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Revising the Absolute Configurations of Coatlines via Density Functional Theory Calculations of Electronic Circular Dichroism Spectra

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ABSTRACT　　Coatline A (**1**) and α-*epi*-coatline A (**4**) co-occur in the trunk extract of *Andira coriacea*. Inspection of their chiroptical properties led to intriguing results. After a careful examination of the experimental data used for the previously reported absolute configuration of these compounds, some uncertainties were identified. A combined theoretical approach including conformational analyses and calculation of electronic circular dichroism (ECD) spectra, in addition with experimental data obtained for schoepfin A (**5**) and the new schoepfin D (**6**) isolated from *Senna quinquangulata*, allowed the revision of the absolute configuration of coatlines A (**1**) and B (**2**). *Chirality 25:180–184, 2013.* © 2012 Wiley Periodicals, Inc.

KEY WORDS: UHPLC/ECD; circular dichroism; absolute configuration; TDDFT ECD; Andira coriacea

INTRODUCTION

C-glycosyldihydrochalcones are unusual plant secondary metabolites among which coatlines and schoepfins are important representatives.[1,2] Even if the chemical structures of these natural products appear quite simple, and despite various published works on their structure elucidation, their absolute configuration remains not clearly assigned. Coatlines A (**1**) and B (**2**), the first *C*-glycosyl-α-hydroxydihydrochalcones, were first isolated in 1980 from the Mexican plant *Eysenhardtia polystachya* and no information was initially given on the absolute configurations of both the osidic and aglycone parts of the molecules (Fig. 1).[2] In 1987, **1** was further isolated from *Pterocarpus marsupium* and the authors proposed a D configuration for the *C*-β-glucosyl moiety without any experimental evidence.[3] The absolute configurations at C-α of **2** and the xylosyl analogue **3** were later assigned as *R* by interpretation of the sign of the Cotton effect at 328 nm in the ECD spectrum.[4] The authors based their conclusion on the comparison of their ECD spectra with those of synthetic non-osidic derivatives.[5] These absolute configurations were then used for both coatlines when compound **2** was proved to be involved in the fluorescence nature of the plant extracts.[6,7] These conclusions further drove the assignment as α*S* for the C-α epimer of coatline A, named α-*epi*-coatline A (**4**), and isolated later from a third Leguminosae, *Crotalaria zanzibarica*.[8] Finally, **4** was also found in *P. marsupium* and the absolute configurations were determined on the basis of the same ECD data.[9]

Although *Andira coriacea* (also named Saint-Martin rouge in French Guyana) is known for its antifungal bioactivity, no chemical study has so far been reported to the authors' knowledge. The first chemical investigation of the trunk of this species led to the isolation of both coatline A (**1**) and α-*epi*-coatline A (**4**) (Figure 1). In view of the clear discrepancies on the determination of the absolute configurations of these compounds, we decided to compare experimental and theoretical ECD spectra of both compounds including the osidic part of the molecule. New advances in theoretical calculation of electronic

circular dichroism (ECD) tremendously facilitate its use for the determination of the absolute configuration of chiral compounds. Since the first use of empirical sector rules or the exciton coupling circular dichroism (ECCD),[10,11] several quantum chemistry methods, such as time-dependent density functional theory (TDDFT), have been developed to predict ECD spectra of chiral compounds.[12] Despite numerous failures in the attribution of the absolute configuration of synthetic and natural compounds,[13–15] 13 acquisition and prediction of ECD spectra remain a method of choice in the determination of the absolute configuration of natural products.[16] In continuation of our ongoing work on the determination of the absolute configurations of natural products, we applied TDDFT calculations on the *C*-glucosyl-α-hydroxydihydrochalcones isolated from the trunk of *Andira coriacea*. Additional experimental data were given by the isolation of C-α dehydroxy analogues of coatlines A (**1**) and B (**2**) named schoepfin A (**5**)[1] and the new schoepfin D (**6**) from the creeper *Senna quinquangulata*.

