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Synthesis of Regioselectively Protected Protocatechuic Acid Derivatives by Biomimetic Transformation of Quinic Acid.

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Abstract: 3- and 4-monoesterified protocatechuic acid methyl ester (**5** and **7** respectively) have been synthesised from quinic acid by a high yields biomimetic rearrangement.

Keywords: protocatechuic acid, quinic acid, diastereoselective synthesis

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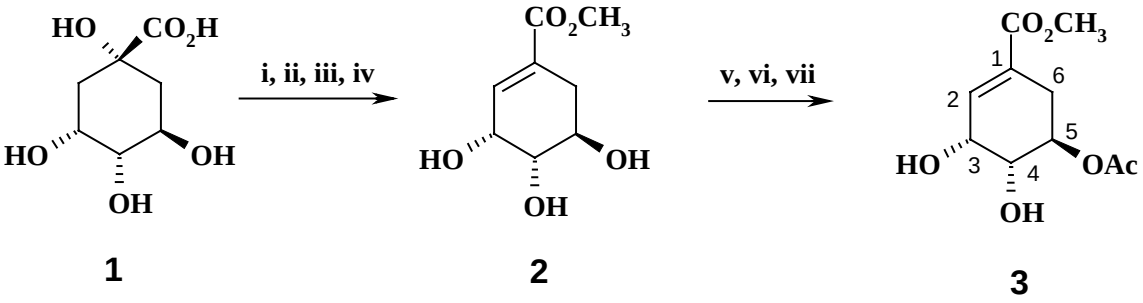
Introduction

The preparation of regioselectively protected protocatechuic acid derivatives has not been previously described, owing to the difficulty of discriminating between the two very similar, from a chemical reactivity point of view, phenolic hydroxyls. Ciamician et al. [1] described, for the first time, the preparation, by partial esterification, of the mixture of the two monoacetyl derivatives of protocatechuic acid. Later Fischer et al. [2] reported the preparation of 3-acetyl-protocatechuic acid by partial alkaline hydrolysis of protocatechuic acid diacetate. A similar procedure was also reported by Lesser et al. [3]. Chromatographic detection of 3-acetyl-protocatechuic acid in natural sources [4] or in synthetic mixtures [5] has also been described.

4-acetyl-protocatechuic acid, on the contrary, was only detected in 1966 as a microbial degradation metabolite of chloramphenicol [6].

Results and discussion

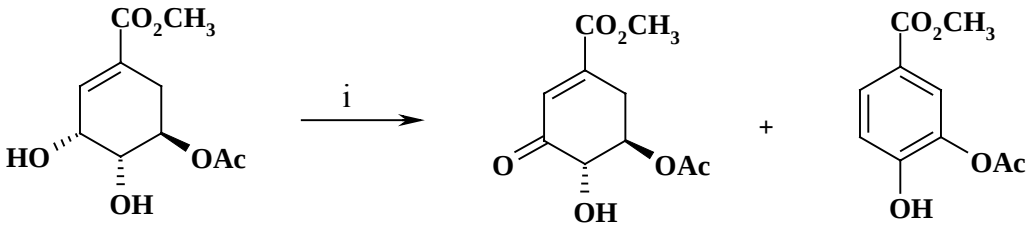
We obtained high yield transformations of the quinic acid skeleton, with formation of aromatic protocatechuic acid derivatives, during the course of our research work to develop antiviral drugs active against influenza viruses [7]. Compound **3**, obtained from quinic acid **1**, as described in Scheme A, was a key intermediate in our synthetic strategy.



1 **2** **3**

Scheme A. Reagents and conditions: i, CH_3OH, H_2SO_4; ii, Ac_2O, pyr; iii, $SOCl_2$, pyr; iv, CH_3OH, H_2SO_4; v, 2,2-dimethoxypropane, acetone, Dowex-50 H^+; vi, Ac_2O, pyr; vii, $AcOH/H_2O$, □.

The next step of our synthetic project made provision for the regioselective oxidation of the allylic hydroxyl group with Jones's reagent, to afford the keto derivative **4** (see scheme B). Nevertheless we have not succeeded in obtaining significant amounts of compound **4**. In fact, even when we utilised oxidative conditions other than Jones' reagent, the oxidation of **3** to **4** is always overcome by the quite complete aromatization of ring, yielding 3-acetyl-protocatechuic acid methyl ester, **5** (scheme B).

