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AN EFFICIENT COVERSION OF CATECHINE INTO 3,4-*trans*-LEUCOCYANIDIN

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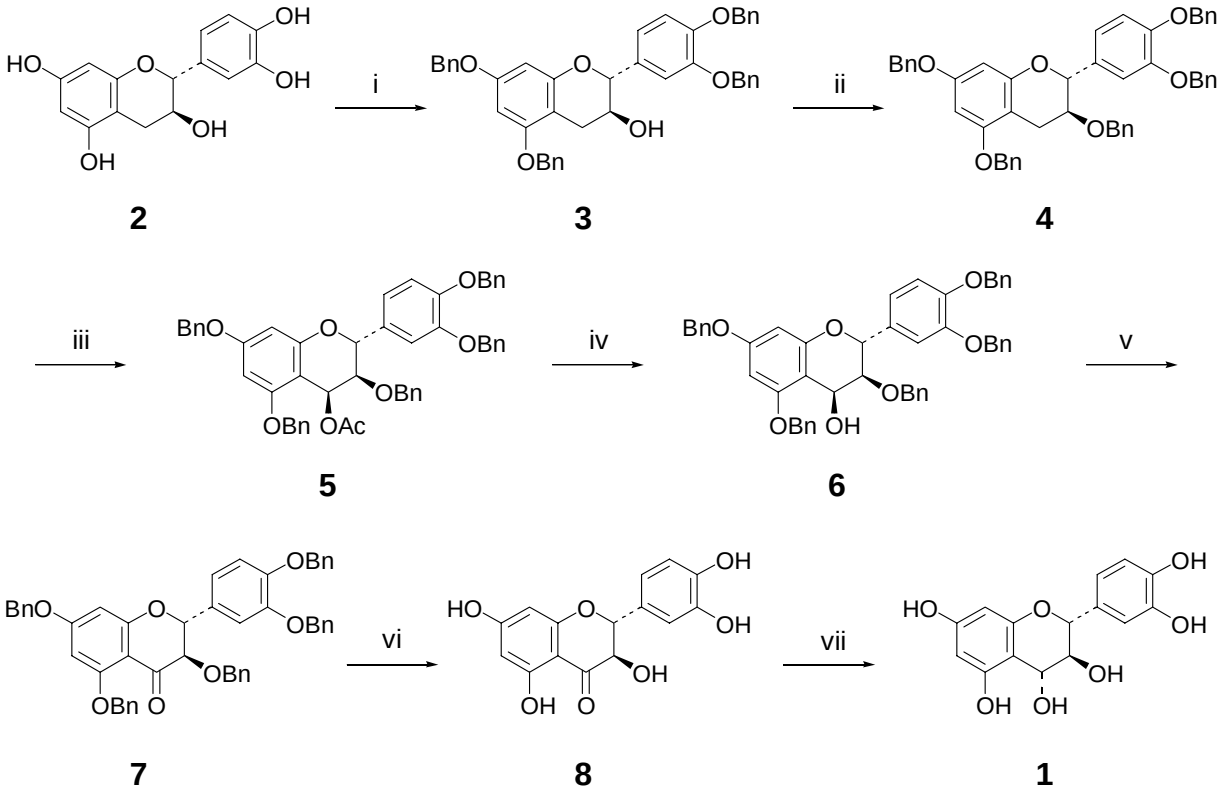
Abstract – Catechine was efficiently converted into 3,4-*trans*-leococyanidin by seven steps involving an acetoxylation at the benzylic position of catechine pentabenzyl ether, followed by hydrolysis, oxidation, deprotection, and stereoselective reduction, successively.

Leucocyanidin (**1**), a member of flavan-3,4-diols, has been recognized as the important biosynthetic precursor of flower color pigments, anthocyanins.[1] Although this compound is widely distributed in nature, its isolation and purification accompanied with some troubles, since this compound is sensitive especially to acids. To the best of our knowledge none of synthesis of leucocyanidin itself has been reported, although a number of synthetic methods for its methyl ether have been established to date.[2]

In the course of our study on flower color pigments, we needed leucocyanidin, which, however, was not commercially available at present. Thus, we decided to develop a facile synthetic procedure for leucocyanidin, and here report our successful results. In order to synthesize leucocyanidin itself, catechine (**2**) is chosen as the starting material, since catechine, also a widely distributed natural product, has the

same stereochemistry with leucocyanidin at the 2 and 3 positions. Moreover, a methodology for introducing an oxygen function to the benzylic position of catechine derivatives was established by using lead tetraacetate or DDQ,[3] and a reduction of dihydroquercetin (taxifolin) to leucocyanidin was also well investigated.[4] We, therefore, decided to apply these reactions to catechine pentabenzyl ether (**4**) to accomplish the synthesis of leucocyanidin.



