Pergamon

Tetrahedron Vol. 50, No. 43, pp. 12477-12488, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00791-8

Oligomeric Flavanoids. Part 17[a]. Absolute Configurations of Flavan-3-ols and 4-Arylflavan-3-ols *via* the Mosher Method

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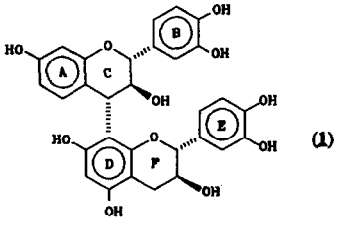
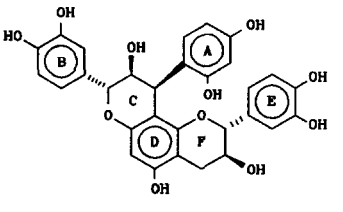
Abstract: ^{1}H NMR analysis of *R*-(+)- and *S*-(-)-α-methoxy-α-trifluoromethylphenyl acetic acid (MTPA) esters of flavan-3-ols and 4-arylflavan-3-ols permits assessment of the absolute configurations at C-3 of these condensed tannin structural units.

Despite its impact on the assessment of the absolute configuration at the point of the interflavanyl linkage in biflavanoid proanthocyanidins[1-3], the circular dichroic approach is hampered by several inherent deficiencies. Most prominent among these are the influence of the C-ring conformation on the sign of the



(1)



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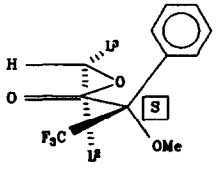

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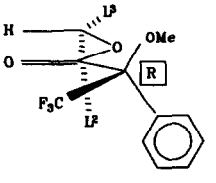


(4)

crucial high-amplitude Cotton effect at low wavelength (220-240 nm) which often leads to incorrect assignments for 4-arylflavan-3-ols[4] and phlobatannins[5,6], its inconsistency at the triflavanoid level[7], and the inability to facilitate assignment of the absolute configuration at the stereocentres of the DEF moiety in biflavanoids, *e.g.* (1) and phlobatannins, *e.g.* (2).

a Part 16. Cronjé A.; Steynberg, J.P.; Brandt, E.V.; Young, D.A.; Ferreira, D. *J. Chem. Soc., Perkin Trans. 1*, 1993, 2467.

The Mosher ester technique[8,9], using α-methoxy-α-trifluoromethylphenyl acetic acid (MTPA) esters, represents a convenient chemical process for establishing the absolute configuration of secondary alcohols[8-15]. In the configuration correlation model for correlating ^{1}H NMR shifts and absolute stereochemistry of *S*-(-)- and *R*-(+)-MTPA esters (3) and (4) the α-trifluoromethyl group, carbonyl, and carbinyl hydrogen are approximately eclipsed. The protons of the substituent which eclipses the phenyl ring [L^3 for the *S*-(-)-MTPA ester (3) and L^2 for the *R*-diastereomer (4)] are, therefore, more highly shielded, presumably as a result of the diamagnetic shielding by the phenyl moiety. The difference in chemical shift of any set of like protons in the diastereomeric *S*- and *R*-MTPA esters ($\Delta\delta_H = \delta_S - \delta_R$) will thus be positive in value when associated with L^2 and negative in value when associated with L^3.

The unique structural features in condensed tannin constituent units raised some fundamental issues concerning the applicability of the Dale and Mosher protocol for assigning absolute configuration, *e.g.* the effect(s) of the juxtaposed aromatic ring(s) in flavan-3-ols (5), 4-arylflavan-3-ols (22), biflavanoids (1), and phlobatannins (2) on the preferential alignment of carbinyl hydrogen, carbonyl, and α-trifluoromethyl group, and of the influence of *bis*-MTPA ester[15] in *e.g.* biflavanoids (1) and phlobatannins (2). Results relevant to a Mosher's approach on a series of flavan-3-ols and 4-arylflavan-3-ols as models for representative classes of oligomeric proanthocyanidins are discussed here. *R*-(+)-MTPA esters, *e.g.* (7) were first prepared in low yield by the standard procedure[8] while both diastereomers were recently accessable in excellent yield *via* a modified method[14].

RESULTS AND DISCUSSION

In order to circumvent the necessity of utilizing both *R*-(+)- and *S*-(-)-MTPA esters, initial efforts were directed towards the less expensive acetyl- and *R*-(+)-MTPA esters. Thus, comparison of the ^{1}H NMR data (Table 1) at 300 MHz in $CDCl_3$ of the catechin acetyl- and *R*-(+)-MTPA esters (6) and (7) reveals a

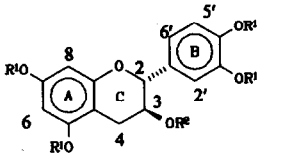
Table 1. ^{1}H NMR peaks (p.p.m.) of the acetyl, *R*-(+)-, and *S*-(-)-MTPA esters of catechin (6), (7), (8), and epicatechin (10), (11), and (12) in $CDCl_3$ (24°C) at 300 MHz. Splitting patterns and J-values (Hz) are given in parentheses.

