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Synthesis of modified proanthocyanidins: easy and general introduction of a hydroxy group at C-6 of catechin; efficient synthesis of elephantorrhizol

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Abstract—A general procedure for the oxidation of catechin derivatives is described, leading to the introduction of a new hydroxy group at C-6. This procedure has been applied for the synthesis of elephantorrhizol, a natural flavan-3-ol exhibiting a fully substituted cycle A.

Proanthocyanidins are known as condensed or non-hydrolyzable tannins.[1–3] Many biological activities, particularly a powerful free-radical scavenging[4–9] activity, have been reported for flavonoids, and their investigation is now increasingly important. Most of the described procyanidins **1** involve oligomerization of catechin derivatives **2a**–**d** (Fig. 1). However, other flavan-3-ols have also been described with additional hydroxy groups on their aromatic rings. Gallocatechins **2c**,**d**, exhibiting three hydroxy groups on the B ring, are the most encountered. However, 11 hydroxylation patterns have been reported in the literature involving in some cases the presence of up to four free phenolic groups on the A ring. Recently indeed, two new flavan-3-ols with new hydroxylation patterns on ring A have been described. (+)-3′, 4′, 5, 6, 7, 8-hexahydroxyflavan-3-ol **3** (elephantorrhizol) was identified in *Elephantorrhiza goetzei*[10,11] and 3-acetyl-5-methoxy-7,3′,4′-trihydroxy-8-*O*-glucoside-flavan-3-ol, barbatoflavan **4**, from *Campanula barbata* (Fig. 1).[12] Due to the increasing interest devoted to this type of compounds, according to their potential pharmacological properties, it is of interest

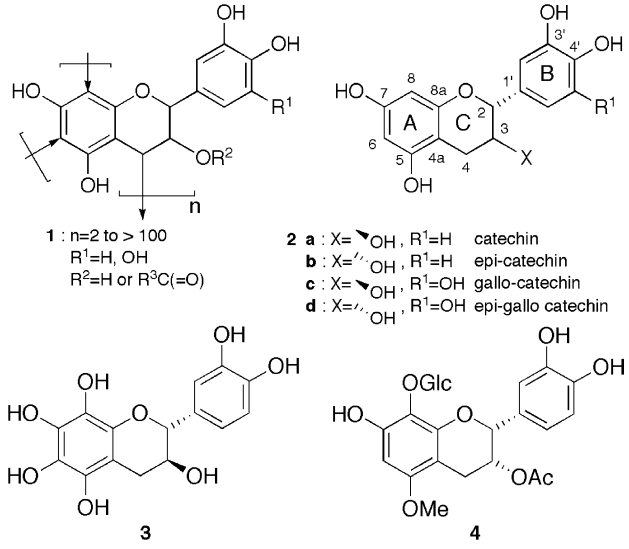

Figure 1.

to investigate structure–activity relationships and, therefore, to have access to synthetically modified flavanols.

Several reports have been already published about the oxidation of flavanoids using various oxidizing reagents[13–15] but, surprisingly, none of them was devoted

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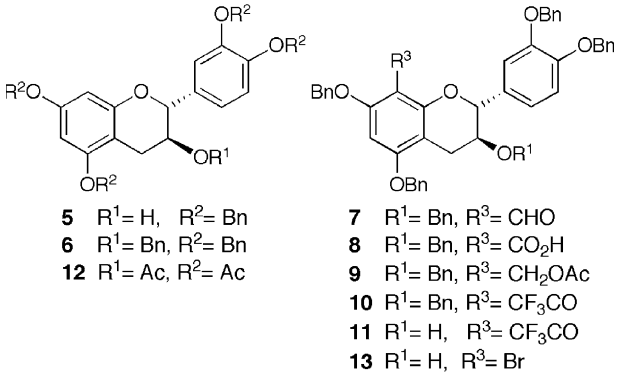
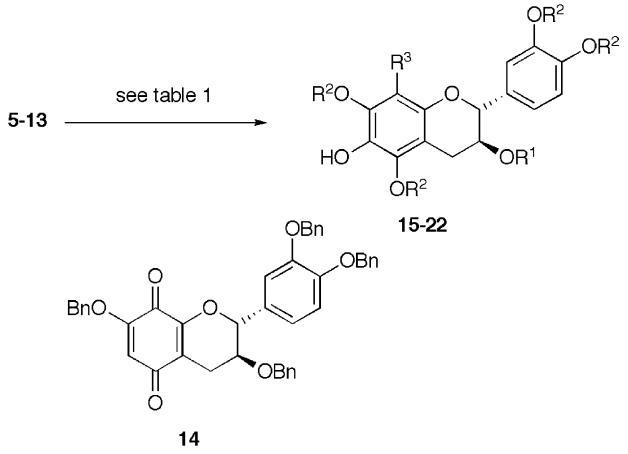


Figure 2.



Scheme 1.

to the hydroxylation of the aromatic ring A of catechin derivatives. Indeed, most of these studies were devoted to the oxidation of flavanoids exhibiting an oxygenated function at C-4, which are known to be very important for the chemical reactivity of flavanoids.

