Absolute Configuration of Atropisomeric *m*-Terphenyl-type Flavan-3-ols

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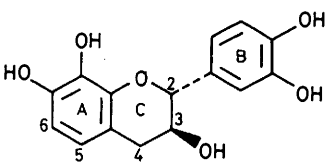
The absolute configuration about both biphenyl linkages in a series of atropisomeric (2*R*,3*S*)-2,3-*trans*-3-acetoxy-6,8-bis-[(2*R*,3*S*)-2,3-*trans*-3-acetoxy-3′,4′,7,8-tetramethoxyflavan-5-yl]-3′,4′,5,7-tetramethoxyflavans {[5,6:5,8]-bis-(+)-[mesquitol]-(+)-catechins} were established by nuclear Overhauser effect difference spectroscopy. This approach is based on association of relevant heterocyclic acetoxy protons with aromatic methoxy groups in close proximity of the bonding axes.

The natural occurrence and biomimetic synthesis of a novel class of condensed tannins based on bi- and *m*-ter-phenyl-type flavan-3-ols have recently been demonstrated by us.[1–3] These oligomers presumably originate from oxidative phenol coupling of the predominant metabolite, (2*R*,3*S*)-2,3-*trans*-3′,4′,7,8-tetrahydroxyflavan-3-ol [(+)-mesquitol (1)], to give [5,6]-bis-(+)-mesquitol and similar condensation with (+)-catechin (2) [(2*R*,3*S*)-2,3-*trans*-3′,4′,5,7-tetrahydroxyflavan-3-ol], leading to atropisomeric [5,8]-(+)-mesquitol-(+)-catechins (3) and (4), and eventually also to the [5,6:5,8]-bis-[(+)-mesquitol]-(+)-catechins [*m*-terphenyl-type flavan-3-ols (5)]. Definition of [*P*]-helicity [(*S*)-conformation] about the biphenyl bond for one of the [5,8]-(+)-mesquitol-(+)-catechins (3) was accomplished by nuclear Overhauser effect (n.O.e.) difference spectroscopy (^{1}H homonuclear), while [*M*]-helicity for the remaining atropisomer (4) was inferred from absence of stereochemically significant interflavanyl n.O.e. effects. The latter phenomenon also precluded assignment of absolute configuration to the four atropisomeric [5,6:5,8]-*m*-terphenyls (5) and a single synthetic [5,6]-(+)-mesquitol-(+)-catechin (6).



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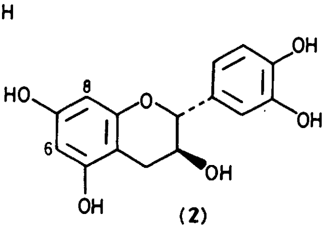

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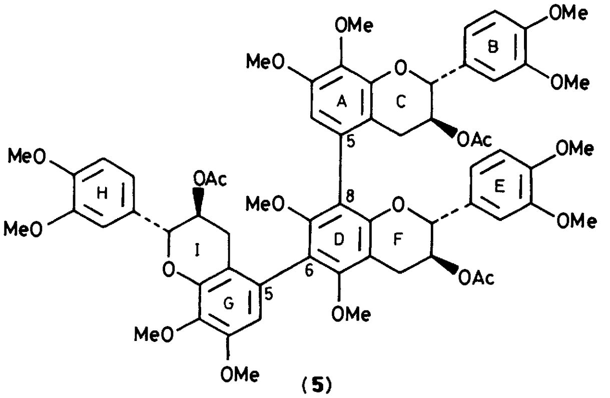

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Initially these studies were based on n.O.e. associations originating from ^{1}H dipolar interactions between aromatic–heterocyclic and methoxy protons. Subsequent elaboration of these effects to heterocyclic acetoxy protons was successfully implemented in defining the absolute configuration of biphenyl-type bis-(+)-catechins (*cf.* ref. 3), such experiments, however, requiring an increased number of scans for each resonance. A similar approach on the *m*-terphenyls now results in the definition of conformation about both biphenyl linkages in all four atropisomers.