MATERIALS AND METHODS
General

UHPLC/DAD/ECD was performed with a 1290 Agilent system coupled with a Jasco XLC 3195CD detector. Optical rotations were measured on a Jasco P-2000 polarimeter. UV and CD spectra were measured using a Jasco J-810 spectropolarimeter. HPLC purifications were carried out on a Varian system equipped with two SD1 pumps. All NMR experiments were recorded at 25 °C on a Bruker Avance 500-MHz spectrometer. Chemical shifts were reported in ppm using residual CD$_3$OD (δ 3.31 for ^{1}H and 49.0

R = H, (αS corrected config): coatline A (**1**)
R = OH, (αR): coatline B (**2**)
R = H, (αR corrected config): α-*epi*-coatline A (**4**)

3

R$_1$ = OH R$_2$ = H: schoepfin A (**5**)
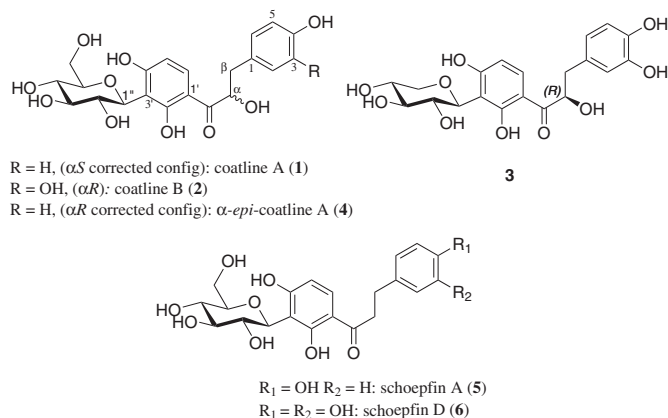R$_1$ = R$_2$ = OH: schoepfin D (**6**)

Fig. 1. Chemical structures of *C*-glycosyldihydrochalcones.

for ^{13}C) as internal reference. ESIMS was performed with a QTRAP 2000 mass spectrometer (ABsciex). HRESIMS were conducted with Accurate-Mass Q-TOF LC/MS 6520 (Agilent).

Plant Material

The trunk of *Andira coriacea* was collected in the Montagne des Chevaux (N04° 44' 0.381", W52° 25' 0.222"), French Guyana, in 2009. The leaves of *Senna quinquangulata* collected in Roura (PK36RN2), French Guyana, in 2010. Taxonomical identifications were performed by Pierre Silland.

Extraction and Isolation

The trunk of *Andira coriacea* (6.2 g) was extracted with ethanol (3 × 500 ml), yielding 386 mg of crude extract after evaporation under reduced pressure. The crude extract was then purified by reverse phase preparative HPLC (C$_{18}$ Varian Pursuit XRS, 250 mm × 41.1 mm × 5 μm) using a gradient of H$_2$O + 0.1%FA and MeOH (from H$_2$O + FA/MeOH 70:30 to 60:40 in 17 min at 60 mL.min^{-1}) to afford pure compounds **1** (12.3 mg) and **4** (40.2 mg). The leaves of *Senna quinquangulata* (5.8 g) were extracted with ethanol (3 × 500 ml) yielding 402 mg of crude extract after evaporation under reduced pressure. Purification of the crude extract was achieved by reverse phase preparative HPLC using a MACHEREY NAGEL Nucleodur C$_{18}$ (HTec, 250 × 40 mm × 5 μm) column. A mixture of H$_2$O + 0.1% FA and MeOH was used during the purification (from 50% to 80% of MeOH in 10 min at 70 mL.min^{-1}). A total of 12 mg and 15 mg of compounds **5** and **6** were obtained, respectively.

Coatline A (1). Pale yellow solid; [α]^{20}$_D$ = −43 (MeOH, *c* 0.20); ^{1}H NMR (CD$_3$OD, 500 MHz): as previously reported by Beltrami et al., 1982;[2] ESIMS: *m/z* = 437.1 [M + H]$^+$.
α-epi-Coatline A (4.) Pale yellow solid; [α]^{20}$_D$ = +54 (MeOH, *c* 0.20); ^{1}H NMR (CD$_3$OD, 500 MHz): as previously reported by by Shitamoto et al., 2010;[8] ESIMS: *m/z* = 437.1 [M + H]$^+$.
Schoepfin A (5). Brown yellow solid; [α]^{20}$_D$ = +42 (MeOH, c 0.25); ^{1}H NMR (CD$_3$OD, 500 MHz): as reported by Huang et al., 2008.[1] ESIMS: *m/z* = 421.2 [M + H]$^+$; HRESIMS *m/z* 421.1498 [M + H]$^+$ (calcd for C$_{21}$H$_{25}$O$_9$, 421.1493, Δ= −1.13 ppm).
Schoepfin D (6). Brown yellow solid; [α]^{20}$_D$ = +45 (MeOH, *c* 0.25); UV (MeOH) λ$_{max}$ (log ε) 282 (3.12), 325 (1.95); ^{1}H NMR (CD$_3$OD, 500 MHz): δ = 2.85 (2H, t, *J* = 7.5 Hz, H-β), 3.18 (2H, t, *J* = 7.5 Hz, H-α), 3.40 (1H, m, H-5"), 3.46 (1H, s, H-4"), 3.47 (1H, s, H-3"), 3.73 (1H, dd, *J* = 12.5, 5.6 Hz, H-6"), 3.85 (1H, dd, *J* = 12.3, 2.4 Hz, H-6"), 4.08 (1H, t, *J* = 9.2 Hz, H-2"), 4.92 (1H, d, *J* = 9.3 Hz, H-1"), 6.40 (1H, d, *J* = 8.9 Hz, H-5'), 6.54 (1H, dd, *J* = 8.0, 2.1 Hz, H-6), 6.66 (1H, d, *J* = 8.1 Hz, H-5), 6.67 (1H, s, H-2), 7.71 (1H, d, *J* = 9.0 Hz, H-6') ppm; ^{13}C NMR (CD$_3$OD, 125 MHz): 31.3 (CH$_2$, C-β), 40.1 (CH$_2$, C-α), 62.7 (CH$_2$, C-6"), 71.7 (CH, C-2"), 72.8 (CH, C-4"), 75.5 (CH, C-1"), 80.1 (CH, C-3"), 82.6 (CH, C-5"), 109.3 (CH, C-5'), 112.6 (C, C-1'), 114.0 (C, C-3'), 116.4 (CH, C-5),

