Phytochemistry, Vol. 31, No. 8, pp. 2909–2910, 1992
Printed in Great Britain.

0031-9422/92 $5.00+0.00

HEMISYNTHESIS OF THE NATURALLY OCCURRING TREMULOIDIN

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(*Received* 2 *December* 1991)

Key Word Index—*Salix*; Salicaceae; salicin; tremulacin; tremuloidin; phenolic glycoside.

Abstract—The hemisynthesis of tremuloidin under mild conditions by 2′-*O*-benzoylation of salicin is described. It appears as an essential step in synthesis of natural phenolic glycosides.

Tremuloidin is a naturally occurring phenolic glycoside which can be obtained from *Salix* or *Populus*. The principal source is the extraction from quaking aspen foliage [1] or from aspen internodes [2] by enzymatic cleavage of tremulacin. Tremuloidin, as tremulacin [3], seems to have an important function, inhibiting, by the presence of the 2′-*O*-benzoyl ester group, the enzymatic detoxication system of some insects such as *Chrysomela* beetles [Augustin, S., unpublished observations]. Moreover, as a derivative of salicin, it has antiinflammatory activity [4].

We have realized a convenient synthesis of tremuloidin under mild conditions by means of selective protection and a 'selective' 2′-*O*-benzoylation followed by a one-step deprotection (Scheme 1).

The choice of this procedure is the consequence of two chemical observations. First, the direct benzoylation of salicin gives with a good yield of populin, a positional isomer of tremuloidin, with 6′-*O*-benzoylation and a mixture of poly-*O*-benzoyl compounds [5]. Moreover, by our method, in the last step, it is possible to control, by TLC, selective deprotection to obtain compound **4**, which is a key intermediate in the synthesis of natural phenolic glycosides like tremulacin.

EXPERIMENTAL

^{1}H NMR spectra: DMSO-d_6 and DMSO-d_6–D_2O with TMS as int. standard. TLC: performed on pre-coated Merck aluminium sheets (silica gel 60 F_{254}, 0.2 mm) with $CHCl_3$–MeOH in different proportions as eluents. $[\alpha]_D$ was determined at 20°.

4′,6′-O-*Benzylidene-7-hydroxy-*O*-tolyl-β-*D*-glucopyranoside* (**1**). A mixture of D-salicin (0.01 mol), 12 g of dry zinc chloride and 60 ml of benzaldehyde was shaken for 8 hr at room temp. The reaction mixture was diluted with H_2O, then the resulting precipitate was filtered, washed with isopropyl ether. The product was obtained with a yield of 85%; mp 187°; $[\alpha]_D$ −54° (Me_2CO; *c* 1); ^{1}H NMR (300 MHz, DMSO-d_6–D_2O): δ3.4–3.8 (5H, *m*, H-2′, H-3′, H-4′, H-5′, H-6′e); 4.2 (1H, *dd*, $J_{6'a,6'e}$ = 9.5 Hz, $J_{6'a,5'}$ = 4.5 Hz, H-6′a); 4.4–4.7 (2H, 2*d*, J_{gem} = 15 Hz, H-7); 5.0 (1H, *d*, $J_{1',2'}$ = 7.5 Hz, H-1′); 5.6 (1H, *s*, H-7′); 7.0–7.6 (9H, *m*, H-ar).

4′,6′-O-*Benzylidene-7-tert-butoxy-*O*-tolyl-β-*D*-glucopyranoside* (**2**). Compound **1** (0.001 mol), trityl chloride (0.0012 mol) and 4 g powdered molecular sieves 4 Å, in 100 ml CH_2Cl_2 were stirred at room temp. for 8–10 hr. About 5 ml of dry pyridine was added to avoid ditritylation. The yellow soln was filtered and concd *in vacuo*. The residue was purified by chromatography on silica gel ($CHCl_3$–MeOH, 19:1) affording 52% yield; mp 98°, $[\alpha]_D$ −12.5° (MeOH; *c* 1); ^{1}H NMR (300 MHz, DMSO-d_6–D_2O): δ3.2–3.7 (5H, *m*, H-2′, H-3′, H-4′, H-5′, H-6′e); 4.05 (1H, *dd*, H-6′a); 4.15 (2H, 2*d*, H-7); 5.0 (1H, *d*, H-1′); 5.6 (1H, *s*, H-7′); 7.1–7.6 (24H, *m*, H-ar).

