Synthesis of Carthamin Acetate, the Red Pigment in Safflower Petals

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Carthamin acetate, (3*S*,3'*S*)-1-[5-(*p*-acetoxycinnamoyl)-3-*C*-(β-D-2",3",4",6"-tetra-*O*-acetylglucopyranosyl)-3,4-dihydroxy-2,6-diketo]cyclohex-4-enylidene-1'-[5'-(*p*-acetoxycinnamoyl)-3'-*C*-(β-D-2"',3"',4"',6"'-tetra-*O*-acetylglucopyranosyl)-2',3',4'-trihydroxy-6'-keto]cyclohexa-1',4'-dienylmethane **7a** and its (3*R*,3'*R*)-epimer **7b** were synthesized via the *C*-glycosylation of 2-acetyl-1,3,4,5-benzenetetrol using acetobromoglucose in the presence of sodium hyride, followed by aldol condensation with *p*-hydroxybenzaldehyde after methyl-protection of the enolic hydroxy group, and subsequent dimerization with triethyl orthoformate after demethylation, in a total yield of 0.6%. Their absolute configurations were determined by X-ray analysis of the key intermediate **4b**.

The structure of carthamin, the red pigment in the flowers of the Safflower plant (*Carthamus tinctorius* L.), was revised as **1** by H. Obara and J. Onodera in 1979,[1] based on some previous structural proposals of some analogues,[2] and has now been proved by the synthesis of model compounds (Figure 1).[3] The absolute configuration of the two-carbinol carbons at the 3- and 3'-positions to which D-glucose is linked has recently been compared with some chiral model compounds and determined to be *S, S*.[4] This red pigment, which is used as a food colorant and as rouge in the cosmetic industry in Japan, is a highly oxidized and complex keto–enol mixture of *C*-glucosylquinochalcone dimers and is strongly acidic. Therefore, it has not been reported to date that the acetate **7a** is derived from **1**.[5] Herein, we wish to report the first total synthesis of carthamin acetate **7a** and its epimer **7b**.

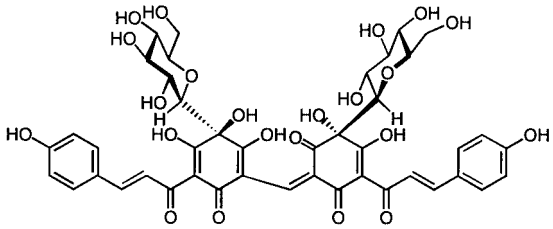
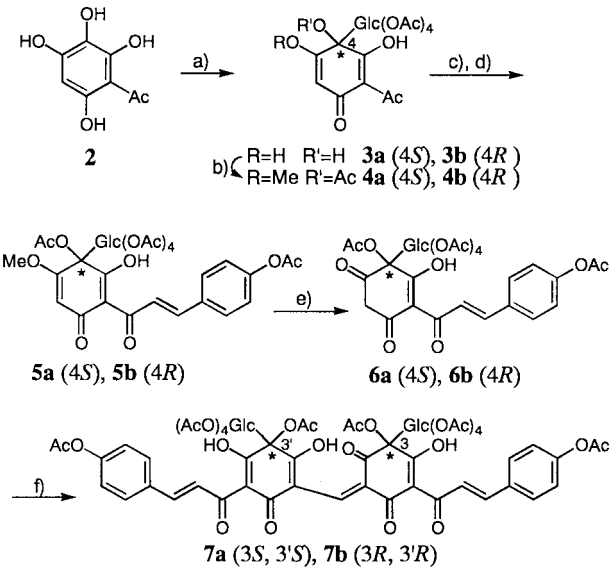