116.6 (CH, C-2), 120.6 (CH, C-6), 133.4 (CH, C-6'), 133.96 (C, C-1), 144.6 (C, C-4), 146.2 (C, C-3), 165.0 (C, C-2'), 165.1 (C, C-4'), 206.1 (C, C = O) ppm; ESIMS: *m/z* = 437.2 [M + H]$^+$; HRESIMS *m/z* 437.1449 [M + H]$^+$ (calcd for C$_{21}$H$_{25}$O$_{10}$, 437.1442, Δ= −1.37 ppm).

Computational Section

Conformational analysis was performed using the conformer research algorithm implemented in the Conflex-Barista software.[17–20] All the density functional theory (DFT) calculations were performed using the Gaussian 03 program package[21] at the B3LYP/6-311 + G* level[22] using the integral equation formalism variant (IEFPCM).[23] TDDFT was employed to calculate excitation energy (in eV) and rotatory strength *R* in dipole velocity (*R*$_{vel}$) and dipole length (*R*$_{len}$) forms on the most stable conformers (*E* < 2 kcal.mol^{-1}). The calculated rotatory strengths were simulated in ECD curve by using the corrected Gaussian function:[24]

$$\Delta\varepsilon(E) = \frac{1}{2.297 \times 10^{-39}} \frac{1}{\sqrt{2\pi}\Delta} \sum_i^A \Delta E_i R_i e^{-\left(\frac{E - \Delta E_i}{2\Delta}\right)^2}$$

where Δ is half the width of the band at $\frac{1}{e}$ height and ΔE_i and R_i are the excitation energies and the rotatory strengths for transition *i*, respectively, *R*$_{vel}$ was used.

RESULTS AND DISCUSSION

Although both compounds **1** and **4** were easily separated by RP HPLC, they presented superimposable ^{1}H NMR spectra, which were similar to those described for coatline A (**1**).[2] A preliminary injection on UHPLC/UV/ECD revealed that both compounds could be discriminated by electronic circular dichroism (ECD). The observation of Cotton effects (CE) of opposite signs at 325 nm together with a clean separation on an achiral column led us to assume they were diastereoisomers on two distant chiral parts of the molecules (Fig. 2). This was consistent with the recent isolation of α-*epi*-coatline A (**4**).[8] In order to fully characterize the configurations of both compounds, we decided to use experimental and theoretical ECD spectra.