Results and Discussion

In order to verify the applicability of the aforementioned approach to the atropisomeric *m*-terphenyls, the dimeric (+)-mesquitol-(+)-catechins (3) and (4) of known absolute configuration were first investigated. Thus, in the (*S*)-atropisomer (3) the anticipated weak n.O.e. association (0.17%) between 3-OAc(F; δ 1.99) and H-6(A; δ 6.42) was observed, while the effect (0.30%)† between 7-OMe(D; δ 3.82) and 3-OAc(C; δ 1.91) confirmed [*M*]-helicity and an (*R*)-conformation for atropisomer (4). The weak n.O.e. association (0.32%) between 7-OMe(A; δ 3.70) and 3-OAc(F; δ 1.96) in conjunction with conformational analysis (Dreiding models), similarly defines [*M*]-helicity and thus (*R*)-absolute configuration for the synthetic (*cf.* ref. 2) [5,6]-(+)-mesquitol-(+)-catechin (6).

Owing to the complexity of the c.d. spectra (*cf.* ref. 2) of the *m*-terphenyl dodecamethyl ether triacetates (7)—(10), and their non-crystallinity, both the exciton chirality approach of Nakanishi[4] and the classical *X*-ray crystallographic method are inapplicable for the determination of the absolute configuration about their biphenyl bond, thus leaving high-resolution n.m.r. the only plausible alternative for solving this problem. Although extensive overlap of signals in both aromatic, heterocyclic, and methoxy regions at 300 MHz renders complete assignment of proton spin systems impossible, the well separated A and G ring 'residual' proton singlets, the strongly shielded 5- and 7-methoxy resonances of ring D, and the three separate acetoxy signals in all four cases (Table 1) provided reference signals for observation of potentially sterochemical significant interflavanyl n.O.e. associations. Owing to anisotropic shielding by both A and G rings, the 7-methoxy protons of the D ring are anticipated to resonate at higher field than those of 5-OMe (anisotropic shielding by ring G only). This was confirmed by observation of an n.O.e. effect from 7-OMe (D) to both residual A and G ring singlets and from 5-OMe(D) to the G ring singlet only, thus unambiguously defining four of the resonances (Table 2) of paramount importance to our present objectives. Finally, n.O.e. associations

