A *C*-Glycosylflavone from *Piper ossanum*, a Compound Conformationally Controlled by CH/π and Other Weak Intramolecular Interactions

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The structure of the known 2″-*O*-α-rhamnosyl-4″-*O*-methylvitexin (apigenin-8-*C*-α-rhamnosyl-(1→2)-*β*-4-*O*-methyl-glucopyranoside), isolated from the leaves of *Piper ossanum*, was revised to acacetin-8-*C*-neohesperidoside (acacetin-8-*C*-α-rhamnosyl-(1→2)-*β*-glucopyranoside or 2″-*O*-α-rhamnosyl-4′-*O*-methylvitexin) (**1**). The NMR data and theoretical calculations established the preferred conformation of **1**, which is controlled by CH/π interactions. This phenomenon explains the unusual chemical shifts of some protons in the molecule, besides other weak intramolecular interactions such as the anomeric effect, the Δ2 effect, and several hydrogen bonds.

The genus *Piper* (Piperaceae), with nearly 2000 species, together with *Peperomia*, with about 1700 species, represent the largest genera of the order Piperales and constitute the core of the Piperaceae family, which comprise some economically important species used as spices such as *Piper nigrum* or ornamental plants such as several *Peperomia* species.[1] Other *Piper* species are used worldwide in folk medicine as diuretic, febrifuge, laxative, and anti-inflammatory remedies.[2] The leaves of *Piper ossanum* Trel., known as "Platanillo de Cuba", are used in folk medicine as hemostatic, antiseptic, cicatrizing, and diuretic agents.[3] Previous chemical studies reported the chemical composition of the essential oil of the leaves[4] and the isolation of a *C*-glycosylflavone with antiulcer and anti-inflammatory activities. Its structure was claimed to be 2″-*O*-α-rhamnosyl-4″-*O*-methylvitexin, with the methoxy group at C-4 of the glucose moiety.[5]

This paper describes the isolation and complete ^{1}H and ^{13}C NMR assignments for acacetin-8-*C*-neohesperidoside (2″-*O*-α-rhamnosyl-4′-*O*-methylvitexin) (**1**). Compound **1** has been previously isolated from the Rutaceae *Fortunella margarita*[6] and *F. japonica*[7] and the Amaranthaceae *Alternanthera maritima*[8] and *A. tenella.*[9] This is the first report about the presence of this rare 8-*C*-glycosylflavone in a *Piper* species. Recently, the closely related apigenin-8-*C*-neohesperidoside (**2**) was isolated from *P. methysticum* (Kava)[10] and *P. umbellatum,*[11] as well as from several species of other families.[12,13]

Compound **1**, also named acacetin-8-*C*-neohesperidoside and margaritene, was first isolated from *Fortunella margarita*[6] and synthesized from acacetin,[6] but spectroscopic data were not given. The same flavonoid was later isolated and reported as a new compound from *F. japonica.*[7] Its structure was established mainly on the basis of ^{1}H and ^{13}C NMR evidence and its acidic hydrolysis products, but only ^{1}H NMR data of the aglycone and ambiguous assignments for C-8, C-10, C-4″, C-2‴, and C-4‴ are available. The isolation of compound **1** from *Alternanthera maritima*[8] and *A. tenella* (Amaranthaceae)[9] was recently reported, but again, no spectroscopic data were given.

The ^{1}H and ^{13}C NMR data of the sugar moiety were assigned by comparison with those of 2″-*O*-α-rhamnosylvitexin (apigenin-8-*C*-neohesperidoside) (**2**)[12] and confirmed by DEPT, ^{1}H, ^{1}H−COSY, TOCSY, NOESY, HSQC, and HMBC NMR experiments. The ^{1}H and ^{13}C NMR spectra of compound **1** clearly indicated the presence of a flavonoid glycoside. The ^{1}H NMR spectrum showed the typical signals of a 4′,5,7,8-tetrasubstituted flavone with a hydroxy group at C-5 as a sharp singlet at δ 13.09 and two AA′XX′ pseudodoublets (J = 9.0 Hz) at δ 8.16 (H-2′, H-6′) and 7.08 (H-3′, H-5′). Three singlets at δ 6.87, 6.26, and 3.86 were assigned to H-3, H-6, and a methoxy group, respectively, and a singlet at δ 10.89 to the presence of an extra phenolic hydroxy group in the aglycone nucleus. As for the glycosyl moiety, the spectrum showed two anomeric proton signals at δ 4.76 (d, J = 9.5 Hz) and 4.96 (d, J = 1.5 Hz), indicating the presence of two sugar moieties. The presence of a doublet at δ 0.46 (d, J = 6.0 Hz) together with the doublet at δ 4.96 (J = 1.5) indicated a rhamnosyl group in the molecule. COSY and TOCSY experiments assisted in the assignment of all signals of the two sugar residues and the identification of the glycosyl moiety as neohesperidoside.

