Synthesis of (+),(−)-Model Compounds and Absolute Configuration of Carthamin; A Red Pigment in the Flower Petals of Safflower

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(+)- and (-)-Model compounds of a carthamin were synthesized. The absolute configuration of carthamin was deduced to be *S*, *S* by means of CD spectroscopy and X-ray analysis.

A red pigment in the flower petals of safflower (*Carthamus tinctorius* L.), carthamin **1**, has been used as dyestuff together with a madder-red and an indigo-blue from ancient times, and recently as a safe coloring agent of food. The structure of **1** has been studied since the 1840's,[1] and eventually was proposed by H. Obara and J. Onodera in 1979 to be a unique dimer of *C*-glucosyl quinochalcone (Figure 1).[2] However, its absolute configuration was still not known.[3]

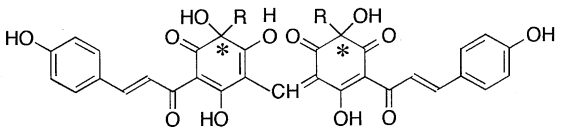
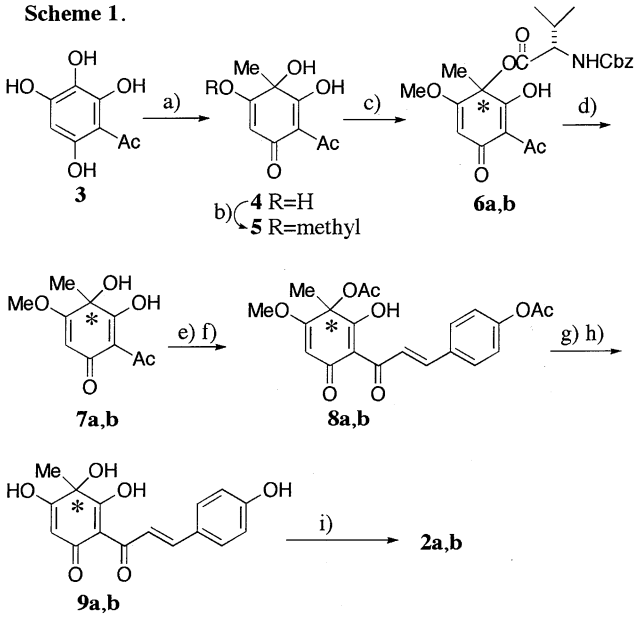


Figure 1. Carthamin **1** R=β-D-glucopyranosyl
Model compound **2** R=methyl.

We would like to report that each enantiomer of the chiral-model compounds of **1** was synthesized, and the absolute configuration of **1** was assumed to be *S*, *S* by comparison of the CD spectra of both enantiomers **2a** and **2b** and that of **1**, and by X-ray crystal structure analysis of the enantiomer.

The synthesis of (+)- and (-)-chiral-model compounds **2a** and **2b**,[4] in which each of the two glucosyl moieties was replaced by a methyl group, was carried out as shown in Scheme 1. Initially, the treatment of methyl iodide and monoacetylbenzene tetrol **3** in the presence of sodium hydride afforded the mono-*C*-methylated product **4** in 56% yield together with bis-*C*-methylated product in 27% yield. Cyclohexadienone **4** was treated with diazomethane for protecting against isomerization under basic conditions to give the **5**.[6] Methylether **5** was then condensed with carbobenzyloxy (Cbz)-L-valine to give a mixture of diastereomers **6a** and **6b**, which were easily separated by silica-gel column chromatography (**6a** and **6b**: silica-gel TLC; toluene/ethyl acetate/acetic acid=5:2:0.5, Rf=0.55 and 0.66, $[\alpha]_D^{24}$ +66°(c 1.18, $CHCl_3$) and $[\alpha]_D^{23}$ -108°(c 1.10, $CHCl_3$)). Each diastereomer was hydrolyzed in 2 N aqueous NaOH / MeOH (1: 2) solution at 40 °C to give chiral cyclohexadienones **7a** and **7b** ($[\alpha]_D^{24}$ +12°(c 1.10) and $[\alpha]_D^{20}$ -11°(c 0.84, $CHCl_3$)) in 91 and 73% yields, respectively. Aldol condensation of each enantiomer **7a** and **7b** with *p*-hydroxybenzaldehyde in the presence of piperidine at 80 °C for 1h and successive acetylation afforded quinochalcones **8a** and **8b** in 71% yields, respectively. Subsequent demethylation with trimethylsilyl iodide and deacetylation with sodium