In an ongoing program aimed at the synthesis of modified proanthocyanidins, we were interested in the preparation of modified catechin derivatives involving introduction of substituents either at C-6 and/or C-8 in order to modify their ability to form oligomers. Several procedures are available for the introduction of various substituents at C-8, including an hydroxy group, allowing in particular the synthesis of compounds **5**-**11**,[16] which will be used, beside already reported peracetyl catechin **12** and bromide **13**,[17] (Fig. 2) as starting materials in the present study devoted to the introduction of an hydroxy group at C-6 of catechin derivatives.

Beside numerous unsuccessful attempts, two very promising sets of conditions were found, resulting in a general introduction of a new hydroxy group at C-6. The main results are gathered in Scheme 1 and Table 1 and involve either use of *m*-CPBA or dimethyldioxirane (DMDO).

The most important fact is the regioselectivity of the reaction when performed on compounds with two possible sites of oxidation, namely compounds **5**, **6** and **12**. Indeed, albeit allowing only moderate yielding transformations (10–20%), both sets of experimental procedures yielded only C-6 hydroxylated compounds. The oxidation of **6** in both conditions allowed the characterization of the yellow quinone **14** (traces) as the only C-8 oxidized compound.

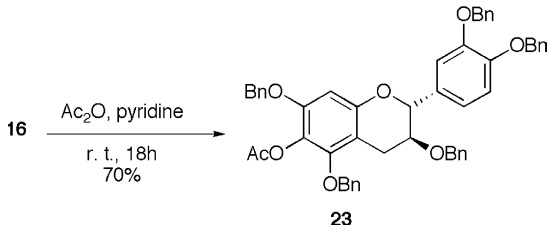
The regiochemistry of the reaction was unambiguously established on compound **23**, obtained through acetylation of **16** (Scheme 2). Indeed, the HSQC/HMBC spectra of **23** allowed a complete attribution of the ^{13}C resonances and the observation, beside other characteristic long range correlations (Fig. 3), of a correlation between the remaining aromatic proton on ring A with C-8a, which is only possible if the proton is located on carbon C-8, thus confirming the structure.

It seems that the experimental conditions involving the use of DMDO as oxidizing agent at low temperature is in most of the cases the more efficient one, as reported for several other flavanoids, and results in good transformation yields, up to 50% in the case of the trifluoroacetylcatechin **10**. Moreover, the presence of an electron-withdrawing group at C-8 seemed to induce a slightly better transformation with DMDO, when yields

Table 1.

	Substrate	Conditions[a]	Temp (°C)	Time (h)	Product	Yield (%)
1	**5**	DMDO	−15	0.6	**15**	10–15
2	**5**	*m*-CPBA, $NaHCO_3$	−10	3	**15**	20
3	**6**	DMDO	−15	0.6	**16**	13
4	**6**	*m*-CPBA, $NaHCO_3$	−10	3	**16**	10–15
5	**7**	DMDO	−40	7.5	**17**	38
6	**8**	*m*-CPBA, $NaHCO_3$	rt	48	**18**	—
7	**8**	DMDO	−15	0.6	**18**	30–45
8	**9**	DMDO	−40	7.5	**19**	34
9	**10**	*m*-CPBA, $NaHCO_3$	rt	48	**20**	9
10	**10**	DMDO	−30	20	**20**	49
11	**11**	*m*-CPBA, $NaHCO_3$	rt	48	**21**	20
12	**11**	DMDO	−30	36	**21**	37
13	**12**	*m*-CPBA or DMDO	—	—	n.r.	—
14	**13**	DMDO	−40	7.5	**22**	33–36

[a] All reactions were carried out in CH_2Cl_2.[18]



Scheme 2.

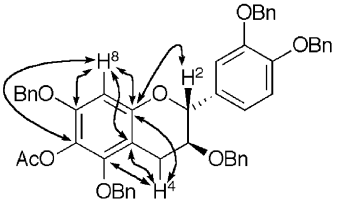


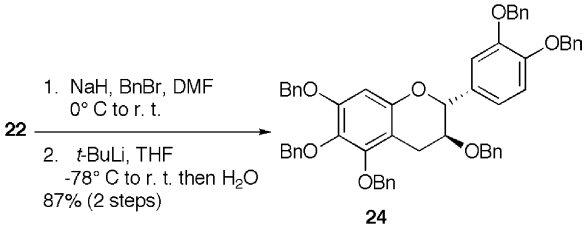
Figure 3. Main ^{1}H–^{13}C long range correlations observed for compound **23**.

obtained with *m*-CPBA were not significantly affected by the substitution pattern at C-8.