On both UV spectra, two bands were clearly identified: at 280 nm for a π → π* transition and at 325 nm for a n → π* transition (Fig. 3 (a)). After inspection of the chemical structure of both compounds, it was noted that two chiral centers are directly connected to this second chromophore associated with 2,6-dihydroxybenzoyl (the sugar moiety and C-α). During the first configurational study, Bezuidenhoudt et al. were unable to assign the absolute configuration at C-α because the ECD spectra, although well defined, were not suitable for comparison with other CD spectra of known compounds due to the presence of chiral sugars located on the aromatic ring.[3] Indeed, it has already been described that the presence of a sugar moiety on aromatic benzoyl moiety affected the n → π* transition of the benzoyl chromophore.[25] The same authors were able to synthesize aglycone analogues of coatlines using chemical synthesis and they recorded the ECD spectra for these compounds.[5] They gave conclusions on the absolute configurations of natural aglycon derivatives but they did not extend their conclusions to the osidic coatlines. Despite the key observations on the role of the osidic part of the molecule on the ECD spectra, all the conclusions dealing with the absolute configuration at the C-α position were further deduced from the comparison between osidic natural product spectra and aglycon congeners. A decade later, Alvarez et al. assigned the *R* configuration at C-α of coatline B (**2**), its aglycon derivative, and its xylosyl analogue (**3**) on the basis of the ECD spectra of aglycon analogues.[4] They did not take into account the influence of the sugar moiety on the Cotton effects.
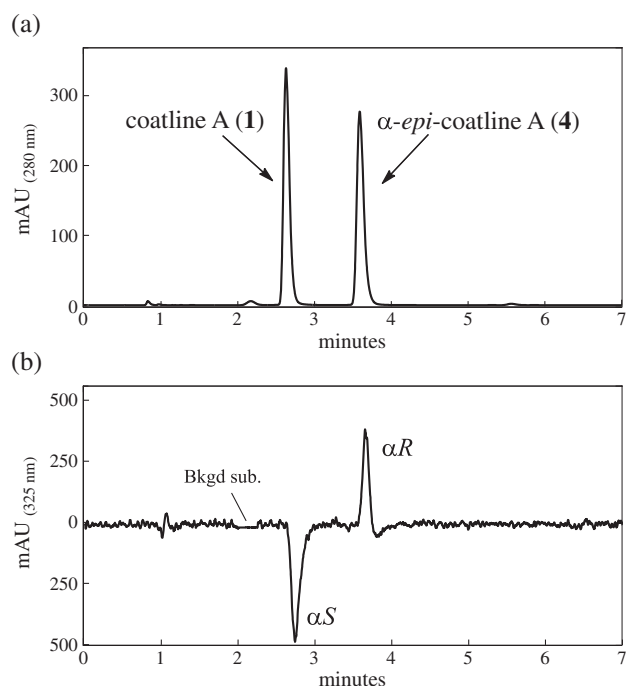
(a)

(b)

Fig. 2. UHPLC/UV/ECD of both coatline A (**1**) and α-*epi*-coatline A (**4**): **(a)** UV at 280 nm, **(b)** ECD at 325 nm. Bkgd sub. = Background subtraction.
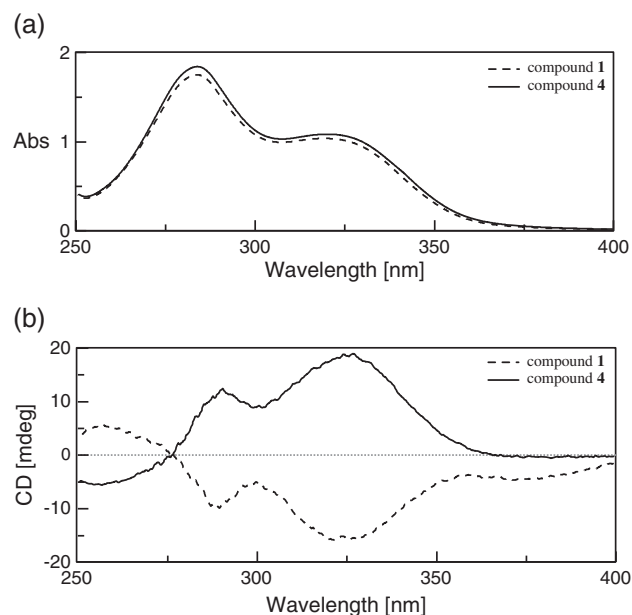
(a)

(b)

Fig. 3. ECD and UV spectra of coatline A (**1**) and α-*epi*-coatline A (**4**).
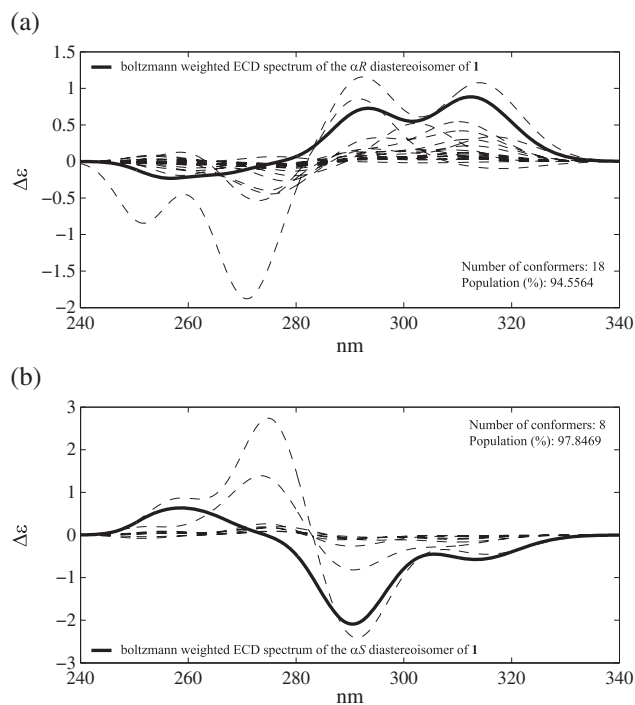
(a)

