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A Total Synthesis of Optically Pure (+)-Catechin Pentaacetate

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A total synthesis of optically pure (+)-catechin pentaacetate has been established using the (-)-chalcon epoxide (100% ee) derived from 3,4,2',4',6'-pentakis(methoxymethoxy)chalcon as the starting material. The optical purity of the product is confirmed by 'H nmr analysis in the presence of a shift reagent.

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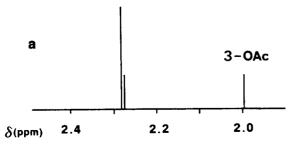
Catechins and related condensed tannins are the representatives of naturally occurring flavanols. It is known that catechins have antihyperlipidemic, antimicrobial and immunostimulating activities [2]. Up to now, a number of synthetic attempts to prepare catechins have been carried out using flavanonols as the starting material or key intermediate. For example, the hydrogenation of (+)-taxifolin tetramethyl ether over Adams catalyst gave (+)-catechin tetramethyl ether in 24% yield [3]. A recent report involved a combination of the sodium borohydride and subsequent sodium cyanoborohydride reductions of (+)-taxifolin to yield (+)-catechin in 90% yield [4]. However, the product formed in this reaction was largely racemized (70%). In a previous paper [1], we reported that the sodium borohydride reduction of (\pm) -flavanonols with 5-OAc furnished (\pm) -catechins in fairly good yields. This paper deals with the application of the above procedure to a total synthesis of optically pure (+)-catechin pentaacetate under the preservation of the stereochemistry.

The synthetic route is shown in Scheme 1. The enantio-selective epoxidation of 3,4,2',4',6'-pentakis(methoxymethoxy)chalcone (1) and chiroptical hplc purification of the (-)-chalcone epoxide 2 to the optically pure state have been established [5,6].

Treatment of (-)-2 (100% ee) with methanolic hydrogen chloride afforded (+)-taxifolin (3) (82%) [5] which was converted into (+)-taxifolin pentaacetate (4) (88%), $[\alpha]_{589}$ + 49.2°, on acetylation with acetic anhydride. Sodium borohydride reduction of (+)-4, followed by acetylation, furnished (+)-catechin pentaacetate (5) (73%), mp 70-73° (hexane), $[\alpha]_{589}$ + 26.5° (chloroform), $[\alpha]_{577}$ + 28.8° (chloroform). As already reported [1], the initial product of the reduction is (+)-catechin 3,7,3',4'-tetraacetate (7) arising from over-reduction of an intermediate 6.

Strange to say, as shown below, melting point and specific rotation of (+)-5 are different from (+)-catechin pentaacetate so far reported [7], mp 132-133° (acetone/ethanol), 130-131° (methanol/water); $[\alpha]_{589}$ + 39.1° (chloroform), $[\alpha]_{577}$ + 35.5° (chloroform).

The ¹H nmr spectrum, melting point and specific rotation of (+)-5 were completely in accord with those of an authentic sample derived from a commercially available (+)-catechin [8]. The ¹H nmr spectrum of (\pm)-5 [1] taken in the presence of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III) (Eu(hfc)₃) showed the separation of the 3-OAc signal at δ 1.998 into two positions at 2.195 and 2.162 (Figure 1). The ¹H nmr spectrum of the authentic sample taken under the same conditions dis-



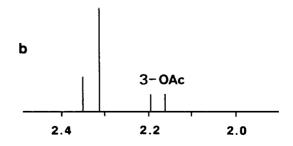


Figure 1. 'H nmr spectrum of (±)-catechin pentaacetate (400 MHz). a) Spectrum was taken in a solution of sample (15.0 mg, 3.00 x 10⁻² mmole) in deuteriochloroform (0.7 ml). b) Spectrum was recorded in the same solution including Eu(hfc)₃ (7.50 mg, 6.28 x 10⁻³ mmole).

Scheme 1

$$R = OCH_2OMe$$
1
(-)-2
(2R, 3S)
(2R, 3R)

R = OAc
(2R, 3S)
(2R, 3R)

$$R = OAc$$
(2R, 3S)

played only one signal at δ 2.190 for 3-OAc, indicating our compound (+)-5 to be optically pure (100% ee). Thus, it was demonstrated that the stereochemistry of (+)-4 and (+)-5 was preserved with no epimerization under the reaction conditions employed.

EXPERIMENTAL

Melting points (uncorrected) were determined on a micro hotstage apparatus. Specific rotations were taken on a JASCO DPI-181 polarimeter. Spectra were recorded on the following spectrometers: ir, Hitachi 260-30; uv, Hitachi EPS-2U; cd, JASCO J-600; 'H nmr, Varian XL-400 (400 MHz) or VXR-300 (300 MHz) (reference, tetramethylsilane); hrms, JEOL JMS DX-300; elemental analysis, Perkin-Elmer 240B.

(+)-Taxifolin Pentaacetate (4).

To a solution of (-)-2 (100% ee) (122.1 mg, 0.233 mmole) in anhydrous methanol (0.5 ml) was added 15% methanolic hydrogen chloride (1 ml), and the mixture was stirred at 50° for 20 minutes. Concentration of the reaction mixture in vacuo, followed by preparative tlc (silica gel, chloroform/methanol = 10:1) of the residue, furnished (+)-3 (58.0 mg, 82%), Rf 0.25, as colorless plates, mp 232-234° (water).