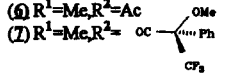
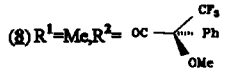
Ring	H	(6)	(7)	(8)	(10)	(11)	(12)
A	6	6.07(d,2.2)	6.10(s)	6.09(d,2.2)	6.09(d,2.2)	6.05(d,2.2)	6.10(d,2.2)
	8	6.15(d,2.2)	6.10(s)	6.11(d,2.2)	6.19(d,2.2)	6.11(d,2.2)	6.15(d,2.2)
B	2	6.86(d,2.0)	6.77(d,2.0)	6.91(d,2.0)	7.02(d,2.0)	7.01(d,2.0)	6.82(d,2.0)
	5	6.80(d,8.0)	6.74(d,8.0)	6.85(d,8.0)	6.84(d,8.5)	6.83(d,8.5)	6.69(d,9.5)
	6	6.89(dd,2.0,8.0)	6.86(dd,2.0,8.0)	6.98(dd,2.0,8.0)	6.95(dd,2.0,8.5)	6.93(dd,2.0,8.5)	6.81(dd,2.0,9.5)
C	2	5.00(d,7.0)	4.85(d,8.5)	4.91(d,9.0)	4.99(br.d,*ca.*1.0)	5.10(br.d,*ca.*1.0)	5.08(br.d,*ca.*1.0)
	3	5.32(ddd,5.5,7.0, 7.0)	5.59(ddd,6.0,8.7, 9.0)	5.49(ddd,6.0,9.0, 9.0)	5.42(m)	5.57(ddd,1.5,2.5, 4.0)	5.59(ddd,1.0,2.5, 4.0)
	4*ax.*	2.64(dd,7.0,17.0)	2.78(dd,9.0,16.0)	2.63(dd,9.0,16.0)	2.92(m)	2.97(dd,4.0,18.0)	2.99(dd,4.0,18.0)
	4*eq.*	2.87(dd,5.5,17.0)	3.18(dd,6.0,16.0)	3.25(dd,6.0,16.0)	2.92(m)	3.09(dd,2.5,18.0)	3.08(dd,2.5,18.0)
	OMe	3.74,3.75,3.83, 3.84, each s	3.73(5-A),3.79 (7-A),3.76(3-B), 3.87(4-B),each s, 3.37 (m, MTPA)	3.73(5-A),3.78 (7-A),3.81(3-B), 3.89(4-B),each s, 3.29(m,MTPA)	3.76,3.77,3.87, 3.89,each s	3.73(5-A),3.74 (7-A),3.75(3-B), 3.88(4-B),each s, 3.23 (m, MTPA)	3.78(5-A),3.77 (7-A),3.65(3-B), 3.86(4-B),each s, 3.24 (m, MTPA)

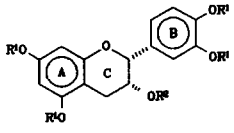
conspicuous shielding of the B-ring protons in the *R*-(+)-MTPA ester (7) relative to the chemical shifts of these protons in the acetyl derivative [Δδ-0.09, 2-H(B); -0.06, 5-H(B); -0.03, 6-H(B)]. Whereas the B-ring

Table 2. ^{1}**H NMR peaks (p.p.m.) of the *R*-(+)- and *S*-(-)-MTPA esters of fisetinidol (14), (15), robinetinidol (17), *ent*-robinetinidol (21), and *ent*-epifisetinidol (19) and (20) in $CDCl_3$ ($24^\circ C$) at 300 MHz. Splitting patterns and J-values (Hz) are given in parentheses**

Ring	H	(14)	(15)	(17)	(21)	(19)	(20)
A	5	6.98(d,8.5)	6.96(d,8.5)	6.99(d,8.5)	6.99(d,8.5)	6.97(d,8.5)	6.92(d,8.5)
	6	6.53(dd,2.5,8.5)	6.52(dd,2.5,8.5)	6.55(dd,2.5,8.5)	6.55(dd,2.5,8.5)	6.53(dd,2.5,8.5)	6.48(dd,2.5,8.5)
	8	6.48(d,2.5)	6.47(d,2.5)	6.49(d,2.5)	6.50(d,2.5)	6.51(d,2.5)	6.47(d,2.5)
B	2	6.80(d,2.5)	6.91(d,2.0)	-	-	6.82(d,2.0)	7.00(d,2.5)
	5	6.75(d,8.5)	6.85(d,8.5)	-	-	6.68(d,8.5)	6.84(d,8.5)
	6	6.88(dd,2.5,8.5)	6.98(dd,2.0,8.5)	-	-	6.80(dd,2.0,8.5)	6.93(dd,2.5,8.5)
	2/6	-	-	6.55(s)	6.66(s)	-	-
C	2	4.95(d,8.5)	4.97(d,9.0)	4.93(d,8.5)	4.96(d,9.0)	5.14(br.d,*ca.*1.0)	5.17(br.d,*ca.*1.0)
	3	5.60(ddd,5.5,8.5, 8.5)	5.51(ddd,5.5,9.0, 9.0)	5.63(ddd,5.5,8.5, 9.0)	5.52(ddd,5.5,9.0, 9.0)	5.55(ddd,1.5,2.5, 4.0)	3.54(ddd,1.5,3.0, 4.0)
	$4_{ax.}$	3.03(dd,8.5,16.0)	2.87(dd,9.0,16.0)	3.05(dd,9.0,15.0)	2.90(dd,9.0,15.0)	3.06(dd,2.5,18.0)	3.07(dd,3.0,18.0)
	$4_{eq.}$	3.18(dd,5.5,16.0)	3.24(dd,5.5,16.0)	3.22(dd,5.5,15.0)	3.29(dd,5.5,15.0)	3.32(dd,4.0,18.0)	3.31(dd,4.0,18.0)
	OMe	3.75,3.78,3.87, each s ,3.36 (m, MTPA)	3.74,3.81,3.99, each s, 3.26 (m, MTPA)	3.76,3.78,3.80, 3.84,each s, 3.36 (m,MTPA)	3.77,3.80,3.84, 3.86,each s, 3.28 (m,MTPA)	3.64,3.77,3.86, each s, 3.20 (m, MTPA)	3.72,3.75,3.89, each s, 3.22 (m, MTPA)



