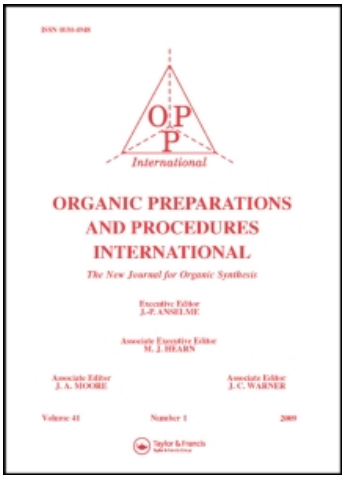


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Jamal Muskifa[a]; Riaz A. Khan[a]; Ikhlas A. Khan[ab]; Daneel Ferreira[a]
[a] Nationa1 Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, School of Pharmacy The University of Mississippi, University, MS, USA [b] Department of Phannacognosy, School of Phannacy The University of Mississippi, Universily, MS, USA

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# BENZYLATION OF FLAVAN-3-OLS (CATECHINS)

Jamal Mustafa[†], Riaz Khan[†], Ikhlas A Khan[†,††] and Daneel Ferreira[†,*]

[†]*National Center for Natural Products Research*
*Research Institute of Pharmaceutical Sciences, School of Pharmacy*
*The University of Mississippi, University, MS 38677, USA*

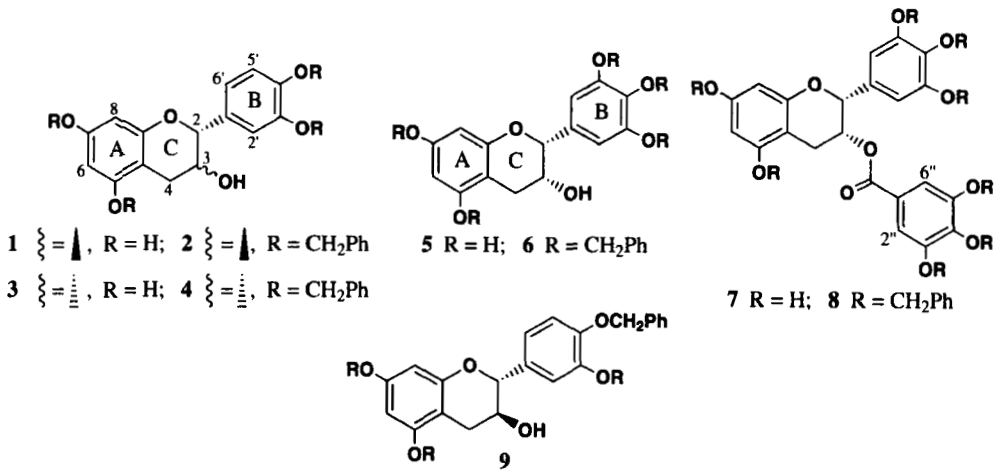
[††]*Department of Pharmacognosy, School of Pharmacy*
*The University of Mississippi, University, MS 38677, USA*

