of idebenone was reported by the workers of Takeda in many years ago,³ and efficient synthesis is still desirable.

In this report, we wish to describe the synthesis of idebenone starting from readily available tetramethoxytoluene $2.^4$ The AlCl₃ catalyzed acylation of **2** with acid chloride 3^5 in CH₂Cl₂ provided **4** (71%). Reduction of **4** with LiAlH₄ followed by acetylation with acetic anhydride gave **5** (88%). Selective removal of the acetyl group on benzylic position under Pd-catalyzed hydrogenation condition was attempted. Even though many examples for the reduction of acetyl group are appeared in literatures,⁶ no reaction was occurred in our system. Thus this problem was solved by two consecutive reactions, elimination using LiBr in DMF (49%)⁷ and then Pd-catalyzed hydrogenation (99%), to provide **7**. Oxidation of **7** with ceric ammonium nitrite (CAN)⁸ in aqueous MeCN followed by hydrolysis with Na₂CO₃ provided **1** (54%). In summary, we accomplished the synthesis of idebenone from readily available tetramethoxytoluene **2**. Two main transformations in this procedure are Friedel–Crafts acylation of **2** to **4** and CAN assisted oxidation of **7** to the quinone **8**.

EXPERIMENTAL

All reactions were carried out under N₂ atmosphere unless otherwise noted. MeCN was distilled from CaH₂ prior to use. Organic extracts or filtrates were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. Flash chromatography was performed with Merck-EM Type 60 (230–400 mesh) silica gel (flash). ¹H NMR spectra were measured by Varian Gemini 200 MHz and Bruker AM-300 NMR spectrometers. Chemical shifts are reported in ppm (δ) relative to TMS as internal standard. Mass spectrometric data determined by use of the electron impact (EIMS) method are reported as *m*/*z* (relative intensity). Elemental analyses were performed with CE Instruments-ea 1110 Automatic Elemental Analyzer. Melting points were uncorrected.

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Methyl 10-(2,3,4,5-Tetramethoxy-6-methylphenyl)-10undecenoate (4)

To a mixture of AlCl₃ (944 mg, 7.02 mmol) in CH₂Cl₂ (10 mL) was added acid chloride **3** (1.6 mL, 7.02 mmol) followed by 1,2,3,4-tetramethoxy-5-methylbenzene **2** (1.27 g, 5.4 mmol) in CH₂Cl₂ (10 mL) at 0°C and then the mixture was refluxed for 24 h. The reaction mixture was quenched with cold water and extracted with CH₂Cl₂. The organic extracts were dried over Na₂SO₄. Evaporation of solvents afforded a crude, which was purified by flash chromatography (silica gel, hexane : EtOAc = 4:1) to



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provide **4** (1.57 g, 71%). ¹H NMR (200 MHz, CDCl₃) δ 1.28 (br s, 8H, 4CH₂), 1.60–1.64 (m, 4H, 2CH₂), 2.02 (s, 3H, ArCH₃), 2.27 (t, *J*=7.4 Hz, 2H, CH₂), 2.69 (t, *J*=7.3 Hz, 2H, CH₂), 3.64 (s, 3H, CO₂CH₃), 3.76 (s, 3H, ArOCH₃), 3.77 (s, 3H, OCH₃), 3.87 (s, 3H, OCH₃), 3.89 (s, 3H, OCH₃); ¹³C NMR (75 MHz, CDCl₃) 11.9, 23.4, 24.8, 29.0, 29.2, 34.0, 45.0, 51.4, 60.6, 61.0, 61.1, 61.8, 122.6, 131.9, 144.5, 145.7, 147.6, 148.1, 174.3, 207.1; MS *m*/*z* (rel. intensity) 410 (M⁺, 15), 239 (100); HRMS (EI) calcd for C₂₂H₃₄O₇ 410.23, found 410.23; Elemental analysis, calcd for C₂₂H₃₄O₇: C, 64.37; H, 8.35, found C, 65.13; H, 8.71.

