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SELECTIVE HYDROXY GROUP PROTECTION OF GALLIC ACID

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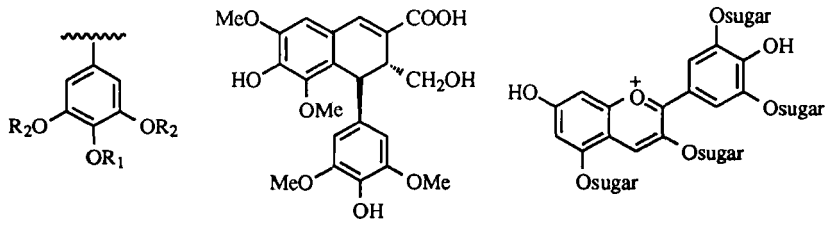
ABSTRACT: An efficient procedure allowing selective differentiation of the 4-hydroxy group of methyl gallate was reported.

The selective derivatization in multifunctionalities of similar reactivity is an important step in synthetic methodology. While a large body of research work has been reported in selective protection of polyol systems , especially in carbohydrate and nucleoside chemistry,[1] little attention has been paid to the selective protection of polyphenols.

Tetrasubstituted aromatics of type **1** are frequently encountered as subunit in natural products, such as lignanes (thomasic acid **2**),[2] anthocyanins (lobelinin **3**),[3] and vancomycin[4] family glycopeptides. Obviously, the selective differentiation of three hydroxy functions of methyl gallate (**4**) constitutes the simpliest way to reach type **1** compounds.

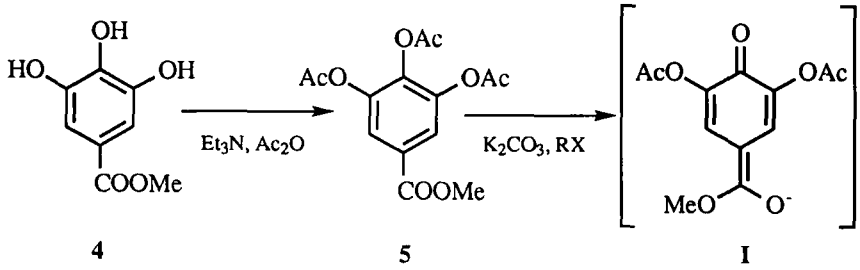


1 2 3

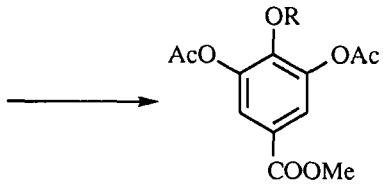
Figure 1

It has been reported that benzylation of methyl gallate **4** (NaH, BnCl)[5] gave predominantly methyl 4-benzyl-3,5-dihydroxybenzoate, while acetylation with Ac_2O-pyridine[6] afforded methyl 3,5-diacetoxy-4-hydroxybenzoate. However, we[7a, b] and others[7c] have been unable to reproduce these results and thus, an alternative way *via* a two step sequence has been described by Pearsons[7c] and us[7b] in the selected examples. We report herein the further modification and the generality of this procedure as shown in scheme 1.

Acetylation of **4** with Ac_2O in the presence of Et_3N gave methyl 3,4,5-triacetoxy benzoate **5** in quantitative yield. Employing Et_3N instead of pyridine increased the yield of **5** significantly and simplified the work-up procedure. When **5** was heated in DMF at 40°C in the presence of K_2CO_3 and an alkyl halide (MeI, EtI, iPrBr, Allyl bromide, BnBr), regioselective alkylation occurred to give methyl 4-alkyloxy-3,5-diacetoxybenzoate **6** in high yield. Higher reaction temperature (100°C) led to lower isolated yield. Acetone could also be used as solvent, however, DMF was found to be the solvent of choice for alkylation of hindered alkyl halides. Addition of KI had some beneficial effect in the preparation of compounds **6c** and **6e**. The regioselectivity observed may be explained by the conjugating effect of ester function leading to formation of the intermediate **I**, alkylation of which gave then the compound **6**.



