DOI: 10.1002/ejoc.201101587

Assignment of Absolute Configuration of Bis-γ-pyrone Polypropionates from Marine Pulmonate Molluscs

Jian-Rong Wang,[a] Marianna Carbone,[b] Margherita Gavagnin,[b] Attila Mándi,[c] Sándor Antus,[c] Li-Gong Yao,[a] Guido Cimino,[b] Tibor Kurtán,*[c] and Yue-Wei Guo*[a]

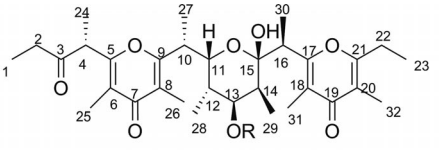
Keywords: Natural products / Configuration determination / Polyketides / Circular dichroism

The absolute configurations of onchidione (**1**), previously reported from the marine pulmonate *Onchidium* sp., and the related alcohols onchidiol (**2**) and 4-*epi*-onchidiol (**3**), first described as methanolysis products of **1**, were assigned by X-ray diffraction analysis and solid-state time-dependent density functional theory electronic circular dichroism. Alcohol **3** was incorrectly reported as the C-16 epimer of **2**.

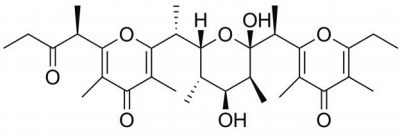
Introduction

Polypropionates represent a group of bioactive secondary metabolites of both marine and terrestrial organisms that show prominent pharmacological activities such as cytotoxic, antiviral, antiproliferative, and antifungal properties.[1,2] These natural products belong to the polyketide group, and their biosynthesis involves the condensation of propionate units through a polyketide synthase (PKS) enzymatic pathway.[2] Marine polypropionates have been mostly reported from gastropod molluscs and, in particular, from species belonging to the orders Sacoglossa and Cephalaspidea of the subclass Opisthobranchia as well as to the families Syphonariidae and Onchidiidae of the subclass Pulmonata.[3] Among these metabolites, there are large flexible molecules, the stereochemical assignment of which is an enormously challenging task.[2] The presence of several contiguous stereogenic centers in these molecules has often generated incorrect assignments but it has also constituted an intriguing target for synthetic studies, sometimes leading to the determination of the absolute configuration.[4] More recently, statistical[5] and computational[6] approaches have been showed to be effective alternative methods for the assignment of the relative stereochemistry in acyclic polypropionates. However, the definition of the absolute configuration remains an outstanding aspect for most of these molecules.

Recently, we reported the isolation of bis-γ-pyrone polypropionate, onchidione (**1**), from both the mucus and the mantle of the pulmonate *Onchidium* sp. collected in the intertidal zone along the coast of Hainan in the South China Sea.[7] The relative stereochemistry of **1** exhibiting eight stereogenic centers was fully elucidated by X-ray analysis, whereas the absolute configuration remained unassigned. In fact, we tried to apply the Mosher method to the expected alcohol derivative obtained by methanolysis of **1**, but this compound was unstable under the reaction conditions and underwent an interconversion, giving a mixture of two molecules that were suggested to be epimers at C-16,[7] according to the racemization mechanism already described for denticulatins.[8]



(–)-onchidione (**1**) R = $CH_3(CH_3)CHCH_2CO$
(–)-onchidiol (**2**) R = H



(+)-4-*epi*-onchidiol (**3**)

Later, we chemically investigated a different population of *Onchidium* sp. subsequently collected in the same place.

[a] State Key Laboratory of Drug Research,
Shanghai Institute of Materia Medica,
Chinese Academy of Sciences,
Zu Chong Zhi Road 555 Zhangjiang Hi-Tech Park,
Shanghai 201203, P. R. China
Fax: +86-21-50805813
E-mail: ywguo@mail.shcnc.ac.cn
[b] Istituto di Chimica Biomolecolare,
Consiglio Nazionale delle Ricerche,
via Campi Flegrei, 34-80078 Pozzuoli, Naples, Italy
[c] Department of Organic Chemistry, University of Debrecen,
POB 20, 4010 Debrecen, Hungary
Fax: +36-52-512-744
E-mail: kurtant@tigris.klte.hu

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201101587.

This study led us again to isolate onchidione (**1**) from the external part of the mollusc as a main metabolite, along with minor related alcohols onchidiol (**2**) and its C-4 epimer **3**. The two alcohols were found to be the same derivatives as those previously obtained by methanolysis of **1**.[7] In this communication, we describe the determination of the absolute configuration of onchidione (**1**), onchidiol (**2**), and 4-*epi*-onchidiol (**3**) by solid-state time-dependent density functional theory electronic circular dichroism (TDDFT ECD) for **1** and **2**, and by X-ray diffraction analysis with the final refinement on the Cu-K_α data for **3**.