(5) R^1=R^2=H
(6) R^1=Me,R^2=Ac
(7) R^1=Me,R^2= 
(8) R^1=Me,R^2= 

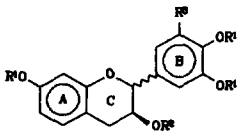


(9) R^1=R^2=H
(10) R^1=Me,R^2=Ac
(11) R^1=Me,R^2= 
(12) R^1=Me,R^2= 

protons of the *R*-(+)-MTPA ester (28) of the fisetinidol-(4β,2)-phloroglucinol (26) are shielded compared to those of the acetate (27) [Δδ -0.15, 2-H(B); -0.18, 5-H(B); -0.11, 6-H(B)] (Table 3), the shielding/deshielding phenomena are inconsistent or less convincing for the fisetinidol-(4α,2)-phloroglucinol esters (24) and (23) [Δδ -0.05, 2-H(B); -0.01, 5-H(B); +0.03, 6-H(B)] (Table 3) and for the epicatechin esters (11) and (10) [Δδ -0.01, 2-H(B), -0.01, 5-H(B); -0.02, 6-H(B)] (Table 1). Such discrepancies discriminate against the utilization of these parameters in constructing a correlation model for assessment of the absolute stereochemistry of these classes of flavanoids.

A different picture, however, emerges on comparison of the chemical shifts of the B-ring protons in the *R*-(+)- and *S*-(-)-MTPA esters of the methyl ethers of the flavan-3-ols, catechin (5), epicatechin (9) (Table 1),

fisetinidol (13), and *ent*-epifisetinidol (18), and of the *R*-(+)-MTPA methyl ether ester (17) of robinetinidol (16) and its diastereomer (21) (Table 2). These protons are consistently shielded in the *R*-(+)-MTPA esters (7), (14), and (19) of the flavan-3-ols with 3*S* configuration [catechin (5), fisetinidol (13), and *ent*-epifisetinidol (18)] relative to their chemical shifts in the *S*-(-)-MTPA esters (8), (15), and (20) [Δδ -0.22, 2-H(B); -0.11, 5-H(B); -0.12, 6-H(B) for esters (7) and (8), Δδ -0.11, 2-H(B); -0.10, 5-H(B); -0.10, 6-H(B)



(13) ≡ , R^1=R^2=R^3=H

(14) ≡ , R^1=Me,R^3=H,R^2= 

(15) ≡ , R^1=Me,R^3=H,R^2= 

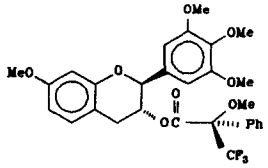
(16) ≡ , R^1=R^2=H,R^3=OH

(17) ≡ , R^1=Me,R^3=OMe,R^2= 

(18) ≡ , R1=R^2=R^3=H

(19) ≡ , R^1=Me,R^3=H,R^2= 

(20) ≡ , R^1=Me,R^3=H,R^2= 

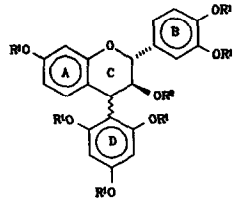


(21)

for esters (14) and (15), Δδ -0.18, 2-H(B); -0.16, 5-H(B); -0.13, 6-H(B) for esters (19) and (20)]. On the contrary, for epicatechin (9) with its 3*R* configuration the B-ring protons are substantially deshielded in the *R*-(+)-MTPA ester (11) compared to their shifts in the *S*-(-)-diastereomer (12) [Δδ +0.18, 2-H(B); +0.14, 5-H(B); +0.12, 6-H(B)]. An interesting case, the principle of which formed the foundation of our initial communication[16], is exemplified by the chemical shifts of the B-ring protons in the *R*-(+)-MTPA esters (17) and (21) of the robinetinidol-type analogues with their enantiomerically related flavan-3-ol moieties. The pyrogallol-type B-ring protons in the *R*-(+)-ester (17) exhibit similar shielding effects [Δδ -0.11, 2-/6-H(B)] compared to those of ester (21) which constitutes the enantiomer of the *S*-(-)-MTPA ester of the methyl ether of robinetinidol (16). By the same token the catechin and epicatechin *S*-(-)-MTPA esters (8) and (12) represent the enantiomers of the *R*-(+)-MTPA esters[16] of the methyl ethers of *ent*-catechin and *ent*-epicatechin respectively hence eliminating the necessity to use both enantiomers.