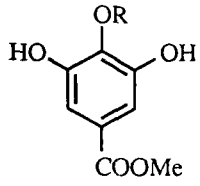
4 5 I



6

6a R = Me, 99%
6b R = Et, 98%
6c R = ^{i}Pr, 98%
6d R = allyl, 96%
6e, R = Bn, 89%

Scheme 1



7a R = Me
7b R = Allyl

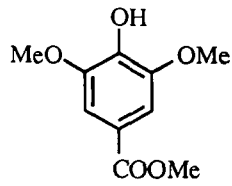


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Figure 2

While selective hydrolysis of **6a** (K_2CO_3, MeOH-H_2O, 10 min) gave quantitatively methyl 3,5-dihydroxy-4-methoxy benzoate **7a**, which was used in our synthesis of (D)-*R*-3,5-diisopropyloxy-4-methoxy phenylglycine;[7b] **6d** was efficiently transformed into methyl 3,5-dimethoxy-4-hydroxy benzoate **8**, *via* hydrolysis, methylation and deallylation[8], in 80% overall yield.

In conclusion, an efficient procedure for selective protection of 4-hydroxy group of gallic acid has been developed and should prove useful in the manipulation of polyphenol systems.

Experimental

Melting points were determined with a Koffler apparatus and were uncorrected. Infrared (IR) spectra were recorded on a Nicolet-205 spectrometer. ^{1}HNMR spectra were measured on a Brucker AC-200 (200 MHz) spectrometer with tetramethylsilane as internal standard (δ ppm). Solvents and reagents were purified according to standard laboratory techniques. All reactions requiring anhydrous conditions were conducted under an argon atmosphere.

Methyl 3,4,5-triacetoxybenzoate 5. To the solution of **4** (51.5 g, 0.28 mol) in Ac_2O (105 mL, 1.12 mol), Et_3N (234 mL, 1.68 mol) was added slowly at 0°C. After stirring for 2 h at room temperature, the excess of Ac_2O was destroyed by careful addition of EtOH (16.3 mL, 0.28 mol) at 0°C. The reaction mixture was diluted with H_2O and extracted with EtOAc, the organic phase was washed with brine, dried over Na_2SO_4, and evaporated to give a white solid. Recrystallization from EtOAc-Heptane gave 85.1 g of **5** (98%): mp. 131°C; IR ($CHCl_3$) ν_{max}: 3050, 1780, 1735 cm^{-1}; ^{1}HNMR ($CDCl_3$, 200 MHz) 2.30 (s, 9H, OAc), 3.88 (s, 3H, OMe), 7.81 (s, 2H, aromatics); Anal. Calcd for $C_{14}H_{14}O_8$: C, 54.20; H, 4.55. Found: C, 54.19; H, 4.55.

Methyl 3,5-diacetoxy-4-methoxy benzoate 6a. To a solution of **5** (31.0 g, 0.1 mol) in DMF was added K_2CO_3 (41.8 g, 0.3 mol) and MeI (12.7 mL, 0.2 mol). The resulting mixture was heated at 40°C for 3h. The inorganic salt was removed by filtration, and the filtrate was diluted with EtOAc. The organic phase was washed with water, dried (Na_2SO_4) and evaporated to give 27.9 g (99%) of

pure compound **6a** after recrystallization from EtOAc-Heptane. mp 83°C; IR ($CHCl_3$) ν_{max}: 3050, 1775, 1730 cm^{-1}; ^{1}HNMR ($CDCl_3$, 200 MHz) 2.35 (s, 6H, OAc), 3.85 (s, 3H, OMe), 3.88 (s, 3H, OMe), 7.67 (s, 2H, aromatics); ^{13}CNMR 20.9, 52.6, 61.3, 122.8, 125.5, 144.0, 148.5, 165.4, 168.7; Anal. Calcd for $C_{13}H_{14}O_7$: C, 55.32; H, 5.00. Found: C, 55.24; H, 4.97.