Figure 1. Carthamin **1.**

The synthesis of the key intermediate, cyclohexadienone, attached to a sugar moiety is very difficult and still remains, although the synthesis of the model compound in which the sugar moiety is replaced by a methyl group was achieved.[3d,4] By *C*-glycosylation of 2,6-diacetyl-1,3,4,5-benzenetetrol with acetobromoglucose in the presence of sodium hyride, the synthesis of *C*-β-glucosylcyclohexadienone has been reported in a yield of 12%.[6] However, since the subsequent mono-deacetylation step failed, we attempted the direct *C*-glycosylation of 2-acetylbenzene-1,3,4,5-tetrol. When 3.5 equivalents of sodium hydride were used, the key intermediate, *C*-β-D-glucopyranosylcyclohexadienone was obtained. After protection of the enol-hydroxy function of **3** with diazomethane, in order to prevent an aldol reaction between the 1,3-diketone and isomerization,[7] followed by acetylation with Ac_2O/pyridine, the desired *C*-β-D-glucopyranosylcyclohexadienone acetate **4** was readily isolated from the diastereomixture (**4a**:**4b**=1.1:1.0),[8] in a low yield of 11% from **2**. Fortunately, by means of an X-ray crystal structure analysis of **4b**, the absolute configuration of **4b** was determined to be *R* (Figure 2), and, thus, its epimer **4a** to be *S*. Compounds **4a** and **4b** were deacetylated with NaOMe, followed by aldol condensation with *p*-hydroxybenzaldehyde in the presence of piperidine at 80 °C and then re-acetylated with Ac_2O/pyridine to give acetylated *C*-β-glucosylquinochalcones **5a** (3*S*) and **5b** (3*R*) in 50 and 37% yield respectively.[8] Each chalcone **5a** and **5b** was next subjected to demethylation by treatment with trimethylsilyl iodide in CH_3CN at room temperature for 4 h to afford **6a** and **6b**. Each activated monomer acetate **6a** and **6b** was then dimerized by treatment with triethyl orthoformate in the presence of a catalytic amount of sodium hydride to give the reddish colored carthamine acetate **7a** (3*S*, 3'*S*) and its epimer **7b** (3*R*, 3'*R*) in 26 and 25% yield from **5a** and **5b**, respectively.[8] The electronic spectra of **7a** and **7b** showed an absorption maximum (red) at around 520 nm similar to that of carthamin **1**.[9] A comparison of the CD spectra of **7a**



Reagents and conditions: a) NaH, per-*O*-acetylglucopyranosyl bromide, in DMSO. b) 1. CH_2N_2 in EtOAc, 2. Ac_2O/pyridine, 11% (from **2**, **4a**:**4b**=1.1:1.0). c) 1. NaOMe in MeOH, 2. Dowex 50 $W(H^+)$. d) 1. *p*-hydroxybenzaldehyde, piperidine, at 80 °C, 2. Ac_2O/pyridine, (**5a**: 42%, **5b**: 45%). e) trimethylsilyl chloride/NaI (10 equiv) in CH_3CN at rt. f) NaH, in $CH(OEt)_3$, (**7a**: 26%, **7b**: 25%, from **5a** and **5b**).

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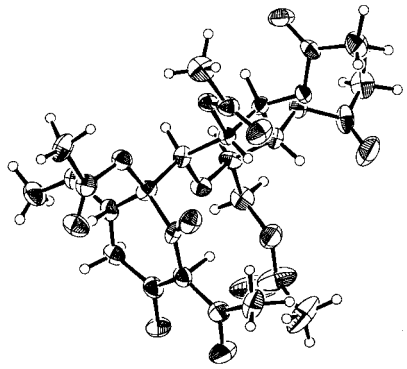

Figure 2. ORTEP drawing of **4b**. $P2_1$ (monoclinic), a=10.70 (1), b=33.02 (4), c=7.962 (5) Å, β=90.51 (8)°, V=2811 (4) Å^3, Z=4, D_C=1.310 g/cm^3, ν=9.31 cm^{-1}, Cu Kα(λ= 1.54178 Å), Crystal dimensions 0.20 × 0.05 × 0.30 mm, $R(R_w)$=0.088 (0109).

