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ABSOLUTE CONFIGURATIONS OF FLAVAN-3-OLS AND 4-ARYLFLAVAN-3-OLS *VIA* A MODIFIED MOSHER'S METHOD

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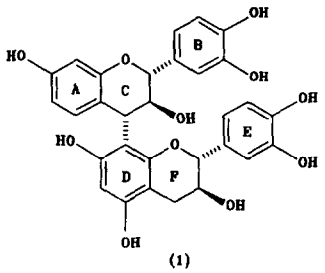
Abstract — ^{1}H NMR Analysis of *R*-(+)-α-methoxy-α-trifluoromethylphenyl acetic acid (MTPA) esters of different sets of enantiomeric flavan-3-ols and 4-arylflavan-3-ols respectively, permits assessment of the absolute configurations at C-3 of these condensed tannin structural units.

Despite its considerable impact on the assessment of the absolute configuration at the point of interflavanyl linkage in biflavanoid condensed tannins[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 crucial high-amplitude Cotton effect at low wavelength (220-240 nm) which often leads to erroneous assignments for 4-arylflavan-3-ols[4] and phlobatannins[5,6], its inconsistency at the triflavanoid level[7], and the inability to facilitate appraisal of the absolute configuration at the chiral centres of the DEF moiety in biflavanoids, *e.g.* 1 and phlobatannins, *e.g.* 2.



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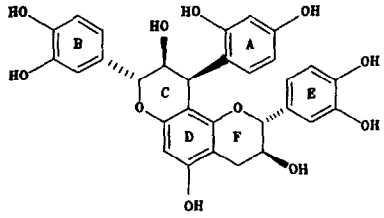

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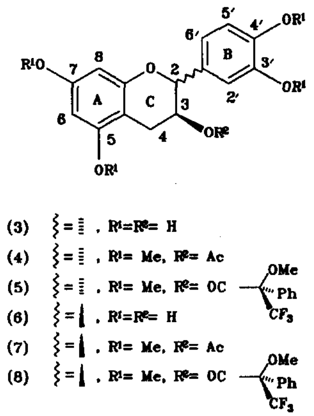
Mosher's method[8], using α-methoxy-α-trifluoromethylphenyl acetic acid (MTPA) esters, represents a convenient chemical process for determining the absolute configuration of secondary alcohols[8-12]. In the configuration correlation model for correlating ^{1}H NMR shifts and absolute stereochemistry of *R*-(+)- and *S*-(-)-MTPA esters the α-trifluoromethyl group, carbonyl, and carbinyl hydrogen are approximately eclipsed, these groups being viewed *via* an 'extended Newman projection' in which the intervening ester linkage is omitted. The protons of the substituent which eclipses the phenyl ring in such an extended Newman projection is then always upfield, presumably as a result of the diamagnetic shielding it experiences by the phenyl ring.

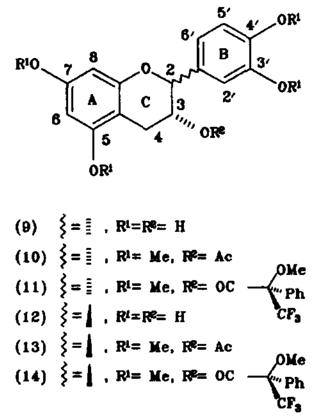
The unique structural features in condensed tannin constituent units raised some fundamental issues concerning the applicability of the Dale and Mosher protocol for assigning absolute configuration, *e.g.* the effect(s) of the juxtaposed aromatic ring(s) in flavan-3-ols 3, 4-arylflavan-3-ols 15, phlobatannins 2, and biflavanoids 1 on the preferential alignment of carbinyl hydrogen, carbonyl, and α-trifluoromethyl group, and of the hitherto unknown influence of *bis*-MTPA ester in *e.g.* biflavanoids 1 and phlobatannins 2. Availability of a variety of enantiomeric flavan-3-ols, 4-arylflavan-3-ols, and phlobatannins hence prompted preliminary