Taking the anomeric proton at δ 4.76 (glucose) as a reference, this proton showed five cross-peaks with protons at δ 4.04, 3.76, 3.55, 3.43, and 3.24 in the TOCSY spectrum, indicating that they belong to the glucose ring. The COSY spectrum allowed all protons belonging to the glucosyl moiety to be unambiguously assigned (see Table 1). Similarly, the C-6‴ methyl group at δ 0.46 was used as a reference for the rhamnose residue. This signal displayed strong cross-peaks with signals at δ 2.11, 2.90, and 3.08 and weak cross-peaks with the signals at δ 3.57 and 4.96 in the TOCSY spectrum, indicating that these protons belong to the rhamnose ring. On the

1) R = Me
2) R = H

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Table 1. NMR Spectroscopic Data (500 MHz, DMSO-d_6) for Compound **1**[a,b]

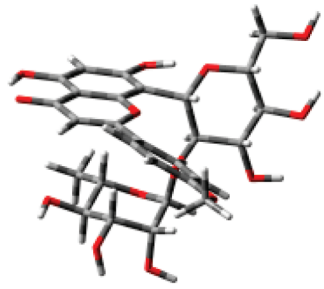
position	δ_H (J in Hz)	δ_C, mult.	δ_C[c]	HMBC
2		163.5 C[c]	163.5	
3	6.87 s	103.1 CH	103.1	C-2, C-10
4		182.1 C	182.0	
5		160.6 C	160.6	
6	6.26 s	98.3 CH	98.2	C-5, C-7, C-8, C10
7		162.4 C	162.2	
8		104.5 C	104.2	
9		155.8 C	155.7	
10		104.2 C	104.4	
1′	-	123.2 C	123.2	
2′, 6′	8.16 d (9.0)	128.8 CH	128.7	C-2, C-4′
3′, 5′	7.08 d (9.0)	114.5 CH	114.4	C-4′
4′		162.3 C	162.2	
OCH_3	3.86 s	55.6 CH_3	55.5	C-4′
1″	4.76 d (9.5)	71.6 CH	71.4	C-7, C-9, C-3″, C-2″, C-5″
2″	4.04 dd (10.0, 9.0)	75.0 CH	75.1	C-3″, C-1″
3″	3.43 td (9.5,5.0)	79.9 CH	79.8	C-4″
4″	3.43 td (9.5, 5.0)	70.6 CH	70.5	C-3″
5″	3.24 brt (5.0)	81.8 CH	81.6	
6″	3.76 ddd (12.0, 6.0, 2.0) 3.55 ddd (12.0, 6.0, 5.5)	61.1 CH_2	61.0	C-4″, C-5″
1‴	4.96 d (1.5)	100.3 CH	100.2	C-2″, C-3‴, C-5‴
2‴	3.57 dd (3.0, 1.5)	70.4 CH	70.2	
3‴	3.08 ddd (9.0, 5.5, 3.0)	70.2 CH	71.6	
4‴	2.90 td (9.0, 4.0)	71.4 CH	70.3	C-3‴, C-5‴
5‴	2.11 dq (9.5, 6.0)	68.2 CH	68.1	C-4‴
6‴	0.46 d (6.0)	17.7 CH_3	17.6	C-4‴, C-5‴
5-OH	13.09 s			C-5, C-6, C-10
7-OH	10.89 s			
3″-OH	5.22 d (5.0)			
4″-OH	5.05 d (5.5)			
6″-OH	4.65 t (5.5)			
2‴-OH	4.40 d (4.0)			
3‴-OH	4.29 d (6.0)			
4‴-OH	4.41 d (4.0)			

[a] ^{1}H assignments were based on ^{1}H−^{1}H COSY, TOCSY, and HSQC experiments. [b] Carbon multiplicities and assignments were determined by DEPT, HSQC, and HMBC experiments. [c] Data from ref 9.