[*]*E-mail: dferreir@olemiss.edu*

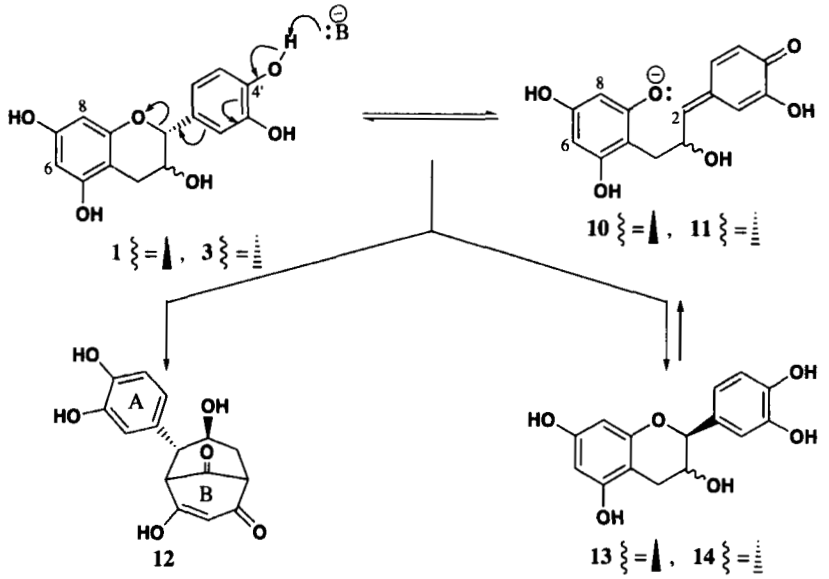


The benzyl functionality is a useful protecting group for the phenolic hydroxyl group in organic synthesis. Benzyl ethers are stable under basic or mildly acidic conditions but readily cleaved by hydrogenolysis.[1] Benzylation of electron-rich phenols such as phloroglucinol gives mixtures of *O*- and *C*-benzylated products which are often difficult to separate, thus leading to reduced yields.[2] Although the phenolic hydroxyl groups of (+)-catechin **1** are readily *O*-methylated by dimethyl sulfate in anhydrous acetone/potassium carbonate,[3,4] the analogous benzylation with a benzyl halide under a variety of conditions[5-7] gives the 5,7,3',4'-tetra-*O*-benzyl ether **2** consistently in less than 50% yield. The analogous benzylation of (-)-epicatechin **3** is even less successful, except for a single report claiming the formation of the perbenzyl aryl ether in 90% yield using benzyl bromide and $K_2CO_3$ in DMF.[8] The 5,7,3',4'-tetra-*O*-benzyl ether **4** was also synthesized from the corresponding (+)-catechin derivative **2** *via* sequential oxidation and reduction of the secondary hydroxyl function at C-3.[6,7] The perbenzyl ethers **6** and **8** of (-)-epigallocatechin **5** and (-)-epigallocatechin-*3-O*-gallate **7** are similarly only accessible *via* multiple step procedures.[9,10] We now report facile access to the perbenzyl aryl ethers **2**, **4**, **6** and **8** of (+)-catechin **1**, (-)-epicatechin **3**, (-)-epigallocatechin **5** and (-)-epigallocatechin-3-*O* -gallate **7** using benzyl chloride/NaH in anhydrous DMF under mild reaction conditions.

Preparative manipulation of the phenolic hydroxyl groups of flavan-3-ols has to take cognizance of the acidity of the 4'-hydroxy function[11] and the subsequent racemization[12-14] and rearrangement reactions[15,16] induced by formation of a *B*-ring quinomethane intermediate (**10** or **11**).




Thus, racemization of (+)-catechin **1** and (-)-epicatechin **3** proceeds through ionization of the 4'-OH group and *B*-ring quinomethane intermediates **10** and **11** *via* a reversible intramolecular 1,6-Michael addition (*Scheme 1*). The ratio of flavan-3-ols in the equilibrium mixture, *e. g.*




Racemization of Flavan-3-ols and Route to the Formation of (+)-Catechinic Acid **12** *via* an ionic (two-electron) mechanism

**Scheme 1**

(+)-catechin **1** and *ent*-epicatechin **13** or (-)-epicatechin **3** and *ent*-catechin **14**, is determined by thermodynamic considerations, the 2,3-*trans*-flavan-3-ol, *e. g.* **1**, generally being more stable than the 2,3-*cis* isomer, e. g. **12**. Quinomethane **10** presumably also serves as precursor to the formation of (+)-catechinic acid **12** through interaction of C-8 (A-ring) and the *si*-face at C-2.

The formation of racemization and rearrangement products at alkaline pH may also proceed *via* a one-electron (radical) mechanism.[17-19]