(b)

Fig. 4. (a) Theoretical ECD spectra of coatline A with αR and D configurations (at the B3LYP/6-311 + G* level). **(b)** Theoretical ECD spectra with αS and D configurations (at the B3LYP/6-311 + G level).

Acquisition of the ECD spectra of **1** and **4** using the same experimental conditions gave unexpected results. Two bands at 280 and 325 nm were indeed easily observed on both spectra but the ECD spectra were almost symmetrical for **1** and **4**, which is usually the case for two enantiomers (Figure 3 (b)). Four stereoisomers are expected for these compounds, giving rise to four pairs of diastereoisomers. One pair of diastereoisomers is already known in the literature: coatline A (**1**) and α-*epi*-coatline A (**4**) that only differ from the configuration at C-α with the same β-D-glucose.[2,8] Changing β-D-glucose for β-L-glucose in both compounds would give a second pair of diastereoisomers with different configurations at C-α. The last two pairs of diastereoisomers, i.e., a mixture of β-D and β-L-glucose with the same absolute configuration at C-α, are unlikely from a biosynthetic point of view. To discriminate between the two possible pairs of diastereo-isomers, we undertook theoretical calculations of ECD spectra. The conformational analysis performed on the proposed stereostructure of **1** (with R at C-α) gave 18 conformers with E 2 kcal.mol^{-1}, while eight conformers were obtained for the expected configurations of **4** (with S at C-α). As drawn in Figure 4, two positive CE were obtained for the C-β-D-glucosyl-(αR)-hydroxydihydrochalcone while the opposite signs are obtained for the S configuration at C-α.

These theoretical spectra are in good agreement with the experimental ECD spectra obtained in Figure 3, especially for the wavelengths of the electronic transitions. Nevertheless, these results do not support the conclusions given in the literature where a negative CE at 325 nm was consistent with an R configuration at C-α.[4,7] To confirm our theoretical approach with previously reported data, we determined the sign of the CE at 325 nm for (αR)-α,2′,4′-trihydroxy-4-methoxydihydrochalcone, an aglycon used in a published report.[8] As shown in Figure 5 (a), two bands with alternative signs are obtained on the ECD spectrum of this compound, a

positive one at ~280 nm and a negative one at 325 nm. Although these data fitted properly with the previously published data of Augustyn and coworkers on the absolute configuration of (αR)-polyoxygenated-α-hydroxydihydrochalcones,[5] they under-lined the key role of the sugar residue on the signs of the CE. We then proceeded with the theoretical calculation of the ECD spectrum of α-dehydroxy analogue of coatline A (**1**), also known as schoepfin A (**5**)[1], to evidence the role of the sugar residue on

the CE observed for **1** (Figure 5 (b)). The results indicated the same two CE observed for **1** and suggested a major contribution of the osidic residue on the sign on the CE at 325 nm.

Because the sugar residue should share the same absolute configurations in both compounds **1** and **4**, both compounds should have the same ECD pattern, but Figures 2 and 3 clearly indicate an opposite sign for the CE at 325 nm. A deeper inspection of the ECD spectra of different conformers of compound **5** (Fig. 5(b)) led to the identification of some conformers with negative CE at 325 nm. Indeed, the different conformers can be classified into two different families as described in Figure 5 (b). Rotamers of types I and II are associated with CE of opposite signs. Changing the configuration at C-α would induce an inversion in the population of type I and type II rotamers, which would be explained by diverse intramolecular hydrogen bonds.