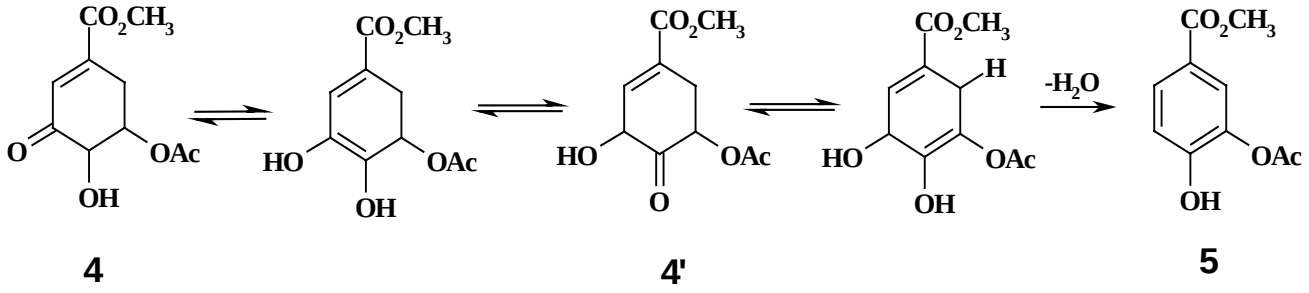


3 **4**, 8% **5**, 92%

Scheme B. Reagents and conditions: i, Jones's reagent, acetone

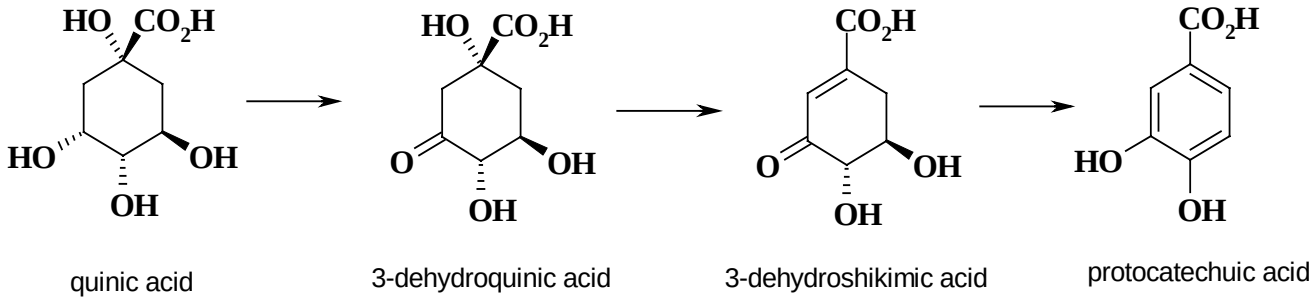
In our opinion this reaction route happens due to a fast 1,4-type elimination of a water molecule from keto derivative **4**, catalysed by the acidic medium. The mechanism of this aromatization, proposed in Scheme C, is based on a series of keto-enol equilibria which, starting from the 3-keto-

derivative **4**, with the catalysis of the strong acidic medium, gives rise to the formation of the 4-keto-derivative **4'**. From compound **4'** a molecule of water is irreversibly eliminated, with the formation of the aromatic protocatechuic acid derivative **5**. An aromatization process of other cyclohexene derivatives that follows a different mechanism in which a lactone intermediate is involved has been described [8].



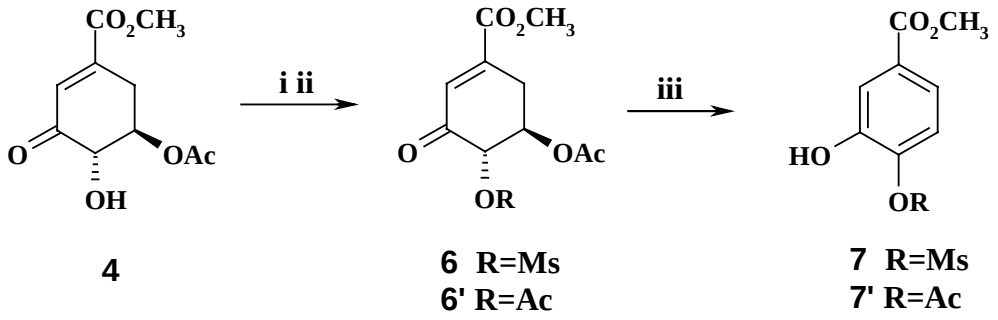
Scheme C. Proposed rearrangement mechanism.