Attention was next focused on 4-arylflavan-3-ols as models for biflavanoid proanthocyanidins, *e.g.* (1) and related analogues with rearranged pyran heterocycles, *e.g.* (2). The fisetinidol-(4,2)-phloroglucinol isomers (22) and (26)[17] were selected to mimic the fisetinidol-catechin profisetinidins[18], the fisetinidol-(4,4)-resorcinol analogues (30) and (33)[17] as models for the bis-fisetinidol profisetinidins[19], and the catechin-(4,2)-phloroglucinol adducts (36) and (39)[17,20], and epicatechin-(4,2)-phloroglucinol (42)[20,21] representing the procyanidins of the B-class[22]. These compounds introduce an unknown feature into the Mosher protocol *i.e.* the effect of steric compression of the ester functionality by the close proximity of the aromatic B- and D-rings.

In the isomeric 4-arylflavan-3-ols (22) and (26) a consistent shielding of B-ring protons is evident in the diastereomeric *R*-(+)-MTPA esters (24) and (28) compared to those of the *S*-(-)-MTPA esters (25) and (29) [Δδ -0.12, 2-H(B); -0.07, 5-H(B); -0.06, 6-H(B) for esters (24) and (25), Δδ -0.20, 2-H(B); -0.19, 5-H(B); -0.14, 6-H(B) for esters (28) and (29)] (Table 3). A similar consistency in the shielding of B-ring protons was also prevalent in the ester derivatives of the remaining profisetinidin-type 4-arylflavan-3-ol isomers (30) and (33) [Δδ -0.13, 2-H(B); -0.08, 5-H(B); -0.02, 6-H(B) for esters (31) and (32), Δδ -0.12, 2-H(B); -0.16,



(22) ≡, $R^1=R^2=H$

(23) ≡, $R^1=Me, R^2=Ac$

(24) ≡, $R^1=Me, R^2=$ 

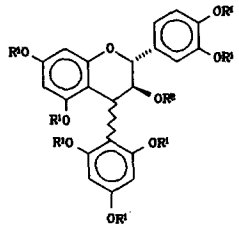
(25) ≡, $R^1=Me, R^2=$ 

(26) ≡, $R^1=R^2=H$

(27) ≡, $R^1=Me, R^2=Ac$

(28) ≡, $R^1=Me, R^2=$ 

(29) ≡, $R^1=Me, R^2=$ 



(36) ≡, $R^1=R^2=H$

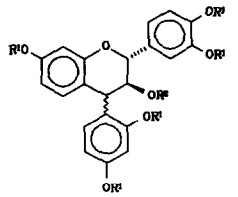
(37) ≡, $R^1=Me, R^2=$ 

(38) ≡, $R^1=Me, R^2=$ 

(39) ≡, $R^1=R^2=H$

(40) ≡, $R^1=Me, R^2=$ 

(41) ≡, $R^1=Me, R^2=$ 



(30) ≡, $R^1=R^2=H$

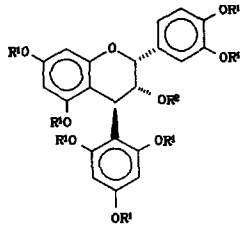
(31) ≡, $R^1=Me, R^2=$ 

(32) ≡, $R^1=Me, R^2=$ 

(33) ≡, $R^1=R^2=H$

(34) ≡, $R^1=Me, R^2=$ 

(35) ≡, $R^1=Me, R^2=$ 



(42) $R^1=R^2=H$

(43) $R1=Me, R^2=$ 

(44) $R^1=Me, R^2=$ 

Table 3. ^{1}H NMR peaks (p.p.m.) of the acetyl, *R*-(+)-, and *S*-(-)-MTPA esters of fisetinidol-(4α,2)-phloroglucinol (23), (24), (25), and fisetinidol-(4β,2)-phloroglucinol (27), (28), and (29) in $CDCl_3$ (24°C) at 300 MHz. Splitting patterns and J-values (Hz) are given in parentheses

