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Simple Syntheses of (+)-Orthosporin and (-)-Semivioxanthin methyl ether$^+$

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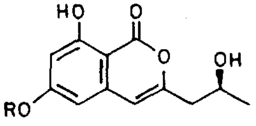
Abstract : Simple syntheses of (+)-orthosporin(1) and (-)-semivioxanthin methyl ether (11) are described from (S)-ethyl 3-hydroxybutyrate (5) and orsellinic acid derivatives 3 and 4 respectively. Copyright © 1996 Published by Elsevier Science Ltd

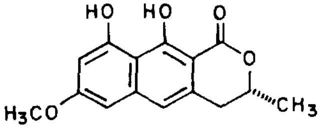
(S)-(+)-Orthosporin (**1**)[1], a phytotoxic metabolite isolated from the culture filtrate of *Rhynchosporium orthosporum* has been shown to be 3-(2'-hydroxypropyl)-6, 8-dihydroxyisocoumarin. Its absolute configuration has been established by synthesis *via* a resolution of the racemic intermediate[1]. Treatment of (1) with diazomethane gave a monomethylated compound which was identical with (+)-diaporthin (**1a**) a phytotoxin isolated from the culture filtrate of *Endothia parasitica*[2]. It should be noted that de-O-methyldiaporthin, a phytotoxin isolated from *Drechslera siccans*[3] and orthosporin (**1**) are structurally identical.

Semivioxanthin (**2**), an antifungal antibiotic isolated from the culture filtrate of *Penicillium citreo veride*[4], has been shown to be 3,4-dihydro-9,10-dihydroxy-7-methoxy-3-methyl-1-oxo-1H-naphtho [2, 3-*c*] pyran and its absolute configuration at C-3 has been assigned (R) on the basis of the correlation of its CD curve with that of (R)-mellein. The first synthesis of (±)-semivioxanthin was reported by Yamaguchi *et al.*[5] *via* a polyketide approach. Subsequently we also reported its synthesis[6]. Recently, a synthetic precursor of semivioxanthin has been reported from a 14-membered lactone by intramolecular aldolactonization[7]. We report here simple syntheses of (S)-(+)-orthosporin (**1**) and unnatural enantiomer, (-)-semivioxanthin methyl ether (**11**).



1 R = H

1a R = CH_3



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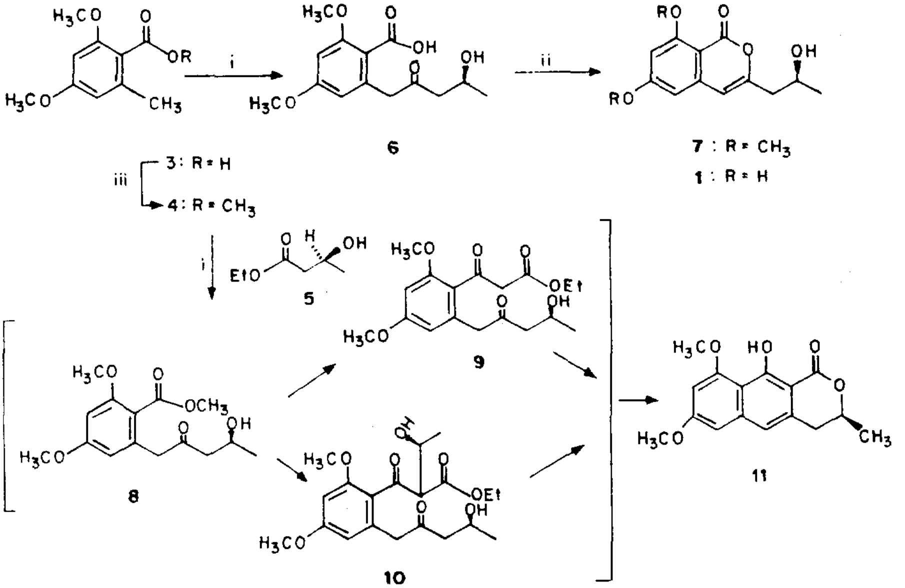
It has been shown[8,9] that the dianion of orsellinic acid generated by using LDA can be reacted with an electrophile such as diethylcarbonate to obtain the corresponding homophthalic acid derivative. Based on this observation, the dianion of orsellinic acid dimethyl ether (**3**), generated with 2 equivalents of LDA in THF at -78°C, on treatment with the desired electrophile (S)-ethyl 3-hydroxybutyrate (**5**)[10] at the same temperature afforded ketoacid (**6**) after acidic workup in 53% yield. The cyclodehydration of (**6**) with p-toluenesulphonic acid in benzene provided (S)-(+)-orthosporin dimethyl ether (**7**) in 79% yield which showed optical rotation $[\alpha]_D^{25}$ +24.86° (c, 2.5 in $CHCl_3$), [Lit[1]. $[\alpha]_D^{25}$ +22.4° (c, 2.7 in $CHCl_3$)]. As the demethylation of (**7**) by aluminium chloride in ethanethiol has been already reported[1], this constitutes a formal total synthesis of (S)-(+)-orthosporin (**1**) (Scheme).

