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Note

Lipase-Catalyzed Kinetic Resolution of (±)-*cis*-Flavan-4-ol and Its Acetate: Synthesis of Chiral 3-Hydroxyflavanones

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Lipase-catalyzed kinetic resolution of (±)-*cis*-flavan-4-ol and its acetate led to enantiomerically enriched flavan-4-ol and its acetate. These chiral compounds were converted to (2*R*, 3*R*)- and (2*S*, 3*S*)-3-hydroxyflavanones.

Key words: kinetic resolution; lipase; 3-hydroxyflavanone

3-Hydroxyflavanones are widely distributed in the plant kingdom[1)] and some of them show interesting biological activities involving a hepatoprotective effect. In association with the synthetic work on condensed tannins,[1,2)] we needed chiral 3-hydroxyflavanones which could be promising monomeric sources for the synthesis of condensed tannins having the oligomeric structure of flavan-3-ols. Three methods for accessing chiral 3-hydroxyflavanones have been reported to date: 1) enzymatic resolution of racemic 3-hydroxyflavanone,[3)] 2) conversion of the epoxy ketones obtained by asymmetric epoxidation of chalcone derivatives,[4,5)] 3) synthesis *via* asymmetric dihydroxylation of cinnamic esters.[6)] These methods, however, involve the disadvantages of low enantiomeric purity of the products and multi-step reaction sequences. We have recently developed a novel approach to accessing enantiomerically enriched 3-hydroxyflavanones.

We have observed earlier that treatment of the enolate derived from racemic flavanone **1** with 2-(phenylsulfonyl)-3-phenyloxaziridine[7)] below −80°C gave 3-hydroxyflavanone **2** in a good yield (Fig. 3). In this case, temperature control was crucial, because elevation of the reaction temperature caused easy opening of the pyranone ring. This useful experimental technique that could afford 3-hydroxyflavanones from flavanones in high yields required the development of a more efficient method for the preparation of enantiomerically enriched flavanones. In this paper, we report the synthesis of enantiomerically enriched 3-hydroxyflavanones *via* lipase-catalyzed kinetic resolution of (±)-*cis*-flavan-4-ol (**3**) and its acetate **4**.

In 1992, Izumi *et al.*[8)] reported that the kinetic resolution of (±)-*cis*-flavan-4-ol acetate (**4**) with lipase PS (Amano) resulted in the formation of (2*R*, 4*R*)-**3** (93% ee) and (2*S*, 4*S*)-**4** (95% ee). On the other hand, the transesterification of (±)-**3** with the same enzyme, using vinyl acetate as the acyl donor afforded acetate **4**, but with no optical rotation. In order to further examine the potent resolving ability of lipases, we conducted a kinetic resolution experiment on some lipases (lipase PS, lipase M, lipase A, lipase R and lipase AY). Among them, lipase AY (Amano) was the most efficient enzyme for both kinetic hydrolysis and transesterification.

When (±)-**3** was treated with lipase AY and vinyl acetate at 25°C for 6 d, (2*R*, 4*R*)-**4** (44% yield, 93% ee) and unreacted (2*S*, 4*S*)-**3** (55% yield, 61% ee) were obtained (Fig. 1). (2*S*, 4*S*)-**3** was oxidized to (*S*)-flavanone (*S*)-**1** with PCC/CH_2Cl_2 to determine the enantiomeric purity by HPLC. Similarly, (2*R*, 4*R*)-**4** was converted to (*R*)-**1** *via* hydrolysis (K_2CO_3/CH_3OH) and subsequent oxidation.

The kinetic hydrolysis of (±)-*cis*-flavan-4-ol acetate **4** in a phosphate buffer (pH 6.8) with the same enzyme gave (2*R*, 4*R*)-**3** (40% yield, 96% ee)

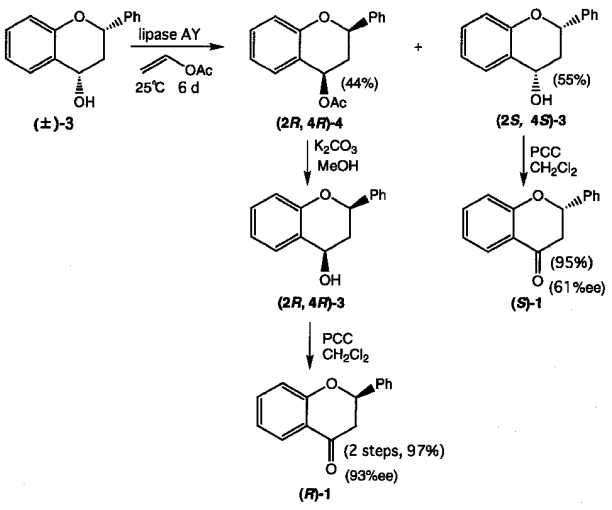

Fig. 1.