other hand, the rhamnose anomeric proton at δ 4.96 showed a cross-peak with the signal at δ 3.57 in the TOCSY and COSY spectra, confirming the chemical shift of the rhamnose H-2‴. All other protons for the rhamnose ring were assigned in accord with the COSY experiment (Table 1). Once the chemical shifts of all protons belonging to the diglycoside moiety were established, the corresponding carbon chemical shifts were assigned through the HSQC spectrum (Table 1). Since H-3″ and H-4″ of the glucose moiety have the same chemical shift in the ^{1}H NMR spectrum, the corresponding carbon chemical shifts were established through the HMBC spectrum. In this spectrum the signal at δ 3.76 (H-6″) showed three- and two-bond connectivities with the signals at δ 70.6 (C-4″) and 81.8 (C-5″), respectively. These data established unambiguously the chemical shift of C-4″ at δ 70.6 and therefore that of C-3″ at δ 79.9. All the carbon chemical shifts of the diglycoside moiety were similar to those published for 2″-*O*-rhamnosylvitexin (apigenin 8-*C*-neohesperidoside), suggesting the presence of a *C*-8-neohesperidosyl moiety in the isolated compound.[12,14] Confirmation of the linkage of glucose at C-8 of the aglycone was based on the HMBC cross-peaks between the anomeric proton of the glucose (H-1″, δ 4.76) and the aromatic carbons C-7 (δ 162.4) and C-9 (δ 155.8) of the aglycone and the large J value of H-1″ in the ^{1}H NMR spectrum. The orientation of the glycosidic attachment was based on the large coupling constant (J = 9.5 Hz) of the glucosyl anomeric proton. Similarly, the rhamnose anomeric proton (H-1‴) showed a cross-peak with the C-2 glucose signal (C-2″, δ 75.0). The HMBC experiment also allowed the determination of the 1→2 interglycosidic union between the rhamnose and glucose moieties. The position of the methoxy group at C-4′ in compound **1** was established through the HMBC spectrum, since the OMe signal at δ 3.86 showed three-bond connectivity with the signal at δ 162.3 (C-4′). Furthermore, in the HMBC spectrum, the 5-OH signal at δ 13.09 clearly showed a cross-peak with the signal at δ 104.2, assigned to C-10, and a cross-peak between the signals at δ 8.16 (H-2′, H-6′) and 162.3 assigned to C-4′. Moreover, the H-6 signal at δ 6.26 showed two-bond connectivity with the signal at δ 162.4, assigned to C-7. These data are consistent with 2″-*O*-α-rhamnosyl-4′-*O*-methylvitexin (**1**).

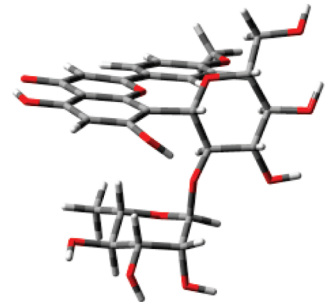
It is important to point out the remarkable chemical shifts of the C-5 methyne and C-6 methyl protons of the rhamnose residue (H-5‴ and H-6‴), which are strongly diamagnetically shifted, with unusual chemical shifts at δ 2.11 and 0.46, respectively. This is very likely due to the anisotropic effects of an aromatic ring of the aglycone moiety, in the preferred conformation of compound **1**. This fact can be observed in several naturally occurring C-8 and C-6 glycosylflavonoids, but this phenomenon has never been explained.[12,13,15−19] Moreover, the same phenomenon can be observed in vitexin 2″-*O*-acyl derivatives.[20] Furthermore, doubling of signals in the NMR spectra due to the presence of two different rotamers has been documented for C-8 glucosides of apigenin, luteolin, and other C-8 and C-6 glycosylflavonoids and has been suggested to be due to interactions between the ring B and the sugar substituent at C-8.[13,15,17,18,21]

On the basis of only steric interactions, this type of compound should adopt an extended (unfolded) conformation, but it is possible that weak intramolecular interactions can take place in order to adopt a folded stable conformation in which the chemical shifts of the end sugar moiety (mainly H-5‴ and H-6‴) could be affected. In order to corroborate and give an explanation for this phenomenon and the above assumption, we carried out a theoretical study of the two possible rotamers of compound **1** produced by rotation around the C-1″(Glu)−C-8(Ar) (A and B, Figure 1) bond. Although weak intramolecular interactions in molecular conformation have been sometimes underestimated, they are relevant for the final



A

Total Energy = -2138.64004 Hartrees
Relative Energy = 0.0 kcal/mol
NImag = 0



B

Total Energy = -2138.65544 Hartrees
Relative Energy = 5.39 kcal/mol
NImag = 0

Figure 1. Conformers produced by rotation around the C-1″−C-8 bond.