Kozikowski and his coworkers[20] synthesized 5,7,3',4'-tetra-*O*-benzylcatechin in poor yield by first treating a solution of (+)-catechin **1** in anhydrous dimethylformamide (DMF) with sodium hydride (4.3 eq.) at room temperature to induce phenolate formation. The mixture is then cooled to –10°C, benzyl bromide (4.5 eq.) is added dropwise and the reaction mixture warmed to room temperature and stirred overnight. Owing to the aforementioned acidity of the 4'-OH function[11] we reasoned that similar conditions could be adapted to utilize its perceived susceptibility to rapid benzylation similar to the observed selectivity for *O*-methylation at the *B*-ring of (+)-catechin **1**.[21,22] Once the 4'-OH group is protected, the racemization and rearrangement reactions (*Scheme 1*) should be suppressed hence leading to a cleaner process for benzylation of the phenolic hydroxyl functions. Thus, to a stirred suspension of NaH (4.25 eq.) in anhydrous DMF under nitrogen at –78°C in a sealed reaction flask, was sequentially added a solution of (+)-catechin **1**(1.0 eq.) in dry DMF and neat benzyl chloride (5.0 eq.)(instead of benzyl bromide used by Kozikowski *et al.*[6,20]) in one batch *via* a syringe. The mixture was stirred at this temperature for 15 minutes, the Dry Ice/acetone bath removed and stirring continued at room temperature for seven hours. During this period the variety of spots on qualitative TLC representing different levels of *O*-benzylation gradually disappeared to leave a single spot comprising 5,7,3',4'-tetra-*O*-benzylcatechin **2**. $^{1}H$ and $^{13}C$ NMR data of the crude product indicated a high degree of purity that would suffice for most preparative purposes. No evidence for the presence of products of racemization and/or rearrangement could be detected. Purification by flash column chromatography on silica gel in hexane-ethyl acetate (2:1) afforded a pure sample of 5,7,3',4'-tetra-*O*-benzylcatechin **2** in 98% yield. Its identity was confirmed by $^{1}H$[20,23] (*Table 1*) and $^{13}C$ NMR (*Table 2*), MS and CD[24] data. Notably, when the *O*-benzylation was performed as indicated in ref. 20, at least six additional spots were visible on qualitative TLC, leading to a reduced yield (30%) of the tetra-*O*-benzylcatechin **2**.



**Table 1.** $^{1}H$ NMR Shifts ($\delta_H$) of Compounds **2**, **4**, **6** and **8** in $CDCl_3$ at 500 MHz.[a]

| | 2-H | 3-H | 4-H | 6/8-H | 2'-H | 5'-H | 6'-H | *O*-$CH_2$ | Benzyl |
|---|---|---|---|---|---|---|---|---|---|
| **2** | 4.68 d (7.2) | 4.04 m | 2.72 dd (8.8, 16.5), 3.17 dd (5.5, 16.50) | 6.36, 6.32, both d (each 2.5) | 7.25 d (2.5) | 7.11 m | 7.11 m | 5.26 s (x2), 5.11 s, 5.03 s | 7.43 m, 20xH |
| **4** | 4.94 s | 4.20 m | 3.05 m | 6.39 s | 7.19 d (2.5) | 7.05 m | 7.05 m | 5.26 (x2), 5.22 s, 4.94 s | 7.42 m, 20xH |
| **6** | 4.93 s | 4.26 s | 3.01 m | 6.36 s | 6.88 s | ---- | 6.88 s | 5.21 s (x2), 5.16 s, 5.08 s (x2) | 7.38, 25xH |
| **8** | Overlapped by $OCH_2Ph$ | 5.76 s | 3.20 m | 6.49, 6.43, both d (each 2.5) | 6.82 s | ---- | 6.82 s | 5.13-4.75, 17xH | 7.40, br m, 42xH |

[a] Coupling constants (Hz) are in brackets

**Table 2.** $^{13}C$ NMR Shifts ($\delta_C$) of Compounds **2**, **4**, **6** and **8** in $CDCl_3$ at 500 MHz

| | 2-C | 3-C | 4-C | 6/8-C | 2'-C | 5'-C | 6'-C | *O*-$CH_2$ | Ring A/B | Benzyl Ph |
|---|---|---|---|---|---|---|---|---|---|---|
| **2** | 82.04 | 68.57 | 28.17 | 94.34 / 94.93 | 114.43 | 115.44 | 121.7 | 70.38, 70.58, 71.69, 71.77 | 102.84, 131.56, 149.53, 149.77, 155.81, 158.27, 159.30 | 127.63, 137.41, 127.75, 137.53, 128.00, 137.44, 128.36, 137.41, 128.47, 129.01 |
| **4** | 78.89 | 66.76 | 28.76 | 94.57 / 95.28 | 114.11 | 115.48 | 120.10 | 70.42, 70.60, 71.76, 71.85 | 101.63, 132.11, 149.33, 149.50, 155.87, 158.83, 159.27 | 127.74, 137.52, 127.83, 137.58, 128.06, 137.44, 128.37, 137.81, 128.49, 128.61, 129.02, 129.11 |
| **6** | 79.04 | 66.86 | 28.62 | 94.65 / 95.30 | 106.75 (2'&6') | ----- | 106.75 | 70.46, 70.64, 71.83 (2xC), 75.72 | 101.56, 134.28, 153.49 (3xC), 155.64, 158.80, 159.30 | 127.69, 137.46, 127.98, 137.50, 128.05, (2xC), 128.28, 138.35, 128.38, 138.89, 128.45, 128.64, 128.95, 129.02, 129.07 |
| **8** | 78.39 | 68.78 | 26.68 | 94.53 / 95.22 | 107.28 (2'&6'), 109.70 (2"&6") of gallate | ---- | 107.28 | 70.51, 70.66, 71.57 (2xC), 71.71 (2xC), 75.51, 75.60 | 101.50, 133.74, 152.88 (3xC), 153.36 (2xC), 156.14, 158.52, 159.39, 143.28 (C-C=O), 165.28 (C=O of gallate) | 127.69, 136.92, 127.95, 137.29 (2xC), 137.39, 128.20, 137.98, 128.28, 138.27, 128.42, 138.99 (2xC), 128.51, 128.55, 128.64, 128.73, 128.84, 128.95, 129.01 |