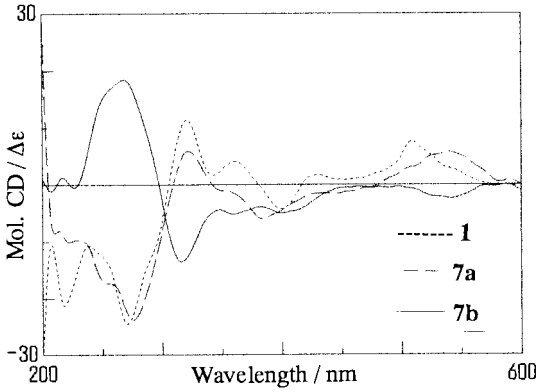

Figure 3. CD spectra of **7a**, **7b**, and **1**.

and **7b** with that of **1** revealed that the curve for **7a** was analogous to that of **1**, on the contrary, that of **7b** yielded a curve which was roughly opposite in sign (Figure 3). Thus, the synthesis of carthamin acetate was achieved for the first time.

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3 a) J. Onodera, T. Saito, and H. Obara, *Chem. Lett.*, **1979**, 1327. b) H. Obara, J. Onodera, and F. Shirasaki, *Chem. Lett.*, **1980**, 1095. c) H. Obara, J. Onodera, S. Abe, and T. Saito, *Bull. Chem. Soc. Jpn.*, **53**, 289 (1980). d) H. Obara, S. Namai, and Y. Machida, *Chem. Lett.*, **1986**, 495.

4 S. Sato, H. Obara, T. Kumazawa, J. Onodera, and K. Furuhata, *Chem. Lett.*, **1996**, 833. In this paper, the direct methylation of 2-acetyl-1,3,4,5-benzenetetrol with methyl iodide, gave the desired cyclohexadinenone in 56% yield.