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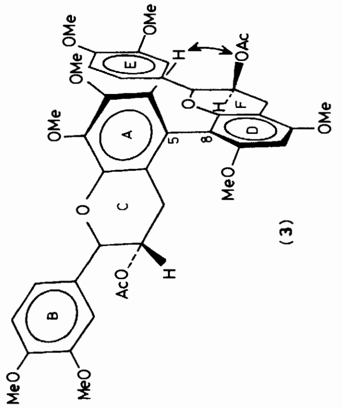
† Approximation due to partial overlap of methoxy resonances.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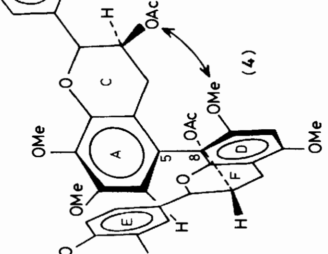
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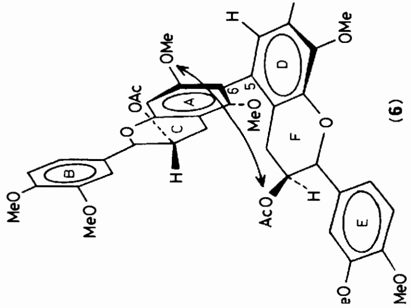
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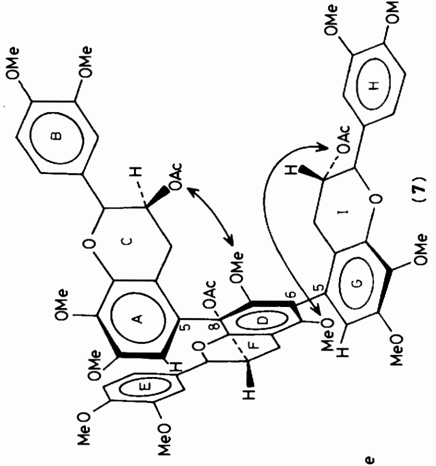
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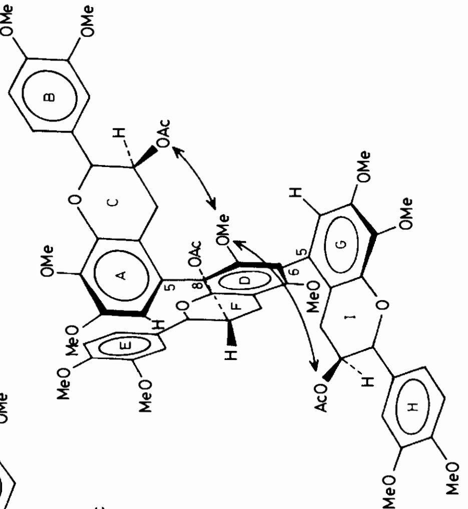
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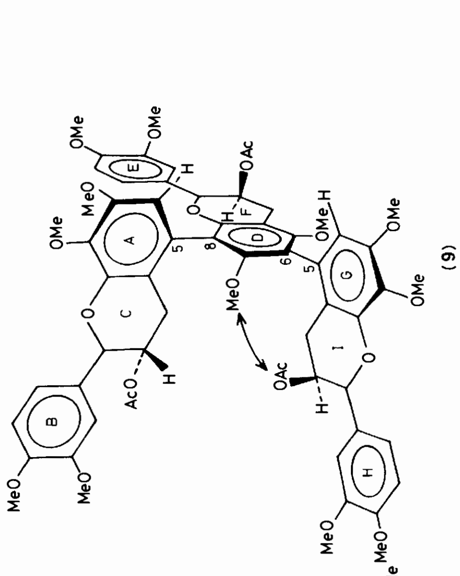
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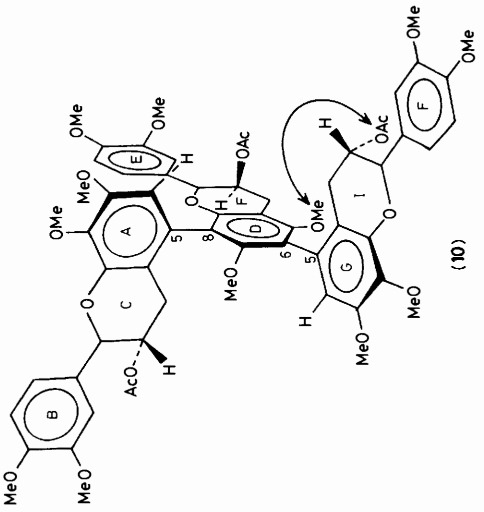
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(10)

Table 1. ^1H Chemical shifts (δ values) of relevant protons at 300 MHz in $CDCl_3$ of atropisomeric [5,6:5,8]-bis-[(+)-mesquitol]-(+)-catechins (**7**)—(**10**)

Protons	(**7**)	(**8**)	(**9**)	(**10**)
6-H(A)	6.52	6.53	6.49	6.38
6-H(G)	6.55	6.56	6.58	6.50
7-OMe(A)	3.81	3.87	3.79	3.75
7-OMe(G)	3.87	3.85	3.86	3.84
5-OMe(D)	3.30	3.17	3.22	3.32
7-OMe(D)	3.03	3.06	3.05	2.90
3-OAc(C)	1.67	1.88		
3-OAc(I)	1.88	1.91	1.76	1.90

