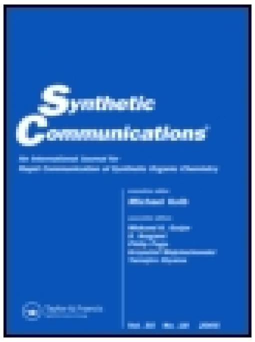


Synthetic Communications

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

Synthesis of Semivioxanthin

V. H. Deshpande , R. A. Khan , B. Rai & N. R. Ayyangar

To cite this article: V. H. Deshpande , R. A. Khan , B. Rai & N. R. Ayyangar (1993) Synthesis of Semivioxanthin, Synthetic Communications, 23:17, 2337-2345, DOI: 10.1080/00397919308011118

To link to this article: http://dx.doi.org/10.1080/00397919308011118

SYNTHETIC COMMUNICATIONS, 23(17), 2337-2345 (1993)

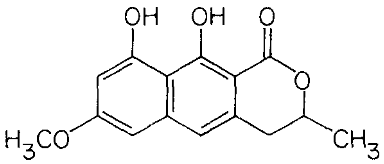
SYNTHESIS OF SEMIVIOXANTHIN[#]

V.H. Deshpande[*], R.A. Khan, B. Rai, and N.R. Ayyangar

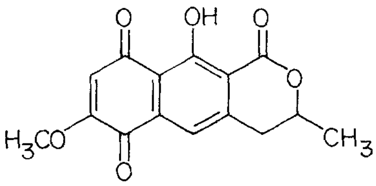
National Chemical Laboratory, Pune 411 008 (INDIA)

Summary : A short route to semivioxanthin (1) is described.

Semivioxanthin (1), an antifungal natural product isolated under different culture conditions from *Penicillium cetreo-viride* by Zeeck et al[1] was shown to be 3,4-dihydro-9,10-dihydroxy-7-methoxy-3-methyl-1-oxo-1H-naptho[2,3-c]pyran. A few of the other examples of natural products having similar basic skeleton are vioxanthin,[1] SC-28762, SC-28763[2] and SC-30532.[3] Although 1 was isolated in 1979, its first synthesis was



1

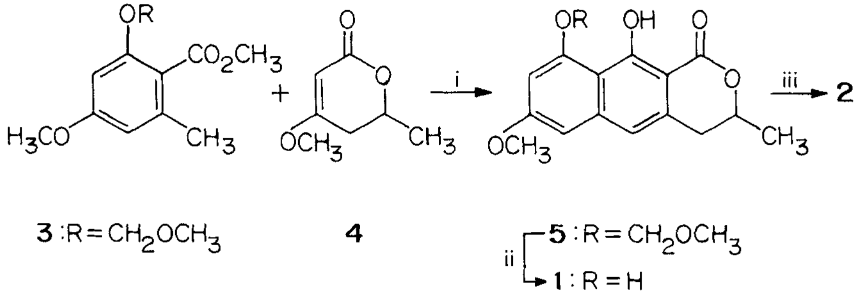


2

---

[*] To whom correspondence should be addressed.

reported in 1990 by Yamaguchi et al[4] via polyketide approach. This prompted us to develop a short and simple synthesis of semivioxanthin as outlined in the Scheme.



Reagents: i) LDA, THF -78°C, ii) Conc. HCl, THF, iii) $K_2Cr_2O_7$, AcOH.

Synthesis of 1 was achieved by the condensation of methyl-4-methoxy-2-methoxymethoxy-6-methylbenzoate (3) with 4-methoxy-6-methyl-5,6-dihydro-2-pyrone (4), followed by deprotection. The orsellinate derivative 3 was prepared by selective demethylation of methyl orsellinate dimethyl ether[5] (CH_2Cl_2, 1.5 equiv. $AlCl_3$, 90%) followed by MOM protection (NaH, $ClCH_2OCH_3$, 80%). The 4-methoxy-6-methyl-5,6-dihydro-2-pyrone (4), m.p. 56°C, was obtained in quantitative yield by methylating (Me_2SO_4, anhyd. K_2CO_3, acetone) the corresponding hydroxy compound[6]. Condensation[7] of 3 (2 equiv. LDA, THF, -78°C) with the lactone 4 afforded MOM protected semivioxanthin 5 in 68% yield. Removal of methoxy methyl protection (conc. HCl, THF) gave 1 in 82% yield.

Oxidation of 1 ($K_2Cr_2O_7$, acetic acid) afforded semixanthomegnin (2) in 77% yield. Spectroscopic data and m.p. of 1 and 2 were in good agreement with those previously reported[1].

GENERAL REMARKS

All melting points were uncorrected. Infrared spectra were recorded on Perkin-Elmer Infrared spectrometer model 683 B. ^{1}H-NMR spectra were recorded in $CDCl_3$ on Varion FT-80 or Bruker WH-90 spectrometer using TMS as internal standard with chemical shifts (δ) expressed in ppm. Mass spectra were recorded on CES-21-110 B spectrometer operating at 70 eV using direct inlet system. All solvents and reagents were purified and dried by standard techniques.

