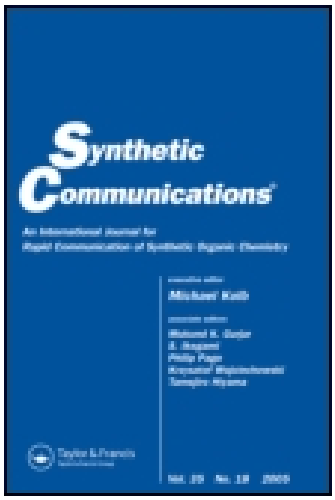

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A Convenient Method for the Synthesis of Dehydroquinic Acid

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ABSTRACT

A convenient synthesis of dehydroquinic acid and its corresponding methyl ester are described. Protection of the trans diol of quinic acid, followed by PCC oxidation, gave fully protected dehydroquinic acid. This gave methyl dehydroquinate on mild acid catalyzed hydrolysis. Ester hydrolysis then gave potassium dehydroquinate which was treated with amberlite to afford dehydroquinic acid.

Key Words: Shikimate pathway; Dehydroquinic acid; Synthesis; Selective protection.

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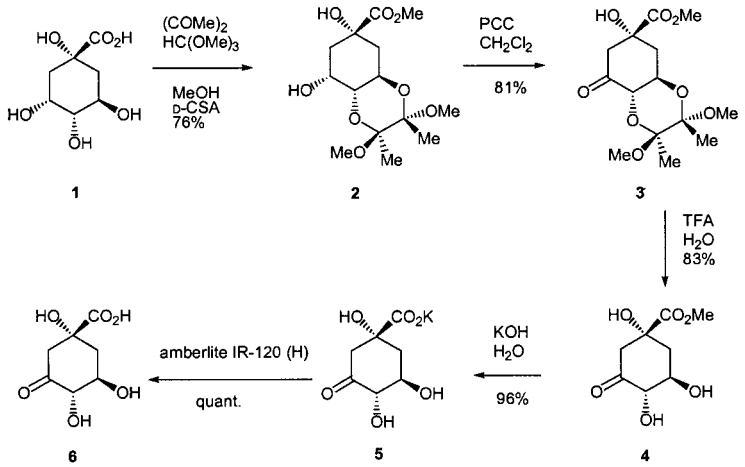
Chorismic acid, a key intermediate to aromatic metabolites such as folate, ubiquinone and the aromatic amino acids is biosynthesized by a sequence of reactions collectively known as the shikimate pathway.[1] A key step in this pathway involves dehydration of dehydroquinic acid **6** to give dehydroshikimic acid in a process that has recently been shown to be catalyzed by either Type I or II dehydroquinases.[1] Inhibitors of these enzymes are now actively being sought to provide leads for the development of new herbicides and antimicrobial agents.[2,3] Therefore, a convenient synthetic source of dehydroquinic acid **6**, and its corresponding methyl ester **4**, is required for use in enzyme inhibition assays[3] and to provide convenient starting materials for the preparation of new inhibitors.[4]

A good deal of effort has gone into trying to develop a convenient method for the preparation of these deceptively simple molecules. Literature methods for the synthesis of dehydroquinic acid, notably oxidation of quinic acid **1** using a platinum–oxygen system[5,6] or nitric acid,[7,8] are difficult to reproduce, invariably require tedious purification, and afford the desired acid in variable yield. Here, we report a convenient and reproducible synthesis of dehydroquinic acid **6**, and its methyl ester **4**, which is amenable to multigram scale. In this method, the acid **6** is prepared from the methyl ester **4** by simple hydrolysis followed by mild acidification. By contrast, the literature preparation of **4** involves a problematic esterification of **6**,[9] which is itself difficult to prepare.

