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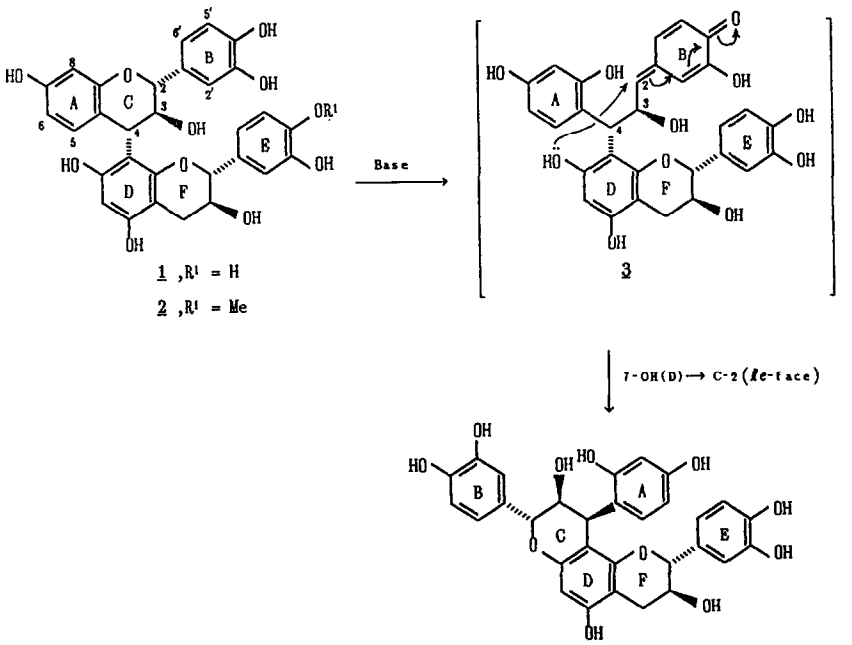
SELECTIVE *O*-METHYLATION OF POLYHYDROXYFLAVAN-3-OLS *via* BENZYL CARBONATES

MARTHA S. VAN DYK, JAN P. STEYNBERG, PETRUS J. STEYNBERG, AND DANEEL FERREIRA*

Department of Chemistry, University of the Orange Free State,
P.O. Box 339, Bloemfontein, 9300 South Africa

Abstract —— The flavan-3-ols (+)-catechin and (-)-epicatechin were selectively transformed to their 3′,4′-di-*O*-methyl- and 5,7-di-*O*-methyl-ethers respectively *via* benzyl carbonates. Such a regioselectivity is facilitated by marked differences in the pKa values of the phenolic hydroxyl groups and by the ability of the *o*-dihydroxy funtionality of the pyrocatechol B-ring to form borate complexes under mild basic conditions.

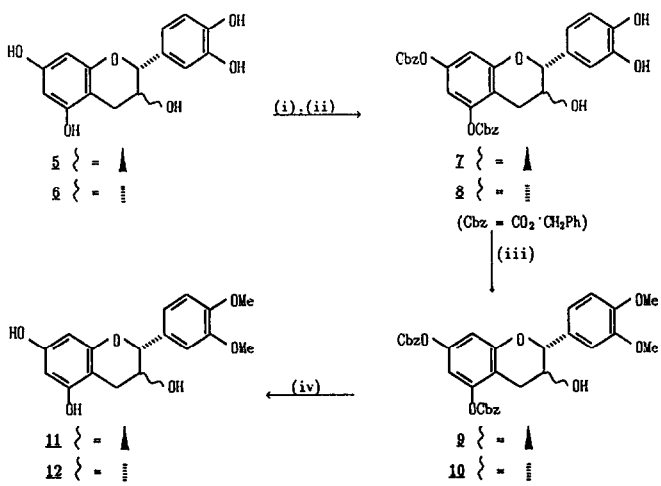
We have recently demonstrated the natural occurrence and biomimetic synthesis of phlobatannins[1-3], a novel class of C-ring isomerized condensed tannins. These compounds, *eg* 4, presumably originate[3] *via* transformation of *eg* a (-)-fisetinidol-(4*α*,8)-(+)-catechin biflavanoid 1 to an intermediate B-ring quinone-methide 3 and subsequent pyran recyclization *via* 7-OH(D) and the *Re*-face at C-2 in 3. The susceptibility of both the B- and E-rings in



