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# Methods in synthesis of flavonoids. Part 2:[1] High yield access to both enantiomers of catechin

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**Abstract**

Resolution of racemic synthetic tetra-*O*-benzylcatechin **2** is described, through the formation of esters **5** and **6** derived from dibenzoyl-L-tartaric acid. The diastereoisomer of the natural series **6** was separated by crystallization, the other one being an oil. This process allowed us to prepare enantiomerically pure (+)-catechin **8** in high yield. The pure isomer in the *ent*-series **9** could be obtained, following the same scheme of reactions. © 2000 Elsevier Science Ltd. All rights reserved.

Asymmetric total synthesis of flavonoids has been challenged over the two last decades, but, probably because of the special reactivity of these polyphenolic compounds, successful examples are scarce.[2–4] Concerning the catechin series, it would be very convenient to have such enantiomerically pure synthetic molecules in order to study the biological as well as the biophysical properties of one or the other enantiomer. Indeed, flavonoids are considered to be responsible for most of the benefits that a well balanced diet can bring to health (diminution of cardiovascular risk,[5] known as the 'French paradox' and cancer,[6] protection against Alzheimer disease,[7] and, as a consequence, increase of the 'Mediterranean' people's life expectancy).

Even though natural catechin is one of the most abundant flavonoid in foods, it proved to be useless in investigating the above mentioned properties at a cellular level. This is the reason why we decided to introduce $^{13}C$ labeling within the skeleton of those molecules. Unfortunately, in our hands, any trial to get directly to optically pure (+)-catechin by enantioselective total synthesis failed. This report deals with the resolution steps of racemic catechin derivatives **2**, as an improvement of our total synthesis of (±)-catechin.[8] Brown and Fuller[9] reported a chemical resolution of (±)-3′,4′,5,7-tetramethoxyflavan-3,4-diol by crystallization of the salt between its carboxyphenylborate ester and (−)-ephedrine, in quite poor yields (about 4% of each chiral diol). While these compounds may be reduced into the corresponding catechins, they are still

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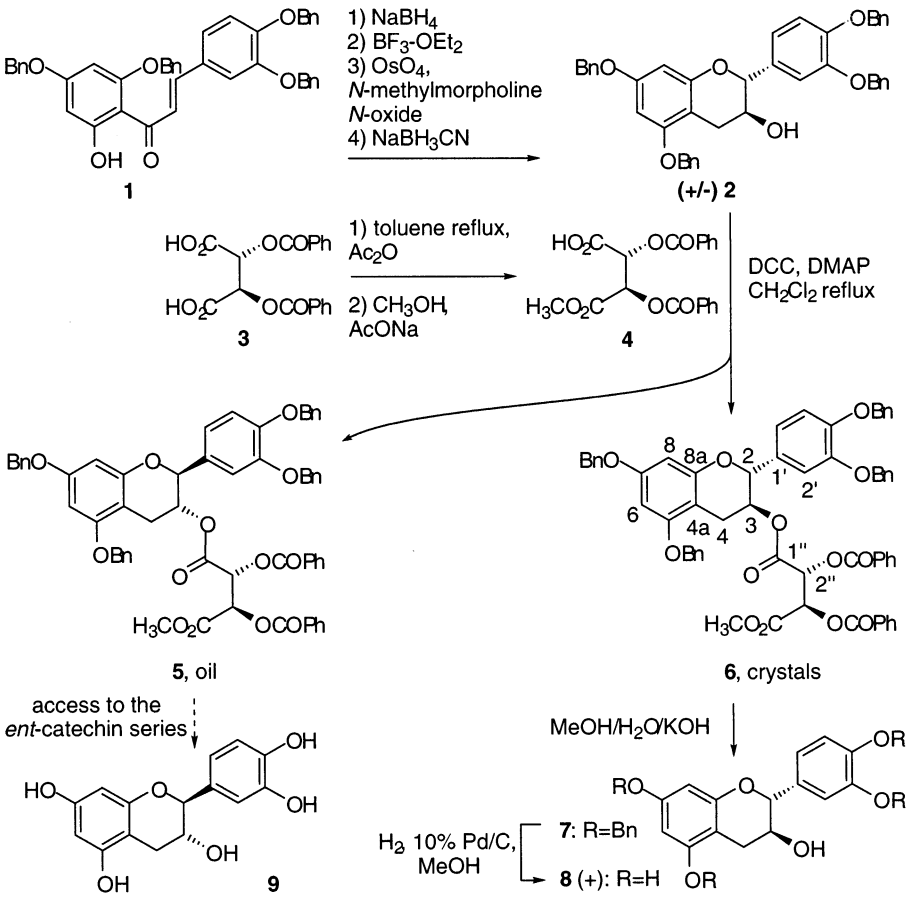
methylated derivatives. It is worthy of note that most of the syntheses in the field were carried out with permethylated phenols, which revealed to be deprotected with much difficulty. Our method describes a preparative resolution of synthetic (±)-tetra-*O*-benzylcatechin **2** (Scheme 1) that fully overcomes this problem and makes possible the obtention of native pure (+)-catechin.