A mixture of (+)-3 (40.0 mg, 0.132 mmole), acetic anhydride (1 ml) and pyridine (2 drops) was stirred at room temperature for 18 hours. Work-up of the reaction mixture, followed by preparative tlc (silica gel, acetone/benzene = 1:10) of the product, afforded (+)-4 (59.2 mg, 88%), Rf 0.65, as colorless needles, mp 132-134° (ethanol); specific rotation (c = 0.31, chloroform): $[\alpha]^{26}$ (nm) +49.2° (589), +49.8° (577), +58.2° (546), +132.9° (435), +726.3° (365); ir (chloroform): ν cm**T** 1780, 1735 (OAc), 1630 (CO); uv (methanol): λ nm (ϵ) 390 (168), 312 (6495), 264 (12103), 216 (61711); cd (c = 1.2 x 10⁻⁴, methanol): $[\theta]^{20.5}$ (nm) O (371), +13964 (333) (positive maximum), O (320), -17476 (302) (negative maximum), -1456 (272) (positive maximum), -1970 (256)

(negative maximum), O (248), +7282 (236) (shoulder), +39835 (215) (positive maximum); 'H nmr (400 MHz) (methanol-d₄): δ 7.500 (1H, dd, J = 8.5, 2.0 Hz, 6'-H), 7.421 (1H, d, J = 2.0 Hz, 2'-H), 7.297 (1H, d, J = 8.5 Hz, 5'-H), 6.880, 6.698 (each 1H, d, J = 2.1 Hz, 6-H, 8-H), 5.793 (1H, d, J = 12.5 Hz, 2-H), 5.600 (1H, d, J = 12.5 Hz, 3-H), 2.328 (3H, s, 5-OAc), 2.282 (9H, s, 3 x OAc), 1.996 (3H, s, 3-OAc); hrms: m/z M⁺, 514.1084 (M, 514.1111 for $C_{0z}H_{0z}O_{1z}$).

Anal. Calcd. for $C_{25}H_{22}O_{12}$: C, 58.37; H, 4.31. Found: C, 58.23; H, 4.38.

(+)-Catechin Pentaacetate (5).

A mixture of (+)-4 (10.0 mg, 0.022 mmole) and sodium borohydride (5.3 mg, 0.140 mmole) in anhydrous dioxane (0.5 ml) was stirred at room temperature for 1 hour, and then 3% acetic acid (0.3 ml) was added. After dilution with water, the reaction mixutre was extracted with ethyl acetate. An oil resulting from the organic layer was treated with acetic anhydride (0.5 ml) and pyridine (2 drops) at room temperature for 18 hours. Work-up of the reaction mixture, followed by preparative tlc (silica gel, acetone/benzene = 1:10) of the product, gave (+)-5 (8.0 mg, 73%), Rf 0.54, as colorless granules, mp 70-73° (hexane) (no depression on admixture with authentic sample with mp 72-73°); specific rotation (c = 0.34, chloroform): $[\alpha]^{25}$ (nm) + 26.5° (589), +28.8° (577), $+35.9^{\circ}$ (546), $+57.7^{\circ}$ (435), $+85.3^{\circ}$ (365); ir (chloroform): ν cm⁻¹ 1770, 1750 (OAc); ¹H nmr (300 MHz) (deuteriochloroform): δ 7.251 (1H, dd, J = 8.5, 2.0 Hz, 6'-H), 7.193 (1H, d, J = 8.5 Hz, 5'-H), 7.166 (1H, d, J = 2.0 Hz, 2'-H), 6.657, 6.595 (each 1H, d, J= 2.1 Hz, 6-H, 8-H, 5.253 (1H, dt, J = 5.0, 6.5 Hz, 3-H), 5.142(1H, d, J = 6.5 Hz, 2-H), 2.864 (1H, dd, J = 16.5, 5.0 Hz, 4-H),2.664 (1H, dd, J = 16.5, 6.5 Hz, 4-H), 2.280 (9H, s, $3 \times OAc$), 2.275 (3H, s, OAc), 1.999 (3H, s, 3-OAc); hrms: m/z M⁺, 500.1302 (M, 500.1318 for C₂₅H₂₄O₁₁). The specific rotation and ¹H nmr data were perfectly in accord with those of an authentic sample. Anal. Calcd. for C₂₅H₂₄O₁₁: C, 60.00; H, 4.83. Found: C, 59.83; H, 4.90.

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- [8] Commercially available catechin (Tokyo Kasei Kogyo Co.): mp 176-178°, $[\alpha]_{b}^{2.6}$ +7.2° (c = 1.0, acetone). Anal. Calcd. for $C_{15}H_{14}O_{6}$; C, 62.07; H, 4.86. Found: C, 61.79; H, 4.97. (+)-Catechin 5,7,3',4'-Tetramethyl Ether: mp 140-141° (ethanol), $[\alpha]_{b}^{2.5}$ -12.8° (c = 0.5, tetrachloroethane); K. Weings, Liebigs Ann. Chem., 615, 203 (1958), mp 143-144° (ethanol), $[\alpha]_{b}$ -13.6° (c = 2.0, tetrachloroethane).