# Determination of the Absolute Configurations of Natural Products Using TDDFT Optical Rotation Calculations: The Iridoid Oruwacin

P. J. Stephens,*[,†] J. J. Pan,[†] F. J. Devlin,[†] and J. R. Cheeseman[‡]

*Department of Chemistry, University of Southern California, Los Angeles, California 90089-0482, and Gaussian Inc., 340 Quinnipiac St., Bldg 40, Wallingford, Connecticut 06492*

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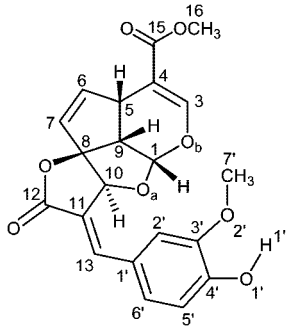
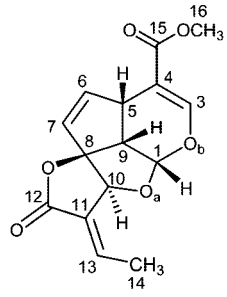
We report the determination of the absolute configuration (AC) of the iridoid natural product oruwacin by comparison of the optical rotations, $[\alpha]_D$, of its two enantiomers, calculated using time-dependent density functional theory (TDDFT), to the experimental $[\alpha]_D$ value, +193. Conformational analysis of oruwacin using density functional theory (DFT) identifies eight conformations which are significantly populated at room temperature. $[\alpha]_D$ values of these eight conformations are calculated using TDDFT at the B3LYP/aug-cc-pVDZ//B3LYP/6–31G* level, leading to the conformationally averaged $[\alpha]_D$ values of −193 for the (1*R*,5*S*,8*S*,9*S*,10*S*)-enantiomer and +193 for the (1*S*,5*R*,8*R*,9*R*,10*R*)-enantiomer. Comparison of the calculated $[\alpha]_D$ values to the value of the natural product proves that naturally occurring oruwacin has the AC 1*S*,5*R*,8*R*,9*R*,10*R*. This AC is opposite to that assigned by Adesogan by comparison of the $[\alpha]_D$ of oruwacin to that of the iridoid plumericin. Our results show that the assignment of the AC of a natural product by comparison of its $[\alpha]_D$ to that of a chemically related molecule can be unreliable and should not be assumed to be definitive.

The iridoid natural product oruwacin was first isolated by Adesogan in 1979 from the leaves of the plant *Morinda lucida*.[1] Chemical and spectroscopic data led to the conclusion that oruwacin has the structure **1**, closely related to that of the iridoid plumericin, whose structure, **2**, was determined by Albers-Schönberg and



(1R,5S,8S,9S,10S)-oruwacin, **1**



(1R,5S,8S,9S,10S)-plumericin, **2**

Schmid.[2,3] The C-14 methyl group of plumericin is replaced in oruwacin by a phenyl ring with OH and $OCH_3$ substituents. Comparison of the NMR data of oruwacin and plumericin led Adesogan to conclude that the relative configuration of oruwacin was identical to that of plumericin. Comparison of the specific rotations, $[\alpha]_D$, of plumericin, +198 ($CHCl_3$),[3] and oruwacin, +193 ($CHCl_3$),[1] led Adesogan to conclude that the AC of oruwacin is also the same as that of plumericin, assuming that the replacement of the C-14 methyl group of plumericin by the *O*-methylcatechol group of oruwacin has little impact on the optical rotation.

The recent applications of *ab initio* density functional theory (DFT) to the calculation of the vibrational circular dichroism (VCD) spectra of chiral molecules[4–7] and of *ab initio* time-dependent density functional theory (TDDFT) to the calculation of the transparent-spectral-region optical rotations (ORs) of chiral molecules[8,9] have greatly facilitated the reliable determination of the ACs of chiral organic molecules using these chiroptical techniques.[10–26] For example, very recently, the AC of plumericin assigned by Albers-Schönberg and Schmid was unambiguously confirmed by comparison of its mid-infrared VCD spectrum and its visible−near UV optical rotatory dispersion (ORD) to DFT and TDDFT calculations of these chiroptical properties.[27] The $[\alpha]_D$ of (1*R*,5*S*,8*S*,9*S*,10*S*)-**2** was predicted to be +195, in excellent agreement with the experimental value (+198).[3]