Scheme 1.

Racemic compound **2** (770 mg) was obtained according to our previously described synthesis from 3,4,4′,6′-tetrabenzyloxy-2′-hydroxychalcone **1**.[8] The best results of chemical resolution were obtained by esterification of **2** by dibenzoyl-L-tartaric acid monomethyl ester **4** (2 equiv., 881 mg) in refluxing $CH_2Cl_2$ (50 mL) in the presence of DCC (2 equiv., 488 mg) and DMAP (0.05 equiv., 7 mg), giving a pair of diastereoisomers in 82% yield (964 mg of mixture **5**/**6**). Compound **6**[10] was able to crystallize selectively in a mixture of hexane/$CH_2Cl_2$ 8/2 (v/v). This crop of crystals was submitted to a single recrystallization (hexane/$CH_2Cl_2$ 8/2) to yield 366 mg of fine white crystals (31% from **2**, de>99%, based on silica gel HPLC, hexane/$CHCl_3$ 85/15). The other isomer **5** did not crystallize, and gave a colorless oil (570 mg, de = 70%) upon concentration of the mother liquids.

Since all attempts to form esters directly from the anhydride of **3** failed, **4** had to be used to produce **5** and **6**. This monoacid methyl ester **4** was synthesized in two steps and 61% overall yield from commercially available dibenzoyl-L-tartaric acid **3**. It was first transformed into the

corresponding anhydride in refluxing toluene (Dean–Stark apparatus) in the presence of acetic anhydride, and then was opened by methanol and sodium acetate (33 wt.%) to give **4**.

Compound **6** (345 mg) was hydrolysed in $CH_3OH/H_2O/KOH$ (27 mL/3 mL/80 mg), leading to 209 mg (94% yield) of (2*R*,3*S*)-tetra-*O*-benzylcatechin **7**, $[\alpha]_D = +1.5$ (*c* 1, $CH_2Cl_2$). Then, hydrogenolysis of **7**[8] gave 80 mg after lyophilisation (92% yield) of (+)-catechin **8**, $[\alpha]_D = +17$ (*c* 1, $H_2O$), with an ee>99% checked by HPLC on a chiral Cyclobond® I column (β-cyclodextrin).

This method provides an efficient way of preparation of (+)-catechin **8** (22% from racemic compound **2**, in three steps), possibly along with its enantiomeric isomer **9** (*ent*-catechin) from **5**. As an extension of it, the decagram-scale preparation of these molecules, incorporating $^{13}C$ labeling, is under progress and will be published elsewhere.