Table 2. Proton associations based on n.O.e. difference spectroscopy*

		N.O.e. (%)			
From	To	(**7**)	(**8**)	(**9**)	(**10**)
5-OMe(D)	6-H(G)	1.43	0.91	1.42	1.18
	3-OAc(I)	0.62			0.44
7-OMe(D)	6-H(A)	1.63	1.02	1.66	1.74
	6-H(G)	1.13	1.21	1.56	1.75
	3-OAc(C)	0.25	0.48		
	3-OAc(I)		0.44	0.31	
6-H(A)	7-OMe(D)	0.62	0.56	0.29	0.53
	7-OMe(A)	*	2.53	1.64	2.12
6-H(G)	7-OMe(D)	0.42	0.62	0.46	0.53
	5-OMe(D)	0.29	0.26	0.48	0.47
	7-OMe(G)	1.03	2.49	1.69	*
3-OAc(C)	7-OMe(D)	0.28	0.46		
3-OAc(I)	6-H(A)		0.36		
	5-OMe(D)	0.55			0.27
	7-OMe(D)		0.47	0.62	

* Quantification not possible due to signal overlap.

between 3-OAc(F) and the D ring methoxys would be highly improbable due to the considerable distance separating these groups.* A similar restriction also applies to the association between 5-OMe(D) and 3-OAc(C). Observed n.O.e. effects between OAc and the high-field methoxys must, therefore, invariably involve associations of 7-OMe(D) to 3-OAc(C) and/or 3-OAc(I), and of 5-OMe(D) to 3-OAc(I) only.

Conformational analysis (Dreiding models), in conjunction with n.O.e. associations between heterocyclic acetoxys and D ring methoxys (Table 2), now permits assessment of the absolute configurations about both biphenyl linkages in the four [5,6:5,8]-bis-[(+)-mesquitol]-(+)-catechins (**7**)—(**10**), previously (*cf.* refs. 2 and 3) differentiated only in terms of R_F values (0.60, 0.56, 0.54, and 0.50) on silica in the same solvent system. In the R_F 0.50 atropisomer (**7**) association between 7-OMe(D; δ 3.03) and 3-OAc(C; δ 1.67) defines [*M*]-helicity and (*R*)-conformation about the C-5(A)—C-8(D) biphenyl bond, while association between 5-OMe(D; δ 3.30) and 3-OAc(I; δ 1.88) similarly defines [*M*]-helicity and an (*R*)-conformation about the C-5(G)—C-6(D) biphenyl linkage.† These observations indicate dihedral angles of *ca.* 90° between the planes of both the biphenyl A and D and G and D rings. Association of both 3-OAc(C; δ 1.88) and 3-OAc(I; δ 1.91) with 7-OMe(D; δ 3.06) in the R_F 0.56 atropisomer (**8**) indicates [*M*]-helicity [(*R*)-conformation] about the C-5(A)—C-8(D) biphenyl bond and [*P*]-helicity [(*S*)-conformation] about the C-5(G)—C-6(D) bond. In the R_F 0.54 isomer (**9**), association between 3-OAc(I; δ 1.76) and 7-OMe(D; δ 3.05) defines [*P*]-helicity and an (*S*)-conformation about the C-5(G)—C-6(D) biphenyl bond, while [*P*]-helicity and an (*S*)-conformation for the C-5(A)—C-8(D) linkage is consistent with the absence of interflavanyl n.O.e. effects between the 5- and 7-methoxys(D) and 3-OAc(C). Similar definition of [*M*]-helicity [(*R*)-conformation] for the C-5(G)–C-6(D) bond in the R_F 0.60 atropisomer (**10**) is evident from association of 5-OMe(D; δ 3.32) and 3-OAc(I; δ 1.90). Absence of interflavanyl n.O.e. associations between the 5- and 7-methoxys(D) and 3-OAc(C), therefore, reflects [*P*]-helicity and an (*S*)-conformation for the C-5(A)—C-8(D) biphenyl linkage.

Despite the fact that only a limited number of key signals could be assigned unequivocally, the above results clearly demonstrate the elegance in which nuclear Overhauser effect difference spectroscopy may be utilized in solving problems previously confined to the more classical *X*-ray crystallographic method. Knowledge of the absolute configuration at C-3 of the constituent flavan-3-ol units and thus of the spatial orientation of their acetoxy groups is, however, a prerequisite for interpretation of observed OMe–OAc n.O.e. associations in terms of the absolute configuration about the biphenyl bonds in the *m*-terphenyl-type flavan-3-ols (**7**)—(**10**).