Ring	H	(23)	(24)	(25)	(27)	(28)	(29)
A	5	6.60(dd,1.2,8.5)	6.62(dd,1.5,8.5)	6.59(d,8.5)	6.76(dd,1.0,8.5)	6.77(d,8.5)	6.72(d,8.5)
	6	6.36(dd,2.5,8.5)	6.37(dd,2.5,8.5)	6.37(dd,2.5,8.5)	6.37(dd,2.5,8.5)	6.39(dd,2.5,8.5)	6.38(dd,2.5,8.5)
	8	6.46(d,2.5)	6.46(d,2.5)	6.46(d,2.5)	6.50(d,2.5)	6.49(d,2.5)	6.52(d,2.5)
B	2	6.99(d,2.0)	6.94(d,2.0)	7.06(d,2.0)	6.91(d,2.0)	6.76(d,2.0)	6.96(d,2.0)
	5	6.84(d,8.5)	6.83(d,8.5)	6.90(d,8.5)	6.80(d,8.5)	6.62(d,8.5)	6.81(d,8.0)
	6	7.04(dd,2.0,8.5)	7.07(dd,2.0,8.5)	7.13(dd,2.0,8.5)	6.95(dd,2.0,8.5)	6.84(dd,2.0,8.5)	6.98(dd,2.0,8.0)
C	2	4.91(d,10.0)	4.96(d,10.0)	5.04(d,10.0)	5.21(d,10.0)	5.33(d,10.0)	5.46(d,9.5)
	3	5.99(t,10.0)	6.55(dd,10.0, 10.0)	6.61(dd,10.0, 10.0)	5.50(dd,6.5,10.0)	5.76(dd,7.5,10.0)	5.68(dd,7.5,9.5)
	4	4.86(dd,1.2,10.0)	5.10(d,10.0)	5.01(d,10.0)	4.92(d,6.5)	5.22(d,7.5)	5.23(d,7.5)
D	4/6	6.14,6.06(both d,2.5)	6.12,6.18(both d,2.2)	6.04,6.09(both d,2.2)	6.14,6.09(both d,2.5)	6.05,6.17(both d,2.5)	5.99,6.10(both d,2.2)
	OMe	3.54,3.71,3.77, 3.81,3.86,3.89, each s	3.63,3.67,3.78, 3.81,3.85,3.92, each s, 2.87 (m, MTPA)	3.61,3.67,3.71, 3.79,3.83,3.90, each s, 2.86 (m, MTPA)	3.32,3.74,3.76, 3.79,3.85(x2), each s	3.31,3.70,3.74, 3.76,3.79,3.83, each s,2.84 (br.s, MTPA)	3.35,3.74,3.75, 3.78,3.80,3.87, each s,3.20(br.s, MTPA)

Table 4. ^{1}H NMR peaks (p.p.m.) of the *R*-(+)-, and *S*-(-)-MTPA esters of fisetinidol-(4α,4)-resorcinol (31), (32) and fisetinidol-(4β,4)-resorcinol (34) and (35) in $CDCl_3$ (24°C) at 300 MHz. Splitting patterns and J-values (Hz) are given in parentheses.

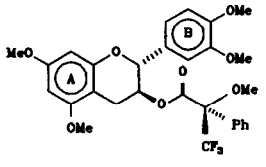
Ring	H	(31)	(32)	(34)	(35)
A	5	6.59(d,8.5)	5.56,6.57[b](d,8.5)	6.81(d,8.5)	6.74(d,8.5)
	6	6.40(dd,2.5,8.5)	6.39(dd,2.5,8.5)	6.45(dd,2.5,8.5)	6.42(dd,2.5,8.5)
	8	6.46,6.48[b](d,2.5)	6.39(d,2.5)	6.53(d,2.5)	6.58(d,2.5)
B	2	6.96,7.00[b](d,2.0)	7.09,7.06[b](d,2.0)	6.77(d,2.5)	6.89(d,2.5)
	5	5.81,6.80[b](d,8.5)	6.89,6.87[b](d,8.5)	6.63(d,8.5)	6.79(d,8.0)
	6	7.04,7.01[b](dd,2.0,8.5)	7.06,7.08[b](dd,2.0,8.5)	6.78(dd,2.5,8.5)	6.91(dd,2.5,8.0)
C	2	5.02,5.01[b](d,10.0)	5.09,5.07[b](d,9.5)	5.28(d,7.5)	5.45(d,6.0)
	3	-[a],6.20[b](t,10.0)	-[a],6.26[b](t,9.5)	5.72(dd,5.0,7.5)	5.66(dd,4.5,6.0)
	4	-[a],4.74[b](d,10.0)	-[a],4.63[b](d,9.5)	4.94(d,5.0)	4.79(d,4.5)
D	2	6.46,6.45[b](d,2.5)	6.46(d,2.5)	6.46(d,2.5)	6.36(d,2.5)
	5	7.14,7.09[b](d,8.0)	7.10,7.03b(d,8.0)	6.34(d,8.5)	6.06(d,8.5)
	6	6.48,6.49[b](dd,2.5,8.0)	6.45(dd,2.5,8.0)	6.83(dd,2.5,8.5)	6.69(dd,2.5,8.5)
	OMe	3.72(x2),3.81,3.83,3.87, each s, 2.85 (m ,MTPA)	3.62,3.72,3.79,3.84,3.90, each s,2.83(m,MTPA)	3.73,3.74,3.76,3.77,3.82, each s,2.99(m,MTPA)	3.67,3.73,3.78,3.80,3.85, each s,3.41(m,MTPA)

[a]Undefinable due to restricted rotation
[b]Chemical shift at 80°C in $CDCl_3$

Table 5. ^{1}H NMR peaks (p.p.m.) of the *R*-(+)-, and *S*-(-)-MTPA esters of catechin-(4α,2)-phloroglucinol (37), (38), and catechin-(4β,2)-phloroglucinol (40), (41), and epicatechin-(4β,2)-phloroglucinol (43) and (44) in $CDCl_3$ (24°C) at 300 MHz. Splitting patterns and J-values (Hz) are given in parentheses.