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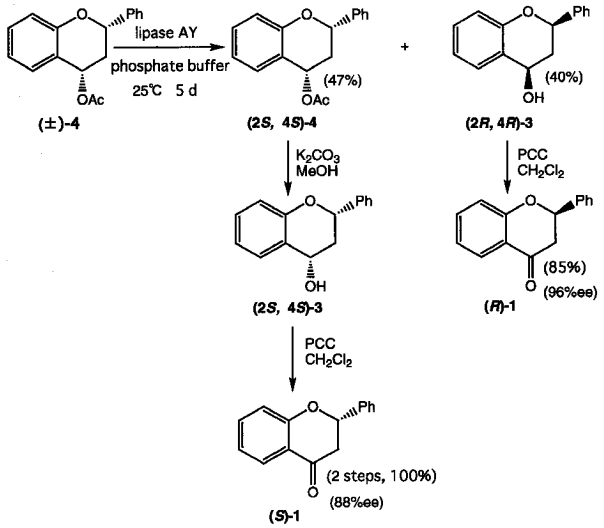

Fig. 2.

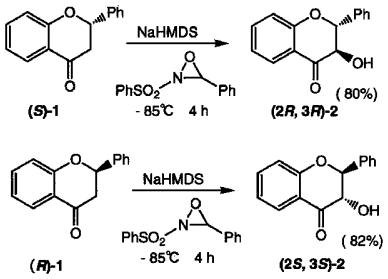

Fig. 3.

and unreacted (2*S*, 4*S*)-**4** (47% yield, 88% ee) (Fig. 2). The ee values of these compounds were also determined by an HPLC analysis of (*R*)- and (*S*)-flavanones (*R*)-**1** and (*S*)-**1** obtained by the same process as that just described.

Finally, the enantiomerically enriched (*S*)- and (*R*)-flavanones (**1**) were transformed into (2*R*, 3*R*)- and (2*S*, 3*S*)-3-hydroxyflavanones (**2**), respectively (Fig. 3). Thus, the reaction between the enolate derived from (*S*)- or (*R*)-**1** and the oxaziridine reagent at −85°C with subsequent hydrolytic work-up led to (2*R*, 3*R*)- or (2*S*, 3*S*)-**2**, each in a good yield.

Experimental

All melting point (mp) data are uncorrected. Optical rotation was measured with a HORIBA SEPA-300 spectrometer, and IR spectra were taken with a JASCO IR-810 spectrometer. ^{1}H-NMR spectra were measured with a JEOL JNM-LA 400 spectrometer. HPLC analyses were conducted with SHIMADZU LC 10AD apparatus equipped with a UV/VIS detector and CHIRALCEL OD (DAICEL) column.

Kinetic Resolution of Racemic cis-Flavan-4-ol (±)-3 with Lipase AY. A suspension of (±)-*cis*-flavan-4-ol[9] (±)-**3** (60 mg, 0.265 mmol), vinyl acetate (4 ml) and lipase AY (Amano) (600 mg) was stirred at 25°C for 6 d. Filtration through a Celite® pad and evaporation of the solvent left a mixture of products which was separated by preparative TLC (hexane:AcOEt = 3:1) to give (2*R*, 4*R*)-**4** (29 mg, 44%) and unreacted (2*S*, 4*S*)-**3** (33 mg, 55%).

The enantiomeric purity of these compounds was determined to be 93% ee for (2*R*, 4*R*)-**4** and 61% ee for (2*S*, 4*S*)-**3** by their conversion to (*R*)- and (*S*)-flavanones (*R*)-**1** and (*S*)-**1** and by an HPLC analysis.