Additional experimental data were provided by the chemical investigation of *Senna quinquangulata*, a creeper found in French Guyana. Indeed, this study led to the discovery of the known schoepfin A (**5**)[1] and the new schoepfin D (**6**), which are C-α dehydroxy analogues of coatlines A (**1**) and B (**2**), respectively. Inspection of the ^{1}H NMR spectrum indicated that compound **6** was clearly related to compound **5**. The signals at δ_H 4.08 (1H, t, H-2"), 3.85 (1H, dd, J = 12.3, 2.4 Hz, H-6"), 3.73 (1H, dd, J = 12.5, 5.6 Hz, H-6"), 3.47 (1H, s, H-3"), 3.46 (1H, s, H-4"), and 3.40 (1H, m, H-5") ppm were identical to those identified for **5** and assigned to the osidic moiety of both

compounds. Although no changes were observed for the signals of aromatic cycle attached to the glycosidic moety at δ_H 7.71 (1H, d, J = 9.0 Hz, H-6') and 6.40 (1H, d, J = 8.9 Hz, H-5') ppm, an ABX system of three protons in a 1,3,4-trisubstituted phenyl ring was clearly identified on the second aromatic cycle at δ_H 6.54 (1H, dd, J = 8.0, 2.1 Hz, H-6), 6.66 (1H, d, J = 8.1 Hz, H-5), and 6.67 (1H, s, H-2) ppm. The last two signals of the ethylene moiety connecting both parts of the structure at δ_H 3.18 (2H, t, J = 7.5 Hz, H-α) and 2.85 (2H, t, J = 7.5 Hz, H-β) ppm confirmed that compound **6** was a schoepfin.

Looking back to the chiroptical properties of compounds **5** and **6**, their experimental ECD spectra evidenced the presence of a unique positive band at c.a. 320 nm (Fig. 6). Because of the absence of the hydroxyl group at C-α, this band should only be induced by the presence of the sugar residue as a consequence of the chiral perturbation of the molecular orbital implicated in n→π* transition. The positive sign is in agreement with the

(a)

(b)

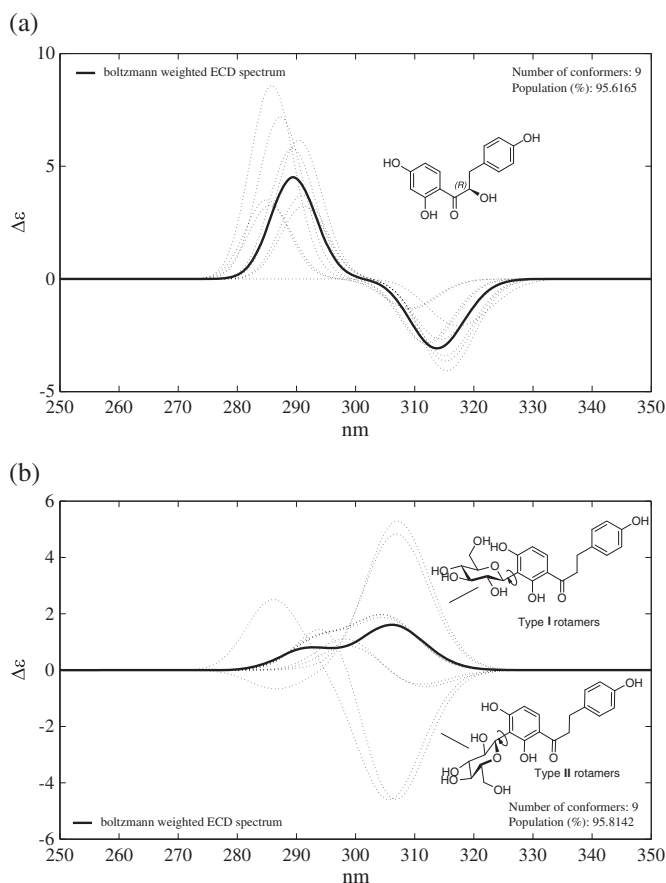**Fig. 5. (a)** Theoretical ECD spectra of α(*R*)-α,2',4'-trihydroxy-4-methoxydihydrochalcone (at the B3LYP/6-311 + G* level). **(b)** Theoretical ECD spectra of the *C*-D-glycosyl moeity (at the B3LYP/6-311 + G* level).
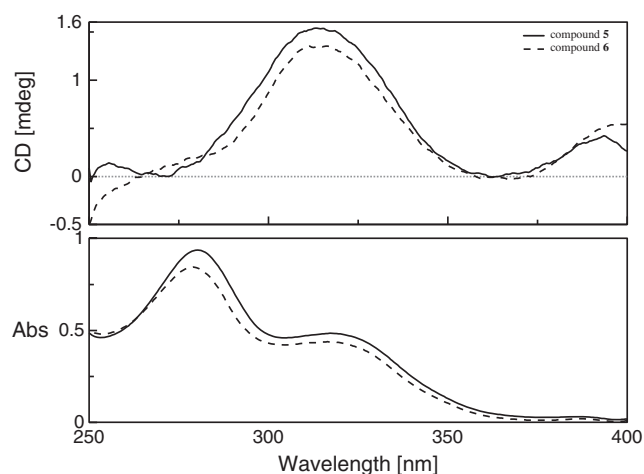