Ring	H	(37)	(38)	(40)	(41)	(43)	(44)
A	6 8	5.94(d,2.5) 6.09(d,2.5)	5.94(d,2.5) 6.10(d,2.5)	6.01(d,2.5) 6.15(d,2.5)	5.89(d,2.5) 6.17(d,2.5)	6.21(d,2.5) 5.98(d,2.5)	6.22(d,2.5) 6.04(d,2.5)
B	2 5 6	6.88(d,2.0) 6.72(d,8.0) 6.97(dd,2.0,8.0)	6.98(d,2.0) 6.83(d,8.5) 7.04(dd,2.0,8.5)	6.70(d,2.00) 6.58(d,8.5) 6.79(dd,2.0,8.5)	6.91(d,2.0) 6.78(d,8.0) 6.95(dd,2.0,8.0)	7.00(d,2.0) 6.80(d,8.5) 6.90(dd,2.0,8.5)	6.81(d,2.0) 6.66(d,8.5) 6.78(dd,2.0,8.5)
C	2 3 4	4.69(d,8.5) 6.22(dd,8.5,10.0) 4.89(d,10.0)	4.78(d,7.5) 6.33(dd,7.5,8.5) 4.82(d,8.5)	5.28(d,10.5) 5.68(dd,6.5,10.5) 5.30(d,6.5)	5.41(d,10.5) 5.66(dd,6.5,10.5) 5.27(d,6.5)	5.45(d,2.0) 5.48(dd,2.0,2.5) 4.71(d,2.5)	5.42(d,2.0) 5.48(dd,2.0,2.5) 4.70(d,2.5)
D	4/6	6.05(br.s)	5.97(br.s)	6.06,6.17(each d,2.5)	6.06,6.09(each d,2.5)	6.10(br.s)	6.09(br.s)
	OMe	3.34,3.66(x2), 3.74(x2),3.76, 3.79,each s,2.98 (m,MTPA)	3.31,3.55(x2), 3.66,3.72,3.77, 3.84,each s,2.97 (m,MTPA)	3.30,3.57,3.65, 3.74,3.78(x2), 3.82,each s,2.84 (m,MTPA)	3.33,3.55,3.71, 3.75,3.76,3.77, 3.86,each s,3.29 (m,MTPA)	3.54,3.77(x2), 3.79(x2),3.82, 3.88,each s,3.24 (m,MTPA)	3.57,3.65,3.80, 3.82(x2),3.86, each s,3.23 (m, MTPA)

5-H(B); -0.13, 6-H(B) for esters (34) and (35)] (Table 4), and for the procyanidin-type analogues (36) and (39) [Δδ -0.10, 2-H(B); -0.11, 5-H(B); -0.07, 6-H(B) for esters (37) and (38), Δδ -0. 21, 22-H(B); -0.20, 5-H(B); -0.16, 6-H(B) for esters (40) and (41)] (Table 5) all with 3*S* absolute stereochemistry. In the procyanidin-type 4-arylflavan-3-ol with 3*R* absolute configuration (42), however, the B-ring protons are



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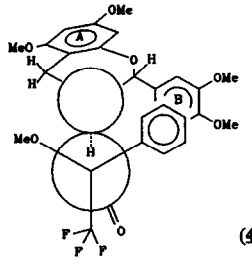

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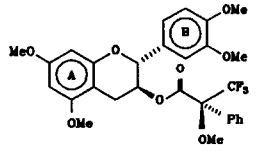

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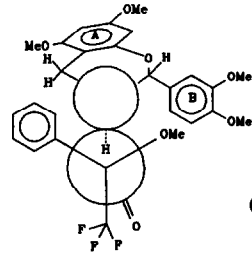

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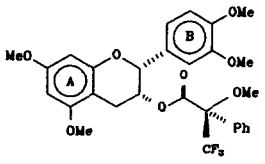

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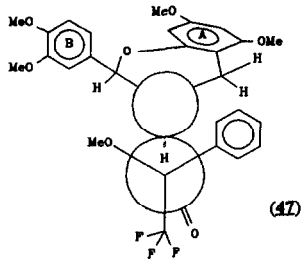

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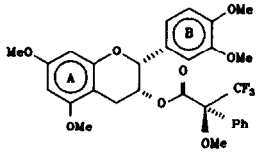

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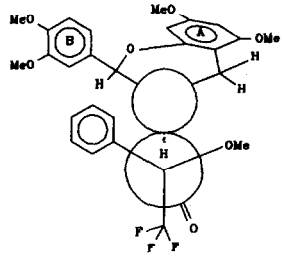

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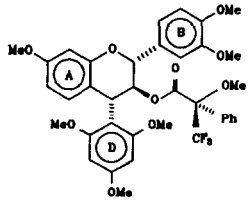

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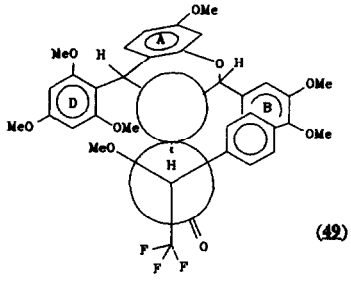

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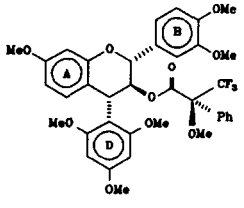

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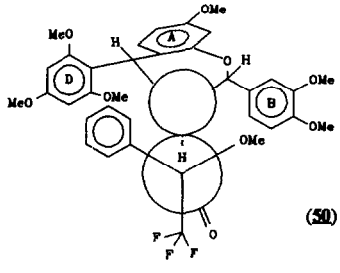