**Table 1.** Relative Energies and Free Energies,[a] Equilibrium Populations,[b] Dihedral Angles,[c] and $[\alpha]_D$ Values[d] of Conformations **a**−**d** of (1*R*,5*S*,8*S*,9*S*,10*S*)-**2**

| conformer | $\Delta E$ | $\Delta G$ | P (%) | D1 | D2 | D3 | $[\alpha]_D$ |
|---|---|---|---|---|---|---|---|
| **a** | 0.0 | 0.0 | 59.3 | 171.9 | 155.4 | −89.8 | +227.7 |
| **b** | 0.4 | 0.4 | 30.7 | −5.7 | 155.3 | −89.5 | +215.5 |
| **c** | 0.9 | 1.2 | 7.6 | −173.1 | 87.7 | −161.0 | −51.3 |
| **d** | 1.6 | 1.9 | 2.5 | 6.9 | 90.3 | −161.3 | −87.2 |
| | | | | Conformational average | | | +194.9 |

[a] B3LYP/6-31G*, in kcal/mol. [b] From $\Delta G$ values at 298 K. [c] D1: O(=)C15C4C3, D2: $C3O_bC1O_a$, D3: $O_bC1O_aC10$. [d] B3LYP/aug-cc-pVDZ//B3LYP/6-31G*; specific rotations in degrees·[dm·g/cm$^3$]$^{-1}$.

Here, we report the TDDFT calculation of the $[\alpha]_D$ of oruwacin, using the same methodology used for plumericin.[27] Our results demonstrate that the AC of oruwacin is in fact the opposite of that of plumericin.

Oruwacin is a conformationally flexible molecule, and its conformational analysis is therefore prerequisite to the calculation of its OR. DFT conformational analysis of plumericin, **2**, at the B3LYP/6-31G* level showed that there are four conformers, **a**−**d**, in equilibrium at room temperature, as a result of the flexibility of its tetracyclic core and of the methoxy-carbonyl substituent.[27] The relative energies, relative free energies, room-temperature equilibrium populations, and key dihedral angles of conformers **a**−**d**[27] are given in Table 1.

Replacement of the C-14 methyl group of plumericin by the *O*-methylcatechol group of oruwacin increases the conformational flexibility, since the phenyl group can rotate around the C-13/C-1′ bond, the O-methyl group can rotate around the C-3′/O-2′ bond and the OH group can rotate around the C-4′/O-1′ bond. In order to define the number and geometries of the conformations resulting from these rotations, we have carried out a DFT B3LYP/6-31G* calculation of the variation in energy of phenylplumericin, **3**, obtained by replacing the C-14 methyl group of conformation **a** of

* Corresponding author. E-mail: pstephen@usc.edu. Tel: 213-740-4119. Fax: 213-740-3972.
† University of Southern California.
‡ Gaussian Inc.

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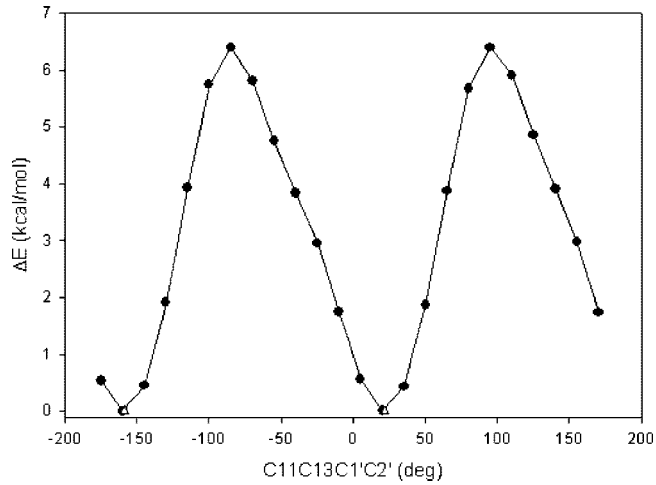
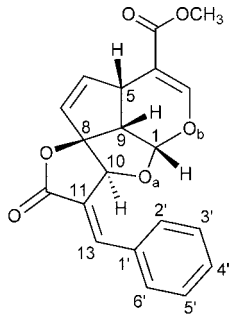
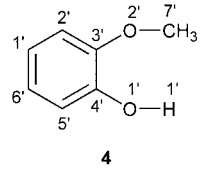



**Figure 1.** B3LYP/6-31G* energy of phenylplumericin, **3** (with the conformation **a** of **2**), as a function of the dihedral angle C11C13C1′C2′. The triangles are the B3LYP/6-31G* optimized conformations.

plumericin by a phenyl group, with respect to the dihedral angle C11C13C1′C2′, and a DFT B3LYP/6-31G* calculation of the variation in energy of *O*-methylcatechol, **4**, with respect to the dihedral angles C2′C3′O2′C7′ and C5′C4′O1′H1′.