Data for (2*R*, 4*R*)-**4**: mp 95–96°C; $[\alpha]_D^{20}$ −33.4 (*c* 1.68, $CHCl_3$); IR (nujol) ν_{max} cm^{-1}: 1740, 1610, 1580, 1240, 1060, 1030, 750, 700; ^{1}H-NMR ($CDCl_3$) δ: 2.11 (3H, S), 2.21 (1H, ddd, *J* = 10, 11, 13 Hz), 2.64 (1H, ddd, *J* = 2, 6, 13 Hz), 5.22 (1H, dd, *J* = 2, 11 Hz), 6.20 (1H, dd, *J* = 6, 10 Hz), 6.92–6.99 (2H, m), 7.20–7.25 (2H, m), 7.28–7.58 (5H, m). Data for (2*S*, 4*S*)-**3**: mp 125–126°C; $[\alpha]_D^{20}$ +7.9 (*c* 1.0, $CHCl_3$) {lit.,[8] mp 115–116°C; $[\alpha]_D^{20}$ +11.2 ($CHCl_3$)}; IR (nujol) ν_{max} cm^{-1}: 3300, 3200, 1605, 1580, 1230, 900, 750, 700; ^{1}H-NMR ($CDCl_3$) δ: 1.75 (1H, d, *J* = 9 Hz), 2.14 (1H, ddd, *J* = 10, 11, 13 Hz), 2.54 (1H, ddd, *J* = 2, 8, 13 Hz), 5.12 (1H, dd, *J* = 9, 16 Hz), 5.19 (1H, dd, *J* = 2, 12 Hz), 6,90 (1H, dd, *J* = 1, 8 Hz), 6.99 (1H, dt, *J* = 1, 7 Hz), 7.21 (1H, m), 7.33–7.47 (5H, m), 7.52 (1H, d, *J* = 8 Hz).

Kinetic Resolution of Racemic cis-Flavan-4-ol Acetate 4 with Lipase AY. A solution of (±)-*cis*-flavan-4-ol acetate[9] (**4**; 30 mg, 0.133 mmol) in toluene (0.5 ml) was stirred with a mixture of lipase AY (150 mg), a phosphate buffer (pH 6.8, 2 ml) and H_2O (5 ml) at 25°C for 5 d. The reaction mixture was filtered through a Celite® pad and extracted with $CHCl_3$. Purification of the crude mixture by preparative TLC (hexane:AcOEt = 3:1) afforded (2*R*, 4*R*)-(**3**) (12 mg, 40%) and unreacted (2*S*, 4*S*)-(**4**) (14 mg, 47%).

The enantiomeric purity [(2*R*, 4*R*)-(**3**): 96% ee; (2*S*, 4*S*)-(**4**): 88% ee] of these compounds was determined by the same procedure as that just described. Data for (2*R*, 4*R*)-**3**: mp 118–119°C; $[\alpha]_D^{20}$ −13.7 (*c* 0.98, $CHCl_3$) {lit.,[8] mp 115–116°C; $[\alpha]_D^{20}$ −14.4 ($CHCl_3$)}.

Data for (2*S*, 4*S*)-**4**: mp 96–97°C; $[\alpha]_D^{20}$ +34.6 (*c* 1.26, $CHCl_3$) {lit.,[8] mp 94–95°C; $[\alpha]_D^{20}$ +23.9 ($CHCl_3$)}.

*Conversion of (2S, 4S)- and (2R, 4R)-Alcohols, (2S, 4S)- and (2R, 4R)-***3**, to (S)- and (R)-Flavanones, (S)- and (R)-***1***.

a) *Synthesis of (S)-1 from (2S, 4S)-3.* (2*S*, 4*S*)-alcohol **3** (12 mg, 0.053 mmol) was treated with PCC (34 mg) and molecular sieves 4A (50 mg) in CH_2Cl_2 (2 ml) at room temperature for 15 min. Ether was added, and the solution was filtered through a

Celite® pad. Evaporation of the solvent gave a residue which was passed through a short SiO_2 column using ether. The crude sample was purified by preparative TLC to give pure (*S*)-**1** (10 mg, 85%), which was then submitted to an HPLC analysis to determine the enantiomeric purity.

Data for (*S*)-**1**: mp 75–76°C; $[\alpha]_D^{20}$ −39.0 (*c* 0.49, $CHCl_3$) {lit.,[8] mp 75–77°C; $[\alpha]_D^{20}$ −54.1 ($CHCl_3$)}

b) *Synthesis of (R)-1 from (2R, 4R)-3.* This reaction was carried out by the same procedure as that just described for (*S*)-**1**.

