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SYNTHESIS OF (±) - 6,8-DIHYDROXY-3-ISOPROPYL-7-METHYLISOCHROMAN

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Abstract

The title isochroman (8) was synthesized as a suitable substrate for acetoxylation studies leading to an intermediate of type (4), expected to afford, on condensation with diketen, the fungal metabolite "rotiorin" type linear product (1). Cyclocondensation of alcohol (6), obtained by the reduction of ketone (5) with paraform in the presence of anhydrous aluminum chloride afforded the dimethoxyisochroman (7). Demethylation of (7) using boron tribromide in dichloromethane furnished the title isochroman (8).

Introduction

Rotiorin [1, 2] (1, R=-CH=CH.CMe=CH.CHMeEt), isolated from *Penicillium sclerotiorum*, belongs to the sclerotiorin group of fungal metabolites. Previous synthetic attempts towards rotiorin, based on the acetoacetylation of an intermediate of aposclerotiorin type (2), in which the C-6 carbonyl is conjugated, invariably resulted in angular analogue of isorotiorin type (3) [4]. In this article, we wish to describe the synthesis of (±)-6, 8-dihydroxy-3-isopropyl-7-methylisochroman (8) as a suitable substrate for acetoxylation studies leading to an intermediate of monascin [3] type (4,R'=Ac, R=$CHMe_2$) in which the C-8 instead of the C-6 carbonyl is conjugated. The compound (4, R'=H) is expected to undergo condensation with diketen, from C-6 carbonyl direction resulting in a linear product of rotiorin type (1, R=$CHMe_2$).

Results and Discussion

Anhydrous iron(III) chloride catalyzed coupling of the 2-(3,5-dimethoxy-4-methylphenyl) ethanoyl chloride [5] with isopropyl magnesium bromide (Grignard reagent) and afforded 1-(3, 5-dimethoxy-4-methylphenyl)-3-methylbutane-2-one (5). IR spectrum of (5) showed a strong carbonyl absorption at 1716 cm^{-1} and the ^{1}H-NMR a 2H singlet at δ 3.70 for the benzylic protons. Reduction of ketone (5) furnished (±)-1-(3, 5-dimethoxy-4-methylphnyl)-3-methylbutan-2-ol (6). A broad hydroxylic absorption at 3430 cm^{-1} in IR and in the ^{1}H-NMR characteristic splitting of the C-4 benzylic protons, (now diastereotopic due to being adjacent to a chiral centre) with C-3 methine proton forming an ABX system was observed. The splitting pattern was not clear in (6).

Cyclocondensation of the alcohol (6) to 6,8-dimethoxy-3-isopropyl-7-methylisochroman (7) was carried out using paraform in dichloromethane in the presence of anhydrous aluminum chloride as catalyst [6]. The ^{1}H-NMR showed the characteristic 2H singlet for C-1 methylene at δ 4.40 and a clear ABX pattern. Thus, each of the benzylic protons at C-4 gave a doublet due to geminal coupling which was split further to another doublet due to vicinal coupling with C-3 methine proton [7]. The C-3 proton showed a multiplet at δ 3.22 - 3.29 ppm.

Demethylation was carried out using 1.0 M solution of boron tribromide in dichloromethane [4] at -78°C to afford the title isochroman (8). IR showed the phenolic hydroxyl absorptions at 3466 and 3298 cm^{-1} and in ^{1}H-NMR the peaks for methoxy protons

Keywords: Sclerotiorin; Rotiorin; Isochroman

disappeared and an overall downfield shift of remaining peaks was observed. The acetoxylation studies are in progress.

Experimental Section

Melting points determined using MEL-TEMP MP-D apparatus are uncorrected. IR spectra were recorded on a Hitachi spectrophotometer model-270 as KBr discs or neat liquids. ^{1}H-NMR (360MHz) was recorded on a Bruker AM-300 using TMS as internal standard. EIMS was obtained on a MAT-112-S machine at 70 ev.