Scheme: *Reagents and conditions*; i, BnCl, K_2CO_3, DMF, 120ºC, 3 h; ii, BnBr, NaH, DMF, rt, 3 h (81% from **2**); iii, Pb_3O_4, AcOH, 75-80ºC, 3 h (85%); iv, K_2CO_3, MeOH, rt, 2 h (90%); v, TPAP, NMO, CH_2Cl_2, rt, 3 h (85%); vi, 10% Pd/C, H_2, MeOH-THF, rt, 24 h (90%); vii, $NaBH_4$, EtOH, rt, 2 h (75%).

Thus, catechine (**2**) was treated with benzyl chloride in DMF at 120°C in the presence of potassium carbonate to afford the known tetrabenzyl ether (**3**),[5] which, on further treatment with sodium hydride and benzyl bromide in DMF at room temperature gave the pentabenzyl ether (**4**)[6] in 81% yield from **2**. Introduction of an oxygen function at the 4-position was successfully achieved by employing Pb_3O_4 in acetic acid at 75-80°C providing the acetate (**5**)[3] as the sole product, in 85% yield. The stereochemistry at

the 4-position of **5** was determined to have 3,4-*cis* relationship based on the analysis of its ^{1}H NMR spectrum.

The preparation of the acetate **(5**) from catechine was also reported by different synthetic route very recently, where DDQ was employed as the oxidation reagent in acetic acid.[6] Hydrolysis of the acetate (**5**) with potassium carbonate in MeOH gave the alcohol (**6**), in 90% yield, which, on oxidation with tetrapropylammonium perruthenate (TPAP) and 4-methylmorphiline *N*-oxide (NMO) afforded the ketone (**7**) in 85% yield. Removal of the benzyl group of **7** under catalytic hydrogenation conditions, followed by reduction of the resulting phenol derivative, taxifolin (**8**), with sodium borohydride according to the literature[4e] furnished the desired compound (**1**) in 68% yield from **7**. The spectroscopic data for the synthesized 3,4-*trans*-leucocyanidin were identical with those reported.[4e]

Thus, we could establish the facile synthetic procedure for 3,4-*trans*-leucocyanidin starting from catechine by 7 steps in 36% overall yield. It is noteworthy that the protecting group for the hydroxy functions is recognized to be a crucial factor in this conversion, where only pentabenzyl ether is found to be an efficient precursor. This synthesis would make a great contribution to the biosynthetic research works in the field of flower color pigments.[7]

EXPERIMENTAL

Melting points were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were obtained using a JASCO FT/IR-200 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were obtained on JEOL LAMBDA-270 (^{1}H-NMR: 270 MHz, ^{13}C-NMR: 67.8 MHz) instrument for solutions in $CDCl_3$ unless otherwise noted, and chemical shifts are reported on the δ scale from internal TMS. MS spectra were measured with a JEOL JMS-D 300 spectrometer. Elemental analyses were performed on a Yanaco-MT5.

(+)-3',4',3,5,7-Penta-*O*-benzylcatechine (4): A stirred solution of catechine (5.8 g, 0.02 mol), benzyl chloride (12.6 g, 0.1 mol), and K_2CO_3 (16.8 g, 0.12 mol) in DMF (50 mL) was heated at 130°C for 3 h, and then poured into water (150 mL). The resulting solution was extracted with ethyl acetate and the extract was dried over Na_2SO_4. Evaporation of the solvent gave tetra-*O*-benzylcatechine (**3**) (11.7 g),