On the other hand, our result is not surprising because the biogenesis of protocatechuic acid starts from quinic acid [9] and the key intermediates are keto derivatives, as described in Scheme D. Quinic acid is in fact metabolised by initial conversion to 3-dehydroquinic acid and, after elimination of a water molecule to form 3-dehydroshikimic acid, is then converted to protocatechuic acid by a 1,2 type elimination of a proton and C-5 hydroxyl group induced by the enzyme 3-dehydroshikimate dehydratase [10].



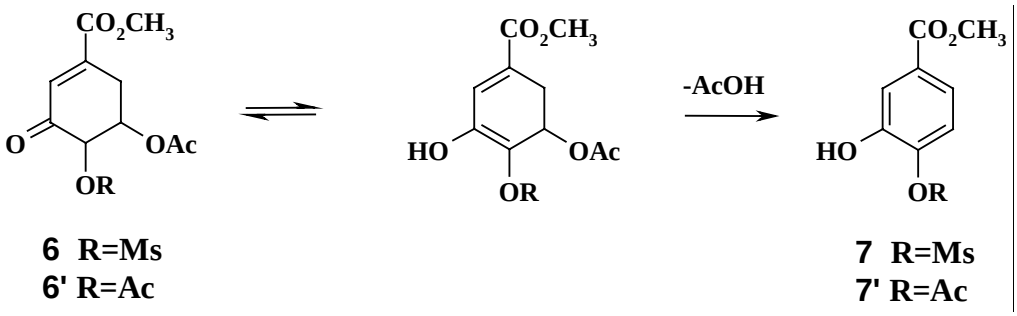
Scheme D. Biosynthesis of protocatechuic acid.

At this point, we decided to verify the possibility of directing the reaction also towards the 1,2-type elimination. In order to do that, the free 4-OH of compound **4** was protected with a different ester and for this we chose the mesyl group. The hydroxyl at C-4 was esterified with methanesulfonyl chloride, as depicted in Scheme E leading to the quantitative formation of product **6**. Subsequent treatment of compound **6** at moderately high temperature (80 ^{o}C) in dimethylformamide brought about the predominant formation of the totally unsaturated product **7** (Scheme E) in 93% yield.



Scheme E. Reagents and conditions: i, CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0°C; ii, Ac_2O, pyr; iii, DMF, .

The same reaction, performed on the diacetyl derivative **6'**, obtained from **4** by esterification with acetic acid, afforded the monoacetate **7'**, with comparable yields. In this case the proposed mechanism (see Scheme F) is a 1,2-type elimination of acetic acid from the enolic form of the keto derivative **6**.



Scheme F. Proposed rearrangement mechanism

Conclusions

In conclusion, it is possible to direct the dehydration of shikimic acid derivatives acid towards a regioselective water elimination, which may be considered an acid catalysed aromatization, or towards a type 1,2 thermal elimination, probably occurring with an Ei mechanism. These procedures afford monoprotected protocatechuic acid methyl esters in very high yields. Even though these protocols do not appear to be very short, owing to the interest of protocatechuic acid as antioxidants, the complete regioselectivity observed in the preparation of monoprotected derivatives overcomes this inconvenience.

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Experimental

General

^{1}H-NMR spectra were measured with a Varian Gemini 200 MHz spectrometer and chemical shifts are expressed in ppm from TMS. Product purification was accomplished by solid-liquid column chromatography on Merck 0.063 - 0.20 nm silica gel; using the elution mixtures listed under each heading. Merck TLC plates coated with Kiesel-Gel 60 F_{254} were employed to monitor the reactions. Detection was done using 2N H_2SO_4, heating at 120°C or 2,4-DNF for the carbonyl compounds.

Syntheses

*Methyl 5-acetyl shikimate (**3**)*: Synthesis of compound **3** was described in ref. 11. ^{1}H-NMR (200 MHz, $CDCl_3$), δ 2.09 (s, 3H, AcO), 2.25-2.35 (dd, 1H, H-6*ax*), 2.81-2.91 (dd, 1H, H-6*eq*), 3.73 (s, 3H, CO_2CH_3), 3.85 (dd, 1H, H-4), 4.42 (m, 1H, H-3), 5.18 (m, 1H, H-5), 6.85 (m, 1H, H-2).

