SHORT PAPER

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Theoretical studies on the configuration of a chalcanol derivative

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The relative configuration of a naturally occurring monobenzoylated diol was assigned to *erythro* by comparing the weighted average of calculated ^{1}H NMR coupling constants with the experimental values.

Keywords: molecular mechanics, benzoylated diol, *erythro*, coupling constant

The genus *Erythrina* (Leguminosae) is widely distributed in tropical and subtropical regions of the world, and numerous compounds isolated from this genus have demonstrated biological activities.[1–4] We have investigated the secondary metabolites of the roots and wood of *Erythrina variegata* and reported isolation of several new isoflavonoids.[5,6] Furthermore, we also described the isolation and the structural elucidation of two novel α′-chalcanols.[7] In the course of this structure determination, we took an interest in the configuration of α-benzoyloxy-α′-chalcanol, but we could not deduce its stereochemistry by analyses of NMR and IR spectral data. Therefore, we undertook determination of the relative configuration of 4, 4′-dihydroxy-α-(4″-hydroxy-3″, 5″-dimethoxybenzoyloxy)-2′-methoxy-3-(γ, γ-dimethylallyl)-α′-chalcanol (**1**) by theoretical procedures.

Methods

The isolation, structure determination and the spectroscopic data of compound **1** have been reported separately.[7] The structure of this compound is shown in Fig. 1. The ^{1}H NMR measurements were carried out in a CD_3OD solution on a JEOL JNM-A 600 MHz spectrometer.

The starting coordinates of the *erythro* and *threo* isomers were constructed by inspection of the Dreiding molecular model using standard bond lengths and angles. The molecular mechanics calculations were performed using the MM3(96) program package downloaded from QCPE.[8] The dihedral driver routine of MM3 was used in systematic production of numerous conformations. The dihedral angle of the $C_{\alpha'}$–C_α bond was driven from 0°to 330° in increments of 30° and that of the C_α–C_β bond was rotated from 0 to 300°in increments of 60°. Moreover, the dihedral angle of C_α–O–C–Ar was altered as 60°, 180°and 300°. Thus 216 total conformations were generated for the *erythro* and *threo* isomers, respectively. Then, all geometric values except for the above-mentioned dihedral angles were completely optimised by the block diagonal method.

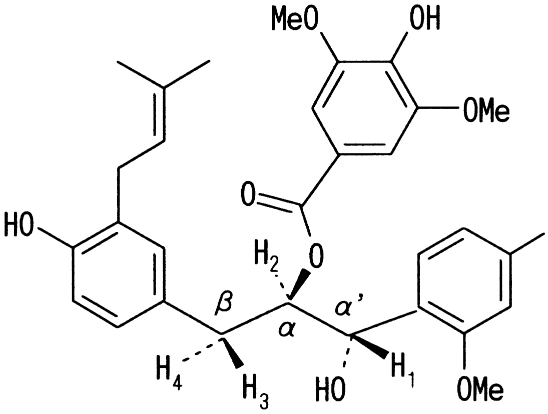

Fig.1 The structure of the compound **1** (the *erythro* configuration is shown).

Table 1 Experimental and calculated coupling constants (Hz)

	Experimental[a]	*Erythro*	*Threo*
$^3J_{H1,H2}$	5.1	5.04	1.89
$^3J_{H2,H3}$	8.8	10.73	11.36
$^3J_{H2,H4}$	3.7	2.26	1.92

[a]Measured in a CD_3OD solution.

Using the steric energy thus obtained, the relative population of an individual conformation was calculated on the assumption of the Boltzmann distribution. The $^3J_{H1,H2}$, $^3J_{H2,H3}$ and $^3J_{H2,H4}$ values were calculated applying the Haasnoot–Altona procedure[9] using the dihedral angles obtained from the molecular mechanics calculations. This method is favourable to distinguish between the *erythro* and *threo* isomers because it takes into consideration the electron negativity of the substituents as well as their relative positions.

Subsequently, the coupling constants were multiplied by the relative population, then the weighted average of the coupling constants was calculated as the sum of these products for the *erythro* and *threo* isomers, respectively.

All calculations were performed on an IBM RS/6000 UNIX work station (OS: AIX var. 4).

Results

The weighted averages of the coupling constants estimated by the process described above are listed in Table 1. The calculated values for the *erythro* configuration were always closer to the experimental values than that of the *threo* isomer. The conformation type, steric energy, relative population, H_1–H_2 dihedral angle and estimated coupling constant of the five most stable conformers of the *erythro* and *threo* isomers are also shown in Table 2.

