A Simplified Synthesis of Peniolactol

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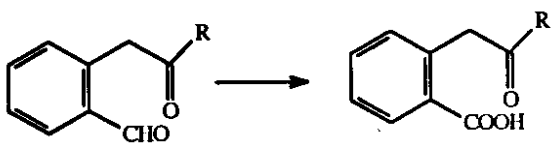
Summary: Two markedly simplified synthetic approaches towards peniolactol, the metabolite of wood-attacking fungus *Peniophora sanguinea* are being reported. The key step involves the achievement of direct oxidation of the ortho-formyl ketones (3 & 6) using sodium chlorite-sulfamic acid. The pre requisite o-formyl ketones (3) and (6) were prepared by the vilsmeier formylation of dimethoxy ketone (2) and orthoformate formylation of the dihydroxy ketone (5) respectively.

Introduction

Peniolactol [1] is a fungal metabolite of the wood attacking fungus *Peniophora sanguinea* Bress. It can exist in two tautomeric forms *viz.* the lactol form, 3,4-dihydro-3,6,8-trihydroxy-3-pentadecylisocoumarin (**1a**) and keto acid, 2,4-dihydroxy-6-(2-oxoheptadecyl)benzoic acid (**1b**). Spectroscopic and x-ray crystallographic evidence [2] indicates that it exists predominantly in lactol form (**1a**) both in organic solvents and in crystalline state. We have already reported the total synthesis of peniolactol [3] using the standard synthetic route established during synthesis of the principal dihydroisocoumarins of *Ononis natrix* [4]. In this article we wish to report a markedly simplified synthesis of peniolactol involving the direct oxidation of o-formyl benzyl ketones (A) to corresponding keto acids (B).



(A) (B)

The direct oxidation of ketones (A) to keto acids (B) was found to be complex and could not be achieved earlier, hence a longer, indirect but safer synthetic route [3,4] was adopted. The use of oxidizing agents like potassium permanganate, silver oxide in alkaline solution, manganese doxide in n-hexane and Collin's reagent etc were found to be quite ineffective. The selective oxidation of aldehydic function leaving the ketonic carbonyl intact had long been a problem. L. Lino *et al.* [5] successfully carried out this oxidation during synthesis of lactols as possible biogenetic intermediates towards colchiquinones and stemphone. These researchers tried Corey's method involving sodium cyanide, freshly prepared manganese dioxide and acetic acid and the sulfamic acid-sodium chlorite method. The latter reagents were found to be more effective and efficient; we have also adopted the use of sulfamic acid-sodium chlorite for selective oxidation of our o-formylbenzyl ketones. Thus, the ketone (**2**) prepared by the standard route [3,4] was subjected to the vilsmeier Haack formylation to afford the 1-(2-formyl-3,5-dimethoxyphenyl)heptadecan-2-one (**3**). The IR spectrum of (**3**) showed the aldehydic absorption at 1665 cm^{-1} in addition to the ketonic carbonyl peak at 1701 cm^{-1}. Oxidation of 2-formyl group in (**3**) using sulfamic acid and sodium chlorite directly afforded the 2,4-dimethoxy-6-(2-oxoheptadecyl)benzoic acid (**4**), which may be regarded as 6,8-di-O-methyl ether of peniolactol. The IR spectra of this keto acid (**4**) showed the characteristic envelope of carboxylic hydroxyl band from 2500-3000 cm^{-1} in contrast to peniolactol, which predominantly exists in lactol tautomeric form. Complete demethylation of keto acid (**4**) using borontribromide in dichloromethane afforded the peniolactol (**1a** and **1b**) identical in all respects to that prepared by the established route [4] (Scheme-1). Alternatively, the ketone (**2**) was demethylated to the 1-(3,5-dihydroxyphenyl) heptadecan-2-one (**5**). Formylation of the dihydroxy ketone (**5**) using triethyl orthoformate and dry hydrogen chloride gas afforded the 1-(2-formyl-3,5-dihydroxyphenyl)heptadecan-2-one (**6**) probably via the hydrolysis of 6,8-dihydroxy-3-pentadecyl-2-benzopyrylium chloride (**6a**), which