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10. Data for **6**: $[\alpha]_D = -35$ (*c* 1, $CH_2Cl_2$). UV/vis ($CH_3OH$): 205 nm, 227, 274. IR (KBr): 3062 $cm^{-1}$, 3032, 2945, 2870, 1768, 1738 (s), 1619, 1594, 1509, 1499, 1452, 1439, 1378, 1315, 1252 (s), 1180, 1124 (s), 1071, 1020, 912, 853, 808, 743, 707, 697. $^1H$ HR-NMR (500 MHz, $CDCl_3$), $\delta$ ppm: 2.62 (dd, $J=5$, 17 Hz, 4-Ha), 2.69 (dd, $J=5$, 17 Hz, 4-Hb), 3.73 (s, $COOCH_3$), 4.73 and 4.83 (2 d, $J=12$ Hz, 5-*O*-$CH_2$-$C_6H_5$), 5.00 (s, 7-*O*–$CH_2$–$C_6H_5$), 5.05 and 5.12 (2 s, 3′ and 4′-*O*–$CH_2$–$C_6H_5$), 5.13 (d, $J=5$ Hz, 2-H), 5.38 (m, 3-H), 5.97 (m, 2″ and 3″-H), 6.09 (d, $J=2.5$ Hz, 6-H), 6.21 (d, $J=2.5$ Hz, 8-H), 6.78 (dd, $J=2$, 8.5 Hz, 6′-H), 6.85 (d, $J=8.5$ Hz, 5′-H), 6.90 (d, $J=2$ Hz, 2′-H), 7.22–7.48 (m, 20 *O*–$CH_2$–$C_6H_5$ and 4 *meta*-*O*–CO–$C_6H_5$), 7.53 and 7.58 (2 m, 2 *para*-*O*–CO–$C_6H_5$), 8.02 and 8.06 (2 m, 4 *ortho*-*O*–CO–$C_6H_5$). $^{13}C$ NMR (125 MHz, $CDCl_3$), $\delta$ ppm: 22.3 (C-4), 52.8 ($COOCH_3$), 69.7 (5-*O*–$CH_2$–$C_6H_5$), 70.1 (7-*O*-$CH_2$–$C_6H_5$), 71.1 (C-3), 71.3 (C-2″ and C-3″), 71.4 (3′-*O*- and 4′-*O*–$CH_2$–$C_6H_5$), 77.2 (C-2), 93.8 (C-6), 94.4 (C-8), 100.4 (C-4a), 113.1 (C-2′), 115.2 (C-5′), 119.4 (C-6′), 126.9, 127.2, 127.4, 127.5, 127.7, 127.9, 128.3, 128.4, 128.5 and 128.6 (4 *para*-, 8 *ortho*- and 8 *meta*-*O*–$CH_2$–$C_6H_5$ and 4 *meta*-*O*–CO–$C_6H_5$), 128.6 (2 *ipso*-*O*–CO–$C_6H_5$), 129.9 and 130.0 (4 *ortho*-*O*–CO–$C_6H_5$), 130.7 (C-1′), 133.4 and 133.5 (2 *para*-*O*–CO–$C_6H_5$), 136.8 (*ipso*-5-*O*–$CH_2$–$C_6H_5$), 136.9 (*ipso*-7-*O*–$CH_2$–$C_6H_5$), 137.0 and 137.2 (*ipso*-3′ and 4′-*O*–$CH_2$–$C_6H_5$), 149.1 (C-3′, C-4′), 154.3 (C-8a), 157.4 (C-5), 158.9 (C-7), 164.9 (3″-*O*–CO–$C_6H_5$), 165.0 (2″-*O*–CO–$C_6H_5$), 165.2 (C-1″), 166.3 (C-4″). MS (FAB+, glycerol) *m*/*z* (%): 1004.6 [$M^+$] (5), 632.0 (80), 542.4 (100). Anal. calcd for $C_{62}H_{52}O_{13}$: C, 74.09; H, 5.21. Found: C, 74.61; H, 5.09.