1-(3, 5-Dimethoxyphenyl)-3-methylbutan-2-one (5)

Prepared by treatment of a solution of 3,5-dimethoxy-4-methylphenylacetic acid (5 g, 0.024 mol) in dry benzene (100 ml) with oxalyl chloride (12.1 g, 0.096 mol) at room temperature 3,5-dimethoxy-4-methylphenylethanoyl chloride formed a crystalline residue (m.p. 61°C), which was taken up in dry ether. A Grignard reagent was prepared from isopropyl bromide (15.0 g, 0.048 mol) and magnesium turnings (1.1 g, 0.048 g-atom) in sodium dried ether (150 ml). The Grignard reagent was added dropwise under nitrogen to a stirred solution of the acid chloride and anhydrous iron(III) chloride (100 mg) in dry ether (100 ml) at 0-5°C. The resulting reddish solution was stirred at 20°C for 1/4 h and then heated under reflux for 2 h and poured into aqueous sodium carbonate (5%, 250 ml). Ice was added and the reaction mixture stored at 0°C overnight. The emulsion was acidified with diluted sulfuric acid, the aqueous layer was separated and extracted with ether (3×100 ml). The combined ethereal extract was washed with saturated brine (100 ml), aqueous sodium carbonate (5%, 100 ml), distilled water and dried (Na_2SO_4). The solvent was evaporated *in vacuo* to leave a red oil which was adsorbed on silica (150 g). Elution with pure petroleum ether (40-60°) gave the 1-(3,5-dimethoxy-4-methylphenyl)-3-methylbutan-2-one (3) (2.24 g, 0.0095 mol, 40%) as an oil.

IR(Neat): 2842, 1716, 1584, 1140, 816 cm^{-1}

^{1}H-NMR δ($CDCl_3$): 1.05 (6H, d, $(CH_3)_2$, J=7.0Hz), 1.96 (1H, septet, $CH(CH_3)_2$), 2.06(3H, s, Ar-CH_3), 3.70(3H, s, Ar-CH_2), 3.80(6H, s, OCH_3x2), 6.36 ppm (2H, s, H-2, H-4).

Found: C, 71.7 H, 8.8, $C_{14}H_{20}O_3$ requires C, 71.2, H, 8.5%

(±)-1-(3,5-Dimethoxy-4-methylphenyl)-3-methylbutan-2-ol (6)

1-(3,5-dimethoxy-4-methylphenyl)-3-methylbutan-2-one (5) (2.36 g, 0.01 mol) and sodium borohydride (0.4 g, 0.01 mol) in absolute ethanol (100 ml) were heated under reflux for 2.5 hours and worked up to leave a yellow oil which was adsorbed on silica (60 g). Elution with ether and petroleum ether (1:25) afforded (±)-1-(3,5-dimethoxy-4-methylphenyl)-3-methylbutan-2-ol (6) (1.9 g, 0.008 mol, 80%) as a colorless oil.

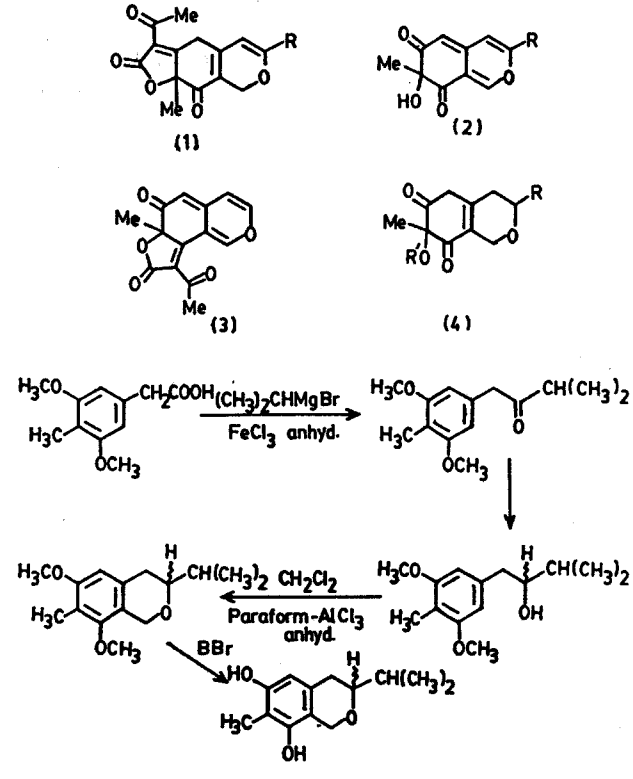
IR (Neat): 3262, 2848, 1587, 1149, 1056 cm^{-1}