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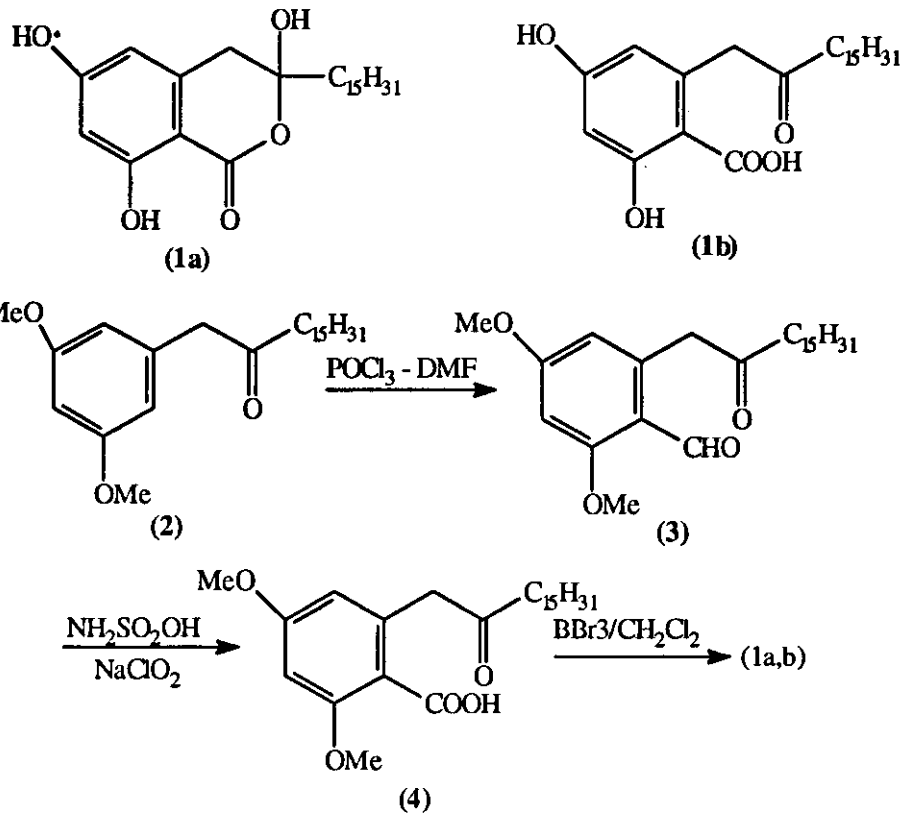
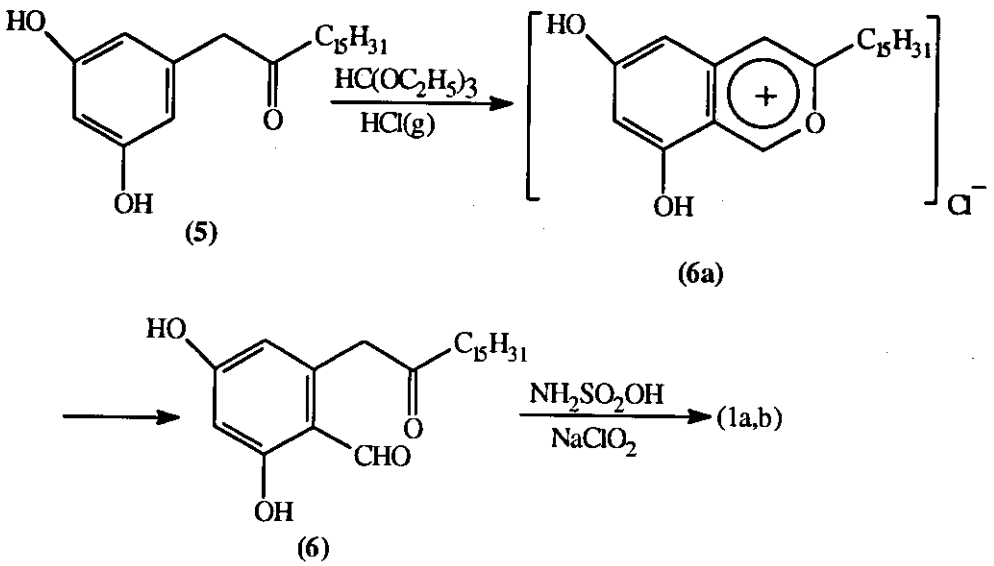