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Table 2 The calculated lowest five conformers of *erythro* and *threo* isomers

	Dihedral angle (deg)			Type[a]	Relative energy	Relative population	Dihedral angle (deg)	Calculated coupling constant
	$C_{\alpha'}$–C_α	$C_{\alpha'}$–C_β	C_α–O		(kJ/mol)	(%)	H_1–$C_{\alpha'}$–C_α–H_2	(Hz)
Erythro	60	180	–60	(A)	0.0000	22.8	63.7	1.8
	–60	180	180	(B)	0.1535	17.6	–60.1	2.4
	180	180	–60	(C)	0.1750	16.9	–173.8	9.0
	180	180	180	(C)	0.2411	15.1	–178.8	9.2
	90	180	–60	(A′)	0.6070	8.2	90.2	0.9
Threo	180	180	180	(D)	0.0000	41.1	–60.7	0.7
	180	180	60	(D)	0.0054	40.7	–60.7	0.7
	60	180	180	(F)	1.2581	4.9	177.3	9.0
	60	180	60	(F)	1.2658	4.8	177.3	9.0
	60	180	–60	(F)	1.7409	2.2	178.5	9.1

[a] See Fig. 2.

Discussion

As reported previously,[7] the proton of an oxygenated methine group at δ5.16 (1H, d, *J*=5.1Hz, α′) coupled with the proton of another oxygenated methine group at δ5.46 (1H, ddd, *J*=8.8, 5.1, 3.7 Hz, α). Moreover, this proton coupled with a methylene group at δ2.79 (1H, dd, *J*=14.7, 8.8 Hz, β) and δ3.91 (1H, dd, *J*=14.7, 3.7 Hz, β). Therefore, the $^3J_{H1,H2}$ of 5.1 Hz was intermediate between the reported values of 2.7–4.4 Hz for the *erythro* configuration and 8.0–8.6 Hz for the *threo* configuration.[10] The IR (KBr) absorption maximum at 3400 cm^{-1} could not be assigned to an intermolecular or intramolecular hydrogen-bonded hydroxyl group nor a free hydroxyl group.

In consideration of the staggered forms of the *erythro* (A)–(C) and the *threo* (D)–(F) isomers (shown in Fig. 2 as Newman projections), Wallis ascribed the major conformation of *erythro* to the rotamer (B) and that of *threo* to the rotamer (F) in view of the possibility of an intramolecular hydrogen bonding and small ^{1}H chemical shifts of the methine groups.[11] He inferred that the predominant dihedral angle of H_1–$C_{\alpha'}$–C_α–H_2 was approximately –60° and 180° for the *erythro* and *threo* isomers, respectively. Consequently, he concluded the observed values of 2.6 Hz of the *erythro* isomer and 8.4 Hz of the *threo* isomer were consistent with the inferred rotamers. Braga *et al.* also assigned the $^3J_{H,H}$ value of 3.2 Hz to *erythro* form because this value is too small for the antiperiplanar protons of the predominant (F) conformation of the *threo* isomer.[12] Similarly, Forrest *et al.* postulated that the $^3J_{H,H}$ of *threo* is larger than that of *erythro* by analogous consideration of the above.[13]

Contrarily, our calculation estimated the $^3J_{H1,H2}$ of *erythro* to be 5.04 Hz and this was larger than the corresponding value of 1.89 Hz estimated for *threo*. This can be accounted for by the bulky substituents on the asymmetric carbons of compound **1**; accordingly, the conformational stability is different from that of the previously reported compounds.

Everything can be explained reasonably, if it can be accepted that the *gauche*-orientation between the –Ar and –CH_2Ar groups is not preferable due to some steric reason. The rotamers (A) and (B) of *erythro* are expected to form an intramolecular hydrogen bond between the –OH and –OCOAr groups. At the same time, they have also the –Ar and –CH_2Ar groups in the *gauche*-orientation. Consequently, these conformations contribute only 40% to the observed coupling constant. Oppositely, the (C) conformation, which has neither a hydrogen bond nor *gauche*-oriented aromatic groups, comprises more than 30%, and this conformation must make the observed $^3J_{H,H}$ of *erythro* larger. However, both the (D) and (F) conformers of *threo* can form the hydrogen bonding, but the conformer (F) is destabilised by the *gauche*-oriented –Ar and –CH_2Ar groups. Thus, the conformer (D) comprises more than 80% and this makes the weighted average of the $^3J_{H,H}$ of *threo* smaller than usual.

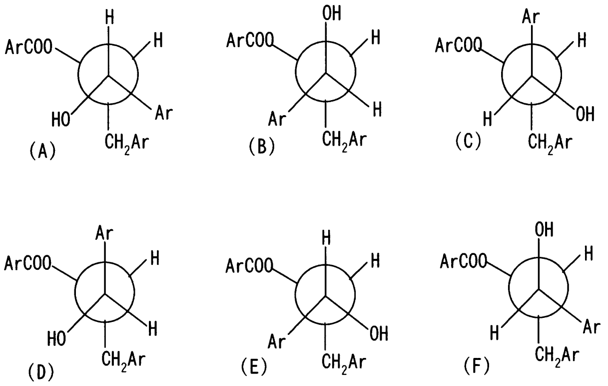

Fig.2 Newman projection of the staggered forms of the *erythro* isomer of compound **1** (A)–(C) and the *threo* isomer (D)–(F) viewed along the axis of the $C_{\alpha'}$–C_α bond.

From the above results, compound **1** was determined as rel-(*erythro*)- 4, 4′-dihydroxy-α-(4″-hydroxy-3″, 5″-dimethoxybenzoyloxy)-2′-methoxy-3-(γ, γ-dimethylallyl)-α′-chalcanol.

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