δ($CDCl_3$): 0.97(6H, d, $(CH_3)_2$, J=6.8Hz), 1.59(1H, brs, OH, D_2O, exch.) 1.76-1.83(1H, septet, $CH(CH_3)_2$), 2.1(3H, s, Ar-CH_3), 2.47-2.52 (1H, dd, Ar-CH, J=complex), 2.64-2.69(1H, dd, Ar-CH, J=complex), 3.22-3.29(1H, m, H-3), 3.78(6H, s, OCH_3x2), 6.54 ppm(2H, s, Ar-Hx2).

MS m/z: 238 (M^+), 197, 196, 165 (base).

(±)-6,8-Dimethoxy-3-isopropyl-7-methylisochroman (7)

Anhydrous aluminum chloride (2.35 g, 0.0176 mol) was added to a stirred solution of (±)-1-(3,5-dimethoxy-4-methylphenyl)-3-methylbutan-2-ol (6) (2 g, 0.0084 mol) and paraformaldehyde (0.25 g, 0.0084 mol) in anhydrous dichloromethane (10 ml). The reaction mixture began to reflux gently and this continued for 3-4 h. The reddish aluminum chloride complex was decomposed by pouring onto ice-sulfuric



Synthetic Scheme

acid mixture and extracted with dichloromethane (3×50 ml). The organic layer was washed successively with aqueous sodium carbonate (5%, 100 ml) and distilled water. The crude product obtained on concentration was purified by thick layer chromatography on silica gel, using ether-petroleum ether as eluent to afford (±)-6,8-dimethoxy-3-isopropyl-7-methylisochroman (7) (1.68 g, 0.0067 mol, 80%) as viscous oil.

IR (Neat): 2908, 1587, 1452, 1098 cm^{-1}

$\delta(CDCl_3)$: 0.97(6H, d, $(CH_3)_2$, J=6.8Hz), 1.76-1.83 (1H, m, $CH(CH_3)_2$) 2.1(3H, s, Ar-CH_3), 2.47-2.52(1H, dd, Ar-CH, J_{gem}=9.6Hz, J_{vic}=4.9Hz), 2.64-2.69(1H, dd, Ar-CH, J_{gem}=9.6Hz, J_{vic}=3.7Hz), 3.22-3.29(1H, m, H-3), 3.76(3H, s, OCH_3), 3.78(3H, s, OCH_3), 4.40(2H, s, CH_2-1), 6.39 ppm (1H, d, Ar-H).

m/z: 251(M^++1), 250(M^+), 207(base), 179.

(±)-6,8-Dihydroxy-3-isopropyl-7-methylisochroman (8)

1.0 molar solution of boron tribromide in dichloromethane (1.50 g, 0.006 mol) was added dropwise to a stirred solution of (±)-6,8-dimethoxy-3-isopropyl-7-methylisochroman (7) (0.5 g, 0.002 mol) at -78°C for 4h. After stirring overnight, the reaction mixture was poured onto ice-water, filtered, and extracted with dichloromethane (3×50 ml). The combined extracts were washed, dried, and concentrated to a red semisolid. Thick layer chromatography gave (±)-6,8-dihydroxy-3-isopropyl-7-methylisochroman (8) (0.26 g, 0.0012 mol, 60%) as light yellow thick oil.

IR: 3466, 3298, 2866, 1578, 1422, 1098 cm^{-1}

$\delta(CDCl_3)$:0.97(6H, d, $(CH_3)_2$, J=6.8Hz), 1.76-1.83 (1H, m, $CH(CH_3)_2$), 2.1(3H, s, Ar-CH_3), 2.43-2.48(1H, dd, Ar-CH, J_{gem}=9.6 Hz, J_{vic}=4.9 Hz), 2.67-2.74(1H, dd, Ar-CH, J_{gem}=9.6Hz, J_{vic}=3.7 Hz), 3.32-3.39(1H, m, H-3), 4.85(2H, s, CH_2-1), 6.39 ppm (1H, d, Ar-H).

MS m/z: 222 (M^+), 207, 165 (base).

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