Scheme-1



Scheme-2

could not be isolated. Oxidation of (6) using sulfamic acid and sodium chlorite directly furnished the peniolactol (1a and 1b) (Scheme-2).

Experimental

^{1}H and ^{13}C-NMR: Bruker AM 400, $CDCl_3$ solution with TMS as internal standard. EI-MS: Jeol Ax505W, 70 eV. - IR: Hitachi model 270 Spectrophotometer, KBr discs or neat liquid - Melting points: MELTEMP MP-D apparatus, uncorrected values.

1-(2-Formyl-3,5-dimethoxyphenyl)heptadecan-2-one(3)

Phosphorus oxychloride (1.8g, 0.012 mol) was added dropwise to a stirred solution of the ketone (2) (4.0g, 0.01 mol) in freshly distilled DMF (7.5 ml) at 0°, under nitrogen. The reaction mixture was heated at 55° for 30 min. and then at 100° for 10 minutes. Work up gave an oil which solidified on standing. Recrystallization from aqueous methanol afforded 1-(2-formyl-3,5-dimethoxyphenyl)heptadecan-2-one (3) (2.34 g, 0.0056 mol, 55%) as bright yellow crystals m.p. 90°. IR (KBr): 2886, 1710, 1665, 1595, 1128 cm^{-1}. ^{1}H-NMR: δ = 0.80 (3H, t, H17′, J=7.0Hz), 1.18 (18H, s, H4′-H16′), 1.62 (2H, m, H3′)3.70 (2H, s, H1′), 3.87 (3Hs, s, 3-OCH_3), 3.89 (3H, s, 5-OCH_3), 6.44 (1H, s, H2), 6.45 (1H, s, H4), 10.46 (1H,s,Ar-CHO) ppm. MS m/z : 418 (M^+), 406, 390 (base, 263.

2,4-Dimethoxy-6-(2-oxoheptadecyl)benzoic acid (4)

A stirred mixture of 1-(2-formyl-3,5-dimethoxyphenyl)heptadecan-2-one (3) (1.5g, 0.0036 mol) in water (280 ml) and acetone (48 ml) was treated with sulphamic acid (0.32g, 0.0049 mol) and 85% sodium chlorite (0.5g, 0.0056 mol). After 2 hour at room temperature, the reaction mixture was extracted with ethyl acetate (3x50 ml), dried (anhyd. Na_2SO_4) and evaporated to afford 2,4-dimethoxy-6-(2-oxoheptadecyl)benzoic acid (4) (1.36, 0.0031 mol, 87%) m.p. 69-72°. IR (KBr): 2902, 1716, 1605, 1599, 831 cm^{-1}. ^{1}H-NMR: δ = 0.88 (3H, t, H17′, J=7.0Hz), 1.25 (26H, brs.H2′-H10′), 1.82 (2H, m, H3′), 3.70 (2H, s,H1′), 3.77 (3H, s, 2-OMe), 3.85 (3H, s, 4-OMe), 6.28 (1H, s, H5), 6.29 (1H, s, H3) ppm.