5 A typical acetylation of **1** with Ac_2O/pyridine or acid did not give the acetate **7a.**

6 H. Obara, Y. Namai, and Y. Machida, *Chem. Lett.*, **1984**, 1397.

7 H. Obara, Y. Machida, S. Namai, and J. Onodera, *Chem. Lett.*, **1985**, 1393.

8 **4a**: colorless syrup. $[\alpha]_D^{25}$ –22.0° (*c* 1.00 $CHCl_3$). EI-MS (*m/z*) 570 (M^+), 510, 468, 331, 268, 167. ^{1}H NMR (500MHz, $CDCl_3$) δ = 1.99 (6H, s, OAc × 2), 2.02, 2.05 and 2.11 (each 3H, s, OAc × 3), 2.55 (3H, s, Ac), 3.56 (1H, ddd, *J* = 9.5, 2.0, and 6.5 Hz, H-5'), 3.78 (3H, s, OCH_3), 3.88 (1H, dd, *J* = 6.5 and 13.5 Hz, H-6'a), 3.98 (1H, d, *J* = 9.5 Hz, H-1'), 4.07 (1H, dd, *J* = 2.0 and 13.5 Hz, H-6'b), 4.95 (1H, t, *J* = 9.5 Hz, H-4'), 5.11 (1H, t, *J* = 9.5 Hz, H-3'), 5.17 (1H, t, *J* = 9.5 Hz, H-2'), 5.58 (1H, s, olefinic H), 18.37 (1H, s, OH). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 20.1–21.0 ($OCO\underline{CH}_3$ × 5), 27.0 (C-$CO\underline{CH}_3$), 56.9 (OCH_3), 62.1, 67.8, 69.0, 69.9, 74.5, and 79.8 (sugar moiety), 92.0 (C4), 99.1 (C2), 108.3 (C5), 168.7–172.5 ($O\underline{CO}CH_3$ ×5), 188.7 (C3), 189.6 (C7), 198.6 (C1). **4b**: colorless prism. mp = 176–178 °C. EIMS (*m/z*) 570 (M^+), 331, 268, 196, 167. $[\alpha]_D^{25}$ –31.9° (*c* 1.00 $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ = 2.00 (9H, s, OAc × 3), 2.06 and 2.09 (each 3H, s, OAc × 3), 2.57 (3H, s, Ac), 3.56 (1H, ddd, *J* = 3.5, 7.5, and 9.5 Hz, H-5'), 3.81 (3H, s, OCH_3), 4.02 (1H, dd, *J* = 7.5 and 13.5 Hz, H-6'a), 4.02 (1H, d, *J* = 9.5 Hz, H-1'), 4.04 (1H, dd, *J* = 3.5 and 13.5 Hz, H-6'b), 4.92 (1 H, dd, *J* = 9.5 Hz, H-4'), 5.16 (1H, t, *J* = 9.5 Hz, H-3'), 5.41 (1H, t, *J* = 9.5 Hz, H-2'), 5.55 (1 H, s, olefinic H-5), 18.31 (1H, s, OH). **5a**: pale-yellow syrup. TLC: R_f = 0.38 (toluene–EtOAc–AcOH = 5:2:0.5). $[\alpha]_D^{24}$ –6.23° (*c* 0.995 $CHCl_3$). FABMS (*m/z*) 717(M+H). ^{1}H NMR (270 MHz, $CDCl_3$) δ = 2.01, 2.09, 2.11, 2.16, and 2.23 (each 3H, s, OAc × 5), 2.42 (3H, s, ArOAc), 3.68 (1 H, ddd, *J* = 2.0, 6.4, 9.8 Hz, H-5'), 3.89 (3H, s, OCH_3), 3.97 (1H, dd, *J* = 6.4 and 12.2 Hz, H-6'a), 4.10 (1H, d, *J* = 9.8 Hz, H-1'), 4.14 (1H, dd, *J* = 2.0 and 12.2 Hz, H-6'b), 5.05 (1H, t, *J*=9.8 Hz, H-4'), 5.18 (1H, t, *J* = 9.8 Hz, H-3'), 5.24 (1H, t, *J* = 9.8 Hz, H-2'), 5.75 (1H, s, olefinic H), 7.31 and 7.76 (each 2H, *J* = 8.5 Hz, *p*-substituted ArH × 4), 7.79 and 8.31 (each 1H, *J* = 15.6 Hz, *trans*-vinyl H × 2), 18.64 (1H, s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 56.9, 62.1, 67.8, 69.0, 74.6, 76.1, 77.4, 79.7, 80.7, 100.9, 107.5, 120.2 (× 2), 130.0, 132.7, 144.1, 152.5, 184.5, 189.2, 191.7, and OAc × 6. **5b**: pale-yellow crystal. mp = 110 °C. TLC: R_f = 0.42 (toluene–EtOAc–AcOH = 5:2:0.5). $[\alpha]_D^{24}$ –49.8° (*c* 1.02 $CHCl_3$). FABMS (*m/z*) 717 (M+H). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.92, 1.99, 2.00, 2.06, and 2.11 (each 3H, s, OAc × 4), 2.32 (3H, s, ArOAc), 3.56 (1H, ddd, *J* = 2.5, 5.0, and 9.0 Hz, H-5'), 3.81 (3H, s, OCH_3), 4.01 (1H, dd, *J* = 5.0 and 12.5 Hz, H-6'a), 4.03 (1H, d, *J* = 9.0 Hz, H-1'), 4.06 (1H, dd, *J* = 2.5 and 12.5 Hz, H-6'b), 4.95 (1 H, t, *J* = 9.0 Hz, H-4'), 5.16 (1H, t, *J* = 9.0 Hz, H-3'), 5.42 (1H, t, *J* = 9.0 Hz, H-2'), 5.61 (1H, s, olefinic H), 7.16 and 7.71 (each 2H, d, *J* = 8.5 Hz, *p*-substituted ArH × 4), 7.90 and 8.10 (each 1H, d, *J* = 16.0 Hz, *trans*-vinyl H × 2), 18.40 (1H, s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 57.1, 61.5, 67.5, 68.1, 74.6, 75.7, 77.5, 78.8, 80.6, 100.4, 107.8, 122.0, 122.1, 130.2, 132.6, 144.0, 152.5, 184.3, 187.3, 191.5, and OAc × 6. **7a**: red solid. TLC: R_f = 0.47 ($CHCl_3$–MeOH = 8:1). ESIMS (negative) (*m/z*) 1413.4 (M – H), 729, 701. UV/vis (EtOH) (log ε) 230 (4.53), 354 (4.47), 529 (4.72) nm. CD (EtOH) λ_{ext}(Δε) 275 (–13.9), 322 (+5.84), 384 (–6.06), 540 (+5.71) nm. ^{1}H NMR (500 MHz, DMSO-d_6, at 50 °C) δ = 1.91 (12H, s, OAc × 4), 1.94 (12H, s, OAc × 4), 2.02 (6H, s, OAc × 2), 2.28 (6H, s, ArOAc × 2), 3.86 (2H, ddd, *J* = 9.0, 5.5, and 3.5 Hz, H-5" × 2), 3.95 (4H, m, H-6"a, b × 2), 4.41 (2H, d, *J* = 9.0 Hz, H-1" × 2), 4.80 (2H, t, *J* = 9.0 Hz, H-4" × 2), 5.25 (2H, t, *J* = 9.0 Hz, H-2" × 2), 7.22 (4H, d, *J* = 8.5 Hz, *p*-substituted ArH × 4), 7.70 (4H, d, *J* = 8.5 Hz, *p*-substituted ArH × 4), 7.78 (2H, d, *J* = 15.9 Hz, *trans*-vinyl H × 2), 8.13 (2H, d, *J* = 15.9 Hz, *trans*-vinyl H × 2), 8.23 (1H, s, =CH–), 19.22 (2H, s, OH× 2). **7b**: red solid. TLC: R_f = 0.25 ($CHCl_3$–MeOH = 8:1). ESIMS (negative) (*m/z*) 1413 (M – H), 729, 701. UV/vis (EtOH) (log ε) 230 (4.44), 352 (4.43), 523 (4.71) nm. CD (EtOH) λ_{ext}(Δε) 268 (+18.3), 316 (–13.6), 400 (–5.05), 542 (–2.44) nm. ^{1}H NMR (500 MHz, DMSO-d_6, at 40 °C) δ = 1.81, 1.90, 1.93, 1.99, and 2.05 (each 6H, s, OAc × 10), 2.29 (6H, s, ArOAc × 2), 3.77 (2H, d, *J* = 11.8 Hz, H-6"a × 2), 3.83 (2H, m, H-5" × 2), 3.91 (2H, dd, *J* = 11.8 and 4.9 Hz, H-6"b), 4.45 (2H, d, *J* = 8.5 Hz, H-1" × 2), 4.77 (2H, t, *J* = 9.4 Hz, H-4" × 2), 5.22 (4 H, m, H-2" and -3" × 2), 7.21 and 7.70 (each 4H, d, *J* = 8.5 Hz, *p*-substituted ArH × 8), 7.75 and 7.84 (each 2H, d, *J* = 16.4 Hz, *trans*-vinyl H × 4), 8.16 (1H, br. s, =CH–), 19.2 (2H, s, OH × 2).

9 Natural carthamin **1**: UV/vis (EtOH) (log ε) 244 (4.33), 373 (4.48), 515 (4.99) nm. CD (EtOH) λ_{ext}(Δε) 218 (–21.4), 271 (–24.6), 321 (+11.3), 361 (+4.02), 400 (–4.2), 509 (+7.61) nm.