2′-O-*Benzoyl-4′,6′-O-benzylidene-7-tert-butoxy-*O*-tolyl-β-*D*-glucopyranoside* (**3**). Compound **2** (3 mmol) and benzoyl cyanide (3 mmol) were stirred in acetonitrile (10 ml). Two drops of triethylamine were added. The reaction was followed by TLC ($CHCl_3$–MeOH, 9:1) and was complete in about 30 min. The soln was stirred in MeOH for 1 hr, then filtered and concd. Purification by elution from a silica gel column ($CHCl_3$–MeOH, 9:1) afforded the 2′-*O*-benzoylated compound in 35% yield; mp 112°; $[\alpha]_D$ −17° (MeOH; *c* 1); ^{1}H NMR (300 MHz, DMSO-d_6–D_2O): δ3.6–5.7 (9H, *m*, H-1′, H-2′, H-3′, H-4′, H-5′, H-6′a, H-6′e, H-7); 7.1–7.6 (27H, *m*, H-ar); 8.00 (2H, *d*, $J_{9,10}$ = 8 Hz, H-9).

2′-O-*Benzoyl-7-hydroxy-*O*-tolyl-β-*D*-glucopyranoside, tremuloidin*. Compound **3** was warmed in 80% HOAc at 40° for 1 hr, then stirred at room temp. for 6–8 hr. The reaction is controlled by TLC with $CHCl_3$–MeOH (9:1) as eluents. The partially deprotected compound (**4**) was obtained after 1 hr. After concn of mixture, the residue was diluted in water and extracted successively with petrol and EtOAc (×2), dried, filtered. The solvent was evapd *in vacuo* and tremuloidin (**5**) was finally obtained in 90% yield; mp 210°; $[\alpha]_D$ −22.5° (Me_2CO–H_2O, 8:2; *c* 1); ^{1}H NMR (300 MHz, DMSO-d_6–D_2O): δ3.3–3.8 (5H, *m*, H-3′, H-4′, H-5′, H-6′); 4.05–4.4 (2H, 2*d*, H-7); 5.04 (1H, *dd*, H-2′); 5.17 (1H, *d*, H-1′) 6.9–7.7 (7H, *m*, H-ar); 8.0 (2H, *d*, H-9).

Compound **4**. Mp 240°; ^{1}H NMR (300 MHz; DMSO-d_6–D_2O): δ3.7–3.9 (4H, *m*, H-3′, H-4′, H-5′, H-6′e); 4.2 (1H, *d*, H-6′a); 4.4–4.65 (2H, 2*d*, H-7); 5.2 (1H, *d*, H-1′); 5.5 (1H, *dd*, $J_{2',3'} = J_{1',2'}$ = 8.2 Hz, H-2′); 5.6 (1H, *s*, H-7′); 7.0–7.7 (12H, *m*, H-ar); 8.0 (2H, *d*, H-9).

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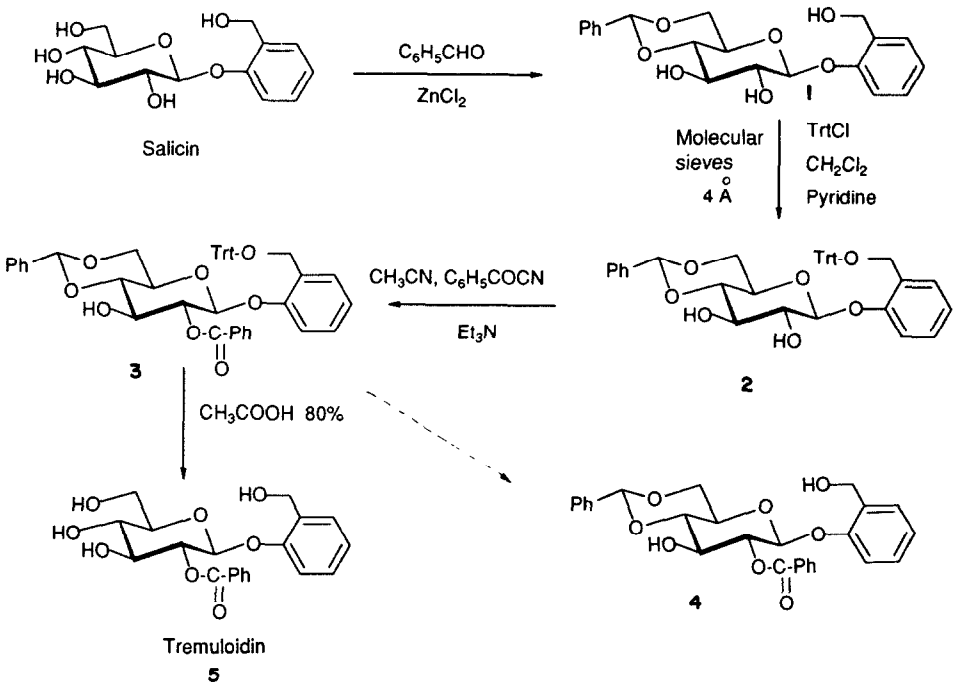

Scheme 1

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