1 ,R¹ = H
2 ,R¹ = Me
3
4

oligoflavanoids of type 1 to quinone-methide formation, however, causes undesired epimerization and regio-isomerization[2,3]. Substantial differences in the pKa values[4] of the phenolic hydroxy groups of (+)-catechin 5 allowed these complications to be resolved by selective methylation of the 4'-OH function[5] prior to acid-catalyzed coupling with (2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*-flavan-3,3',4,4',7-pentaol, hence leading to the 'protected' profisetinidin 2 incapable of quinone-methide formation at the E-ring[3]. The utility of such an approach is, however, limited by the formation of the 3'-*O*-methyl ether in equal proportions and its further methylation preferentially at 7-OH(A). Since a 3',4'-di-*O*-methyl-(+)-catechin moiety in the biflavanoid precursor would serve the same goal as the 4'-*O*-methyl ether, an alternative approach towards the synthesis of derivative 11 had to be adopted. We now disclose our results of relevance to the selective methylation of (+)-catechin 5 and (-)-epicatechin 6 *via* benzyl carbonates[6], such an approach being based on the ability of the *o*-dihydroxy functionality of the pyrocatechol B-ring to form borate complexes[7] under mild basic conditions.

Thus, treatment[8] of (+)-catechin 5 [(2*R*,3*S*)-2,3-*trans*-flavan-3,3',4',5,7-pentaol] in an aqueous solution of sodium hydroxide/boric acid (adjusted to pH 9 with conc. HCl) with two molar equivalents of benzyl chloroformate at ambient temperature, afforded the 5,7-di-*O*-benzyloxy carbonyl derivative 7 in *ca* 50% yield (Scheme). Subsequent methylation with ethereal diazomethane at 0°C (*ca* 1h) gave the 3',4'-di-*O*-methyl-5,7-di-*O*-benzyloxy carbonyl derivative 9 which was deprotected by catalytic hydrogenation (10% Pd/C, MeOH) to afford 3',4'-di-*O*-methyl-(+)-catechin 11; both these steps occurring in quantitative yields. A



Scheme

Reagents and Conditions: (i) $NaOH/H_3BO_3/HCl$ (pH 9), r.t.; (ii) $PhCH_2OCOCl$ (2 eq.), r.t., 1.5h (iii) CH_2N_2/MeOH, 0°C, *ca* 1h; (iv) H_2, Pd/C, MeOH, 12h.

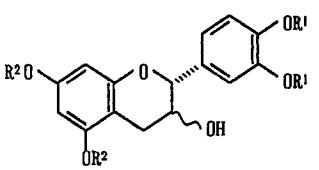
similar sequence applied to (-)-epicatechin 6 [(2*R*,3*R*)-2,3-*cis*-flavan-3,3',4',5,7-pentaol]

gave derivatives 8 and 10, and eventually the 3′,4′-di-*O*-methyl-(-)-epicatechin 12 in a yield comparable to that of the (+)-catechin derivative 11. The locations of the methyl groups in both 11 and 12 were confirmed by NOE techniques (^{1}H NMR in $CDCl_3$) which indicated the selective association of H-5′ (δ6.896 and 6.898 for 11 and 12 respectively) with 4′-OMe [δ3.783 (3.5%[a]) and 3.782 (4.1%[a]) for 11 and 12 respectively] and of 2′-H (δ7.012 and 7.171 for 11 and 12 respectively) with 3′-OMe [δ3.783 (1.7%[a]) and 3.777 (5.8%[a]) for 11 and 12 respectively.

Although the esterification step for both (+)-catechin 5 and (-)-epicatechin 6 proceeded in only 50% yields, the recovery from flash chromatography on silica represented *ca* 85% of the starting mass. The mass differences may be ascribed to the presence of phenols 5 and 6 as well as mono-, tri-, and tetra-*O*-benzyloxy carbonyl derivatives of both 5 and 6; the benzyl carbonates could be recycled successfully *via* hydrogenation of the respective mixtures over 10% Pd/C.