The initial step in the synthesis involved a one-pot protection of the vicinal trans diol and acid groups of quinic acid **1** to give **2**, which was purified by treatment with decolorizing charcoal and recrystalization. We found that optimum yields of **2** were obtained after vigorous reflux with trimethylorthoformate, butanedione and methanol in the presence of camphorsulfonic acid catalyst for 18 h. This contrasts with the literature method of Gotor et al.[10] who reported a reaction time of 1 h. The masked quinic acid **2** was then oxidized using a four-fold excess of pyridinium chlorochromate (PCC) to furnish the protected form of dehydroquinic acid **3** in 88% after treatment with decolorizing charcoal and recrystalization.[10] Subsequent cleavage of the acetal protecting group with trifluoroacetic acid[11] proceeded smoothly to afford the methyl dehydroquinate **4**[9] that was purified by column chromatography on deactivated silica gel.[12] Hydrolysis of the methyl ester **4**, with aqueous KOH, furnished the potassium dehydroquinate **5** as an off-white solid that did not require further purification. The deprotection and hydrolysis steps were carefully monitored by thin layer chromatography, because prolonged exposure of the dehydroquinates **4** and **5** to strongly acidic or basic conditions readily led to the elimination of the hydroxyl group at C-1



Scheme 1.

to form dehydroshikimate, which is susceptible to aromatization. The potassium salt **5** was finally stirred over amberlite[3] to give dehydroquinic acid **6** (hygroscopic solid) in excellent yield (Sch. 1). The acid hence obtained gave satisfactory analytical data and all spectroscopic data was consistent with the proposed structure where reported in the literature.[6] The optical rotation was equivalent to that reported by Grewe and Jeschke at a similar concentration and in the same solvent.[7]

In conclusion, we report a convenient and reproducible method for the preparation of dehydroquinic acid **6** and its corresponding methyl ester **4**. The preparation of **4** is conveniently carried out on gram scales (see experimental), however, **6** is particularly hygroscopic and is best prepared from a stock pile of **4** as required.

EXPERIMENTAL

General: ^{1}H-NMR spectra were obtained using a 300 MHz Varian Unity 300 NMR spectrometer. ^{13}C-NMR spectra were recorded at a frequency of 75 MHz. ^{1}H–^{13}C-NMR Correlation experiments were carried out on an Inova 500 spectrometer at 500 MHz. Chemical shifts (δ) are given in part per million (ppm). Mass spectra were recorded on a Kratos MS80RFA instrument for electron impact (EI) and fast atom bombardment (FAB) techniques, or a micromass LCT spectrometer for the time-of-flight (TOF) method. Infrared spectra were obtained on a

Shimadzu Hyper FT-IR instrument. Optical rotations were measured using a Perkin 341 spectrometer. Melting points were taken on an Electrothermal apparatus and are uncorrected.

Methyl (1*S*,3*R*,4*R*,5*R*)-1,3-dihydroxy-4,5-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy)]cyclohexan-1-carboxylate 2

2,3-Butanedione (4.65 mL, 53 mmol), trimethylorthoformate (13.9 mL, 127 mmol) and D-camphorsulfonic acid (302 mg, 1.3 mmol) were added to a suspension of quinic acid **1** (5 g, 26 mmol) in methanol (40 mL). The mixture was heated to vigorous reflux for 18 h, then left to cool to room temperature and treated with sodium bicarbonate (200 mg, 2 mmol). The solvent was removed under reduced pressure to give a paste that was dissolved in ethyl acetate. Activated charcoal was added and the mixture was heated to reflux for 2 h, then left to cool to room temperature. The mixture was filtered over a thick pad of silica gel which was further washed using ethyl acetate–methanol (9:1), and the resulting colorless filtrate was evaporated in vacuo to give a white solid. The crude ester **2** was recrystalized from ethyl acetate to furnish the protected quinic acid **2** as white shiny crystals (6.3 g, 76%). M.p. 139–140°C [Lit.[11] m.p. 138–140°C], $[\alpha]_D^{20}$ +121.9 (*c* 1.08, CH_2Cl_2) [Lit.[11] $[\alpha]_D^{20}$ +116.3 (*c* 1.06, CH_2Cl_2); δ_H ($CDCl_3$) 1.30 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.92 (1H, dd, *J* 12.5, 12.5, 6-*H*H), 2.03 (1H, dd, *J* 14.5, 14.5, 2-*H*H), 2.10 (1H, ddd, *J* 12.5, 4.5, 3, 6-H*H*), 2.18 (1H, ddd, *J* 14.5, 3, 3, 2-H*H*), 3.18 (1H, d, *J* 3, OH), 3.26 (3H, s, CHCH_3), 3.27 (3H, s, CHCH_3), 3.60 (1H, dd, *J* 10, 3, 4-H), 4.20 (1H, m, 3-H), 4.31 (1H, ddd, *J* 12.5, 10, 4.5, 5-H); δ_C 17.5 (CH_3), 17.6 (CH_3), 37.3 (C-2), 38.5 (C-6), 47.8 (2 × CO*C*H$_3$), 52.8 (CO_2CH_3), 62.3 (C-5), 69.0 (C-5), 76.2 (C-4), 75.7 (C-1), 99.6 (*C*OCH$_3$), 100.2 (*C*OCH$_3$), 174.2 (*C*O$_2$CH$_3$); *m*/*z* (EI) Found 289.1287 ($C_{13}H_{21}O_7$ requires 289.3016); 289 (M-OMe, 5%), 193 (10), 178 (25), 154 (30), 94 (52), 70 (100), 57 (81).