(1R,5S,8S,9S,10S)-phenylplumericin, **3**



**4**

The results, shown in Figures 1 and 2, demonstrate that there are two equivalent stable conformations of the phenyl ring in **3**, interconverted by a 180° rotation, and that there are four stable inequivalent conformations of **4**, **e**−**h**. Optimization of these conformations of **3** and **4** gives the relative energies and key dihedral angles given in Tables 2 and 3 (and also shown in Figures 1 and 2). In the case of the conformations of **3**, the phenyl ring is approximately coplanar with the olefinic C-11/C-13 bond. Optimizations of the conformations of **3** with the plumericin core in conformations **b**−**d** lead to the structures whose relative energies and key dihedral angles are also given in Table 2. The dihedral angles D1−D3 of the four conformations of phenylplumericin, **3**, are very similar to those of conformations **a**−**d** of plumericin, **2**, showing that substitution of the phenyl group for the C-14 methyl group of **2** causes little change in the structure of the plumericin core. The lowest energy conformation of **4**, **e**, has a hydrogen bond between the OH group and the $OCH_3$ group O atom. The other three conformations, **f**−**h**, do not and are >4 kcal/mol higher in energy.

Altogether, therefore, we predict that there are 32 conformations of oruwacin, each one possessing one of the four conformations **a**−**d** of the plumericin core, one of the two orientations of the phenyl ring in which it is approximately coplanar with the adjacent C=C bond, and one of the four conformations **e**−**h** of the *O*-methylcatechol group. We have built and optimized all 32 conformations using DFT at the B3LYP/6-31G* level and verified

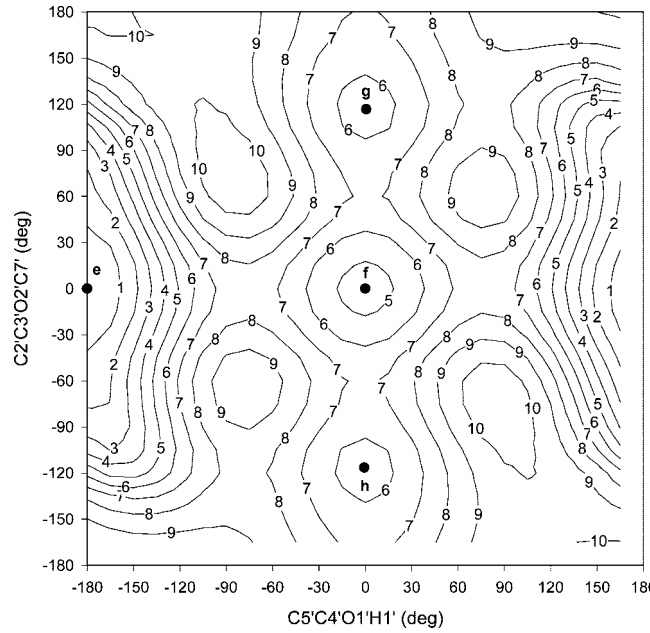



**Figure 2.** B3LYP/6-31G* energy of *O*-methylcatechol, **4**, as a function of the dihedral angles C5′C4′O1′H1′ and C2′C3′O2′C7′. The contours are at 1.0 kcal/mol intervals. The circles are the B3LYP/6-31G* optimized conformations.