Fig. 6. ECD and UV spectra of schoepfine A (**5**) and D (**6**).
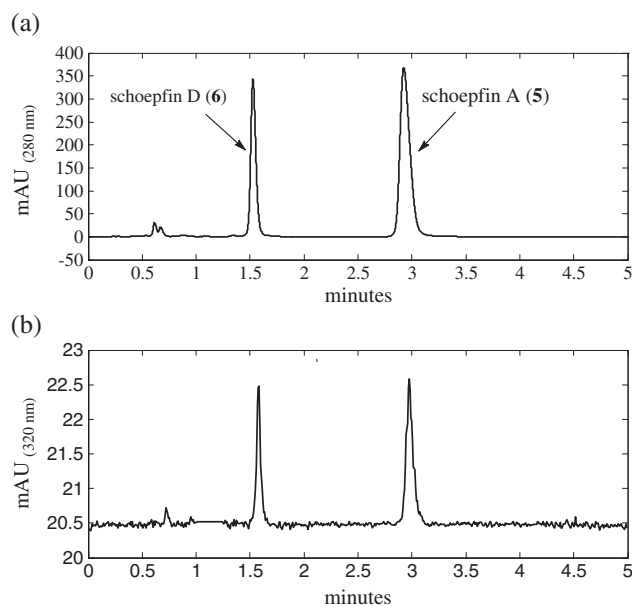
(a)

(b)

Fig. 7. UHPLC/UV/ECD of both schoepfin A (**5**) and schoepfin D (**6**): **(a)** UV at 280 nm, **(b)** ECD at 320 nm.

theoretical Boltzmann weighted spectrum obtained with a D configuration for the sugar moiety (Figure 5 (b)). For the same reason, both compounds **5** and **6** present the same UV and ECD signal when separated by UHPLC/UV/ECD. Only their retention times can help for identification (Fig. 7). These results are also in agreement with our knowledge about the metabolism of higher living organisms, since it is not possible for them to use β-L-glucose as source of energy.[26] These results confirmed the revision of the absolute configurations at C-α for all coatlines.

CONCLUSION

During the first chemical study of *Andira coriacea*, we have been able to isolate both epimers at C-α of coatline A (**1**) and their absolute configurations were unambiguously determined by ECD spectroscopy and theoretical calculations. Our results imply a revision of the absolute configurations of both compounds as well as for coatline B (**2**). The validation of the theoretical calculations approach was obtained by comparison with experimental spectra of schoepfin A (**5**) and the new schoepfin D (**6**) isolated from *Senna quinquangulata*.

ACKNOWLEDGMENTS

LITERATURE CITED

1. Huang CF, Gan XW, Bai HY, Ma L, Hu LH. Schoepfin A, B, C: three new chalcone *C*-glycosides from *Schoepfia chinensis*. Nat Prod Res 2008;22:623–627.

2. Beltrami E, Bernardi MD, Fronza G, Mellerio G, Vidari G, Vita-Finzi P. Coatline A and B, two *C*-glucosyl-α-hydroxydihydrochalcones from *Eysenhardtia polystachya*. Phytochemistry 1980;21:2931–2933.

3. Bezuidenhoudt BCB, Brandt EV, Ferreira D. Flavonoid analogues from *Pterocarpus* species. Phytochemistry 1987;26:531–535.

4. Alvarez L, Delgado G. *C*- and *O*-Glycosyl-a-hydroxydihydrochalcones from *Eysenhardtia polystachya*. Phytochemistry 1999;50:681–687.

5. Augustyn JAN, Bezuidenhoudt BCB, Swanepoel A, Ferreira D. Enantioselective synthesis of flavonoids. Part 2. Poly-oxygenated α-hydroxydihydrochalcones and circular dichroic assessment of their absolute configuration. Tetrahedron 1990;46:4429–4442.

6. Acuña A, Amat-Guerri F. Early history of solution fluorescence: the *Lignum nephriticum* of Nicolás Monardes. In: Berberan-Santos MN, editor. Fluorescence of supermolecules, polymers, and nanosystems. Berlin: Springer; 2008. p. 3–20.

7. Acuna AU, Amat-Guerri F, Morcillo P, Liras M, Rodriguez B. Structure and formation of the fluorescent xompound of *Lignum nephriticum*. Org Lett 2009;11:3020–3023.