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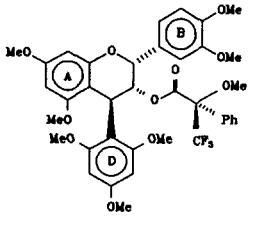

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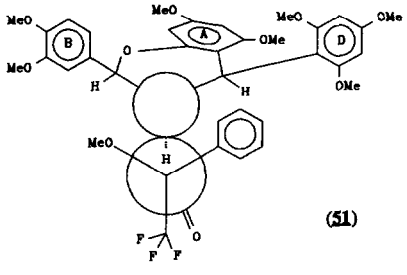

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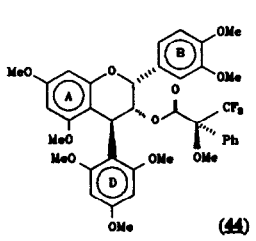

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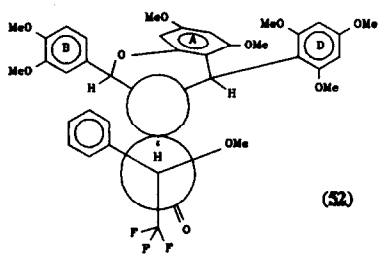

(52)

deshielded in the *R*-(+)-MTPA ester (43) relative to those in the *S*-(-)-MTPA ester (44) [Δδ +0.19, 2-H(B); +0.14, 5-H(B); +0.13, 6-H(B)] (Table 5).

Although a shielding of like magnitude may be anticipated for D-ring protons in the *S*-(-)-MTPA esters (25), (29), (32), and (35) compared to those in the *R*-(+)-diastereomers (24), (28), (31), and (34), the fact that 4- and 6-H(D) cannot be differentiated in the phloroglucinol adducts (24), (25), (28), and (29) (Table 3) in conjunction with the small and inconsistent shielding/deshielding in the resorcinol analogues (31), (32), (34), and (35) (Table 4), would disfavour the utilization of these parameters in the construction of a model for correlating absolute stereochemistry. The irregular shielding/deshielding of D-ring protons is presumably attributable to a less perfect alignment (*vide infra*) of the D-ring and the phenyl ring of the ester moiety compared to that of the latter ring and the B-ring of esters with 3*S*-configuration.

However, the consistency of the shielding/deshielding effects in the different sets of *R*-(+)- and *S*-(-)-MTPA esters of the flavan-3-ols and 4-arylflavan-3-ols is compatible with conformations in which the α-trifluoromethyl group, carbonyl, and carbinyl hydrogen are in the same plane and are approximately eclipsed. In conjunction with the porposals of Dale and Mosher[8], this subsequently permits the construction of configuration correlation models (45) and (46) for the *R*-(+)- and *S*-(-)-MTPA esters (7) and (8) of a flavan-3-ol with 3*S* configuration, and (47) and (48) for Mosher esters (11) and (12) of a flavan-3-ol with 3*R* absolute stereochemistry. Similar correlation models, (49) and (50), are also feasible for the *R*-(+)- and *S*-(-)-MTPA esters, (24) and (25) of 4-arylflavan-3-ols with 3*S* absolute configuration and (51) and (52) for those esters, (43) and (44), of 4-arylfavan-3-ols possessing 3*R* stereochemistry. These conformational models represent crucial arrangements in which the α-phenyl substituent of the *R*-(+)-MTPA ester functionality is preferentially orientated towards the B-ring of both flavan-3-ols and 4-arylflavan-3-ols with 3*S* absolute

Table 6. ^{1}H NMR peaks (p.p.m.) of the B-ring protons of the *R*-(+)- and *S*-(-)-MTPA esters (7) and (8) of catechin at different temperatures and in different solvents

Solvent/Temp.	2-H(*R*)	2-H(*S*)	5-H(*R*)	5-H(*S*)	6-H(*R*)	6-H(*S*)
$CDCl_3$ (23°C)	6.78	6.92	6.74	6.85	6.87	6.98
$CDCl_3$ (40°C)	6.79	6.92	6.74	6.85	6.87	6.98
$CDCl_3$ (60°C)	6.82	6.92	6.75	6.85	6.86	6.96
$CDCl_3$ (80°C)	6.84	6.93	6.76	6.85	6.86	6.95
C_6D_6 (24°C)	6.74	6.89	6.49	6.52	6.83	6.95
$(CD_3)_2CO$ (24°C)	6.98	7.12	6.85	6,98	6.90	7.03

configuration and away from the B-ring or towards the D-ring in respectively flavan-3-ols and 4-arylflavan-3-ols with 3*R* stereochemistry. These orientations are exactly reversed for the α-phenyl substituent of the *S*-(-)-MTPA ester moiety. The protons of that aromatic ring which is juxtaposed with the α-phenyl substituent of the ester unit are then shielded by the mutual anisotropic effect.

