

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

Mieko Urano, Hitoshi Kagawa, and Yoshihiro Harigaya\*

School of Pharmaceutical Sciences, Kitasato University,  
Minato-ku, Tokyo 108, Japan

Shaoshun Li and Masayuki Onda\*

Shenyang College of Pharmacy, Wenhua-Lu  
Shenyang, China

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A total synthesis of optically pure (+)-catechin pentaacetate has been established using the (-)-chalcone epoxide (100% ee) derived from 3,4,2',4',6'-pentakis(methoxymethoxy)chalcone as the starting material. The optical purity of the product is confirmed by  $^1\text{H}$  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 enantioselective 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%),  $[\alpha]_{589} + 49.2^\circ$ , on acetylation with acetic anhydride. Sodium borohydride reduction of (+)-**4**, followed by acetylation, furnished (+)-catechin pentaacetate (**5**) (73%), mp 70-73° (hexane),  $[\alpha]_{589} + 26.5^\circ$  (chloroform),  $[\alpha]_{577} + 28.8^\circ$  (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);  $[\alpha]_{589} + 39.1^\circ$  (chloroform),  $[\alpha]_{577} + 35.5^\circ$  (chloroform).

The  $^1\text{H}$  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  $^1\text{H}$  nmr spectrum of ( $\pm$ )-**5** [1] taken in the presence of tris[3-(heptafluoropropyl)hydroxymethylene](+)-camphorato]europium (III) ( $\text{Eu}(\text{hfc})_3$ ) showed the separation of the 3-OAc signal at  $\delta$  1.998 into two positions at 2.195 and 2.162 (Figure 1). The  $^1\text{H}$  nmr spectrum of the authentic sample taken under the same conditions dis-

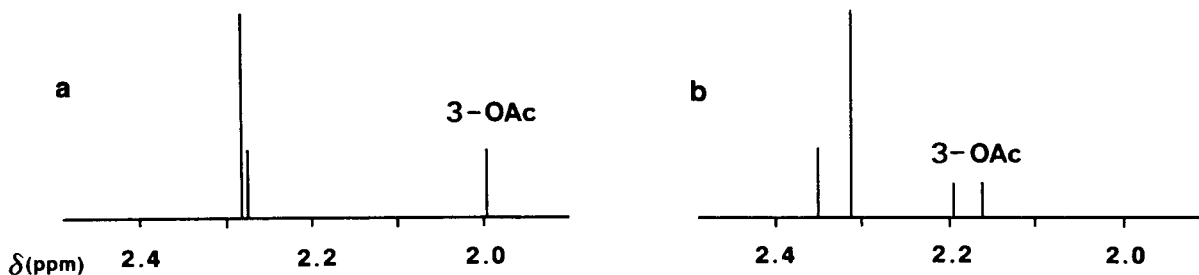


Figure 1.  $^1\text{H}$  nmr spectrum of (+)-catechin pentaacetate (400 MHz). a) Spectrum was taken in a solution of sample (15.0 mg,  $3.00 \times 10^{-2}$  mmole) in deuteriochloroform (0.7 ml). b) Spectrum was recorded in the same solution including  $\text{Eu}(\text{hfc})_3$  (7.50 mg,  $6.28 \times 10^{-3}$  mmole).



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[8] Commercially available catechin (Tokyo Kasei Kogyo Co.): mp 176-178°,  $[\alpha]_D^{25} +7.2^\circ$  (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),  $[\alpha]_D^{25} -12.8^\circ$  (c = 0.5, tetrachloroethane); K. Weings, *Liebigs Ann. Chem.*, **615**, 203 (1958), mp 143-144° (ethanol),  $[\alpha]_D -13.6^\circ$  (c = 2.0, tetrachloroethane).