The high susceptibility of procyanidins [5-OH(A) analogues of profisetinidins, *eg* 1] to interflavanyl bond cleavage at alkaline pH[9], hampers their study under these conditions[10]. Since this bond rupture, occurring *via* an A-ring quinone-methide[9], may be prevented by protection at both 5- and 7-OH of the 'upper' (+)-catechin or (-)-epicatechin moieties, adaptation of the above protocol towards the synthesis of 5,7-di-*O*-methyl-(+)-catechin 17 and (-)-epicatechin 18 became an objective.

Separate treatment[11] of (+)-catechin 5 and (-)-epicatechin 6 with benzyl chloroformate in a KH_2PO_4/NaOH buffer solution (pH 8) at ambient temperature afforded the 3′,4′-di-*O*-ben-



13 ≀ = ▲ , R¹ = $CO_2{\cdot}CH_2Ph$, R² = H
14 ≀ = ⋮ , R¹ = $CO_2{\cdot}CH_2Ph$, R² = H
15 ≀ = ▲ , R¹ = $CO_2{\cdot}CH_2Ph$, R² = Me
16 ≀ = ⋮ , R¹ = $CO_2{\cdot}CH_2Ph$, R² = Me
17 ≀ = ▲ , R¹ = H, R² = Me
18 ≀ = ⋮ , R¹ = H , R² = Me

[a]Approximate values due to overlap or close proximity of signals.

zyloxy carbonyl derivatives 13 and 14 in 40% yield, such regioselectivity being attributable to higher pKa values of 3'- and 4'-OH compared to those of 5- and 7-OH[4]. Flash chromatography on Silica again facilitated *ca* 75% mass recovery hence permitting deprotection of mono-, tri-, and tetra-*O*-benzyloxy carbonyl derivatives and recycling as before. Methylation of the dibenzyl carbonates 13 and 14 with diazomethane for *ca* 6h at 0°C afforded the 5,7-di-*O*-methyl-3',4'-di-*O*-benzyloxy carbonyl derivatives 15 and 16 which were quantitatively transformed to the 5,7-di-*O*-methyl derivatives 17 and 18 by catalytic hydrogenation (10% Pd/C). The locations of the methyl groups were again confirmed by NOE experiments which indicated the selective association of 7-OMe (δ3.723 and 3.737 for 15 and 16 respectively) with both H-8 [δ6.060 (15.8%) and 6.103 (15.8%) for 15 and 16 respectively] and H-6 [δ6.137 (4.6%) and 6.130 (5.5%) for 15 and 16 respectively], and of 5-OMe (δ3.785 and 3.777 for 15 and 16 respectively) with H-6 (16.6 and 16.5% for 15 and 16 respectively).

These results demonstrate the utility of benzyl carbonates as selective protecting groups in polyhydroxyflavan-3-ols. The utilization of the (+)-catechin and (-)-epicatechin derivatives 17 and 18 in our study of the mechanism of base-catalyzed conversions of procyanidin-type condensed tannins will be the subject of a full paper.

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8. General procedure: A 50% solution of benzyl chloroformate (2 molar equivalents) in toluene was added dropwise over a period of 30 min. with vigorous stirring to a solution of (+)-catechin (100 mg) in a mixture of NaOH (0.5 g)/H_3BO_3 (1 g) in H_2O (50 ml) (pH adjusted to 9 with conc. HCl) at ambient temperature. Stirring was continued for 1h, the mixture was acidified (3M HCl) and extracted with EtOAc. The extract was dried (Na_2SO_4), evaporated to dryness, and the mixture resolved by flash chromatography on silica (EtOAc-hexane, 11:10).
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11. The benzyl chloroformate solution (2 molar equivalents) was added to a solution of (+)-catechin (200 mg) in a mixture of KH_2PO_4 (0.68 g), NaOH (0.183 g), and H_2O (96 ml). Work-up and purification were according to the procedure in 8.

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