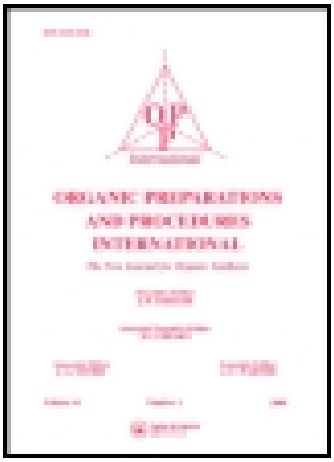


Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

BENZYLATION OF FLAVAN-3-OLS (CATECHINS)

Jamal Muskifa [a] , Riaz A Khan [a] , Ikhlas A Khan [a b] & Daneel Ferreira [a]

[a] Nationa1 Center for Natural Products Research , Research Institute of Pharmaceutical Sciences, School of Pharmacy The University of Mississippi , University, MS, 38677, USA

[b] Department of Phannacognosy , School of Phannacy The University of Mississippi , Universily, MS, 38677, USA E-mail:

Published online: 26 May 2010.

To cite this article: Jamal Muskifa , Riaz A Khan , Ikhlas A Khan & Daneel Ferreira (2004) BENZYLATION OF FLAVAN-3-OLS (CATECHINS), Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 36:1, 61-67, DOI: 10.1080/00304940409355371

To link to this article: http://dx.doi.org/10.1080/00304940409355371

ORGANIC PREPARATIONS AND PROCEDURES INT., 36 (1), 61-67 (2004)

BENZYLATION OF FLAVAN-3-OLS (CATECHINS)

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

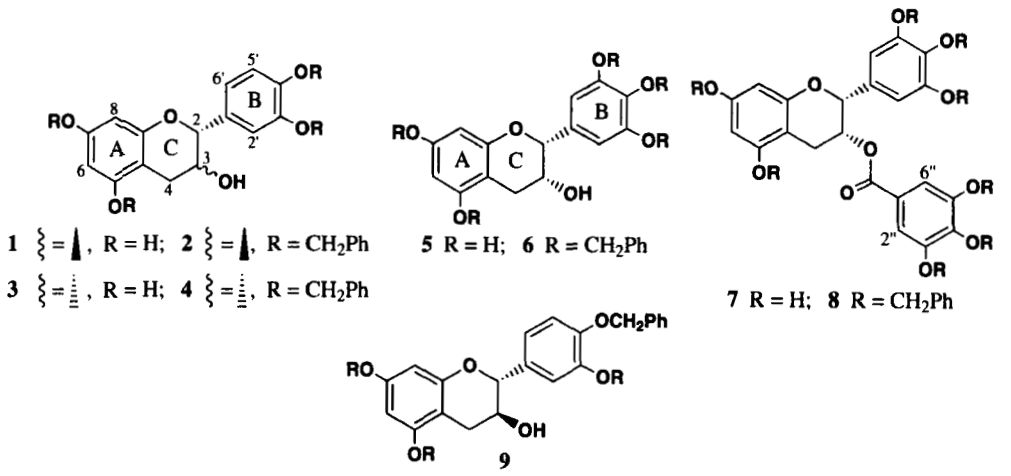
[†]*National Center for Natural Products Research*
Research Institute of Pharmaceutical Sciences, School of Pharmacy
The University of Mississippi, University, MS 38677, USA