Scheme 1.



a) MeI/NaH, 53% b) CH_2N_2 in AcOEt, 100% c) Cbz-(L)-valine/DCC/DMAP, 80% (**6a** : **6b** = 1 : 1). d) 2 N NaOH/MeOH(1:2)/50 °C for 0.5 and 3 h, 73 and 91% e) p-hydroxybenzaldehyde/piperidine, 85 °C, 50min, 75% f) Ac_2O/py, 95% g) Me_3SiI in CH_3CN, 40 °C, 16h, 75% h) NaOMe/MeOH, r.t., 1 h, 56% i) NaH/$CH(OEt)_3$, r.t., 6 h, 76 and 72%.

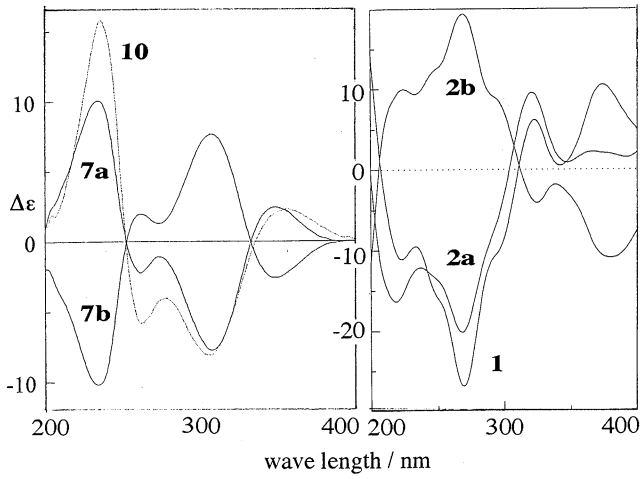


Figure 2. CD spectra of (+)- and (-)-model compounds **7a**, **b** and **2a**, **b**, and *C*-β-D-glucopyranosylclohexadienone **10** and carthamin **1**.

methoxide gave chiral monomers **9a** and **9b** in 42% yields, respectively.[6] These chiral monomers **9a** and **9b** were dimerized in triethyl orthoformate in the presence of sodium hydride[5b] to give the chiral dimers **2a** and **2b**[7] in 76 and 72% yields, respectively. By the comparison of the cyclohexadienone **7a** and **7b**, and the monomer **9a** and **9b**, and the dimer **2a** and **2b**, and *C*-β-D-glucopranosylcyclohexadienone **10**[8] and **1** using CD spectroscopy, it was observed that the CD spectra of both enantiomers showed a good symmetry, respectively, and those of the monomer and dimer displayed the same curvature. That is, the chiral dimer also had the same Cotton effect as the chiral monomer between 200 to 400 nm. Since the CD spectra of the cyclohexadienone **7a**, **7b** and **10** had the same Cotton effect, it was assumed that the Cotton effect is unchangeable by the replacement of a glucosyl to a methyl group. Furthermore, it was observed that the CD spectra of other enantiomers **7a** and **2a** and that of **1** displayed a downward curvature, and were very analogous, as shown in Figure 2.[9] Since this Cotton effect at around 270 nm is due to a common cyclohexadienone skeleton, it was assumed that the absolute configuration of another chiral-model dimer and that of **1** are identical. Furthermore, based on the X-ray crystal structure analysis of 4-*O*-[(1*S*)-(-)-camphanoyl] cyclohexadienone **12b**[10] which was condensed **7b** and (1*S*)-(-)-camphanic acid using dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP), it was found that the absolute configuration of C(4)-asymmetric carbon is *R* (Figure 3).

From these results, it was deduced that the absolute configuration of the two asymmetric carbons in the aglycon moiety of **1** is *S*, *S*.

The authors are grateful to Mr. Akihiro Shibata of JASCO International Co., Ltd., for his measurement of HR-FAB/LSI mass spectroscopy.