8. Shitamoto J, Matsunami K, Otsuka H, Shinzato T, Takeda Y. Crotalionosides A-C, three new megastigmane glucosides, two new pterocarpan glucosides and a chalcone *C*-glucoside from the whole plants of *Crotalaria zanzibarica*. Chem Pharm Bull(Tokyo) 2010;58:1026–1032.

9. Achari B, Dutta PK, Roy SK, Chakraborty P, Sengupta J, Bandyopadhyay D, Maity JK, Khan IA, Ding Y, Ferreira D. Fluorescent pigment and phenol glucosides from the heartwood of *Pterocarpus marsupium*. J Nat Prod 2012;75:655–660.

10. Harada N, Ohashi M, Nakanishi K. The benzoate sector rule, a method for determining the absolute configurations of cyclic secondary alcohols. J Am Chem Soc 1968;90:7349–7351.

11. Harada N, Chen S-ML, Nakanishi K. Quantitative definition of exciton chirality and the distant effect in the exciton chirality method. J Am Chem Soc 1975;97:5345–5352.

12. Diedrich C, Grimme S. Systematic investigation of modern quantum chemical methods to predict electronic circular dichroism spectra. J Phys Chem A 2003;107:2524–2539.

13. Furche F, Ahlrichs R, Wachsmann C, Weber E, Sobanski A, Vögtle F, Grimme S. Circular dichroism of helicenes investigated by time-dependent density functional theory. J Am Chem Soc 2000;122:1717–1724.

14. Hopmann KH, Šebestík J, Novotná J, Stensen W, Urbanová M, Svenson J, Svendsen JS, Bouř P, Ruud K. Determining the absolute configuration of two marine compounds using vibrational chiroptical spectroscopy. J Organ Chem 2011;77:858–869.

15. McCann DM, Stephens PJ. Determination of absolute configuration using density functional theory calculations of optical rotation and electronic circular dichroism: chiral alkenes. J Org Chem 2006;71:6074–6098.

16. Pescitelli G, Kurtán T, Krohn K. Assignment of the absolute configurations of natural products by means of solid-state electronic circular dichroism and quantum mechanical calculations. Comprehensive chiroptical spectroscopy. Hoboken: John Wiley; 2012. p 217–249.

17. Goto H, Osawa E. Corner flapping: a simple and fast algorithm for exhaustive generation of ring conformations. J Am Chem Soc 1989;111:8950–8951.

18. Goto H, Osawa E. Further developments in the algorithm for generating cyclic conformers. Test with cycloheptadecane. Tetrahedron Lett 1992;33:1343–1346.

19. Goto H, Osawa E. An efficient algorithm for searching low-energy conformers of cyclic and acyclic molecules. J Chem Soc, Perkin Trans 1993;2:187–198.

20. Goto H, Ohta K, Kamakura T, Obata S, Nakayama N, Matsumoto T, Osawa E. CONFLEX. Tokyo-Yokohama: Conflex Corp.; 2004.

21. Frisch MJT, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Montgomery JA, Jr., Vreven T, Kudin KN, Burant JC, Millam JM, Iyengar SS, Tomasi J, Barone V, Mennucci B, Cossi M, Scalmani G, Rega N, Petersson GA, Nakatsuji H, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene M, Li X, Knox JE, Hratchian HP, Cross JB, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Ayala PY, Morokuma K, Voth GA, Salvador P, Dannenberg JJ, Zakrzewski VG, Dapprich S, Daniels AD, Strain MC, Farkas O, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ortiz JV, Cui Q, Baboul AG, Clifford S, Cioslowski J, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng AC, Nanayakkara Y, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Gonzalez C, Pople JA. Gaussian 03, Revision C.01. Wallingford, CT: Gaussian, Inc.; 2003.

22. Lee C, Yang W, Parr RG. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. Phys Rev B Condens Matt 1988;37:785–789.

23. Tomasi J, Mennucci B, Cammi R. Quantum mechanical continuum solvation models. Chemical Rev 2005;105:2999–3094.

24. Stephens PJ, Harada N. ECD cotton effect approximated by the Gaussian curve and other methods. Chirality 2010;22(2):229–233.

25. Gaffield W. Circular dichroism, optical rotatory dispersion and absolute configuration of flavanones, 3-hydroxyflavanones and their glycosides: determination of aglycone chirality in flavanone glycosides. Tetrahedron 1970;26:4093–4108.

26. Sasajima K-I, Sinskey AJ. Oxidation of L-glucose by a pseudomonad. Biochim Biophys Acta 1979;571:120–126.