conformation observed. For example, it is well known that the preferred axial orientation of the hydroxy group in 5-hydroxy-1,3-dioxane is attributed to an intramolecular hydrogen bond, one of the strongest interactions in the group of weak interactions that includes others such as CH/π, $\pi-\pi$, etc.[22,23] It has also been considered that the preferred arrangement of hydroxy groups in carbohydrates is due to an additive hydrogen-bonding arrangement.[24] Furthermore, the stereoelectronic interaction $n_O \rightarrow \sigma^*_{C-O}$ has been identified as a possible origin of the anomeric effect in the O−C−O segment in carbohydrates.[25−27] It is also known that CH/π interactions have a significant role in the molecular recognition between carbohydrates and aromatic compounds[28−30] and are important for the protein−carbohydrate recognition processes, as in case of galactose by galectines.[31]

In this paper we demonstrated by theoretical calculations at the M06-2X/6-31++G(d,p) level of theory, a functional recently developed by Truhlar,[32] that compound **1** is conformationally restricted due to several additional weak interactions. In this conformation the α-rhamnose with an axial glucose substituent shows an *endo*-anomeric effect that produces a C1‴−O_{endo} distance of 1.394 Å and the C1‴−O_{exo} of 1.421 Å in conformer A and a C1‴−O_{endo} distance of 1.392 Å and the C1‴−O_{exo} of 1.425 Å in conformer B, these distances being in good agreement with the stabilization through the $n_O \rightarrow \sigma^*_{C-O}$ interaction. Energy values are in agreement with the determined geometric patterns. For conformer A the $n_{O(s)endo} \rightarrow \sigma^*_{C\text{-}Oexo}$ and $n_{O(p)endo} \rightarrow \sigma^*_{C\text{-}Oexo}$ stereoelectronic interactions are 1.49 and 12.36 kcal/mol, respectively [determined by NBO calculation[33] at the M06-2X/6-31G(d,p) level], while for conformer B the values are 1.97 and 10.98 kcal/mol. The *exo*-anomeric effect is a little bit stronger, with values of 2.26 and 15.07 kcal/mol for $n_{O(s)exo} \rightarrow \sigma^*_{C\text{-}Oendo}$ and $n_{O(p)exo} \rightarrow \sigma^*_{C\text{-}Oendo}$ stereoelectronic interactions for conformer A and 1.73 and 15.99 kcal/mol for conformer B. The values are almost the same for each conformer, proving that factors other than the *endo*- and *exo*-anomeric effect are responsible of the observed preference, but they are the origin of the global arrangement that allows the participation of weak interactions.[25−27] The axial hydroxy group at C-2‴ of the rhamnose moiety results in the so-called Δ2 effect, incrementing the anomeric effect by ca. 1 kcal/mol as was previously described;[34] this effect is similar in both conformers. The antiperiplanar alignment required for the operation of the stereoelectronic interactions avoids the free rotation of C−O bonds, reducing the number of possible conformers.

As expected, the aromatic moiety keeps an equatorial orientation, and the hydroxy groups were oriented in order to keep additive interactions. There is a difference of 5.39 kcal/mol in stability between the two studied conformers due to an extra hydrogen bond between the C-7 hydroxy group of the aromatic group and the endocyclic oxygen of the glucopyranoside moiety in conformer A,

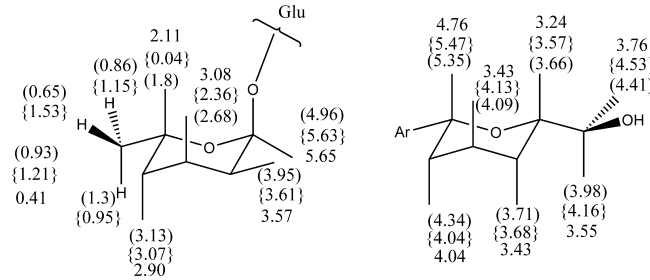


Figure 2. Chemical shift data of the glycosyl moieties for compound **1**: calculated [at energy level (B3LYP/6-311++G(2d,2p)//mPWB95/6-31+G(d,p)), {M06-2X/6-31++G(d,p)} and experimental.

restricting the free rotation of this conformer. In comparison the energy of the rotamer B is increased by the proximity of two oxygen atoms, i.e., O-1 of the flavone ring and the endocyclic oxygen O-2 of the glucose moiety, with an interaction of repulsive nature.