2,4-Dihydroxy-6-(2-oxoheptadecyl)benzoic acid (1a) 3,4-Dihydro-3,6,8-trihydroxy-3-pentadecyl-isocoumarin (1b)≡Peniolactol (1a and 1b)

Two ml of a 1.0 M solution of boron tribromide in dichloromethane was added dropwise to a stirred solution of 2,4-dimethoxy-6-(2-oxoheptadecyl)benzoic acid (4) (0.87 g, 0.002 mol) in dry dichloromethane (5ml) at 0° under nitrogen. The mixture was refluxed for 2 hours. After cooling, the reaction mixture was poured into ice-water and extracted with dichloromethane (3x50 ml). The concentrated residue was crystallized from methanol to afford peniolactol (1a and 1b) (0.36g, 0.009 mol, 45%) as ash coloured solid m.p. 142-145° (decomp.) (lit. [1] 150° decomp.). IR (KBr): 2902, 1716, 1605, 1599, 831 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ =0.88 (t, J=7.0Hz, 17′-H), 1.25 (br,s,26H,2′-14′-H), 1.65 (m, 1H,1′-H), 1.92 (m, 1H,1′-H) 3.81 (s, 2H,4-H), 6.30 (d, J=2.4Hz, ArH), 6.39 (d, J=2.4 Hz, ArH) ppm. ^{13}C-NMR ($CDCl_3$) δ = 171.2 (C=O), 166.2 165.5, 150.6, 108.1, 107.15, 103.2, 101.9, 37.8, 35.5, 31.9, 29.67, 29.65, 29.64,29.63, 29.62, 29.59, 29.57, 29.55, 29.50, 29.34, 24.94, 22.7, 14.0 ppm. MS (70 eV); m/z (%) = 406 [M^+], 388 (100).

1-(3,5-Dihydroxyphenyl)heptadecan-2-one (5)

Five ml a 1.0M solution of boron tribromide in dichloromethane was added dropwise to a stirred solution of 1-(3,5-dimethoxyphenyl)-heptadecan-2-one (2) (2.0g, 0.005 mol) in dry dichloromethane (5 ml) at 0° under nitrogen. The mixture was refluxed for 2h. After cooling, the reaction mixture was poured into ice-water, and extracted with dichloromethane (3x100 ml). The concentrated residue was crystallized from methanol to afford 1-(3,5-dihydroxyphenyl)-heptadecan-2-one (5) (0.84 g, 0.002 mol, 45%) as thick brown oil, which could not be recrystallized. IR (Neat): 2842, 1701, 1584, 1140, 816 cm^{-1}. ^{1}H-NMR δ: 0.87 (3H, t, H-17′ J=6.5Hz), 1.25 (26H, s, H4′-H16′), 1.55 (2H, m, H-3′), 3.60 (2H, s, H1′), 6.35 (2H, s, H-2,H-4), 6.37 (1H, s, H3) ppm. EIMS: m/z 364 (M^+, base), 320, 302, 196.

1-(2-Formyl-3,5-hydroxyphenyl)heptadecan-2-one (6)

A solution of 1-(3,5-Dihydroxyphenyl) heptadecan-2-one (5) (0.84g, 0.002 mol) in triethyl orthoformate (9ml) was treated with dry hydrogen

chloride gas at 0° for 15 minutes, the resulting precipitate was collected. It was dissolved in 5% aqueous sodium carbonate. ^{1}H-NMR δ: 0.87 (3H, t, H17′, J=7.0Hz), 1.25 (18H, s, H4′-H16′), 1.56 (2H, m, H3′), 3.40 (2H, s, H1′), 6.31 (1H, d, H2, J=2.2Hz), 6.34 (1H, d, H4, J=2.3 Hz), 10.46 (1H, s, Ar-CHO)ppm. MS m/z: 392 (M^+), 364 (base), 279.

Peniolactol (1A and 1b)

A stirred mixture of 1-(2-formyl-3,5-dihydroxyphenyl)heptadecan-2-one (6) (1.41g, 0.0036 mol) in water (280 ml) and acetone (48 ml) was treated with sulphamic acid (0.32 g, 0.0049 mol) and 85% sodium chlorite (0.5 g, 0.0056 mol). After 2 hour at room temperature, the reaction mixture was extracted with ethyl acetate (3x50 ml), dried (anhydr. Na_2SO_4) and evaporated to afford peniolactol (1a and 1b) (1.14 g, 0.0028 mol, 78%) m.p. 154-157°. (decomp.) (lit. [1] 150° decomp). The analytical data is already given.

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