In order to simplify the synthesis of (7), methyl orsellinate dimethyl ether (4), prepared from the corresponding acid (3) (Me_2SO_4, K_2CO_3, acetone), on similar treatment with LDA in THF at -78°C and (S)-ethyl 3-hydroxybutyrate (5) did not give the desired product (7) after acidic workup. However, the product isolated in 35% yield was characterized as the unnatural enantiomer, (-)-semivioxanthin methyl ether (11) which showed optical rotation $[\alpha]_D^{25}$ -18.0°(c, 0.3 in $CHCl_3$). The formation of semivioxanthin methyl ether was confirmed by its racemic synthesis from methyl orsellinate dimethyl ether (4) and 4-methoxy-6-methyl-5,6-dihydro-2-pyrone according to the method described by us[6].

SCHEME



Reagents : (i) LDA,THF,-78°C,(S)-ethyl 3-hydroxybutyrate (5) in THF, then 10% HCl; (ii) pTSA, benzene; (iii) Me_2SO_4, K_2CO_3, acetone, reflux.

The formation of semivioxanthin methyl ether (11) clearly indicates that two molecules of ethyl 3-hydroxybutyrate have reacted with methyl orsellinate (4) in which the aromatic ester group plays an important role[11]. The benzylic anion of methyl orsellinate (4) first reacts with the ester carbonyl of ethyl 3-hydroxybutyrate (5) to form keto ester (8) which can further react with the another molecule of ethyl 3-hydroxybutyrate (5) by generating an anion at its active methylene group. Ethyl 3-hydroxybutyrate (5) can undergo retroaldol cleavage to generate CH_3CHO and an anion ($^-CH_2COOEt$) which would attack the ester carbonyl of (8) to give an intermediate (9) which in turn would cyclise to give (11) after acidic workup. Alternatively, the anion of ethyl 3-hydroxybutyrate(5) can first attack the ester carbonyl of (8) to form an intermediate (10) (scheme) which would rearrange intramolecularly by eliminating CH_3CHO and cyclise on acidic workup to give semivioxanthin methyl ether (11). While in the case of orsellinic acid (3) although the dianion is formed, the benzylic anion attacks the ester carbonyl of ethyl 3-hydroxybutyrate thereby leading to the formation of ketoacid (6) which has been isolated after acidic workup and then cyclised with pTSA in benzene to orthosporin dimethyl ether (7). It should be noted that the intermediates suggested in the scheme for the formation of semivioxanthin skeleton could not be isolated and confirmed.

The synthesis of (S)-(-)-semivioxanthin methyl ether (11) from (S)-ethyl 3-hydroxybutyrate suggested that condensation of (R)-ethyl 3-hydroxybutyrate with methyl orsellinate dimethyl ether (4) would lead to the natural (R)-semivioxanthin methyl ether.