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

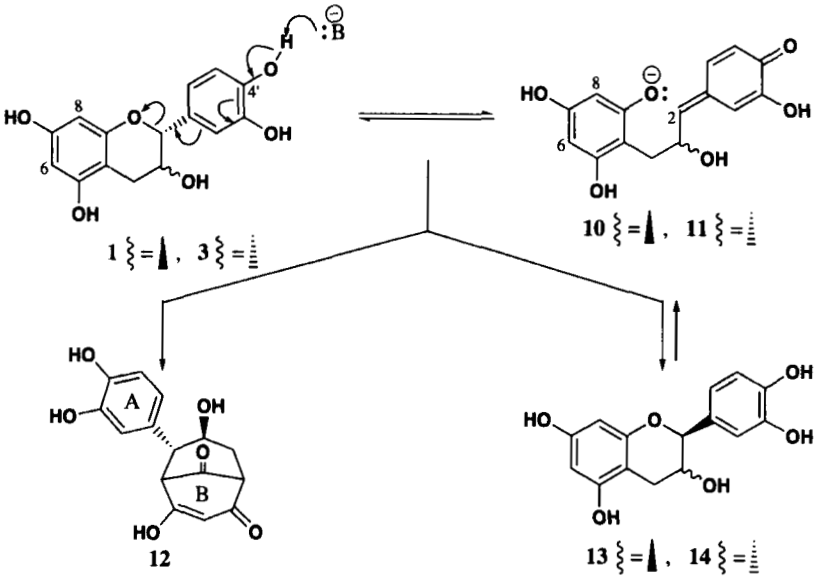
[*]*E-mail: dferreir@olemiss.edu*

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 (δ_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 (δ_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

Acknowledgements.- This work is supported in part by the United States Department of Agriculture Research Service Specific Cooperation Agreement no. 58-6408-2-0009. We thank Mr. Frank Wiggers for assistance with NMR spectroscopy.

REFERENCES

1. T. W. Greene and P. G. M. Wuts, "*Protective Groups in Organic Synthesis*", 3rd ed, p. 266, John Wiley and Sons, Inc., New York, (1999).

2. E. J. Deme, *J. Org. Chem.*, **41**, 3769 (1976).

3. St. V. Kostanecki and J. Tambor, *Ber.*, **35**, 1867 (1902).

4. P. P. Mehta and W. B. Whalley, *J. Chem. Soc.*, 5327 (1963).

5. H. Kawamoto, F. Nakatsubo and K. Marakami, *Mokuzai Gakkaishi*, **37**, 488 (1991); *Chem. Abstr.*, **115**, 279643y (1991).

6. W. Tückmantel, A. P. Kozikowski and L. J. Romanczyk, *J. Am. Chem. Soc.*, **121**, 12073 (1999).

7. S. Miura, T. Midorikawa and N. Awata, *Radioisotopes*, **32**, 225 (1983).

8. G. Goetz, F. Fkyerat, N. Metais, M. Kunz, R. Tabbachi, R. Pezet and V. Pont, *Phytochemistry*, **52**, 759 (1999).

9. L. Li and T. H. Chan, *Org. Lett.*, **3**, 739 (2001).

10. N. T. Zaveri, *Org. Lett.*, **3**, 843 (2001).

11. N. P. Slabbert, *Tetrahedron*, **33**, 821 (1977).

12. K. Freudenberg, O. Bohme and L. Purrmann, *Ber.*, **55**, 1734 (1922).

13. K. Freudenberg and L. Purrmann, *Ber.*, **56**, 1185 (1923).

14. K. Freudenberg and L. Purrmann, *Ann.*, **437**, 274 (1924).

15. K. D. Sears, R. L. Casebier, H. L.Hergert, G. H. Stout and L. E. McCandlish, *J. Org. Chem.*, **39**, 3244 (1974).

16. P. Courbat, A. Weith, A. Albert and A. Pelter, *Helv. Chim. Acta*, **60**, 1665 (1977).

17. J. A. Kennedy, M. H. G. Munro, H. K. J. Powell, L. J. Porter and L. Y. Foo, *Australian J. Chem.*, **37**, 885 (1984).

18. J. A. Kuhnle, J. J. Windle and A. C. Waiss, *J. Chem. Soc. (B)*, 613 (**1969**).

19. O. H. Jensen and J. A. Pedersen, *Tetrahedron*, **39**, 1609 (1983).

20. L. J. Romanczyk, A. P. Kozikowski, W. Tückmantel and M. E. Lippman, *US Patent*, 6,420,572 (2002); *Chem. Abstr.*, **137**, 109159g (2002).

21. J. G. Sweeny and G. A. Iacobucci, *J. Org. Chem.*, **44**, 2298 (1979).

22. J. P. Steynberg, J. F. W. Burger, D. A. Young, E. V. Brandt, J. A. Steenkamp and D. Ferreira, *J. Chem. Soc. Perkin I*, 3323 (**1988**).

23. A. P. Kozikowski, W. Tückmantel and C. George, *J. Org.Chem*, **65**, 5371 (2000).

24. R. J. J. Nel, H. van Rensburg, P. S. van Heerden and D. Ferreira, *J. Chem. Res*, (S), 606, (M), 2610 (**1999**).

(Received September 22, 2003; in final form January 14, 2004)