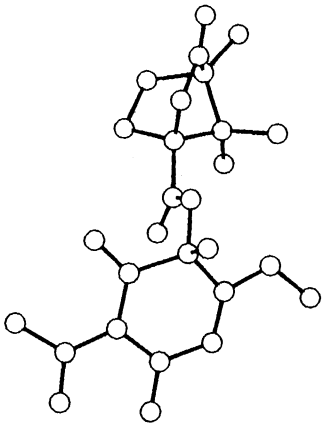


Figure 3. Crystal data for **12b**. $P2_1$ (monoclinic), a=11.881 (4), b=7.3774 (2), c=12.310 (2), β=113.86 (2), V=986.8 (5) Å^3, Z=2, Dc=1.32 g/cm^3, μ=8.19 cm^{-1}, CuKα(l=1.54178 Å), Crystal dimensions 0.40 x 0.20 x 0.20 mm, *R*(*Rw*)=0.068(0.058).

References and Notes

1 Preiser, J. Pr. Chem., [i]**32**, 142(1844). C. Kuroda, *Nippon Kagaku Kaishi*, **51**, 237(1930). C. Kuroda, *J. Chem. Soc.*,**1930**, 752. T. R. Seshadri and R. S. Thakur, *Curr. Sci.*, **29**(2), 54(1960).

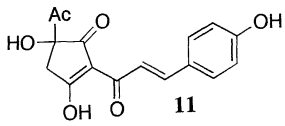
2 H. Obara and J. Onodera, *Chem. Lett.*, **1979**, 201. J. Onodera, T. Saito, and H. Obara, *Chem. Lett.*, **1979**,1327.

3 An adequate crystal for X-ray analysis has not been obtained hitherto.

4 This model compound was already synthesized as a diastereo-mixture, but the yield was very poor.[5a]

5 a) H. Obara, S. Namai, and Y. Machida, *Chem. Lett.*,**1986**, 495.
b) H. Obara, J. Onodera, and F. Shirasaki, *Chem. Lett.*,**1980**,1095.

6 W. Windish, P. Kolbach, and R. Scheicher, *Wochschr. Brau.*, **44**, 453(1927). G. A. Howord, *J. Inst. Brewing*, **65**, 417(1959). H. Obara, Y. Machida, S. Namai, and J. Onodera, *Chem. Lett.*, **1985**, 1393. After demethylation of **8**, treatment under basic conditions gave the corresponding isomerized product **11** as a by-product.
Compounds **9a**, **b** : yellow prism. mp 171~172 °C. UV/VIS (EtOH, log ε) λ 230(4.23), 395(4.53) nm. CD(EtOH) $\lambda_{ext}(\Delta\varepsilon)$ nm **9a**: 223(-5.3), 265 (-4.4), 289(-3.2), 335(+1.8), 400(+3.3). **9b**: 227(+6.2), 254(+6.1), 291(-0.8), 339(-1.5), 399(-2.6). ^{1}H NMR (DMSO-d_6) δ=1.40(3H, s, CH_3) 5.19 (1H, s, olefinic H), 6.85 and 7.53(each 2H, d, *J*= 8.5 Hz, *p*-substituted PhH x 4), 7.70 and 7.96(each 1H, d, *J*=15.7 Hz, trans-vinyl H x 2), 10.11(1H, br.s, OH), 18.57(1H, br.s, chelated OH). ^{13}C NMR(DMSO-d_6) δ=196.1, 190.7, 185.0, 178.6, 160.4, 144.1, 130.7, 125.8, 118.6, 116.1, 104.2, 97.0, 74.2, 27.0. HR-FAB/LSI MS (-) : 301.0682, Calcd. 301.0712.
Compound **11**: yellow prism. mp 223~224 °C. FAB-MS(+) *m/z* 303(M+H)$^+$. UV/VIS(EtOH, logε) λ 248(4.10), 426(4.39)nm. ^{1}H NMR(DMSO-d_6) δ=2.28 (3H, s, Ac), 2.54 (1H, d, *J*=18.0 Hz, CH_2), 3.08(1H, d, *J*=18.0 Hz, CH_2), 6.89 and 7.64(each 2H, d, *J*=8.8 Hz, *p*-substituted PhH x 2), 7.70 and 7.96 (each 1H, d, *J*=15.8 Hz, *trans*-vinyl H x 2), 10.48 (1H, s, PhOH) . ^{13}C NMR(DMSO-d_6) δ=208.8, 203.0, 198.3, 179.6, 162.0, 148.6, 132.0, 125.1, 116.4, 113.6, 108.1, 85.1, 45.0, 25.9.