The existence of stabilizing CH/π carbohydrate−aromatic interactions in the range of 1 to 3 kcal/mol has been demonstrated experimentally and theoretically by using NMR experiments and MP2 calculations. It was established that in the ^{1}H NMR spectra the CH/π interactions can be associated with diamagnetic shifts of the protons in the shielding zone of the aromatic ring.[28,29] In accord with the above assumption, chemical shifts of protons associated with the glycosyl moiety in conformer A of compound **1** were calculated using the "gauge-independent atomic orbitals" method at the B3LYP/6-311++G(2d,2p)//mPWB95/6-31+G(d,p)[35,36] and M06-2X/6-31++G(d,p) levels (Figure 2). The first level of theory describes in a better form the chemical shifts; however the level M06-2X/6-31++G(d,p) is properly used for the study of weak interactions. The theoretical results indicate that the methyl protons (H-6‴) and mainly the methyne proton (H-5‴) show unusual diamagnetic shifts, due to CH/π interactions with the aromatic ring A of the flavone moiety. The interaction distances are 2.51, 2.50, 2.69, 2.83, 2.83, and 2.66 Å, similar to those obtained for the fucose-benzene interaction.[29] Interestingly, in conformer B the same distances are 3.01, 2.90, 2.60, 2.56, 2.54, and 2.82 Å.

An electron density study[37] was performed to understand the nature of the interactions mentioned above. Figure 3 shows the molecular graph of A and B, where it is possible to observe two CH/π interactions in each conformation. Additionally, conformer A shows an O/π interaction. It is well known that the properties of the bond critical point (BCP) can be used to characterize atomic interactions.[38] Table 2 presents the properties of the BCP. In general the interactions have a BCP with a density around 0.01. The Laplacian of electron density, which describes the charge concentration and depletion, is greater than 0.03 au, and the bond ellipticity is an

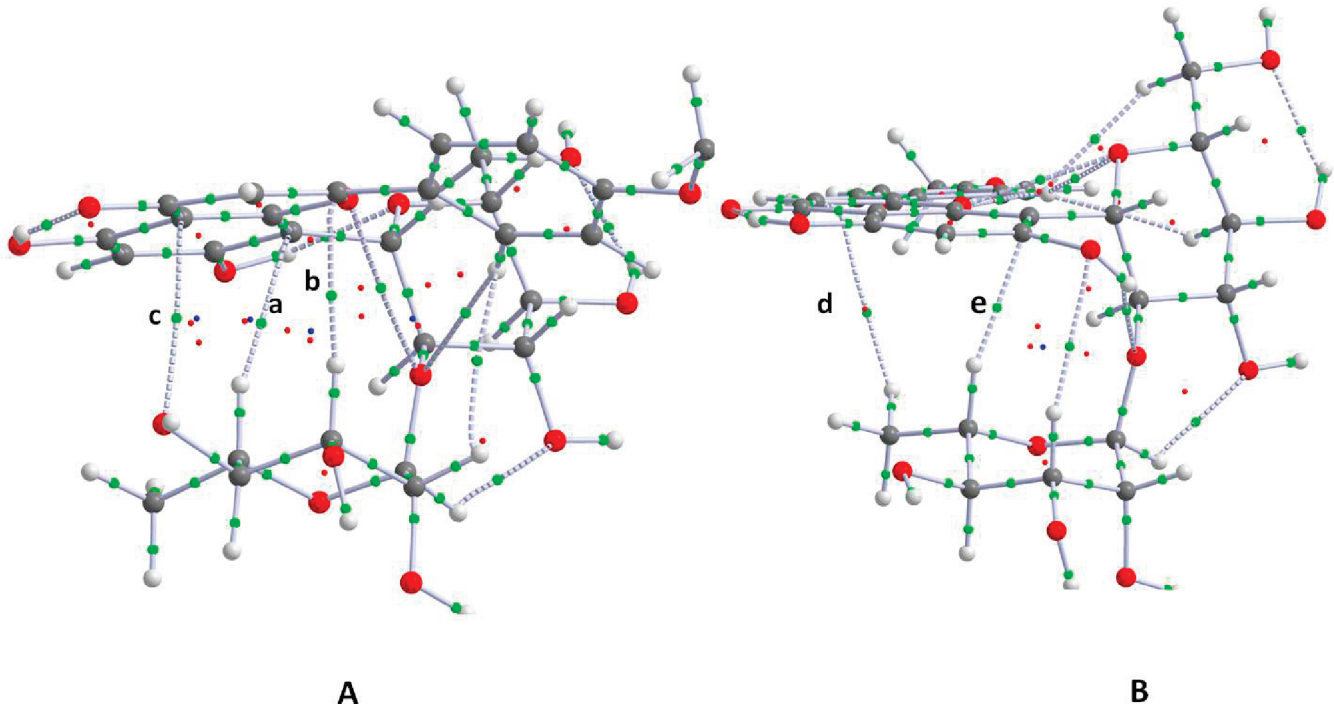


Figure 3. Molecular graphics of conformers A and B.