EXPERIMENTAL

Methyl 4-methoxy-2-methoxymethoxy-6-methylbenzoate (3):

To the stirred solution of methyl orsellinate dimethyl ether (1.5 g, 7.15 mmol) in dry dichloromethane (25 ml) at 0°C was added powdered anhydrous $AlCl_3$ (1.43 g, 10.7 mmol). After 30 min. the mixture was allowed to warm to room temperature and stirred further 2.5 h. It was then poured slowly into cold dilute HCl solution, warmed on water bath for 20 min. After cooling to room temperature, colourless crystalline solid separated was filtered, washed thoroughly with water, dried and crystallised from pet ether to obtain Methyl 2-hydroxy-4-methoxy-6-methylbenzoate (1.26 g, 90%); m.p. 67°C (Lit.[8], m.p. 67°C).

To a stirred suspension of sodium hydride (0.086 g, 3.6 mmol) [50% sodium hydride (0.172 g) emulsion in paraffin was washed with dry benzene (5 ml) under argon atmosphere] in dry benzene (25 ml) was injected a solution of <u>ortho</u>-hydroxy ester (0.700 g, 3.6 mmol) in dry benzene (5 ml). It was stirred at room temperature for 30 min and then cooled to 10°C. To the resulting sodium phenoxide suspension, chloromethyl methyl ether (0.43 g, 5.4 mmol) was added with vigorous stirring. It was stirred at 5-10°C for 1 h and then at room temperature for 4 h. The solvent was removed under reduced pressure and the residue after workup was purified by column chromatography on silica gel (eluent: 5% acetone-pet. ether) to afford compound **3** as a colourless viscous oil, (0.685 g, 80%). **IR** (Neat): ν max 1740 and 1620 cm^{-1}. ^{1}**H-NMR** : δ 2.26 (s, 3H), 3.44 (s, 3H), 3.75 (s, 3H), 3.85 (s, 3H), 5.11 (s, 2H), 6.35 (d, J = 2.5 Hz, 1H) and 6.57 (d, J = 2.5 Hz, 1H).**MS** (m/e): 240 (M$^+$). Analysis cal. for $C_{12}H_{16}O_5$: C, 60.00; H, 6.67; Found : C, 59.90; H, 6.66%.

4-Methoxy-6-methyl-5,6-dihydro-2-pyrone (4):

A mixture of 4-hydroxy-6-methyl-5,6-dihydro-2-pyrone[6] (1.28 g, 10 mmol), dimethyl sulphate (1.51 g, 12 mmol) and anhydrous potassium carbonate (2.1 g, 15 mmol) in dry acetone (50 ml) was heated to reflux for 8 h. The acetone was distilled off from the reaction mixture, water (50 ml) was added to the residue and extracted with dichloromethane (3 x 25 ml). The organic extracts were combined, dried (Na_2SO_4) and evaporated to leave a viscous oil. Chromatographic purification of the crude product on silica gel using 5% acetone-pet. ether as an eluent afforded the methoxypyrone 4 (1.35g,95%); m.p. 56°C. **IR** (Nujol):ν max 1735 and 1620 cm^{-1}. **^{1}H-NMR** : δ 1.39 (d, J = 6.8 Hz, 3H), 2.93 (m, 2H), 3.69 (s, 3H), 4.48 (m, 1H) and 5.10 (s, 1H).**MS** (m/e): 142 (M^+). Analysis cal. for $C_7H_{10}O_3$: C, 59.15; H, 7.04; Found : C, 59.20; H, 7.00%.

3,4-Dihydro-10-hydroxy-7-methoxy-9-methoxymethoxy-3-methyl-1-oxo-1H-naphtho[2,3-c]pyran (5):

To the solution of LDA [prepared from 1.6 M n-BuLi in hexane (2 ml) and diisopropyl amine (0.44 ml, 3.15 mmol) at 0°C under argon atmosphere] in THF (10 ml), a solution of 3 (0.378 g, 1.57 mmol) in THF (2 ml) was injected at -78°C. After 15 min. the resultant orange-red anionic solution was treated with dihydropyrone 4 (0.223 g, 1.57 mmol) in THF (2 ml) and the reaction mixture was stirred further for 30 min. at -78°C. It was then allowed to warm to room temperature and stirred for 20 min. The reaction mixture was poured into an ice cold dilute hydrochloric acid solution and extracted with dichloromethane. The organic extract was washed with saturated brine solution, dried (Na_2SO_4) and evaporated to give brown thick oily residue. It was chromatographed (silica gel, eluent: 15% acetone-pet. ether) to yield compound 5 (0.340 g, 68%) as a pale yellow crystalline solid; m.p. 138°C. **IR** ($CHCl_3$):ν max 1654 and 1633 cm^{-1}. **^{1}H-NMR**: δ 1.53 (d, J = 6.4 Hz, 3H), 2.92 (d, J = 6.8 Hz, 2H), 3.53 (s, 3H), 3.86 (s, 3H), 4.65 (m, 1H), 5.31 (s, 2H), 6.59 (d, J = 2.5 Hz, 1H), 6.68 (d, J = 2.5 Hz, 1H), 6.81 (s, 1H) and 9.03 (s, 1H). **MS** (m/e): 318 (M^+). Analysis cal. for $C_{17}H_{18}O_6$: C, 64.15; H, 5.66; Found : C, 64.09; H, 5.62%.