Results and Discussion

Polypropionates **1**–**3** were isolated as described in the Experimental Section. The identity of the main metabolite, onchidione (**1**), was easily confirmed by spectroscopic data including the ECD spectra recorded in MeOH.[9] With the aim to assign the absolute configuration of **1**, we decided to use the solid-state TDDFT ECD approach. This method is especially useful in determining the absolute geometry of conformationally flexible natural[10,11] and synthetic compounds,[12,13] as the conformational analysis step of the ECD calculation could be skipped. The ECD spectra of **1** were recorded in MeOH and as a KCl disk showing almost identical curves (Figure 1) that proved that the solid-state conformers are also prevalent in solution. The TDDFT ECD spectrum calculated at the PBE0/TZVP level for the optimized X-ray structure[7] of the enantiomer (4*R*,10*R*,11*R*,12*R*,13*S*,14*S*,15*S*,16*S*)-**1** (Figure 1) well reproduced the main experimental bands. Thus, the absolute configuration of onchidione was determined as that depicted in formula **1**.

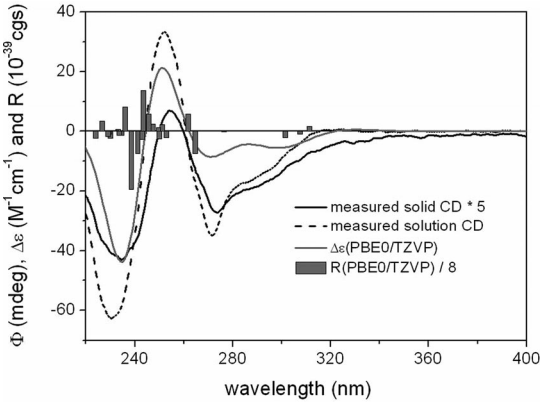


Figure 1. Experimental solid-state ECD spectrum of onchidione (**1**) recorded as KCl disk, TDDFT calculated ECD spectra (PBE0/TZVP) for (4*R*,10*R*,11*R*,12*R*,13*S*,14*S*,15*S*,16*S*)-**1** using X-ray geometry as input; vertical bars represent rotational strengths.

Alcohols **2** and **3** were submitted to careful NMR spectroscopic analysis that resulted in definition of their planar structures and full carbon and proton assignment (see the Experimental Section). The two molecules differed only in the configuration of one or more chirality centers. Comparison of the spectroscopic data with those we collected for the methanolysis derivatives of **1** revealed that **2** and **3** were identical to the alcohols described in the previous paper.[7] With the aim to complete the assessment of the relative configuration of the unassigned chiral centers[7] in addition to the aim to determine the absolute configurations of both **2** and **3**, a stereochemical study was conducted on these molecules by using X-ray and TDDFT ECD techniques.

Onchidiol (**2**) was crystallized from EtOH, and a suitable single crystal was analyzed by X-ray diffraction. The final X-ray model is depicted in Figure S1 (Supporting Information), thus confirming that it was the alcohol derivative of onchidione (**1**). Two slightly different conformers in a 1:1 ratio were identified in the crystal lattice, which differed only in the rotation of the ethyl groups (Figure S1). The two γ-pyrone moieties, located on the top of each other somewhat tilted, adopt an equatorial orientation forcing the 15-OH, 12-Me, and 13-OH groups into the axial position.

As for onchidione (**1**) the solid-state TDDFT ECD approach was applied to determine the absolute stereochemistry of **2**. The ECD spectra of **2** were recorded in MeOH and as a KCl disk showing very similar curves (Figure 2), which proved that the solid-state conformers are also prevalent in solution. The experimental ECD spectra were dominated by negative, positive, and negative Cotton effects (CE) at 273, 255, and 239 nm, respectively. The ECD spectrum was then calculated for the DFT-optimized X-ray geometries of the enantiomer (4*R*,10*R*,11*R*,12*S*,13*S*,14*S*,15*S*,16*S*)-**2** with the TDDFT method at the B3LYP/TZVP level (Figure 3). It clearly reproduced the main experimental bands very well, confirming the expected absolute configuration of **2** as (4*R*,10*R*,11*R*,12*S*,13*S*,14*S*,15*S*,16*S*), the same as that of onchidione (**1**).[14]