which without further purification, was used in the next reaction. To a stirred solution of **3** (2.7 g, 4 mmol) in DMF (10 mL) was added 60% NaH in mineral oil (0.18 g, 4.5 mmol) at 0°C, and the resulting solution was stirred at rt for 1 h. To this solution was added benzyl bromide (0.74 g, 4.3 mmol), and the whole was stirred at the same temperature for further 3 h. After treatment with water (150 mL), the solution was extracted with ethyl acetate, and the extract was dried over $MgSO_4$. Evaporation of the solvent gave a solid, which was recrystallized from ethyl acetate-hexane to give the known penta-*O*-benzylcatechine (**4**) (2.66 g, 81% from **2**), as a colorless solid.[6] $[\alpha]_D$ +32.1° (c=1.0, MeOH); IR 1620, 1600 cm^{-1}; ^1H NMR δ 2.68 (1H, dd, *J*=16.4 and 8.6 Hz), 3.04 (1H, dd, *J*=16.4 and 5.5 Hz), 3.68-3.72 (1H, m), 4.10 (1H, d, *J*=11.8 Hz), 4.28 (1H, d, *J*=11.8 Hz), 4.76 (1H, d, *J*=8.1 Hz), 4.97-5.15 (9H, m), 6.20 (1H, d, *J*=2.3 Hz), 6.24 (1H, d, *J*=2.3 Hz), 6.93-7.46 (28H, m).

(+)-(4*S*)-Acetoxy-3',4',3,5,7-penta-*O*-benzylcatechine (5): To a stirred solution of **4** (2.5 g, 3.4 mmol) in benzene (20 mL) were added acetic acid (5 mL) and Pb_3O_4 (3.0 g, 4.4 mmol), and the resulting mixture was heated at reflux for 3 h. After cooling to rt, the mixture was treated with ethyl acetate, and insoluble materials were removed off through a pad of Celite. The filtrate was dried over $MgSO_4$ and concentrated to give a residue, which was purified by column chromatography on silica gel. Elution with hexane-ethyl acetate (7:3 v/v) afforded **5** (2.3 g, 85%) as a colorless oil. $[\alpha]_D$ +90.3° (c=0.7, $CHCl_3$); IR 1740, 1620, 1600 cm^{-1}; ^1H NMR δ 2.04 (3H, s), 3.68 (1H, dd, *J*=3.6 and 10.4 Hz), 4.08 (1H, d, *J*=11.5 Hz), 4.50 (1H, d, *J*=11.5 Hz), 4.91-5.21 (10H, m), 6.15 (1H, d, *J*=2.1 Hz), 6.25 (1H, d, *J*=2.1 Hz), 6.62-7.50 (28H, m); EIMS 798 (M^+). Anal. Calcd for $C_{52}H_{46}O_8 \cdot 0.5H_2O$: C, 77.30; H, 5.86. Found: C, 77.42; H, 5.96.

(+)-3',4',3,5,7-Penta-*O*-benzyl-(4*S*)-hydroxycatechine (6): To a solution of the acetate (**5**)(1.4 g, 1.75 mmol) in MeOH-THF (6:5, v/v) (30 mL) was added K_2CO_3 (4.2 g, 0.03 mol), and the resulting solution was stirred at rt for further 2 h. After removal of the solvent, a residue was treated with water and extracted with ethyl acetate. The extract was dried over $MgSO_4$ and concentrated to give a residue, which was purified by column chromatography on silica gel. Elution with hexane-ethyl acetate (7:3 v/v) afforded **6** (1.19 g, 90%) as a colorless oil. $[\alpha]_D$ +50.2° (c=0.8, $CHCl_3$); IR 3550-3500, 1620, 1600 cm^{-1}; ^1H NMR δ 3.61 (1H, dd, *J*=3.5 and 10.0 Hz), 4.06 (1H, d, *J*=12.0 Hz), 4.23 (1H, d, *J*=12.0 Hz), 4.94-5.19 (10H, m), 6.14 (1H, d, *J*=2.1 Hz), 6.22 (1H, d, *J*=2.1 Hz), 6.62-7.50 (28H, m); HRMS *m/z* found:

756.3117. Calcd for $C_{50}H_{44}O_7$: 756.3087 (M^+). Anal. Calcd for $C_{50}H_{44}O_7 \cdot 0.5H_2O$: C, 78.41; H, 5.92. Found: C, 78.44; H, 5.63.