Table 2. Properties of Bond Critical Points Associated with C−H/π and O/π Interactions at the M06-2X/6-31++G(d,p) Level of Theory

	conformer A			conformer B	
property	**a**	**b**	**c**	**d**	**e**
$\rho(r)^a$	0.0126	0.0098	0.0075	0.0032	0.0117
$\nabla^2\rho(r)^b$	0.0407	0.0346	0.0242	0.0092	0.0373
ε^c	1.9227	0.7189	2.1240	0.8349	1.8730
BPL[d]	4.9127	4.8137	6.2875	6.7123	4.9796
$H(r)^e$	0.0012	0.0014	0.0007	0.0005	0.0012

[a] Electron density. [b] Laplacian of electron density. [c] Ellipticity. [d] Bond path length. [e] Energy density at BCP.

average of 1.5 au. The energy density, $H(r)$, is around 0.001 au. These values are features of closed-shell interactions, typical of weak interactions.[39]

The obtained theoretical data indicated that compound **1** prefers the folded conformation stabilized by the anomeric effect, the Δ2 effect, and the CH/π interaction, locating the C-6‴ methyl and the C-5‴ methyne groups in close proximity to the aromatic ring A, which is responsible for the unusual diamagnetic chemical shifts of the C-5 methyne (H-5‴) and the methyl group (H-6‴) of the rhamnose moiety, observed in the ^{1}H NMR spectra of C-8 and C-6 neohesperidosyl flavonoids (see Table 1 and Figure 2). The interaction between aromatic proton H-6 and the C-4‴ hydroxy group observed in the NOESY spectrum supports the above assumption. The anomeric effect is the origin of the axial preference of the hydroxy group; it is stabilized by the Δ2 effect, which increases the anomeric preference, and the CH/π interaction controls the position of the aromatic ring.

The unambiguous and complete ^{1}H and ^{13}C NMR assignments for acacetin-8-*C*-neohesperidoside (2″-*O*-α-rhamnosyl-4′-*O*-methylvitexin) (**1**) were accomplished. A sample of compound **1** used for this study was characterized by comparison of TLC and mixed melting point with an authentic sample and shown to be identical. The combined NMR data and theoretical calculations permitted establishment of the preferred conformation in solution of compound **1**, being controlled by CH/π interactions. This explains the unusual chemical shifts of H-5 and H-6 associated with the rhamnosyl moiety. Weak intramolecular interactions as well as stereoelectronical effects (anomeric effect, the Δ2 effect, and several hydrogen bonds) assist in the stabilization of a folded conformational arrangement.

Experimental Section

General Experimental Procedures. The melting point is uncorrected. The ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded in a Varian-Unity Inova 500 MHz spectrometer in DMSO-d_6 (Cambridge Isotope Laboratories, Inc.) with TMS as internal standard. The mass spectrum was determined at 70 eV on a JEOL JMS-SX102A mass spectrometer. The IR (in KBr pellets) and UV (in EtOH) spectra were recorded on a Bruker Tensor 27 and a Shimadzu UV 160U spectrophotometer, respectively. The CCs were carried out in polyamide and TLC on precoated silica gel 60 F_{254} (Merck, 1.0 mm), using UV (254 nm) and 10% $CeSO_4$−H_2SO_4 reagent followed by heating for visualization of spots.

Plant Material. Leaves of *Piper ossanum* Trel. were collected in an area next to the Instituto Superior de Medicina Militar "Dr. Luis Díaz Soto" in Habana, Cuba. The herbarium voucher specimen (number 220) is deposited at the herbarium of the Instituto Nacional de Investigaciones Tropicales "Alejandro Humboldt", Ciudad de la Habana, Cuba.

Extraction and Isolation. The dried and ground leaves (200 g) were extracted with H_2O (4 L) at 100 °C for 30 min. The aqueous extract was concentrated to 100 mL and partitioned between EtOAc and H_2O. The combined EtOAc solutions were evaporated to dryness under reduced pressure. The resulting crude EtOAc extract (4 g) was dissolved in H_2O, filtered, and fractionated on a polyamide column (80 g). The column was eluted with H_2O and H_2O−EtOH with gradually increasing portions of EtOH.