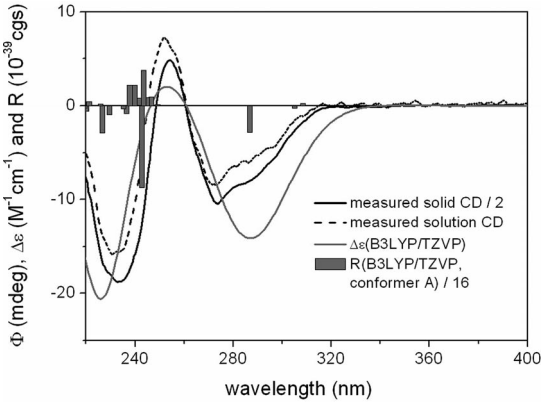


Figure 2. Experimental solid-state (KCl) and solution (MeCN) ECD spectrum of **2** compared with the TDDFT calculated ECD spectra (B3LYP/TZVP) of (4*R*,10*R*,11*R*,12*S*,13*S*,14*S*,15*S*,16*S*)-**2** using the two X-ray geometries as input (1:1 ratio); vertical bars represent rotational strengths.

4-*epi*-Onchidiol (**3**) showed an ECD spectrum slightly different from those of **1** and **2**, consistent with an opposite absolute configuration of one or more chiral centers in **3** with respect to **1** and **2** (Figure 4). In order to determine

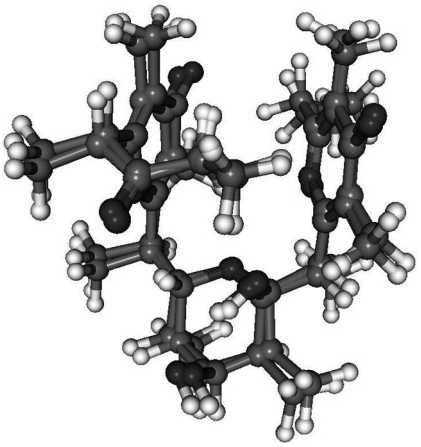


Figure 3. Overlapped DFT optimized structures of the X-ray analysis of **2** used as input for the TDDFT ECD calculation.

the configuration, a suitable single crystal of **3** was grown by careful crystallization from EtOH and used for X-ray diffraction analysis. The X-ray structure of **3** is shown in Figure 5. On the basis of the eight oxygen atoms, the final refinement on the Cu-K_α data resulted in a Flack parameter of 0.09(8), allowing unambiguous assignment of the absolute configuration of **3** as 4*S*,10*R*,11*R*,12*S*,13*S*,14*S*,15*S*,16*S*,

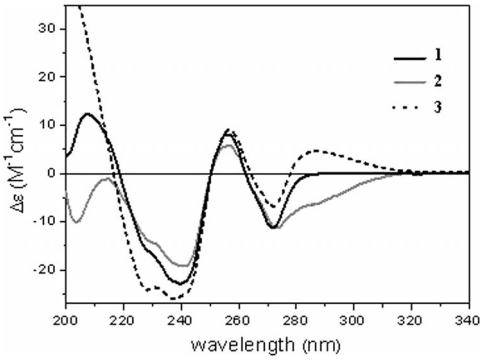


Figure 4. Experimental solution ECD profiles of **1**–**3** in methanol.

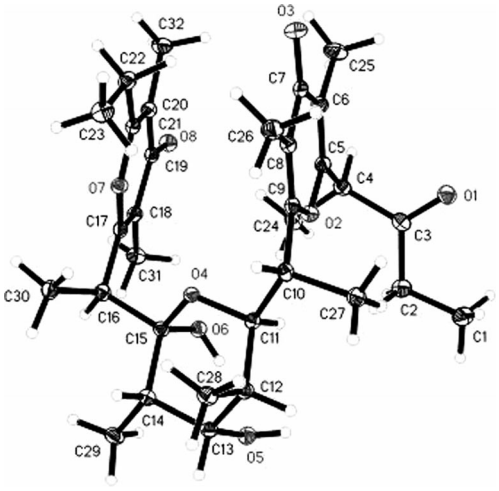


Figure 5. ORTEP diagram for the X-ray structure of **3**.

in agreement with the results obtained for **1** and **2**. Thus, compound **3** is the C-4 epimer of onchidiol (**2**).

Onchidiols **2** and **3** were identical to the previously reported molecules obtained by methanolysis of **1**,[7] which were incorrectly suggested to be epimeric at C-16. This implies that the main epimerization mechanism of onchidione alcohol derivatives involves the enolization of H-4 rather than inversion at C-16 as it was observed for denticulatins.[5] It is interesting to note that such racemization does not occur in onchidione (**1**). In the previous paper we reported that an intramolecular hydrogen bond between the hydroxy group at C-15 and the carbonyl group at C-3 stabilized the folded conformation of the crystal structure of **1**.[7] If the similarity of the solid-state and solution conformers is assumed, the intramolecular hydrogen bond should be formed also in solution by engaging the carbonyl at C-3 and making the enol formation difficult to occur. Alternatively, such an intramolecular hydrogen bond seems to be absent in **2** due to its different conformation in which the carbonyl at C-3 and the 15-OH group appear to be too far away from each other (Figure S1). This could explain the racemization at C-4 observed in onchidiol (**2**).