**Table 2.** Relative Energies,[a] Dihedral Angles,[b] and $[\alpha]_D$ Values[c] of Conformations **a**−**d** of (1*R*,5*S*,8*S*,9*S*,10*S*)-**3**[a]

| conformer | Δ*E* | D1 | D2 | D3 | D4 | $[\alpha]_D$ |
|---|---|---|---|---|---|---|
| **a** | 0.0 | 171.5 | 156.1 | −89.2 | 21.6 | −97.3 |
| **b** | 0.4 | −5.9 | 155.9 | −88.9 | 21.8 | −96.1 |
| **c** | 1.4 | −172.7 | 87.0 | −160.1 | 14.3 | −430.0 |
| **d** | 2.0 | 7.9 | 88.4 | −160.4 | 14.0 | −463.3 |

[a] B3LYP/6–31G*, in kcal/mol. [b] D1: O(=)C15C4C3, D2: $C3O_bC1O_a$, D3: $O_bC1O_aC10$, D4: C11C13C1′C2′. [c] B3LYP/aug-cc-pVDZ//B3LYP/6-31G*; specific rotations in degrees·[dm·g/cm$^3$]$^{-1}$.

**Table 3.** Relative Energies[a] and Dihedral Angles[b] of Conformations **e**−**h** of **4**[a]

| conformer | Δ*E* | D5 | D6 |
|---|---|---|---|
| **e** | 0.0 | 0.0 | −180.0 |
| **f** | 4.6 | 0.0 | 0.0 |
| **g** | 5.6 | 116.6 | 0.6 |
| **h** | 5.6 | −116.6 | −0.7 |

[a] B3LYP/6–31G*, in kcal/mol. [b] D5: C2′C3′O2′C7′, D6: C5′C4′O1′H1′.

that this expectation is indeed correct. The relative energies and free energies (obtained from harmonic frequency calculations) of all 32 conformations, given in Table 4, lie within a range of 0–9 kcal/mol. Eight of the 32 conformations have energies and free energies within 3 kcal/mol of the lowest energy/free-energy conformation. Only eight conformations are significantly populated at room temperature therefore. The room-temperature equilibrium populations of these eight conformations are given in Table 4. The key dihedral angles of these eight conformations are also given in Table 4. In all eight conformations, the hydroxy and methoxy substituents of the phenyl ring have the same hydrogen-bonded conformation as the lowest energy conformation of **4**, **e**. In conformations 1, 2, 5, and 6, the plumericin core conformations are the same as those of conformations **a**, **b**, **c**, and **d** of plumericin, respectively, and the phenyl ring is oriented so that O2′ is closer to $O_a$ and $O_b$ than O1′. In conformations 3, 4, 7, and 8, the plumericin core conformations are the same as those of conformations **a**, **b**, **c**, and **d** of plumericin, respectively, and the phenyl ring is oriented so that O1′ is closer to $O_a$ and $O_b$ than O2′.

**Table 4.** Relative and Free Energies,[a] Equilibrium Populations,[b] Dihedral Angles,[c] and $[\alpha]_D$ Values[d] of Conformations 1–32 of (1*R*,5*S*,8*S*,9*S*,10*S*)-**1**