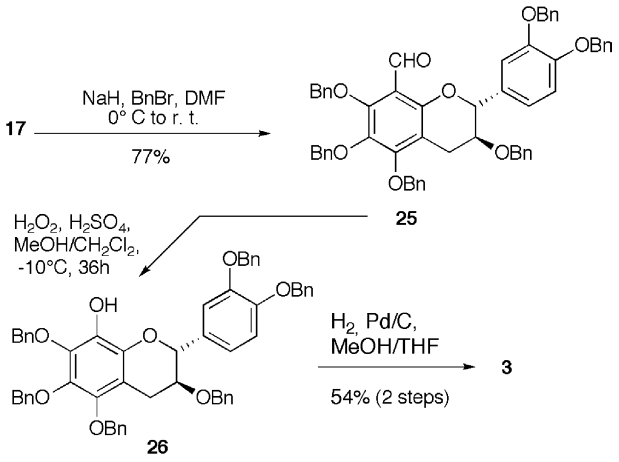
Another important feature of this transformation lies in its versatility. Indeed, the oxidation of bromide **13** results in the formation in ca. 35% yield (Table 1, entry 14) of the desired 6-hydroxy-8-bromocatechin derivative **22**. Hydroxy group at C-6 can be thereafter protected as its benzyl ether and the bromide hydrolyzed (*t*-BuLi, H_2O), finally affording pentahydroxy flavan-3-ol **24**[19] in 87% yield (two steps, Scheme 3). The overall yield of this synthetic sequence is furthermore better than the yield obtained directly from **5**. This result shows that, even if C-6 has been proven to be the more reactive site of catechin derivatives in these conditions, introduction of a bromine atom on carbon C-8 allows the protection of C-8, which is easily removed later through hydrolysis.

The synthesis of elephantorrhizol was thereafter obviously achieved through protection of the hydroxy group at C-6 of aldehyde **17** followed by a Dakin reaction[20] performed on aldehyde **25** (Scheme 4) to furnish hexa-*O*-benzyl elephantorrhizol **26**. Total hydrogenolysis of benzyl groups led to (+)-elephantorrhizol, spectroscopic data of which were in agreement with those reported for the natural product.[11]

These results clearly show the importance of the protection pattern of the phenolic groups of the catechin derivatives in the course of such oxidation reactions, since we were not able to isolate any compounds with an oxidized B ring when other studies[15–17] have demonstrated the sensitivity of this ring to similar oxidative procedures in the presence of free phenolic groups; moreover, the protecting groups used for the protection of the phenolic groups have to be carefully chosen, since the penta-*O*-acetyl catechin **12** did not react in these conditions. Secondly, we have demonstrated the importance of the substituent at C-8 in the yield of the transformation.



Scheme 3.



Scheme 4.

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18. Typical procedure for DMDO mediated oxidation of catechin derivatives: to a solution of **7** (300 mg, 0.39 mmol) in CH_2Cl_2 (6 mL) at −40 °C was added dropwise under argon a solution of DMDO (Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377–2377) (12 mL). The resultant mixture was stirred at −40 °C for 7 h 30 min and evaporated under reduced pressure without warming. The residue was purified by chromatography on silica gel (EtOAc/cyclohexane, 2:8) to give 113 mg (38%) of **17** as a colourless oil.
19. Compound **23**: ^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.22 (CH_3CO), 152.43 (C-8a), 150.52 (C-7), 150.00 (C-5), 149.17 (C-3′, C-4′), 138.00, 137.56, 137.46, 137.37, 136.76 (s, Bn), 132.33 (C-1′), 128.62–127.29 (Bn + C-6), 120.78 (C-6′), 115.29 (C-5′), 114.11 (C-2′), 107.36 (C-4a), 97.99 (C-8), 80.47 (C-2), 75.36 (t, Bn), 74.47 (C-3), 71.79 (t, Bn), 71.61 (t, Bn), 71.35 (t, Bn), 70.93 (t, Bn), 26.75 (C-4), 20.51 (CH_3CO). **24**: ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.06 (s), 150.87 (s), 150.44 (s), 149.04 (s), 138.07 (s), 137.87 (s), 137.80, 137.42 (s), 137.38 (s), 136.99 (s), 136.10 (s), 132.50 (s), 128.73 (d), 128.59 (d), 128.38 (d), 128.16 (d), 128.02 (d), 127.90 (d), 127.72 (d), 127.56 (d), 127.48 (d), 127.41 (d), 120.65 (d), 115.21 (d), 114.04 (d), 107.28 (s), 98.02 (d), 80.25 (d), 75.90 (t), 75.24 (t), 74.55 (d), 71.61 (t), 71.55 (t), 71.32 (t), 70.96 (t), 26.61 (t). **26**: ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.16 (s), 149.07 (s), 142.40 (s), 139.96 (s), 138.84 (s), 137.97 (s), 137.87, 137.80 (s), 137.76 (s), 137.72 (s), 137.51 (s), 137.31 (s), 134.76 (s), 132.14 (s), 128.61 (d), 128.54 (d), 128.21 (d), 128.11 (d), 127.92 (d), 127.56 (d), 127.46 (d), 120.64 (d), 115.21 (d), 114.15 (d), 110.55 (s), 80.33 (d), 76.22 (t), 75.73 (t), 75.47 (t), 74.67 (d), 71.74 (t), 71.61 (t), 71.43 (t), 26.58 (t).
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