Data for (*R*)-**1**: mp 76–77°C; $[\alpha]_D^{20}$ +61 (*c 0.86, $CHCl_3$) {lit.,[8] mp 76–77°C; $[\alpha]_D^{20}$* +66.5 ($CHCl_3$)}.

*Conversion of (2R, 4R)- and (2S, 4S)-Acetates **4** to (R)- and (S)-Flavanones **1**.*

a) *Synthesis of (R)-1 from (2R, 4R)-4.* (2*R*, 4*R*)-acetate **4** (26 mg, 0.097 mmol) was then treated with K_2CO_3 (19 mg) in MeOH (0.5 ml) at room temperature for 15 min. A sat. NaCl solution was added and the solution was extracted with $CHCl_3$. Evaporation of the solvent gave a crude alcohol which was dissolved in CH_2Cl_2 (2 ml) and treated with PCC (62 mg) and molecular sieves 4A (70 mg) as just described. Purification of the crude product by preparative TLC furnished pure (*R*)-**1** (21 mg, 97% from acetate). The enantiomeric purity of this sample was determined by the HPLC analysis already described.

Data for (*R*)-**1**: mp 78–79°C; $[\alpha]_D^{20}$ +57 (*c* 0.38, $CHCl_3$) {lit.,[8] mp 76–77°C; $[\alpha]_D^{20}$ +66.5 ($CHCl_3$)}.

b) *Synthesis of (S)-1 from (2S, 4S)-4.* This reaction was carried out by the same procedure as that just described for (*R*)-**1**.

Data for (*S*)-**1**: mp 76–77°C; $[\alpha]_D^{20}$ −55.0 (*c* 0.20, $CHCl_3$) {lit.,[8] mp 75–77°C; $[\alpha]_D^{20}$ −54.1 ($CHCl_3$)}.

(2R, 3R)- and (2S, 3S)-3-Hydroxyflavanones (2R, 3R)- and (2S, 3S)-2.

a) *Synthesis of (2R, 3R)-2 from (S)-1.* To a stirred solution of (*S*)-**1** (63 mg, 0.281 mmol) in THF (3 ml) was added sodium bis(trimethylsilyl)amide (NAHMDS) (0.39 ml, 1 M in THF, 0.393 mmol) below −80°C and, after 5 min, a solution of 2-(phenylsulfonyl)-3-phenyloxaziridine[10] (102 mg, 0.393 mmol) in THF (1 ml) was added. Stirring was continued for 4 h at −85°C and the reaction was quenched with sat. NH_4Cl. After stirring at room temperature for 2 h, the aq. solution was extracted with $CHCl_3$, and the organic layer was dried (Na_2SO_4). Evaporation and preparative TLC (hexane:AcOEt = 2:1) gave pure (2*R*, 3*R*)-**2** (54 mg, 80%), mp 187–188°C; $[\alpha]_D^{20}$ −18 (*c* 0.34, CH_2Cl_2) {lit.,[2] mp 189–190°C for 59%ee; lit.,[6] $[\alpha]_D^{20}$ −25.0 (CH_2Cl_2)}; IR (nujol) ν_{max} cm^{-1}: 3450, 1680, 1610, 1580, 1310, 1230, 1150, 1040, 760, 700; ^{1}H-NMR ($CDCl_3$) δ: 3.67 (1H, d, *J* = 2 Hz, OH), 4.65 (1H, dd, *J* = 2, 12 Hz), 5.15 (1H, d, *J* = 12 Hz), 7.06 (1H, d, *J* = 12 Hz), 7.12 (1H, t, *J* = 7 Hz), 7.42–7.50 (3H, m), 7.54–7.60 (3H, m), 7.94 (1H, dd, *J* = 2, 8 Hz).

b) *Synthesis of (2S, 3S)-2 from (R)-1.* (2*S*, 3*S*)-3-Hydroxyflavanone **2** was obtained from (*R*)-**1** in an 82% yield by the same procedure as that just described for (2*R*, 3*R*)-**2**.

Data for (2*S*, 3*S*)-**2**: mp 186–187°C; $[\alpha]_D^{20}$ +22.8 (*c* 0.6, CH_2Cl_2).

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