| conformer | Δ*E* | Δ*G* | *P* (%) | D1 | D2 | D3 | D4 | D5 | D6 | $[\alpha]_D$ | core[e] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.0 | 0.0 | 44.4 | 171.8 | 155.2 | −89.2 | 21.4 | 3.5 | −178.8 | −89.6 | **a** |
| 2 | 0.2 | 0.3 | 26.3 | −5.8 | 155.6 | −88.9 | 20.9 | 3.0 | −178.7 | −90.8 | **b** |
| 3 | 1.0 | 0.7 | 12.8 | 171.9 | 155.7 | −89.4 | −160.8 | −0.9 | 179.1 | −353.6 | **a** |
| 4 | 1.4 | 1.2 | 5.6 | −5.9 | 155.9 | −89.4 | −161.1 | −0.9 | 179.1 | −357.4 | **b** |
| 5 | 1.5 | 1.1 | 6.5 | −173.0 | 88.0 | −161.4 | 12.5 | −0.1 | −179.2 | −583.6 | **c** |
| 6 | 1.9 | 1.7 | 2.6 | 7.7 | 89.2 | −161.7 | 12.6 | 0.0 | −179.2 | −619.8 | **d** |
| 7 | 2.4 | 2.0 | 1.5 | −172.6 | 86.7 | −160.4 | −166.7 | −0.2 | 179.5 | −551.5 | **c** |
| 8 | 3.0 | 2.7 | 0.5 | 7.5 | 88.9 | −161.1 | −167.3 | −0.7 | 179.5 | −583.0 | **d** |
| 9 | 4.7 | 4.7 | | 171.8 | 155.0 | −89.1 | 21.3 | 2.4 | −0.1 | | **a** |
| 10 | 5.00 | 5.0 | | −5.9 | 155.6 | −88.8 | 20.8 | 2.1 | −0.1 | | **b** |
| 11 | 5.5 | 5.2 | | 171.8 | 155.6 | −89.4 | −160.3 | −0.6 | −0.40 | | **a** |
| 12 | 5.8 | 5.7 | | −5.8 | 155.8 | −89.5 | −160.5 | −0.5 | −0.4 | | **b** |
| 13 | 6.2 | 5.9 | | −173.0 | 87.8 | −161.2 | 12.6 | −0.2 | 0.0 | | **c** |
| 14 | 6.7 | 6.5 | | 7.5 | 89.3 | −161.7 | 12.5 | −0.1 | 0.0 | | **d** |
| 15 | 6.7 | 6.0 | | 171.9 | 155.4 | −89.4 | −160.3 | −116.4 | −1.0 | | **a** |
| 16 | 6.8 | 6.0 | | 171.6 | 155.0 | −89.8 | 18.2 | 113.9 | 0.5 | | **a** |
| 17 | 6. 8 | 6.0 | | 171.8 | 156.0 | −89.5 | −160.1 | 116.8 | 0.3 | | **a** |
| 18 | 6.9 | 6.5 | | −172.6 | 86.8 | −160.5 | −166.5 | −0.2 | −0.3 | | **c** |
| 19 | 7.0 | 6.2 | | 171.6 | 155.6 | −89.6 | 18.9 | −114.7 | −1.0 | | **a** |
| 20 | 7.0 | 6.5 | | −5.8 | 155.8 | −89.6 | −160.7 | −116.3 | −1.0 | | **b** |
| 21 | 7.1 | 6.5 | | −5.8 | 156.3 | −89.6 | −160.5 | 117.3 | 0.2 | | **b** |
| 22 | 7.1 | 6.6 | | −6.1 | 155.8 | −89.3 | 18.4 | 114.1 | 0.6 | | **b** |
| 23 | 7.3 | 6.7 | | −5.9 | 156.3 | −89.1 | 18.8 | −114.8 | −0.9 | | **b** |
| 24 | 7.4 | 7.2 | | 7.7 | 88.9 | −161.1 | −167.1 | −0.6 | −0.2 | | **d** |
| 25 | 8.2 | 7.3 | | −172.8 | 87.1 | −160.7 | −166.5 | −116.1 | −0.9 | | **c** |
| 26 | 8.2 | 7.3 | | −172.9 | 87.4 | −160.6 | −166.2 | 116.0 | 0.4 | | **c** |
| 27 | 8.2 | 7.3 | | −172.9 | 87.1 | −160.5 | 11.8 | 113.8 | 0.8 | | **c** |
| 28 | 8.3 | 7.5 | | −172.7 | 86.8 | −160.5 | 12.4 | −114.0 | −0.7 | | **c** |
| 29 | 8.7 | 7.9 | | 7.5 | 89.1 | −161.1 | −167.0 | −116.0 | −0.9 | | **d** |
| 30 | 8.7 | 7.9 | | 7.6 | 89.2 | −161.1 | −166.5 | 116.0 | 0.5 | | **d** |
| 31 | 8.8 | 8.2 | | 7.2 | 90.0 | −160.9 | 11.8 | 113.5 | 0.7 | | **d** |
| 32 | 9.0 | 8.3 | | 7.8 | 88.5 | −160.7 | 12.5 | −114.0 | −0.8 | | **d** |
| | | | | | | | | | Conformational average[f] | −193.3 | |
| | | | | | | | | | expt[g] | 193.0 | |

[a] B3LYP/6-31G*; in kcal/mol. [b] From Δ*G* values at 298 K. [c] D1: O(=)C15C4C3, D2: C3$O_b$C1$O_a$, D3: $O_b$C1$O_a$C10, D4: C11C13C1′C2′, D5: C2′C3′O2′C7′, D6: C5′C4′O1′H1′. [d] B3LYP/aug-cc-pVDZ//B3LYP/6-31G*; specific rotations in degrees·[dm·g/cm$^3$]$^{-1}$. [e] Conformation of the plumericin core. [f] $\sum_i [\alpha]_D^i$ , ($P^i$), where $[\alpha]_D{}^i$ and $P^i$ are the values of $[\alpha]_D$ and *P* for the *i*th conformation. [g] ref 1.