10-Methylcarbonyloxy-1-(2,3,4,5-tetramethoxy-6-methylphenyl)decylacetate (5)

To a mixture of LAH (550 mg, 14.4 mmol) in THF (10 mL) was added a solution of 4 (740 mg, 1.8 mmol) in THF (5 mL) at 0° C. After stirring at 0° C for 1 h, the mixture was quenched with MeOH. Filtration followed by evaporation of solvents afforded a crude, which was purified by flash chromatography (silica gel, hexane: EtOAc = 1:1) to provide 1-(2,3,4,5-tetramethoxy-6-methylphenyl)-1,10-decenediol (639 mg, 92%). To a solution of the diol (639 mg, 1.6 mmol) and DMAP (20 mg, 0.16 mmol) in CH₂Cl₂ (10 mL) was added acetic anhydride (0.4 mL, 4 mmol) and Et₃N (1 mL, 7 mmol) at 0° C. After being stirred at *r.t.* for 7 h, the mixture was diluted with CH₂Cl₂. The resulting solution was washed with water and the organic fraction was dried over Na₂SO₄. Evaporation of solvent afforded a crude, which was purified by flash chromatography (silica gel, hexane : EtOAc = 2:1) provided **5** (721 mg, 96%). ¹H NMR (200 MHz, CDCl₃) δ 1.27 (br s, 12H, 6CH₂), 1.57–1.80 (m, 4H, 2CH₂), 2.05 (s, 3H, OCOCH₃), 2.06 (s, 3H, OCOCH₃), 2.30 (s, 3H, ArCH₃), 3.77 (s, 3H, OCH₃), 3.87 (s, 3H, OCH₃), 3.89 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.04 (t, J = 6.7 Hz, 2H, CH_2), 6.20 (t, J = 6.4 Hz, 1H, CH); ¹³C NMR (75 MHz, CDCl₃) 12.0, 20.9, 21.2, 25.8, 26.0, 28.5, 29.1, 29.2, 29.3, 29.3, 34.0, 60.5, 60.9, 60.9, 61.1, 64.6, 71.4, 125.4, 127.3, 144.7, 146.4, 148.2, 170.5, 171.2; MS m/z (rel. intensity) 468 $(M^+, 91), 408 (100), 377 (26), 266 (29), 241 (73), 225 (47), 105 (26); HRMS$ (EI) calcd for C₂₅H₄₀O₈ 468.27, found 468.27; Elemental analysis, calcd for C₂₅H₄₀O₈: C, 64.08; H, 8.60, found C, 65.28; H, 9.07.

10-(2,3,4,5-Tetramethoxy-6-methylphenyl)-9-decenylacetate (6)

A mixture of the acetate 5 (25 mg, 0.05 mmol) and LiBr (108 mg, 1.25 mmol) in DMF (0.5 mL) was heated at 120° C for 24 h. Water (5 mL)

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was added and the mixture was extracted with diethyl ether (5 mL×3). The organic extracts were dried over Na₂SO₄. Evaporation of solvents afforded a crude, which was purified by flash chromatography (silica gel, hexane : EtOAc = 4:1) to provide **6** (10 mg, 49%). ¹H NMR (200 MHz, CDCl₃) δ 1.33 (br s, 12H, 6CH₂), 1.44–1.62 (m, 4H, 2CH₂), 2.04 (s, 3H, OCOCH₃), 2.19 (s, 3H, ArCH₃), 3.74 (s, 3H, OCH₃), 3.78 (s, 3H, OCH₃), 3.90 (s, 3H, OCH₃), 3.92 (s, 3H, OCH₃), 4.05 (t, *J* = 6.7 Hz, 2H, AcOCH₂), 5.92–6.03 (m, 1H, ArCH = C<u>H</u>), 6.24 (d, *J* = 16.0 Hz, 1H, ArC<u>H</u> = CH); ¹³C NMR (75 MHz, CDCl₃) 12.9, 20.9, 25.9, 28.6, 29.0, 29.2, 29.4, 33.8, 60.4, 60.6, 61.1, 61.2, 64.6, 123.1, 124.8, 127.2, 136.4, 144.8, 145.4, 146.6, 147.9, 171.2; MS *m/z* (rel. intensity) 408 (M⁺, 100), 377 (7), 334 (4); HRMS (EI) calcd for C₂₃H₃₆O₆ 408.25, found 408.25; Elemental analysis, calcd for C₂₃H₃₆O₆: C, 67.62; H, 8.88, found C, 67.39; H, 9.02.