It can be concluded that a short synthesis of (S)-(+)-orthosporin (1) and a novel single step condensation methodology for the synthesis of (S)-(-)-Semivioxanthin methyl ether (**11**) have been developed. The methodology could be extended for the synthesis of other molecules possessing similar skeleton.

Experimental Section

General Remarks:

H^1-NMR spectra were recorded either on FT-80 or Bruker WH 90 or WH- 200 FT spectrometer in CDCl$_3$ solution containing TMS as an internal standard with chemical shift (δ) expressed in ppm downfield from TMS. Infra- red spectra (νmax in cm^{-1}) were recorded as either thin film or nujol mulls on Perkin Elemer Infra -red 683 -B spectrometer with sodium chloride optics. Mass spectra were recorded on a CES - 21 1108 double focussing mass spectrometer operating at 70 eV using direct inlet system.

(S)-Ethyl-3-hydroxybutyrate (5): Baker's Yeast (2.8 gm, Blue Bird make) was introduced in distilled water (50 ml) and then ethanol (0.58 ml, 200 mmol) and glucose (1.8 gm, 200 mmol) were added and the contents were shaken at 25-30°C for 3 hr. Then ethyl acetoacetate (0.5 gm, 77 mmol) was introduced and the shaking was continued for 48 hr. The reaction mixture was filtered through a Celite pad and the filtrate was extracted with ethyl acetate (3 x 50 ml). The combined extracts were washed with brine, dried over Na$_2$SO$_4$ and concentrated. The oily residue was distilled between 65-67°C at 10 mm (lit.[10] 70-71°C at 12 mm) to afford (S)-ethyl-3-hydroxybutyrate (**5**) (0.3 gm, 60%) with 95% optical purity $[\alpha]_D^{25}$ +41.1° (c 2, CHCl$_3$); {lit[10]$[\alpha]_D^{25}$ + 43.5° (c 1, CHCl$_3$)}.

Condensation of orsellenic acid (3) with (S)-ethyl 3-hydroxybutyrate (5): A solution of LDA was prepared by reacting n-BuLi in hexane (1.6 M, 6.18 ml, 9.9 mmol) with dry diisopropylamine (0.99 gm, 9.9 mmol) in dry THF (10 ml) at 0°C under argon atmosphere. It was then cooled to -78°C and 2,4-dimethoxy-6-methylbenzoic acid (**3**) (0.588 gm, 3 mmol) dissolved in THF (5 ml) was added during 20 min. The stirring was continued at the same temperature for 2 more hr. and then a solution of **5** (0.504 gm, 3.5 mmol) in THF (5 ml) was added slowly. The reaction mixture was further stirred for 2 hr. and then warmed to room temperature and stirred overnight. The reaction mixture was then poured into ice cold hydrochloric acid solution (10%) and extracted with dichloromethane (2 x 50 ml). The combined extracts were washed with brine, dried (Na$_2$SO$_4$) and concentrated. The residue was subjected to column purification on silica gel (hexane-acetone; 7:2) to yield **6** (0.45 gm, 53%) as a sticky solid; $[\alpha]_D^{25}$ + 11° (c 2, CHCl$_3$);**IR**(Nujol): 3416 (br), 1680 and 1606 cm^{-1} ;**^{1}H-NMR** (CDCl$_3$): δ 1.18 (d, J = 6Hz, 3H); 2.50 (m, 2H); 3.81 (s, 5H); 3.93 (s, 3H); 4.06 - 4.56 (m, 1H); 6.31 (d, J = 2Hz, 1H); 6.43 (d, J = 2Hz, 1H);**Ms** (m/z): 282 (M$^+$)**Analysis calc. for $C_{14}H_{18}O_6$**: C, 59.5; H, 6.4; **Found**: C, 59.4; H, 6.5.