A notable feature of the shielding/deshielding of B- and D-ring protons is the greater consistency of these effects, where applicable, at the B-ring. Dreiding models indicate improved alignment between the α-phenyl substituent of the ester unit and the B-ring in the *R*-(+)-MTPA ester (24) compared to that between the phenyl group and the D-ring in the *S*-(-)-MTPA ester (25). The geometry of the former alignment involving the B-ring conforms with an offset face-to-face arrangement required for π-stacking (stabilizing π-σ-attraction)[23]. Such an attracting interaction presumably stabilizes an eclipsed conformation of type (45) which is essential for the preferential and consistent shielding of B-ring protons in the *R*-(+)-MTPA esters of flavan-3-ols and 4-arylflavan-3-ols with 3*S* absolute configuration and in the *S*-(-)-MTPA esters of these oligoflavanoid constituent units with 3*R* stereochemistry. In order to define the chemical shifts of 3- and 4-H(C) in the esters (31) and (32) their ^{1}H NMR spectra had to be recorded at 80^{0}C. At this elevated temperature the shielding of B-ring protons in the *R*-(+)-MTPA ester (31) relative to that in the *S*-(-)-MTPA ester (32) is maintained thus demonstrating that conformations of type (45) are predominant over a wide temperature range. Such a consistency in the shielding of B-ring protons in *R*-(+)-MTPA esters with varying temperature, was confirmed by comparison of chemical shifts of these protons in the *R*-(+)- and *S*-(-)-MTPA esters (2) and (8) of catechin at different temperatures (Table 6). The same consistency is apparently also maintained in different solvents, *e.g.* $CDCl_3$, C_6D_6, and $(CD_3)_2CO$ (Table 6). Both these observations are significant since the accumulation of ^{1}H NMR data at elevated temperatures and in various solvents are often prerequisites for the structural elucidation of condensed tannins.

The Mosher esters of the 2,3-*trans*-3,4-*cis*-4-arylflavan-3-ols (34) and (35) exhibit conspicuously small J-values for C-ring protons [$^3J_{2,3}$ 7.5 and 6.0 Hz for (34) and (35) resp.; $^3J_{3,4}$ 5.0 and 4.5 Hz for (34) and (35) resp.] hence reflecting a significant equilibrium between A- and E-conformers[24]. This phenomenon profoundly effects the Cotton effect at low wavelengths which has often lead to erroneous assignment of absolute configuration at C-4[4-6,24]. The shielding of B-ring protons in the *R*-(+)-MTPA ester (34) relative to that in the *S*-(-)-ester (35) is nevertheless retained thus indicating that the Mosher method is less sensitive to conformational fluctuations than the circular dichroic approach. Introduction of the additional stereocentre in the *R*-(+)- and *S*-(-)-MTPA esters of the flavan-3-ol derivatives appears to enhance the amplitude of the Cotton effects due to the ^1L_a and ^1L_b transitions (at about 240 and around 280 nm respectively) of the aromatic A- and B-ring chromophores[2,25].

We have thus demonstrated the utility of the classical Dale and Mosher method for defining the absolute configuration of flavan-3-ols and 4-arylflavan-3-ols as important constituent units in oligomeric proanthocyanidins. In conjunction with ^{3}J values the unambiguous assignment of stereochemistry at C-3 would facilitate establishment of absolute configurations at all stereogenic centres of condensed tannin nuclei.

EXPERIMENTAL

T.l.c. was performed on DC-Plastikfolien Kieselgel 60 PF_{254} (0.25 mm) and the plates sprayed with H_2SO_4-HCHO (40:1, v/v) after development. Preparative plates (p.l.c.) [Kieselgel PF_{254} (1.0 mm)] were air-dried and used without prior activation. Methylation was performed with an excess of diazomethane in methanol-diethyl ether over 48 h at -15°C. ^{1}H N.m.r. spectra were, unless otherwise specified, recorded on a Bruker AM-300 spectrometer for solution in $CDCl_3$ at 25°C and with TMS as internal standard. Esterification reactions were carried out under nitrogen. All the flavan-3-ols and 4-arylflavan-3-ols mentioned are known compounds and were fully characterised as their methyl ether acetates. Hence, the

MTPA esters of these compounds represent simple derivatives of structures that were unambiguously determined.

Preparation of Mosher Acid Chloride

Oxalyl chloride (7.125 equiv) was added to a solution of *(R)*-(+)- or *(S)*-(-)-MTPA (1.5 equiv) and DMF (1.5 equiv) in hexane (1 ml/0.024 mmol of MTPA) at room temperature. After 1 h the mixture was filtered and concentrated in vacuo and the residu used without further purification.

Preparation and Purification of Mosher Esters

MTPA acid chloride (1.5 equiv) was added to the methyl ether (1 equiv) of the flavan-3-ol or 4-arylflavan-3-ol in DCM (0.1 ml/0.01 mmol of substrate) in triethyl amine (6 equiv). The mixture was left at room temperature for 1 h and the reaction progress monitored by t.l.c. HCl (0.1M, 50 ml) was added, and the products extracted with EtOAc (3 x 100 ml). The organic phase was washed with $NaHCO_3$ (5%, 3 x 50 ml), brine, dried (Na_2SO_4) and concentrated under reduced pressure. Subsequent purification by p.l.c. [hexane-ethyl acetate-acetone (6.3.1)] afforded the product as pale buff amorphous solids.

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(*Received in UK* 15 *August* 1994; *accepted* 9 *September* 1994)