10-(2,3,4,5-Tetramethoxy-6-methylphenyl)decylacetate (7)

A mixture of the olefin **6** (181 mg, 0.44 mmol) and 10% Pd/C (15 mg) in MeOH (5 mL) was stirred under H₂ atmosphere using a balloon at *r.t.* for 1 h. The mixture was passed a celite pad and the filtrate was concentrated *in vacuo* to provide **7** (180 mg, 99%). ¹H NMR (300 MHz, CDCl₃) δ 1.32 (br s, 12H, 6CH₂), 1.50–1.56 (m, 4H, 2CH₂), 2.05 (s, 3H, OCOCH₃), 2.21 (s, 3H, ArCH₃), 2.52 (t, *J* = 7.8 Hz, 2H, ArCH₂), 3.71 (s, 3H, OCH₃), 3.76 (s, 3H, OCH₃), 3.89 (s, 3H, OCH₃), 3.91 (s, 3H, OCH₃), 4.03 (t, *J* = 6.7 Hz, 2H, AcOCH₂); ¹³C NMR (75 MHz, CDCl₃) 11.5, 21.0, 25.9, 26.9, 28.6, 29.2, 29.4, 29.5, 30.1, 30.3, 60.6, 60.9, 61.0, 61.1, 64.6, 124.8, 130.3, 144.5, 144.7, 147.6, 147.7, 171.2; MS *m/z* (rel. intensity) 410 (M⁺, 100), 336 (10), 225 (60); HRMS (EI) calcd for C₂₃H₃₈O₆ 410.27, found 410.27.

10-(4,5-Dimethoxy-2-methyl-3,6-dioxo-1,4cyclohexadienyl)decylacetate (8)

To a solution of 7 (180 mg, 0.44 mmol) in MeCN (2 mL) was added a solution of CAN (554 mg, 1 mmol) in H₂O (1 mL) at 0°C. After the mixture was stirred for 15 min, water was added to the mixture, which was extracted with EtOAc. The organic extract was dried over Na₂SO₄. Evaporation of solvents afforded a crude, which was purified by flash chromatography (silica gel, hexane : EtOAc = 4:1) to provide **8** (148 mg, 88%). ¹H NMR (200 MHz, CDCl₃) δ 1.28 (br s, 12H, 6CH₂), 1.58–1.60 (m, 4H, 2CH₂), 2.01 (s, 3H, OCOCH₃), 2.04 (s, 3H, ArCH₃), 2.44 (br s, 2H, ArCH₂), 3.99 (s, 3H, 2OCH₃), 4.05 (t, *J*=6.6 Hz, 2H, AcOCH₂); ¹³C NMR (75 MHz, CDCl₃)

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11.9, 21.0, 25.9, 26.3, 28.5, 28.7, 29.2, 29.3, 29.4, 29.8, 61.1, 61.8, 64.6, 72.3, 138.6, 143.0, 144.3, 171.2, 184.1, 184.7; MS m/z (rel. intensity) 380 (M⁺, 32), 338 (57), 196 (100), 184 (46); HRMS (EI) calcd for C₂₁H₃₂O₆ 380.22, found 380.22; Elemental analysis, calcd for C₂₁H₃₂O₆: C, 66.29; H, 8.48; O, 25.23, found C, 65.17; H, 8.74; O, 24.18.

2-(10-Hydroxydecyl)-5,6-dimethoxy-3-methylbenzo-1,4-quinone (1)

To a solution of the quinone **8** (98 mg, 0.25 mmol) in MeOH/H₂O (1.6 mL/0.4 mL) was added Na₂CO₃ (6 mg, 0.052 mmol) at 0°C and the mixture was stirred at 0°C for 36 h. Water was added and the mixture was extracted with EtOAc. The organic extract was dried over Na₂SO₄. Evaporation of solvents afforded a crude, which was purified by recrystallization (EtOAc/hexane) to provide the idebenone 1 (52 mg, 61%). ¹H NMR (300 MHz, CDCl₃) δ 1.28–1.62 (m, 16H, 8CH₂), 2.04 (s, 3H, ArCH₃), 2.44 (br s, 2H, ArCH₂), 3.63 (t, *J* = 6.7 Hz, 2H, AcOCH₂), 3.98 (s, 6H, 2OCH₃); ¹³C NMR (75 MHz, CDCl₃) 11.9, 25.7, 26.3, 28.6, 29.3, 29.3, 29.5, 29.8, 32.8, 61.1, 63.1, 138.6, 143.1, 144.2, 184.1, 184.7; MS *m/z* (rel. intensity) 338 (M⁺, 81), 308 (21), 197 (100), 183 (47); HRMS (EI) calcd for C₁₉H₃₀O₅ 338.21, found 338.21; Elemental analysis, calcd for C₁₉H₃₀O₅: C, 67.43; H, 8.93; O, 23.64, found C, 67.06; H, 9.15; O, 21.44; m.p. 50–53°C.

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