*Methyl 5-acetyl-3-keto shikimate (**4**) and methyl 3-acetyl-protocatechuicate (**5**)*: compound **3** (200 mg) was dissolved in acetone (10 mL) under stirring and, Jones' reagent was added dropwise. When the solution became persistent orange-brown coloured, the reaction was complete as the evidence by TLC. Sodium tiosulphate was added until a green colour was observed, then the reaction mixture was neutralised with barium carbonate and filtered through Celite. Volatile materials were evaporated *in vacuo* and the residue purified by Si gel chromatography, eluting with ethyl acetate / chloroform (6:4) to give **4** (15 mg, 8% yield) and compound **5** (166 mg, 92% yield), both as colourless oils. ^{1}H-NMR compound **4** (200 MHz, $CDCl_3$): δ 2.15 (s, 3H, AcO), 2.60 (m, 1H, H-6*ax*), 3.30 (dd, 1H, H-6*eq*), 3.85 (s, 3H, CO_2CH_3), 4.30 (d, 1H, H-4), 5.10 (m, 1H, H-5), 6.90 (d, 1H, H-2). ^{1}H-NMR compound **5** (200 MHz, $CDCl_3$): δ 2.33 (s, 3H, AcO), 3.62 (s, 3H, CO_2CH_3), 6.3 (s, 1H, OH), 7.69 (d, 1H, J= .8 Hz), 7.82 (dd, 1H, J=1.8, 7.9 Hz), 8.12 (d, 1H, J=7.9 Hz).

*Methyl 5-acetyl-3-keto-4-mesyl shikimate (**6**):* Compound **4** (50 mg) was dissolved in dichloromethane (2.5 mL) and the solution cooled at 0 °C. triethylamine (0.1 mL) was added, followed by dropwise addition of methanesulfonyl chloride (0.05 ml). The reaction mixture was stirred at 0 °C for 2 h. The mixture was then diluted with dichloromethane, the organic phase washed with water and dried over anhydrous sodium sulphate. The volatile materials were removed *in vacuo* and the residue was purified by Si gel chromatography, eluting with chloroform / ethyl acetate (7:3), to give **6** (58 mg, 86% yield) as a colourless oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.12 (s, 3H, AcO), 2.60 (m, 1H, H-6*ax*), 3.11 (s, 3H, SO_2CH_3), 3.31 (m, 1H, H-6*eq*), 3.82 (s, 3H, CO_2CH_3), 4.81 (m, 1H, H-4), 5.05 (m, 1H, H-5), 6.91 (d, 1H, H-2).

*Methyl 4,5-diacetyl-3-keto shikimate (**6'**):* Compound **4** (50 mg) was dissolved in pyridine (0.1 mL) and acetic anhydride (0.2 mL) was added. The reaction mixture was allowed to stand at room temperature. After 1 h compound **6'** was formed, as shown by TLC using chloroform / ethyl acetate (8:2) as eluent. Methanol was added to the reaction mixture and the volatile materials were removed *in vacuo*. The residue was purified by chromatography eluting with chloroform / ethyl acetate (8:2) to give **6'** (51 mg, 86% yield). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.12, 2.14 (s, 2x3H, 2xAcO), 2.62 (m, 1H, H-6*ax*), 3.28 (m, 1H, H-6*eq*), 3.78 (s, 3H, CO_2CH_3), 4.80 (m, 1H, H-4), 5.03 (m, 1H, H-5), 6.94 (d, 1H, H-2).

*Methyl 4-mesyl-protocatechuicate (**7**)*: compound **6** (100 mg) was dissolved in anhydrous DMF (4 mL) and the reaction mixture was heated at 80°C under stirring for 2 h. The reaction mixture was then diluted with ethyl acetate, successively washed with saturated aqueous ammonium chloride, water and brine, and dried over anhydrous sodium sulphate. The solvents were evaporated *in vacuo* and the residue purified by Si gel chromatography, eluting with chloroform / ethyl acetate (6:4) to give compound **7** (80 mg, 93% yield) as a yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.13 (s, 3H, SO_2CH_3) 3.70 (s, 3H, CO_2CH_3), 6.1 (s, 1H, OH), 7.67 (d, 1H, J=1.8 Hz), 7.91 (dd, 1H, J=1.8, 7.4 Hz), 8.10 (d, 1H, J=7.4 Hz).

*Methyl 4-acetyl-protocatechuicate (**7'**)*: Compound **6'**, under the same reaction conditions as described for compound **6**, afforded compound **7'**, as a colourless viscous oil, in 94% yield. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.25 (s, 3H, AcO), 3.70 (s, 3H, CO_2CH_3), 6.1 (s, 1H, OH), 7.67 (d, 1H, J=1.8 Hz), 7.91 (dd, 1H, J=1.8, 7.4 Hz), 8.10 (d, 1H, J=7.4 Hz).

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Sample Availability: Samples are available from the authors