3,4-Dihydro-9,10-dihydroxy-7-methoxy-3-methyl-1-oxo-1H-naphtho[2,3-c]pyran (Semivioxanthin) (1):

To the stirred solution of naphthopyrone 5 (0.1g, 0.365 mmol) in THF (5 ml) was added 4-5 drops of concentrated hydrochloric acid and stirred at room temperature for 4 h. To the reaction mixture an aqueous 5% sodium bicarbonate solution (10 ml) was added and the resulting solution was extracted with dichloromethane (2 x 15 ml). The dichloromethane extract was washed with water, saturated brine solution, dried over sodium sulphate and evaporated. Purification of the crude product by passing through short column of silica gel (eluent: 5% methanol-chloroform) afforded semivioxanthin (**1**) (0.071g) in 82% yield as a crystalline solid; m.p. 185°C (Lit.[1], m.p. 185°C). **IR** ($CHCl_3$): ν max 1642 and 1585 cm^{-1}. **UV** (MeOH): λ max (ϵ) 371.8 (10,000), 308 (3,600), and 261.2 (48,200) nm. **^{1}H-NMR**: δ 1.53 (d, J=6.5 Hz, 3H), 2.94 (m, 2H), 3.84(s, 3H), 4.72 (m, 1H), 6.47 (d, J=2Hz,1H), 6.50 (d, J=2 Hz, 1H), 6.84 (s, 1H), 9.37 (s, 1H) and 13.57 (s, 1H). **MS** (m/e): 274 (M^+). Analysis cal. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.11; Found : C,65.60; H,5.10%.

3,4,5,9-Tetrahydro-10-hydroxy-7-methoxy-3-methyl-1,6,9-trioxo-1H-naphtho[2,3-c]pyran (Semixanthomegnin) (2):

To the stirred solution of semivioxanthin (**1**) (0.05 g, 0.175 mmol) in glacial acetic acid (5 ml) was added solid potassium dichromate (0.322 g, 1.09 mmol). After stirring for 8 h at room temperature, a mixture of chloroform (10 ml) and water (20 ml) was added. The chloroform layer was separated and the aqueous part was extracted with chloroform (2 x 10 ml). The chloroform extracts were united, washed successively with water, 5% aqueous sodium bicarbonate solution, saturated brine solution, dried (Na_2SO_4) and concentrated. Purification of the product by column chromatography on silica gel (eluent : chloroform) afforded semixanthomegnin (2) as a orange-red solid (0.041 g, 77%). Recrystallization from chloroform-acetone gave orange-red needles; m.p. 225-226°C, (Lit.[1] m.p. 226°C). **IR** ($CHCl_3$): ν max 1730, 1690, 1672, 1620 and 1600 cm^{-1}. **UV** (CH_3OH):λmax (ε): 410 (4,800), 286 (8,600) and 226 (29,500) nm. **^{1}H-NMR**:δ 1.52(d, J = 6.5 Hz, 3H), 2.99(m, 2H), 3.90 (s, 3H), 4.66 (m, 1H), 6.15 (s, 1H), 7.49 (s, 1H) and 13.20 (s, 1H). **MS** (m/e): 288 (M^+). Analysis cal. for $C_{15}H_{12}O_6$: C, 62.50; H, 4.16; Found : C, 62.41; H, 4.16%.

Acknowledgement : The authors are grateful to Prof. M. Yamaguchi for providing NMR and IR spectra of synthetic semivioxanthin. Mr. R.A. Khan and Mrs. Beena Rai are thankful to the CSIR, New Delhi, India for financial support.

REFERENCES :

1. Zeeck, A., Rub, P., Laatch, H., Loeffler, W., Wehrle, H., Zaahner, H. and Holst, H., Chem. Ber., 1979, 112, 957.
2. Jiu, J. and Muzuba, S., J. Antibiot., 1974, 27, 760.
3. Suzuki, K., Nozawa,K. and Kawai, K., Chem. Pharm.

Bull., 1990, 38, 3180.

4. Yamaguchi, M., Okuma, T., Nakamura, T. and Minami, T., J.Chem.Soc., Perkin Trans. I, 1990, 183.

5. Parker, K. A., Spero, D. M., and Koziski, K. A., J.Org.Chem., 1987, 52, 183.

6. Bocardit, R. and Moreno-Manas, M., Tetrahedron Lett., 1980, 21, 551.

7. Carpenter, T. A., Evans, C. E., Leeper, F. J., J. Staunton and Wilkinson, M. R., J.Chem.Soc. Perkin Trans.I, 1984, 1083.

NCL Communication No. 5311.

(Received in UK 25 March 1993)