Methyl (1*R*,4*S*,5*R*)-1-hydroxy-4,5-[(2*S*,3*S*)-2,3-dimethoxybutan-2,3-dioxy)]-3-oxo-cyclohexan-1-carboxylate 3

The protected quinic acid **2** (5.7 g, 19.7 mmol) was added to a suspension of pyridinium chlorochromate (22 g) in dichloromethane (100 mL) over molecular sieves (4 Å). The reaction mixture was stirred at room temperature for 15 h. It was then filtered over a pad of silica gel which was washed with ethyl acetate–methanol (9:1). The resulting brown filtrate was treated with decolorizing charcoal and then heated to reflux

for 1 h. After cooling to room temperature, the mixture was filtered over a thick pad of silica gel which was washed using ethyl acetate–methanol (9:1). The filtrate was concentrated under reduced pressure to afford a pale yellow solid that was recrystallized from ethyl acetate to give the protected dehydroquinic acid **3** as white crystals (4.64 g, 81%). M.p. 212–214°C [Lit.[11] m.p. 212–214°C]; $[\alpha]_D^{20}$ +105.1 (*c* 1.05, $CHCl_3$) [Lit.[11] $[\alpha]_D^{20}$ +82.7 (*c* 1.05, $CHCl_3$)]; ν_{max}/cm^{-1}(KBr) 3485, 2947, 1749, 1732, 1442, 1078; δ_H ($CDCl_3$) 1.30 (3H, s, CH_3), 1.34 (3H, s, CH_3), 2.10 (1H, *J* 13, 13, 6-*H*H), 2.34 (1H, dd, *J* 13, 13, 6-H*H*), 2.51 (1H, dd, *J* 14, 4, 2-*H*H), 2.87 (1H, d, *J* 14, 2-H*H*), 3.21 (3H, s, OCH_3), 3.24 (3H, s, OCH_3), 3.26 (1H, brs, OH), 3.82 (3H, s, CO_2CH_3), 4.23 (1H, ddd, *J* 10, 4, 4, 5-H), 4.40 (1-H, dd, *J* 10, 4-H); δ_C 17.6 (CH_3), 17.7 (CH_3), 37.9 (C-6), 48.1 (OCH_3), 48.4 (OCH_3), 49.1 (C-2), 53.7 (CO_2CH_3), 67.1 (C-5), 74.1 (C-1), 77.2 (C-4), 99.7 ($COCH_3$), 100.6 ($COCH_3$), 174.2 (CO_2CH_3), 199.7 (C-3); *m*/*z* (EI) Found 287.1131 ($C_{13}H_{19}O_7$ requires 287.2858); 287 (10%, M-OMe), 152 (25), 111 (100), 75 (60).