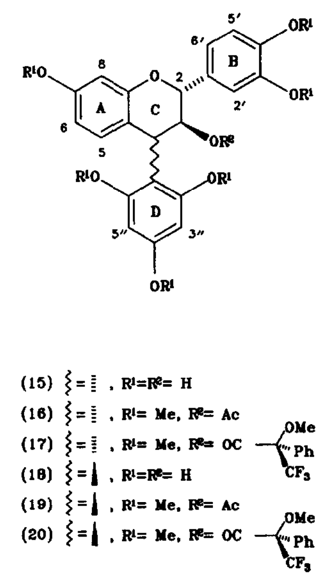
investigations involving comparison of the chemical shifts of appropriate protons in acetyl and *R*-(+)-MTPA esters. Results relevant to such a modified Mosher's approach on the flavan-3-ols (+)- and (-)-catechin 3 and 12[13], (-)- and (+)-epicatechin 9 and 6[13], the 2,3-*trans*-3,4-*trans*-4-arylflavan-3-ols 15[2] and 21[6], and the 2,3-*trans*-3,4-*cis*-4-arylflavan-3-ols 18[2] and 24[6] are discussed here. The *R*-(+)-MTPA esters, *e.g.* 5, were prepared from the methyl ethers and *R*-(+)-MTPA *via* standard literature procedures[8].

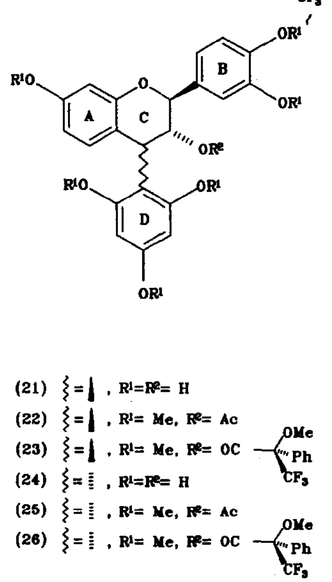
Initial efforts at circumventing the necessity of utilizing both *R*-(+)- and *S*-(-)-MTPA esters were focussed on the acetyl and *R*-(+)-MTPA esters. Thus, comparison of the ^{1}H NMR data at 300 MHz in $CDCl_3$ of the (+)-catechin acetyl and *R*-(+)-MTPA esters 4 and 5 reveals a conspicuous shielding of the B-ring protons in the *R*-(+)-MTPA ester 5 relative to the chemical shifts of these protons in the acetyl derivative 4 [Δδ -0.10, 2-H(B); -0.07, 5-H(B); -0.03, 6-H(B)]. In the (-)-catechin derivatives the B-ring protons are deshielded in the *R*-(+)-MTPA ester 14 relative to those of the acetate 13 [Δδ +0.04, 2-H(B); +0.04, 5-H(B); +0.08, 6-H(B)]. Whereas the B-ring protons of the (+)-epicatechin *R*-(+)-MTPA ester 8 are shielded compared to those of the acetate 7 [Δδ -0.20, 2-H(B); -0.26, 5-H(B); -0.03, 6-H(B)], the shielding/deshielding phenomena are inconsistent for the (-)-epicatechin esters 11 and 10 [Δδ -0.01, 2-H(B); -0.12, 5-H(B); +0.09, 6-H(B)]. Similar disparities are also evident from comparisons of the ^{1}H NMR data of the *R*-(+)-MTPA 17, 23 and acetyl 16, 22 esters of the (2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*-4-arylflavan-3-ol 15 and its enantiomer 21, and of the same derivatives 20, 26 and 19, 25 of the (2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*cis*-4-arylflavan-3-ol 18 and its enantiomer 24. Such inconsistencies 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*-(+)-MTPA esters of the two sets of enantiomeric flavan-3-ols. These protons are conspicuously shielded in the diastereomeric esters 5 and 8 of the



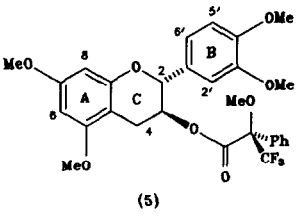






flavan-3-ols with 3*S* configuration [(+)-catechin 3 and (+)-epicatechin 6] relative to their chemical shifts in the esters 11 and 14 of analogues having 3*R* configuration [(-)-catechin 12 and (-)-epicatechin 9] [$\Delta\delta$ -0.19, 2-H(B); -0.14, 5-H(B); -0.12, 6-H(B) for the (+)- and (-)-catechin esters 5 and 14. $\Delta\delta$ -0.14, 2-H(B); -0.11, 5-H(B); -0.11, 6-H(B) for the (+)- and (-)-epicatechin esters 8 and 11].