(S)-(+)Di-O-methyl orthosporin: The keto acid (**6**) (0.282 gm, 1 mmol) was heated at reflux in dry benzene (10 ml) with a catalytic amount of para-toluene sulphonic acid for 30 min. After cooling, the benzene solution was washed with sodium bicarbonate solution and water respectively and dried over Na$_2$SO$_4$. The residue obtained after removal of the solvent was purified on silica gel column (hexane-acetone; 8:2) to give (+)-di-O-methyl orthosporin (**7**) (0.21 gm, 79.5%) as sticky solid; $[\alpha]_D^{25}$ + 24.8° (c 2.5,CHCl$_3$) [lit.[1] $[\alpha]_D^{25}$ + 22.4°(c 2.7, CHCl$_3$);**IR** (Nujol): 3473 and 1713 cm^{-1}; **^{1}H-NMR** (CDCl$_3$): δ 1.23 (d, J = 6Hz, 3H); 2.50 (dd, J = 14.2, 7.7 Hz, 1H); 2.60 (dd, J = 14.2, 5.6 Hz, 1H); 3.80 (s, 3H); 3.86 (s, 3H); 4.15-4.30 (m, 1H); 6.12 (s, 1H); 6.25 (d, J = 2Hz, 1H); 6.35 (d, J = 2Hz, 1H);**Ms** (m/z): 264 (M$^+$), 220 (base peak);**UV** (CHCl$_3$, λ_{max}): 321.4 and 260.4 nm;**Analysis calc. for $C_{14}H_{16}O_5$**: C, 63.62; H,6.1; **Found**: C ,63.64; H ,6.1.

Condensation of methyl orsellinate 4 with (S)-ethyl 3-hydroxybutyrate (5) : A solution of LDA was prepared at 0°C by adding n-BuLi (1M, 3.16 ml) to diisopropylamine (0.32 gm, 3.16 mmole) in THF (2 ml) under argon atmosphere. The solution was cooled to -78°C and a solution of methyl orsellinate (**4**)

(0.33 gm, 1.58 mmole) in THF(2 ml) was added during 10 min. The reddish orange solution was stirred for 15 min. and (S)-ethyl-3-hydroxybutyrate (**5**) (0.21 gm, 1.59 mmole) in THF (1 ml) was added dropwise. The reaction mixture was stirred further for 2 h at -78°C and 1 hr at room temperature. The reaction mixture was poured into ice-cold dilute HCl(10 ml), stirred and extracted with CH_2Cl_2 (2 x 10 ml). The combined organic extracts were washed with water, dried over Na_2SO_4 and concentrated. The residue was purified on silica gel column (hexane-acetone; 8:2) to afford (S)-(-)-semivioxanthin methyl ether (**11**) (0.158 gm, 35%) as a colourless crystalline solid, m.p. 130-131°C;$[\alpha]_D^{25}$ -18° (c 0.3, $CHCl_3$); **IR** (Nujol): 1665 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 1.48 (d, J = 6 Hz, 3H); 2.88 (dd, J = 6 Hz and 1 Hz, 2H); 3.84 (s, 3H); 3.93 (s, 3H); 4.64 (m, 1H); 6.40 (d, J = 2 Hz, 1H); 6.48 (d, J = 2 Hz, 1H); 6.77 (s, 1H); 13.13 (s, 1H, O$\underline{H}$); **^{13}C-NMR** ($CDCl_3$): 20.9 ($C_3\underline{C}H_3$); 35.2 (C_4); 55.6 (C_9-O$\underline{C}H_3$); 56.3 (C_7-O$\underline{C}H_3$); 75.8 (C_3); 98.5 (C_{9a}); 99.1 (C_8); 100.8 (C_6); 110.8 (C_{10a}); 115.4 (C_5); 134.5 (C_{4a}); 141.6 (C_{5a}); 160.8 (C_{10}); 162.0 (C_9); 164.2 (C_7); 171.3 (C_1).**Ms** (m/z): 288 (M^+) (base peak);UV ($CHCl_3$, λ_{max}): 259, 307 and 361 nm. **Analysis calc. for $C_{16}H_{16}O_5$**; C, 66.7; H, 5.5; **Found**: C, 66.6; H, 5.6.

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