Compounds **6b**, **6c**, **6d**, **6e** were prepared as described for **6a** using EtI, iPrBr, allyl bromide and BnBr as alkylating agents.

Methyl 3,5-diacetoxy-4-ethoxy benzoate 6b. IR ($CHCl_3$) ν_{max}: 1769, 1725 cm^{-1}; ^{1}HNMR ($CDCl_3$, 200 MHz) 1.30 (t, J = 7.0 Hz, 3H, $OCH_2\mathit{Me}$), 2.30 (s, 6H, OAc), 3.85 (s, 3H, OMe), 4.05 (q, J = 7.0 Hz, 2H, $OC\mathit{H}_2Me$), 7.65 (s, 2H, aromatics); ^{13}CNMR 16.3, 21.2, 52.9, 70.4, 123.1, 125.7, 144.5, 148.5, 165.8, 169.0; Anal. Calcd for $C_{14}H_{16}O_7$: C, 56.76; H, 5.44. Found: C, 56.59; H, 5.47.

Methyl 3,5-diacetoxy-4-isopropyloxy benzoate 6c. IR ($CHCl_3$) ν_{max}: 1770, 1718, 1621 cm^{-1}; ^{1}HNMR ($CDCl_3$, 200 MHz) 1.25 (d, J = 6.0 Hz, 6H, $OCH\mathit{Me}_2$), 2.35 (s, 6H, OAc), 3.85 (s, 3H, OMe), 4.40 (septet, J = 6.0 Hz, 1H, $OC\mathit{H}Me_2$), 7.68 (s, 2H, aromatics); ^{13}CNMR 20.5, 22.5, 52.1, 77.2, 122. 4, 124.9, 144.3, 146.1, 165.1, 168.0.

Methyl 3,5-diacetoxy-4-allyloxy benzoate 6d. mp 57°C; IR ($CHCl_3$) ν_{max}: 1770, 1718, 1614 cm^{-1} ^{1}HNMR ($CDCl_3$, 200 MHz) 2.30 (s, 6H, OAc), 3.90 (s, 3H, OMe), 4.75 (dt, J = 1.5, 5.3 Hz, 2H, $OC\mathit{H}_2CHCH_2$), 5.21 (qd, J = 1.5, 10.5 Hz, 1H, $OCH_2CHC\mathit{H}_2$), 5.35 (qd, J = 1.5, 17.3 Hz, 1H, $OCH_2CHC\mathit{H}_2$), 5.95 (tdd, J = 5.3, 10.5, 17.3 Hz, 1H, $OCH_2C\mathit{H}CH_2$), 7.70 (s, 2H, aromatics); ^{13}CNMR 20.64, 52.3, 74.4, 117.9, 122.5, 125.4, 133.0, 144.0,

147.2, 165.1, 168.3; Anal. Calcd for $C_{15}H_{16}O_7$: C, 58.44; H, 5.23. Found: C, 58.21; H, 5.27.

Methyl 3,5-diacetoxy-4-benzoxy benzoate 6e. mp 60°C; IR ($CHCl_3$) ν_{max}: 1777, 1733, 1613 cm^{-1} ^{1}HNMR ($CDCl_3$, 200 MHz) 2.20 (s, 6H, OAc), 3.90 (s, 3H, OMe), 5.02 (s, 2H, OCH_2Ph), 7.40 (m, 7H, aromatics); ^{13}CNMR 20.7, 52.5, 75.8, 122.8, 125.7, 127.1, 127.8, 128.5, 128.7, 136.8, 141.1, 144.3, 147.6, 165.4, 168.6