In the two sets of enantiomeric 4-arylflavan-3-ols a similar and consistent shielding of B-ring protons is evident in the diastereomeric *R*-(+)-MTPA esters 17 and 20 of analogues possessing 3*S* configuration 15 and 18 compared to those in the esters 23 and 26 of compounds with 3*R* configuration 21 and 24 [$\Delta\delta$ -0.09, 2-H(B); -0.06, 5-H(B); -0.05, 6-H(B) for the all-*trans* esters 17 and 23. $\Delta\delta$ -0.20, 2-H(B); -0.19, 5-H(B); -0.14, 6-H(B) for the *trans-cis* esters 20 and 26]. By the same token the D-ring protons of the *R*-(+)-MTPA esters 23 and 26 of the 4-arylflavan-3-ols with 3*R* configuration 21 and 24 are shielded relative to the chemical shifts of the corresponding protons in the diastereomeric esters 17 and 20 of analogues with 3*S* configuration 15 and 18 [$\Delta\delta$ -0.09, -0.10 and -0.06, -0.07, 3- and 5-H(D) for the all-*trans*- 23



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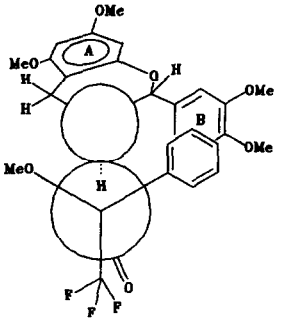

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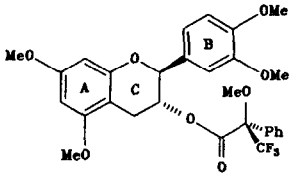

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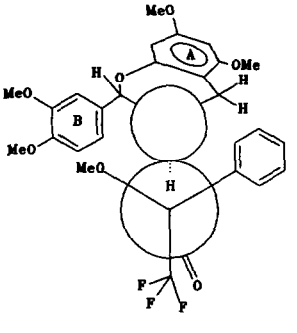

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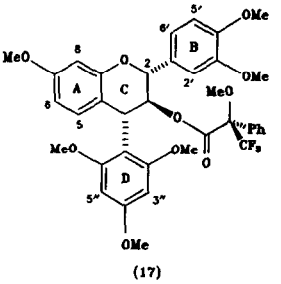

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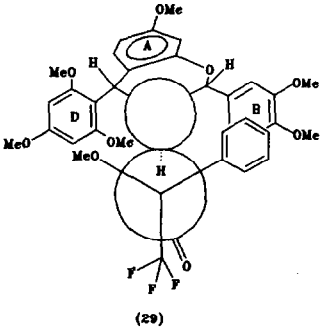

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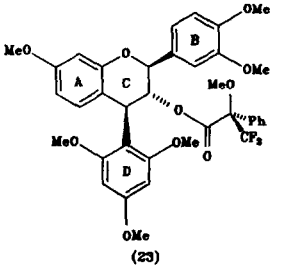

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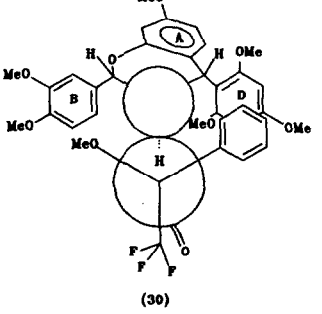

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and 17 and *trans-cis*-esters 26 and 20 respectively].

The consistency of these shielding effects in the *R*-(+)-MTPA esters of the different groups of enantiomeric 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 proposals of Dale and Mosher[8], this subsequently permits the construction of configuration correlation models 27 and 28 for flavan-3-ols with respectively 3*S* 5 and 3*R* 14 configurations and 29 and 30 for 4-arylflavan-3-ols with respectively 3*S* 17 and 3*R* 23 configurations. These conformational models represent crucial arrangements in which the α-phenyl substituent of the *R*-(+)-MTPA ester moiety is preferentially orientated towards the B-ring of both flavan-3-ols and 4-arylflavan-3-ols with 3*S* absolute configuration, and towards the D-ring of 4-arylflavan-3-ols with 3*R* absolute stereochemistry. The protons of that aromatic ring which is juxtaposed with the αphenyl substituent of the ester unit are then shielded by the mutual anisotropic effect.

It should be emphasized that the observed shielding effects on B-ring protons in *R*-(+)-MTPA esters of flavan-3-ols and on B- or D-ring protons in the *R*-(+)-MTPA esters of 4-arylflavan-3-ols were exclusively facilitated by the availability of both enantiomers, *e.g.* 3 and 12, in each instance. These shielding effects would obviously also be induced when using both *R*-(+)- and *S*-(-)-MTPA esters in the classical Dale and Mosher sense. The utility of such an approach is presently being investigated, our ultimate aim being the assessment of absolute configuration at C-3 where only one isomer is available. In conjunction with ^3J values such unambiguous assignment of stereochemistry at C-3 would then permit definition of absolute configurations at all chiral centres of condensed tannin nuclei.

Acknowledgements

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