In addition, when (+)-catechin **1** was treated with NaH (4.25 eq.) and benzyl chloride (1.0 eq.) at -78°C and the mixture stirred at room temperature for 7 hours, only 4'-*O*-benzylcatechin **9** was obtained in *ca.* 90% yield. Such an observation gives credence to conjecture that *O*-benzylation at 4'-OH is rapid thus preventing the formation of racemization and rearrangement products.

Treatment of 1.0 eq. of (-)-epicatechin (**3**), (-)-epigallocatechin (**5**) and (-)-epigallocatechin-3-*O*-gallate (**7**) with NaH (4.25, 5.25 and 8.25 eq., respectively) in anhydrous DMF and benzyl chloride (5.0, 6.0, and 8.0 eq., respectively) in anhydrous DMF, first at -78°C (15 minutes) and then for 7 hours at room temperature (24 hrs for **7**), afforded 5,7,3',4'-tetra-*O*-benzylepicatechin (**4**), 5,7,3',4',5'-penta-*O*-benzylepigallocatechin (**6**) and 5,7,3',4',5'-penta-*O*-benzyl-3-*O*-(3,4,5-tri-*O*-benzylgalloyl)epigallocatechin (**8**) in yields of 90%, 85% and 51%, respectively. The structures of these derivatives are confirmed by $^1H$ and $^{13}C$ NMR, MS and CD data.[23,24] Preservation of the 2*R* absolute configuration in each of derivatives **2**, **4**, **6** and **8** is

unequivocally confirmed by the negative Cotton effect of the $^1L_b$ band in the 280 nm region of their CD spectra.[24] Recorded yields are for the products purified by column chromatography on silica gel. However, qualitative TLC of the reaction mixtures of *O*-benzylation of (-)-epicatechin (**3**) and (-)-epigallocatechin (**5**) again indicated purities for work-up reactions in excess of 90% which would be acceptable for a variety of preparative purposes. We could not find evidence for the formation of racemization products in either of these *O*-benzylation reactions, a remarkable feature in view of the fact that 2,3-*cis*-flavan-3-ols are thermodynamically less stable than their 2,3-*trans* counterparts. This is the first report of the successful direct preparation of the phenolic perbenzyl aryl ethers of (-)-epigallocatechin (**5**) and (-)-epigallocatechin-3-*O*-gallate (**7**). However, this protocol was ineffective when applied to the *O*-benzylation of epicatechin-3-*O*-gallate, an observation which cannot be readily explained.

We have thus developed a facile method to efficiently and selectively *O*-benzylate the phenolic functionalities of (+)-catechin (**1**), (-)-epicatechin (**3**), (-)-epigallocatechin (**5**) and its 3-*O*-gallate (**7**). This procedure should expedite synthetic efforts in proanthocyanidin chemistry that often necessitate the utilization of *O*-benzyl protected flavan-3-ol intermediates.



## EXPERIMENTAL SECTION

Preparative column chromatography was carried out on silica gel. $^1H$ and $^{13}C$ NMR spectra were recorded on a DRX-500 Bruker NMR spectrometer. Molecular weights were determined by electron-spray-ionization (ESI) on a Bruker BioApex Fourier Transform mass spectrometer. Samples were run in ESI positive mode by direct injection with a syringe pump mass spectrometer. FT-IR spectra were recorded in $CHCl_3$ on a Genesis Series FTIR™ spectrometer. CD spectra were recorded on a JASCO J-715 spectrometer. DMF was dried over calcium hydride and freshly distilled under nitrogen prior to use. Benzyl chloride and sodium hydride (60% dispersion in mineral oil) were procured from Aldrich Chemicals, USA.