As in previous studies[8,9,17–19,23–26] (including that of plumericin[27]), in predicting the $[\alpha]_D$ values of the eight conformations of oruwacin using TDDFT, we use the B3LYP functional and aug-cc-pVDZ basis set, together with the B3LYP/6-31G* conformational geometries. The resulting $[\alpha]_D$ values for (1*R*,5*S*,8*S*,9*S*,10*S*)-oruwacin are given in Table 4. The $[\alpha]_D$ values of the conformations of (1*R*,5*S*,8*S*,9*S*,10*S*)-plumericin and (1*R*,5*S*,8*S*,9*S*,10*S*)-phenylplumericin are also given in Tables 1 and 2.

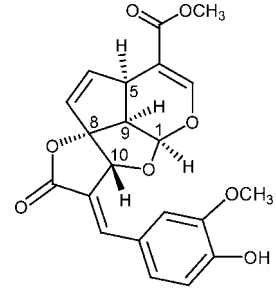
Conformations **a** and **b** of plumericin have similar $[\alpha]_D$ values, showing that $[\alpha]_D$ is insensitive to the orientation of the methoxycarbonyl substituent. Conformations **c** and **d** also have similar $[\alpha]_D$ values, for the same reason. However, the $[\alpha]_D$ values of **c** and **d** are opposite in sign to those of **a** and **b** and different in magnitude by ~250–300. Thus $[\alpha]_D$ is very sensitive to the conformation of the tetracyclic core of plumericin.

In phenylplumericin, all $[\alpha]_D$ values are negative in sign. Relative to plumericin, for each conformation $[\alpha]_D$ is different in magnitude by 300–400. Thus, the electronic interaction of the phenyl group with the plumericin core causes a massive shift in $[\alpha]_D$.

In oruwacin, conformations 1 and 2 have similar $[\alpha]_D$ values to conformations **a** and **b** of phenylplumericin. For conformations 5 and 6, $[\alpha]_D$ differs from conformations **c** and **d** of phenylplumericin by >100. Thus, the impact of the phenyl substituents on $[\alpha]_D$ depends on the conformation of the plumericin tetracyclic core. Rotation of the phenyl ring substantially changes $[\alpha]_D$ when the core conformation is **a** or **b** but not when it is **c** or **d**.

In sum, these calculations show that the oruwacin $[\alpha]_D$ is sensitive to the plumericin core conformation and the orientation of the *O*-methylcatechol group.

The conformationally averaged $[\alpha]_D$ of (1*R*,5*S*,8*S*,9*S*,10*S*)-oruwacin is −193.3; for the other enantiomer, (1*S*,5*R*,8*R*,9*R*,10*R*)-oruwacin, $[\alpha]_D$ is therefore +193.3. The $[\alpha]_D$ of the natural product is +193 ($CHCl_3$).[1] The calculated $[\alpha]_D$ for the (1*S*,5*R*,8*R*,9*R*,10*R*)-enantiomer is identical to the experimental $[\alpha]_D$, while that for the (1*R*,5*S*,8*S*,9*S*,10*S*)-enantiomer differs by 386. Our calculations thus lead unambiguously to the conclusion that the natural product (+)-oruwacin has the AC 1*S*,5*R*,8*R*,9*R*,10*R*, opposite to that of plumericin. This conclusion is opposite to that of Adesogan.[1] It is clear from our calculations that Adesogan's assumption that the optical rotation is insensitive to the replacement of the methyl group of plumericin by a substituted phenyl group is incorrect.




(1S,5R,8R,9R,10R)-oruwacin

This work further documents the power of the TDDFT methodology in predicting the optical rotations of chiral organic molecules and further demonstrates the applicability of the technique to large natural product molecules.

In addition, we have shown that the assignment of the AC of a natural product by comparison of its $[\alpha]_D$ value to that of a

chemically related molecule can be unreliable. Consequently, some natural product ACs in the literature may need to be redetermined.

Lastly, the fact that naturally occurring plumericin and oruwacin have opposite ACs shows that the biosynthetic pathways resulting in these molecules must be different. Further work is required to determine the biosynthetic pathway of oruwacin and its difference from that of plumericin.

## Methods

All DFT calculations were carried out using the GAUSSIAN 03 program.[28]

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