The fractions eluted with H_2O−EtOH (9:1) (825 mL) were concentrated *in vacuo*, and the residue (1.5 g) was rechromatographed on a polyamide column (30 g) and eluted with H_2O (500 mL). The purified fraction was concentrated to 30 mL, left to stand at 0 °C, and then filtered. A yellow solid (390 mg) was obtained, which was recrystallized from a mixture of H_2O−EtOH (1:1), yielding 245 mg of compound **1**.

2″-*O*-α-Rhamnosyl-4′-*O*-methylvitexin (1): yellow needles; mp 220−222 °C (lit. 192−193 °C),[9] UV shifts of **1** after adding $AlCl_3$ and NaOAc were performed as reported, and the data were identical,[7] IR (KBr) ν_{max} 3398, 3363, 1658, 1618, 1571 1510 cm^{-1}; ^{1}H NMR and ^{13}C NMR data see Table 1; FABMS positive *m/z* 593 $[M + H]^+$.

Theoretical Calculations. All calculations were performed using Gaussian 09.[40] Full geometry optimizations were performed at the M06-

2X/6-31++G(d,p) level. The NMR shielding tensor was calculated using the gauge-independent atomic orbitals (GIAO) method at the B3LYP/6-311++G(2d,2p)//mPWB95/6-31+G(d,p), and M06-2X/6-31++G(d,p) levels of theory. The values for hydrogen atoms of TMS are 8.81 and 38.1, respectively. The molecular graphics of electron density were done with the program AIMAII Version 10.07.01.[41] Natural bond orbital analyses (NBO) were carried out with version 3.0, which is included in G09.[33]