**General Procedure for O-Benzylation.**- To a stirred suspention of NaH (4.25 mmol for **1** and **2**; 5.25 and 8.25 mmol for **5** and **7** respectively) in dry DMF (5 mL) under nitrogen at -78°C in a sealed two-neck flask, was sequentialy added a solution of **1**, **3**, **5**, and **7** (1 mmol) in anhydrous DMF (2 mL) and neat benzyl chloride (5.0 mmol for **1** and **2**; 6.0 and 8.0 mmol for **5** and **7**, respectively) in one batch *via* a syringe. The mixtures were stirred at this temperature for an additional 15 minutes, when the Dry Ice/acetone bath was removed. Stirring was continued for 7 hours except for **7** that required 24 hours. Progress of the reaction was monitored by qualitative TLC[Si-gel, hexane/EtOAc (2:1 v/v)]. The reactions were quenched by adding 1N HCl (2 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL) and the organic layer washed with hexane (2 x 5 mL) to remove mineral oil and water (2 x 10 mL) to remove acid. The organic layer was dried over $Na_2SO_4$ and evaporated to dryness. The *O*-benzylated products were purified by silica gel column chromatography using hexane/ethyl acetate (2:1, v/v) as eluent.

**5,7,3',4'-Tetra-O-benzylcatechin (2)**.- Amorphous white solid, mp. 115-116°C, yield 98%; IR: 3030, 1613, 1593, 1512, 1497, 1453, 1377, 1263, 1215, 1139, 1116 $cm^{-1}$. EI-MS found $[M+H]^+$, 651.2769; $C_{43}H_{39}O_6$ $[M+H]^+$ requires 651.2796. $^1H$ and $^{13}C$ NMR data are given in *Tables 1 & 2*.

*Anal.* Calcd for $C_{43}H_{38}O_6$: C, 79.36; H, 5.89. Found: C, 79.31; H, 6.15

**5,7,3',4'-Tetra-O-benzylepicatechin (4)**.- Amorphous white solid, mp. 128-129°C, *lit.* mp. 129.5-130°C,[6] yield 91%; IR: 3031, 1617, 1592, 1512, 1498, 1453, 1441, 1377, 1263, 1217, 1144, 1112 $cm^{-1}$. EI-MS found $[M+H]^+$, 651.2769; $C_{43}H_{39}O_6$ $[M+H]^+$ 651.2796. $^1H$ and $^{13}C$ NMR data are given in *Tables 1 & 2*.

*Anal.* Calcd for $C_{43}H_{38}O_6$: C, 79.36; H, 5.89. Found: C, 79.40; H, 6.18

**5,7,3',4',5'-Penta-O-benzylepigallocatechin (6)**.- Amorphous buff solid, mp. 135-136°C, yield 85%; IR: 3031, 1615, 1593, 1498, 1439, 1376, 1213, 1147, 1116 $cm^1$. EI-MS found $[M+H]^+$ 757.3149; $C_{50}H_{45}O_7$ $[M+H]^+$ requires 757.3159. $^1H$ and $^{13}C$ NMR data are given in *Tables 1 & 2*.

*Anal.* Calcd for $C_{50}H_{44}O_7$: C, 79.34; H, 5.86. Found: C, 79.46; H, 6.04

**5,7,3',4',5'-Penta-O-benzyl-3-O-(3,4,5-tri-O-benzylgalloyl)epigallocatechin (8)**.- Amorphous buff solid, mp. 69-70°C, yield 51%; IR: 3031, 1717, 1658, 1613, 1593, 1498, 1453, 1428, 1368, 1331, 1212, 1148, 1104 $cm^{-1}$. EI-MS found $[M^+]$ 1179.3725; $C_{78}H_{66}O_{11}$ $[M^+]$ requires 1179.3728. $^1H$ and $^{13}C$ NMR data are given in *Tables 1 & 2*.

*Anal.* Calcd for $C_{78}H_{66}O_{11}$: C, 79.44; H, 5.64. Found: C, 79.30; H, 5.90

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