Methyl 3,5-dihydroxy-4-methoxy benzoate 7a. To a solution of **6a** (28.2 g, 0.1 mmol) in MeOH (400 mL) and H_2O (100 mL) was added K_2CO_3 (82.8 g, 0.6 mmol). After stirring for 20 min at room temperature, the volatiles were evaporated. The aqueous solution was acidified to pH 2 and extracted with EtOAc. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated to give **6** (19.6 g, 99%). mp 148°C (EtOAc-Heptane); IR ($CHCl_3$) ν_{max}: 3535, 3260, 1715, 1597 cm^{-1}; ^{1}HNMR ($CDCl_3$, 200 MHz) 3.75 (s, 3H, OMe), 3.85 (s, 3H, OMe), 7.01 (s, 2H, aromatics); ^{13}CNMR 52.3, 60.5, 109.9, 126.3, 140.9, 151.4, 168.3; MS *m/z* 198, 170; Anal. Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09. Found: C, 54.35; H, 5.12.

Methyl 3,5-dihydroxy-4-allyloxy benzoate 7b. 7b was prepared as described for **7a**. mp 120°C; IR ($CHCl_3$) ν_{max}: 3536, 3276, 1722, 1596 cm^{-1}; ^{1}HNMR ($CDCl_3$, 200 MHz) 3.85 (s, 3H, OMe); 4.70 (dt, J = 1.5, 5.2 Hz, 2H, OCH_2CHCH_2), 5.31 (qd, J = 1.5, 10.4 Hz, 1H, OCH_2CHCH_2), 5.45 (qd, J = 1.5, 17.2 Hz, 1H, OCH_2CHCH_2), 6.10 (tdd, J = 5.2, 10.4, 17.2 Hz, 1H, OCH_2CHCH_2), 7.20 (s, 2H, aromatics); Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 58.58; H, 5.53.

Methyl 3,5-dimethoxy-4-hydroxy benzoate 8 A solution of methyl 3,5-dihydroxy-4-allyloxy benzoate **7b** (224 mg, 1 mmol) in DMF containing K_2CO_3 (828 g, 6 mmol) and MeI (310 µl, 5 mmol) was heated at 100°C for 5 h. Following the same work-up procedure as described for **6a**, methyl 3,5-dimethoxy-4-allyloxy benzoate was obtained in 95% yield. mp 76°C; ν_{max}: 1722, 1588 cm^{-1}; ^{1}HNMR ($CDCl_3$, 200 MHz) 3.87 (s, 6H, OMe), 3.88 (s, 3H, OMe), 4.62 (dt, J = 1.5, 5.2 Hz, 2H, OCH_2CHCH_2), 5.15 (qd, J = 1.5, 10.4 Hz, 1H, OCH_2CHCH_2), 5.30 (qd, J = 1.5, 17.2 Hz, 1H, OCH_2CHCH_2), 6.08 (tdd, J = 5.2, 10.4, 17.2 Hz, 1H, OCH_2CHCH_2), 7.25 (s, 2H, aromatics); ^{13}CNMR 52.8, 56.8, 74.7, 107.4, 118.6, 125.8, 134.7, 153.8, 167.3; Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.90; H, 6.25. To the solution of methyl 3,5-dimethoxy-4-allyloxy benzoate (50 mg, 0.20 mmol) in THF was added $Pd(PPh_3)_4$ (11.5 mg, 5% equiv.) and $NaBH_4$ (30 mg, 0.79 mmol). After being stirred for 2h at toom temperature, the reaction mixture was diluted with aqueous NH_4Cl solution and acidified with 3N HCl. The volatiles were removed and the aqueous solution was extracted with EtOAc. Purification by preparative TLC gave **8** (38 mg, 90%). mp 109°C; IR ($CHCl_3$) ν_{max}: 1726, 1626 cm^{-1} ^{1}HNMR ($CDCl_3$, 200 MHz) 3.88 (s, 3H, OMe), 3.96 (s, 6H, OMe), 5.91 (s, 1H, OH), 7.32 (s, 2H, aromatics); ^{13}CNMR 52.5, 56.9, 107.2, 121.5, 139.8, 147.1, 167.3; Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.56; H, 5.72.

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