Tetrahedron Vol. 29, pp. 2849 to 2850. Pergamon Press 1973. Printed in Great Britain

A NEW SYNTHESIS OF FUSCIN

B. PYUSKYULEV, B. RINDONE and C. SCOLASTICO
Istituto di Chimica Organica dell'Università, Via Saldini 50, Milano

(*Received in the UK* 27 *March* 1973; *Accepted for publication* 18 *April* 1973)

Abstract—The prenylation of trihydroxylacton (**6**) with prenyl bromide in the presence of silver oxide yields mainly the C-prenyl derivative with good yield. The intermediate **7** thus obtained is cyclised to dihydrofuscin with formic acid.

Our research on the sequential analysis in the biosynthesis of terpenoid compounds of mixed biogenetic origin induced us to examine the physiologically active mould metabolite fuscin, isolated by Michael[1,2] from a culture of *Oidiodendron fuscum* Robak.

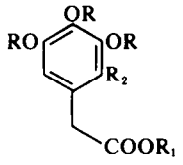
Its structure (**1**) was determined by Barton and Hendrickson,[3] then confirmed by total synthesis[3,4] and the mixed biosynthesis of **1** was at last demonstrated.[5]

Since we needed labelled intermediates, during their preparation we planned a chemical analogue of the biosynthesis of fuscin (similar to the van Tamelen's scheme[6] of "biogenetic-type reactions").

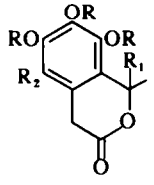
Methyl 3,4,5-trimethoxyphenyl acetate[7] (**2**) was transformed into methyl 2-acetyl-3,4,5-trimethoxyphenyl acetate (**3**) either with acetic anhydride and perchloric acid[8] (low yield as was obtained by other groups[9]), or by treatment of **2** with excess acetyl chloride and aluminium chloride in diethyl ether. In this case the keto-ester (**3**) was obtained in good yield. The corresponding keto-acid (**4**) probably existed in equilibrium with the lactol form (**5**), since it showed (in $CHCl_3$) only the CO band at 1750 cm^{-1}. Reduction of the keto-acid (**4**) with potassium borohydride furnished the lactone trimethylether (**6**), which was demethylated with BBr_3 to the trihydroxylacton (**7**).

As previously reported,[10] the only system to obtain C-prenylation in good yield is the treatment of phenol (**7**) in dioxane solution with prenyl bromide in presence of silver oxide. With this method we observed only C-prenylation to the hydroquinone (**8**).

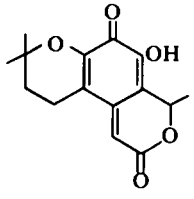
Compound **8** was cyclised and the chromane (**9**) thus obtained was identical with dihydrofuscin and **9** was oxidised to fuscin as previously described.[3]



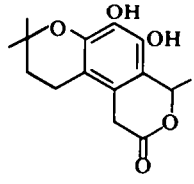
2: $R = R_1 = CH_3$; $R_2 = H$
3: $R = R_1 = CH_3$; $R_2 = COCH_3$
4: $R = CH_3$; $R_1 = H$; $R_2 = COCH_3$



5: $R = CH_3$; $R_1 = OH$; $R_2 = H$
6: $R = CH_3$; $R_1 = R_2 = H$
7: $R = R_1 = R_2 = H$
8: $R = R_1 = H$; $R_2 = (CH_3)_2C{=}CHCH_2{-}$



1



9

EXPERIMENTAL

M.ps are uncorrected. The UV spectra were determined on a Perkin-Elmer mod 137 spectrophotometer. The IR spectra were measured with a Perkin-Elmer 257 spectro-

photometer. The NMR spectra were recorded on a Varian A-60 spectrometer using TMS as internal standard.

Methyl 2-acetyl-3,4,5-trimethoxyphenyl acetate (3). Methyl 3,4,5-trimethoxyphenyl acetate (2·5 g) was dissolved in dry diethyl ether with addition of acetyl chloride (58 ml) and $AlCl_3$ (43 g; added portionwise under reflux). The dark soln was left for 3 hr at room temp with stirring, then poured into 1·4 l. 2N HCl and extracted with diethyl ether. The organic extracts were washed with a sat $NaHCO_3$ aq. The solvent then was removed *in vacuo* and the residue (3·3 g) was chromatographed over silica-gel Merck 0·05–0·2 mm (65 g) eluting with heptane–diethyl ether 7/3, (25 ml each fraction). Fractions 23–40, evaporated and crystallised from benzene-n-hexane yielded 2·2 g, m.p. 44–45°; ν_{max} (Nujol) 1738, 1690 cm^{-1}; δ (ppm) 2·52 (s, 3H, —Ac), 3·67 (s, 5H, $ArCH_2COOMe$), 3·87 (s, 6H, —OMe), 3·91 (s, 3H, $—OCH_3$). (Found: C, 59·6; H, 6·45. $C_{14}H_{18}O_8$ requires: C, 59·57; H, 6·43%).