Experimental

The natural atropisomeric [5,6:5,8]-bis-[(+)-mesquitol]-(+)-catechins from the heartwood of *Prosopis glandulosa* (Mesquite) were isolated as their dodecamethyl ether triacetates (**7**)—(**10**) by methods outlined previously.[2] The same 'trimers' were also synthesized by phenol oxidative coupling [$K_3Fe(CN)_6$] of (+)-mesquitol (**1**) and (+)-catechin (**2**),[3] followed by full methylation with diazomethane and subsequent acetylation with acetic anhydride–pyridine. These derivatives, previously differentiated in terms of their R_F values (0.60, 0.56, 0.54, and 0.50) on silica plates in dichloromethane–acetone [96:4 (v/v); × 2], may now be identified as: R_F 0.60, (2*R*,3*S*)-2,3-*trans*-3-acetoxy-6*R*,8*S*-bis-[(2*R*,3*S*)-2,3-*trans*-3-acetoxy-3′,4′,7,8-tetramethoxyflavan-5-yl]-3′,4′,5,7-tetramethoxyflavan (**10**); R_F 0.56, (2*R*,3*S*)-2,3-*trans*-3-acetoxy-6*S*,8*R*-bis-[(2*R*,3*S*)-2,3-*trans*-3-acetoxy-3′,4′,7,8-tetramethoxyflavan-5-yl]-3′,4′,5,7-tetramethoxyflavan (**8**); R_F 0.54, (2*R*,3*S*)-2,3-*trans*-3-acetoxy-6*S*,8*S*-bis-[(2*R*,3*S*)-2,3-*trans*-3-acetoxy-3′,4′,7,8-tetramethoxyflavan-5-yl]-3′,4′,5,7-tetramethoxyflavan (**9**); R_F 0.50, (2*R*,3*S*)-2,3-*trans*-3-acetoxy-6*R*,8*R*-bis-[(2*R*,3*S*)-2,3-*trans*-3-acetoxy-3′,4′,7,8-tetramethoxyflavan-5-yl]-3′,4′,5,7-tetramethoxyflavan (**7**).

The ^1H n.m.r. spectra of the derivatives of 'trimers' were recorded on a 300 MHz Bruker AM spectrometer for $CDCl_3$ solutions at 25 °C. The methoxy resonances of the D ring (see Table 1) were distinguished by their n.O.e. (difference) associations with 'residual' A and G ring protons (Table 2) (*ca.* 500 scans per resonance). For observation of the OMe–OAc associations the number of scans per resonance was increased to *ca.* 500. The n.O.e. difference spectra were recorded by methods outlined in the literature.[5–7]

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* This was confirmed by observations on the methyl ether acetate of (+)-catechin where n.O.e. associations from 3-OAc were restricted to the heterocyclic and B ring protons.

† Restrictions imposed on the orientation of the 3-OAc groups of rings C and I by the 3*S* absolute configuration and the observed n.O.e. associations simultaneously facilitated assignment of the respective acetoxy signals.

References

1 E. Jacobs, D. Ferreira, and D. G. Roux, *Tetrahedron Lett.*, 1983, **24**, 4627.

2 E. Young, E. V. Brandt, D. A. Young, D. Ferreira, and D. G. Roux, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1737.

3 D. A. Young, E. Young, D. G. Roux, E. V. Brandt, and D. Ferreira, *J. Chem. Soc., Perkin Trans. 1*, in the press.

4 N. Harada and K. Nakanishi, 'Circular Dichroic Spectroscopy, Exciton Coupling in Organic Chemistry,' Oxford University Press, Oxford, 1983, pp. 190—212.

5 L. D. Hall and J. M. K. Sanders, *J. Am. Chem. Soc.*, 1980, **102**, 5704.

6 W. E. Hull, 'Aspect 2000 Application Note No. 1,' *Bruker Rep.*, 1978, **1**, 4.

7 E. G. Chapman, D. B. Abercrombie, P. D. Cary, and E. M. Bradbury, *J. Magn. Reson.*, 1978, **31**, 459.

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