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Supporting Information Available: ^{1}H, ^{13}C, DEPT, COSY, TOCSY, NOESY, HSQC, and HMBC 500 MHz NMR spectra of compound **1**. Full optimized geometries of the conformers A and B and full ref 40 are included. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Wanke, S.; Jaramillo, M. A.; Borsch, T.; Samain, M.-S.; Quandt, D.; Neinhuis, C. *Mol. Phylogenet. Evol.* **2007**, *42*, 477–497.
(2) Núñez, V.; Castro, V.; Murillo, R.; Ponce-Soto, L. A.; Merfort, I.; Lomonte, B. *Phytochemistry* **2005**, *66*, 1017–1025.
(3) Roig, J. T., *Plantas Medicinales Aromáticas o Venenosas de Cuba*; Ciencia y Técnica: La Habana, 1974.
(4) Pino, J. A.; Bello, A.; Urquiola, A. *J. Essent. Oil Res.* **2002**, *14*, 375–379.
(5) Martínez, R. C.; García, M.; Martínez, S. M.; Larionova, M.; Sebazco, C.; Machín, M.; Ruiz, V. *Rev. Cubana Planta Med.* **2004**, *9*, 1, pp. 0−0.
(6) Chopin, J.; Besset, A.; Bouillant, M. L. *C. R. Acad. Sci. Paris, Sér. C* **1977**, *284*, 1007.
(7) Kumamoto, H.; Matsubara, Y.; Iisuka, Y.; Okamoto, K.; Yokoi, K. *Agric. Biol. Chem.* **1985**, *49*, 2613.
(8) Souza, J. G.; Tomei, R. R.; Kanashiro, A.; Kabeya, L. M.; Azzolini, A. E. C. S.; Dias, D. A.; Salvador, M. J.; Lucisano-Valim, Y. M. *Z. Naturforsch.* **2007**, *62c*, 339–347.
(9) Salvador, M. J.; Ferreira, E. O.; Mertens-Talcott, S. U.; De Castro, W. V.; Butterweck, V.; Derendorf, H.; Dias, D. A. *Z. Naturforsch.* **2006**, *61c*, 19.
(10) Jhoo, W. J.; Ang, C. Y. W.; Heinze, T. M.; Deck, J.; Schnackenberg, L. K.; Beger, R. D.; Dragull, K.; Tang, C. S. *J. Food Sci. C* **2007**, *72*, 120–125.
(11) Tabopda, T. K.; Ngoupayo, J.; Liu, J.; Mitaine-Offer, A. C.; Tanoli, S. A. K.; Khan, S. N.; Ali, M. S.; Ngadjui, B. T.; Tsamo, E.; Lacaille-Dubois, M. A.; Luu, B. *Phytochemistry* **2008**, *69*, 1726–1731.
(12) Scharbert, S.; Holzmann, N.; Hofmann, T. *J. Agric. Food Chem.* **2004**, *52*, 3498–3508.
(13) Rayyan, S.; Fossen, T.; Natelang, H. S.; Andersen, O. M. *Phytochem. Anal.* **2005**, *16*, 334–341.
(14) Agrawal, P. K. *Carbon-13 NMR of Flavonoids*; Elsevier: Amsterdam, 1989.
(15) Harborne, J. B. C-glycosylflavonoids. In *The Flavonoids: Advances in Research since 1986*; Chapman and Hall: New York, 1993; pp 57−93.
(16) Zou, J.-H.; Yang, J.-S.; Dong, Y.-S.; Zhou, L.; Lin, G. *Phytochemistry* **2005**, *66*, 1121–1125.
(17) Isayenkova, J.; Wray, W.; Nimtz, M.; Strack, D.; Vogt, T. *Phytochemistry* **2006**, *67*, 1598–1612.
(18) Prinz, S.; Ringl, A.; Huefner, A.; Pemp, E.; Kopp, B. *Chem. Biodiversity* **2007**, *4*, 2920–2931.
(19) Hasegawa, T.; Tanaka, A.; Hosoda, A.; Takano, F.; Ohta, T. *Phytochemistry* **2008**, *69*, 1419–1424.
(20) Cai, S.-Q.; Wang, R.; Yang, X.; Shang, M.; Ma, C.; Shoyama, Y. *Chem. Biodiversity* **2006**, *3*, 343–348.
(21) Rabe, C.; Steenkamp, J. A.; Joubert, E.; Burger, J. F. W.; Ferreira, D. *Phytochemistry* **1994**, *35*, 1559–1565.
(22) Alonso, J. L.; Wilson, E. B. *J. Am. Chem. Soc.* **1980**, *102*, 1248–1251.
(23) Baggett, N.; Bukhari, M. A.; Foster, A. B.; Lehmann, J.; Webber, J. M. *J. Chem. Soc.* **1963**, 4157–4160.
(24) Esquivelzeta-Rabell, M.; Peón, J.; Cuevas, G. *J. Phys. Chem. B* **2009**, *113*, 8599–8606.
(25) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019–5087.
(26) Juaristi, E.; Cuevas, G. *The Anomeric Effect*; CRC Press: Boca Raton, FL, 1994.
(27) Martínez-Mayorga, K.; Cortés, F.; Leal, I.; Reyna, V.; Quintana, D.; Antúnez, S.; Cuevas, G. *Arkivoc* **2003**, 132–148.
(28) Bautista-Ibañez, L.; Ramírez-Gualito, K.; Quiróz-García, B.; Rojas-Aguilar, A.; Cuevas, G. *J. Org. Chem.* **2008**, *73*, 849–857.
(29) Fernández-Alonso, M. C.; Cañada, F. J.; Jiménez-Barbero, J.; Cuevas, G. *J. Am. Chem. Soc.* **2005**, *127*, 7379–7386.
(30) Jiménez-Barbero, J.; Cañada, F.; Cuevas, G.; Asensio, J. L.; Aboitiz, N.; Canales, A.; Chávez, M. I.; Fernández-Alonso, M. C.; García-Herrero, A.; Mari, S.; Vidal, P. In *Protein-Carbohydrate Interactions: A Combined Theoretical and NMR Experimental Approach on Carbohydrate-Aromatic Interactions and on Pyranose Ring Distortion*; Vliegenthart, J. F. G.; Woods, R. J., Eds.; ACS Symposium Series 930; American Chemical Society: Washington, DC, 2006; pp 60−80.
(31) Lis, H.; Sharon, N. *Chem. Rev.* **1998**, *98*, 637–674.
(32) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215–241.
(33) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899–926.
(34) Reeves, L. W.; Schneider, W. G. *Can. J. Chem.* **1957**, *35*, 251–261.
(35) Zhao, Y.; Pu, J.; Lynch, B. J.; Truhlar, D. G. *Phys. Chem. Chem. Phys.* **2004**, *6*, 673–676.
(36) Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2005**, *109*, 5656–5667.
(37) Bader, R. F. W. *Atoms in Molecules−A Quantum Theory*; Oxford University Press: Oxford, 1990.
(38) Bader, R. F. W.; Essen, H. *J. Chem. Phys.* **1984**, *80*, 1943–1960.
(39) Koch, U.; Popelier, P. *J. Phys. Chem.* **1995**, *99*, 9747–9754.
(40) Frisch, M. J.; et al. *Gaussian 09*, Revision A.1; Gaussian, Inc.: Wallingford, CT, 2009.
(41) Keith, T. A. *AIMAll* (Version 10.07.01); 2010 (aim.tkgristmill.com).

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