2-Acetyl-3,4,5-trimethoxyphenylacetic acid (4). A soln of 3 (3 g) in 25 ml MeOH was added to 600 ml of 10% KOH aq. After 4 hr at room temp with stirring the soln was acidified with HCl and extracted 3 times with EtOAc. Evaporation of the solvent under vacuum gave a crystalline residue which was crystallised from benzene–hexane to yield 2·33 g of 4; m.p. 90–91°; ν_{max} 1750 cm^{-1}. (Found: C, 58·14; H, 6·11. $C_{13}H_{16}O_8$ requires: C, 58·2; H, 6·01%).

Conversion of 4 into lacton 6. To a soln of 4 (2·5 g) in MeOH (35 ml) heated under reflux was added KBH_4 (10 g) portionwise over 4 hr. After 18 hr heating under reflux with stirring, the suspension was evaporated under vacuum. The residue was taken with water (100 ml), acidified with 20% H_2SO_4 (53 ml), stirred for 30 min and extracted 3 times with EtOAc (200 ml). The organic extracts were washed with sat $NaHCO_3$ aq, with water until neutral and then evaporated under vacuum. The residue was crystallised from EtOH–water: 1·537 g, m.p. 111–112°; ν_{max} ($CHCl_3$) 1740 cm^{-1}; δ (ppm) 1·54 (d, $J = 7$ c/s, 3H, CH_3CH—O—), 3·62 (s, 2H, $ArCH_2$—), 5·7 (q, 1H, $J = 7$ c/s, CH_3CH—O—), 6·4 (s, 1H, ArH). (Found: C, 61·96; H, 6·42. $C_{13}H_{16}O_5$ requires: C, 61·9; H, 6·39%).

Hydrolysis of trimethoxylacton (6) *to trihydroxylacton* (7). The soln of 6 (1 g) in CH_2Cl_2 (350 ml) was cooled at −10° and BBr_3 (6 ml) was added with stirring. The soln was left at room temp for 27 hr. Decomposition with water (900 ml) and separation of the organic layer followed by washing with water, drying (Na_2SO_4), and evaporation to dryness under vacuum afforded a residue which, crystallised from diethyl ether–hexane, gave 7 (638 mg), m.p. 186–188°; ν_{max} (Nujol) 1710, 1640 cm^{-1}; δ (ppm, C_3D_6O) 1·51 (d, $J = 7$ c/s, 3H, CH_3CH—O—), 3·38 (d, 1H, $J = 19$ c/s, —CH_2—), 3·72 (d, 1H, $J = 19$ c/s, —CH_2—), 5·67 (q, 1H, $J = 7$ c/s, CH_3CH—O—), 6·28 (s, 1H, Ar–H)). (Found: C, 57·21; H, 4·96. $C_{10}H_{10}O_5$ requires: C, 57·14; H, 4·8%).

Prenylation of 7 to hydroquinone 8. To a soln of prenyl bromide (0·9 ml) in 4 ml dioxane, 91 mg of 7 and 2·8 g Ag_2O were added and the resulting suspension was stirred at room temp under N_2 for 25 min. Filtering off the solid and evaporation of the filtrate under vacuum yielded a residue which was crystallised from diethyl ether–hexane; m.p. 141–146°; ν_{max} (Nujol) 1710, 1640 cm^{-1}. (Found: C, 64·82; H, 6·65. $C_{15}H_{18}O_5$ requires: C, 64·74; H, 6·52%).

Dihydrofuscin (9). A soln of 8 (10 mg) in 1·5 ml of HCOOH was kept at room temp for 3 hr under N_2. Evaporation under vacuum yielded a residue which was crystallised from EtOH yielding 9: m.p. 206–208° identical with an authentical sample.* (Found: C, 64·86; H, 6·61. $C_{15}H_{18}O_5$ requires: C, 64·74; H, 6·52%).

*We thank Prof. D. H. R. Barton for the samples of dihydrofuscin and fuscin.

REFERENCES

[1]S. E. Michael, *Biochem. J.* **43**, 528 (1948)

[2]J. H. Birkinshaw, A. Bracken, S. E. Michael and H. Raistrick, *Ibid.* **48**, 67 (1951)

[3]D. H. R. Barton and J. B. Hendrickson, *J. Chem. Soc.* 1028 (1956)

[4]D. H. R. Barton and J. B. Hendrickson, *Chem. & Ind.*, 682 (1955); A. J. Birch, *Ibid.* 682 (1955)

[5]A. J. Birch, A. J. Ryan, J. Schofield and H. Smith, *J. Chem. Soc.*, 1231 (1965)

[6]E. E. van Tamelen, *Accounts of Chem. Res.* **1**, 111 (1968)

[7]J. Cason and Don M. Lynch, *J. Org. Chem.* **31**, 1886 (1966)

[8]H. Burton and P. F. G. Praill, *J. Chem. Soc.* 1203 (1950)

[9]Shinsaku Natori and Yuko Kumada, *Chem. Pharm. Bull.* **13**, 1472 (1965)

[10]L. Canonica, B. Rindone, E. Santaniello and C. Scolastico, *Tetrahedron* **28**, 4395 (1972)