(+)-3',4',3,5,7-Penta-*O*-benzyltaxifolin (7): To a stirred solution of the alcohol (**6**)(1.89 g, 2.5 mmol) in CH_2Cl_2 (20 mL) were added NMO (0.6 g, 5.1 mmol) and $MgSO_4$ (2.0 g), and the resulting mixture was stirred at ambient temperature for 20 min. TPAP (0.035 g, 0.001 mmol) was added to this mixture, and the whole was stirred at the same temperature for further 3 h. The insoluble material was filtered off through a pad of Celite, and the filtrated was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel. Elution with hexane-ethyl acetate (7:3 v/v) afforded **7** (1.6 g, 85%) as a colorless solid. $[\alpha]_D$ +98.7° (c=0.1, $CHCl_3$); IR 1680, 1610 cm^{-1}; ^1H NMR δ 4.01 (1H, d, *J*=10.5 Hz), 4.42 (1H, d, *J*=11.8 Hz), 4.82 (1H, d, *J*=11.8 Hz), 4.99-5.20 (9H, m), 6.15 (1H, d, *J*=2.1 Hz), 6.21 (1H, d, *J*=2.1 Hz), 6.92-7.57 (28H, m); HRMS *m/z* found: 754.2920. Calcd for $C_{50}H_{42}O_7$: 754.2930 (M^+).

(+)-Taxifolin (8): A solution of **7** (1.5 g, 2.0 mmol) in THF-MeOH (7:3, v/v) (100 mL) was hydrogenated over 10% Pd-C (350 mg) under an atmospheric pressure of hydrogen for 24 h. After removal of the catalyst by filtration, the filtrate was concentrated to leave a residue, which was purified by column chromatography on silica gel. Elution with $CHCl_3$-MeOH (10:1, v/v) gave **8** (550 mg, 90%) as colorless amorphous powders. Mp. 216-219°C (lit.,[8a] 220-222°C; lit.,[2c] 232-235°C); $[\alpha]_D$ +22.6° (c=1.1, MeOH) [lit.,[8c] $[\alpha]_D$ +20° (c=0.1, MeOH); lit.,[8a] $[\alpha]_D$ +46.2° (c=1.2, MeOH); lit.,[2c] $[\alpha]_D$ +4.6° (c=0.82, EtOH)]; IR 3400, 1650, 1590 cm^{-1}; ^1H NMR δ 4.50 (1H, d, *J*=12.0 Hz), 4.90 (1H, d, *J*=12.0 Hz), 5.88 (1H, d, *J*=2.0 Hz), 5.92 (1H, d, *J*=2.0 Hz), 6.78-6.83 (2H, m), 6.96 (1H, d, *J*=2.1 Hz); ^{13}C NMR δ 73.66, 85.10, 96.25, 97.28, 101.82, 115.86, 120.89, 129.84, 146.30, 147.13, 164.30, 165.30, 168.69, 198.41. Physicochemical properties of **8** were identical with those reported.[8]

(2*R*,3*S*,4*R*)-(+)-3,4,5,7,3',4'-Hexahydroxyflavan (3,4-*trans*-Leucocyanidin) (1): Reduction of taxifolin was carried out according to the literature procedure as follows.[4e] To a stirred solution of taxifolin (0.5 g, 1.64 mmol) in EtOH (100 mL) was added $NaBH_4$ (0.25 g, 6.6 mmol) in one portion, and the solution was stirred at rt for 2 h. The mixture was poured into water (1 L), and pH of the solution was adjusted to 3-4 with acetic acid. The aqueous solution was extracted with ethyl acetate, and the extract was washed with

brine and dried over $MgSO_4$. The solvent was concentrated *in vacuo* at below 40°C to 10-20 mL, which was immediately subjected to column chromatography on Cephadex LH-20. Elution with EtOH provided the desired product (**1**) (0.5 g, 75%) as amorphous powders. ^{1}H NMR (acetone-d_6) δ 3.86 (1H, m, 3-H), 4.60 (1H, d, *J*=10.0 Hz, 2-H), 4.98 (1H, d, *J*=7.9 Hz, 4-H), 5.82 (1H, d, *J*=2.3 Hz, 8-H), 5.96 (1H, d, *J*=2.3 Hz, 6-H), 6.80 (1H, s, 2'-H), 6.81 (1H, s, 5'-H), 6.94 (1H, s, 6'-H). These data are identical with those reported.[4e]

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