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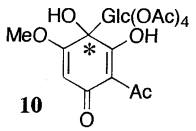
7 Compounds **2a**, **b**: red prism. mp>250 °C. UV/VIS(EtOH, log ε) λ 242(4.36), 375(4.51), 529(4.98) nm; Carthamin **1**: λ 244(4.35), 373(4.54), 529(5.02) nm. CD(EtOH)$\lambda_{ext}(\Delta\varepsilon)$ nm **2a** ; 223(-11.1), 234(-9.56), 270(-27.1), 323(+6.11), 343(+0.46), 375(+10.5). **2b** ; 225(+9.95), 233(+9.32), 269(+19.4), 325(-4.19), 339(-1.89), 381(-11.0). **1**; 219(-16.4), 237(-12.2), 268(-20.3), 321(+9.5), 348(+0.83), 367(+2.13). ^{1}H NMR($CDCl_3$) δ=1.50(6H, s, CH_3 x 2), 6.86 and 7.75(each 4H, d, *J*=8.5 Hz, *p*-substituted PhH x 8), 7.75 and 7.96(each 2H, d, *J*=15.8 Hz, trans-vinyl H x 4), 8.39 (1H, s, =CH-), 10.14(2H, s, OH x 2), 19.40(2H, br.s, chelated OH x 2). HR-FAB/LSI MS(-): 613.1325, Calcd. 613.1346.

8 Compound **10**: mp192.0~192.5 °C. EIMS(*m/z*) 528(M$^+$). UV/VIS (EtOH, log ε) λ 203(3.77), 240(4.19), 275(3.91), 307(3.85) nm. ^{1}H NMR($CDCl_3$) δ=1.99, 2.01, 2.01, and 2.04(each 3H, s, OAc x 4), 2.57(3H, s, Ac), 3.58(^{1}H, ddd, *J*=2.7, 4.9, and 9.2 Hz, H-5'), 3.85(3H, s, OCH_3), 3.93(1H, d, *J*=9.2 Hz, H-1'), 4.02(1H, dd, *J*=4.9 and 12.4 Hz, H-6'a), 4.09(1H, dd, *J*= 2.7 and 12.4 Hz, H-6'b), 4.94(1H, t, *J*=9.2 Hz, H-4'), 5.14(1H, t, *J*=9.2 Hz, H-3'), 5.21(1H, t, *J*=9.2 Hz, H-2'), 5.43(1H, s, olefinic H), 18.15 (1H, s, chelated OH).
The synthesis of **10** will be reported elsewhere.



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9 The CD spectra of each chiral dimer **2a** and **2b**, and **1** had good symmetry between 200 to 400 nm, but could not be measured at around 520nm in the red-absorption region due to being labile. This lability in solution may be attributed to a complexed keto-enol tautomerism of the long-conjugated dimer which was linked with a sp^2 carbon.

10 Compound **12a**: colorless needle. mp 209 °C. $[\alpha]_D^{19}$ +113° (c 1.02, $CHCl_3$). EI-MS(*m/z*) 392(M$^+$). ^{1}H NMR($CDCl_3$) δ= 1.09(3H, s, Me), 1.10(3H, s, Me), 1.14(3H, s, Me), 1.65(3H, s, Me), 2.58(3H, s, $COCH_3$), 3.84(3H, s, OMe), 5.50(1H, s, olefinic H), 18.45(1H, s, chelated OH).
Compound **12b**: colorless needle. mp 251 °C. $[\alpha]_D^{20}$ -106° (c 1.325, $CHCl_3$). EI-MS(*m/z*) 392(M$^+$). ^{1}H NMR($CDCl_3$) δ=1.02(3H, s, Me), 1.13(3H, s, Me), 1.17(3H, s, Me), 1.64(3H, s, Me), 2.57(3H, s, COMe), 3.83(3H, s, OMe), 5.49(1H, s, olefinic H), 18.47(1H, s, chelated OH).