Methyl 3-Dehydroquinate 4

The protected dehydroquinic acid **3** (2 g, 6.28 mmol) was treated with a mixture of trifluoroacetic acid and water (95:5, 30 mL), and stirred at 0°C for 15 min. The resulting yellow mixture was concentrated in vacuo to afford the methyl ester of dehydroquinic acid **4** as a yellow oil. The crude product was purified by column chromatography on deactivated silica gel obtained by rinsing the column of silica gel with 2% triethylamine in the eluent, then rinsing the column with pure eluent. Elution with 1.2% methanol in ethyl acetate afforded methyl dehydroquinate **4** as a very sticky colorless oil (1.06 g, 83%). $[\alpha]_D^{20}$ −34.8 (*c* 1.50, MeOH); ν_{max}/cm^{-1} 3388, 3141, 2958, 1732, 1436, 1041; δ_H (acetone-d_6) 2.32 (1H, dd, *J* 13.5, 10.5, 6-*H*H), 2.36 (1H, ddd, *J* 13.5, 6, 2.5, 6-H*H*), 2.64 (1H, dd, *J* 14, 2.5, 2-*H*H), 3.19 (1H, dd, *J* 14, 1, 2-H*H*), 3.86 (3H, s, CH_3), 4.05 (1H, ddd, *J* 10.5, 9.5, 6, 5-H), 4.27 (1H, dd, *J* 9.5, 1, 4-H); δ_C (acetone-d_6) 40.5 (C-6), 47.6 (C-2), 52.3 (CO_2CH_3), 72.1 (C-5), 74.3 (C-1), 81.7 (C-4), 173.9 (CO_2CH_3), 205.6 (C-3); *m*/*z* (TOF) 189 (100%, M-OMe), 171 (90), 153 (26).

Potassium 3-Dehydroquinate 5

A solution of the methyl dehydroquinate **4** (400 mg, 1.96 mmol) in water (2 mL) was added with a solution of potassium hydroxide (109 mg,

1.96 mmol) in water (1 mL). The reaction mixture was stirred at room temperature for 10 min. It was then concentrated under reduced pressure, dried under high vacuum for 4 h to give potassium dehydroquinate **5** as an off-white solid that gave satisfactory analytical data and was hence used crude in the next step (429 mg, 96%). M.p. 170–172°C; $[\alpha]_D^{20}$ −47.6 (*c* 1.49, H_2O); Anal. calcd. for $C_7H_9O_6K$ C, 36.83; H, 3.94. Found C, 36.72, H, 3.94; ν_{max}/cm^{-1} (Nujol) 3176, 1708, 1045; δ_H (D_2O) 2.12 (1H, ddd, *J* 13.5, 5.5, 3, 6-*H* H); 2.19 (1H, dd, *J* 13.5, 11, 6-H*H*), 2.38 (1H, dd, *J* 14, 3, 2-*H* H), 2.99 (1H, d, *J* 14, 2-H*H*), 3.81 (1H, ddd, *J* 11, 10, 5.5, 5-H), 4.22 (1H, d, *J* 10, 4-H); δ_C (D_2O) 40.4 (C-6), 48.5 (C-2), 72.1 (C-5), 75.4 (C-1), 80.7 (C-4), 179.6 (CO_2K), 209.5 (C-3); *m*/*z* (TOF) Found 189.0401 ($C_7H_9O_6$ requires 189.0399); 189 (75%, $M-K^+$), 171 (100).

3-Dehydroquinic Acid 6

Potassium dehydroquinate **5** (170 mg, 0.74 mmol) was dissolved in water (2 mL), amberlite IR-120 (H) (100 mg) was added, and the mixture was stirred for 5 min. The ion-exchange resin was filtered off, the resulting filtrate was evaporated in vacuo, and then dried under high vacuum for 5 h to give dehydroquinic acid **6** quantitatively as a very hygroscopic white solid (140 mg). $[\alpha]_D^{20}$ −42.6 (*c* 0.35, MeOH) [Lit.[7] $[\alpha]_D^{20}$ −43.2 ± 4 (*c* 0.35, MeOH)]; ν_{max}/cm^{-1} (KBr) 3294, 2933, 2621, 1724, 1091; δ_H (D_2O) 2.20 (1H, m, 6-H_2), 2.46 (1H, brd, *J* 14, 2-*H* H), 3.02 (1H, d, *J* 14, 2-H*H*), 3.79 (1H, brdd, *J* 9.5, 9.5, 5-H), 4.18 (1H, d, *J* 9.5, 4-H); δ_C (D_2O) 39.5 (C-6), 47.5 (C-2), 71.3 (C-5), 74.0 (C-1), 80.6 (C-4), 176.5 (CO_2H), 208.1 (C-3).

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