Conclusions

The absolute configurations of marine polypropionates onchidione (**1**), onchidiol (**2**), and 4-*epi*-onchidiol (3) were unambiguously determined by using physical methods that included solid-state time-dependent density functional theory electronic circular dichroism and X-ray diffraction analysis with the final refinement on the Cu-K_α data. This is the first time that the absolute stereochemistry of acyclic polypropionates was assigned by applying these methodologies; in most cases this is determined by stereospecific synthesis (i.e., peronatriols,[15] onchitriols[16]).

Experimental Section

Biological Material: *Onchidium* sp. (400 individuals, average size 4 cm) were collected in the intertidal zone along the coast of Lingshui Bay, Hainan Province, China, during August, 2010. The molluscs were frozen immediately after collection. A voucher specimen (LS-115) is available for inspection at Herbarium of Shanghai Institute of Materia Medica, CAS.

Extraction and Isolation: The extraction of *Onchidium* sp. specimens was performed according to a previous study.[7] The diethyl ether soluble portion of the acetone extract of the external part (2.1 g) was fractionated on an LH-20 Sephadex column ($CHCl_3$/MeOH, 1:1). Selected fractions were combined (0.8 g) and purified by silica gel column chromatography ($CHCl_3$/MeOH gradient) to give subfractions 1 and 2. Fraction 1 (120 mg) was purified by silica gel column chromatography ($CHCl_3$/MeOH, 97:3) to give onchidione (**1**, 80.5 mg). Fraction 2 (115 mg) was submitted to reverse-phase HPLC chromatography (MeOH/H_2O, 75:25) obtaining onchidiol (**2**, 25.4 mg) and 4-*epi*-onchidiol (**3**, 6.2 mg).

Onchidione (1): ECD (MeCN, $c = 1.30 \times 10^{-4}$): λ_{max} ($\Delta\varepsilon$) = 296 sh. (–12.51), 286 sh. (–16.97), 271 (–34.84), 252 (33.19), 230 (–62.61), 202 (–75.11), positive below 196 nm. ECD (66 μg of **1** in 250 mg

of KCl): λ_{max} ($\Delta\varepsilon$) = 303 sh. (–2.42), 290 sh. (–3.84), 272 (–5.47), 255 (0.99), 233 (–9.04), 204 (–8.09), positive below 196 nm. ^{1}H and ^{13}C NMR in accordance with the literature data.[7]

Onchidiol (2): Colorless crystals; m.p. 158–159 °C. $[\alpha]_D^{20}$ = –37 (c = 0.13, MeOH). UV (MeOH): λ_{max} (logε) = 260 (4.5) nm. ECD (MeOH, $c = 0.89 \times 10^{-3}$): λ_{max} ($\Delta\varepsilon$) = 287 sh. (–6.26), 273 (–11.23), 257 (5.90), 242 (–19.19), 230 sh. (–14.26), 214 (–1.17), 203 (–10.06) nm. ECD (MeCN, $c = 1.19 \times 10^{-4}$): λ_{max} ($\Delta\varepsilon$) = 293 sh. (–4.76), 284 sh. (–6.07), 271 (–8.44), 252 (7.09), 232 (–15.32), 201 (–16.87), positive below 196 nm. ECD (66 μg of **2** in 250 mg of KCl): λ_{max} ($\Delta\varepsilon$) = 296 sh. (–11.4), 288 sh. (–15.49), 273 (–20.89), 254 (9.75), 233 (–37.55), 203 (–16.85), positive below 199 nm. IR (KBr): $\tilde{\nu}$ = 3417, 2979, 2937, 2883, 1724, 1652, 1608, 1460, 1425, 1383, 1184, 1057, 978 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.79 (s, 1 H, OH), 4.51 (dd, J_{HH} = 10.6, 2.1 Hz, 1 H, 11-H), 3.97 (q, J_{HH} = 7.2 Hz, 1 H, 4-H), 3.62 (dd, J_{HH} = 2.8, 2.8 Hz, 1 H, 13-H), 3.31 (q, J_{HH} = 7.2 Hz, 1 H, 16-H), 3.10 (m, 1 H, 10-H), 2.62 (m, 1 H, 2a-H), 2.51 (m, 2 H, 2b-H and 22a-H), 2.15 (m, 1 H, 22b-H), 2.00 (m, 1 H, 14-H), 1.99 (s, 3 H, 26-H), 1.98 (s, 3 H, 31-H), 1.97 (m, 1 H, 12-H), 1.86 (s, 3 H, 25-H), 1.79 (s, 3 H, 32-H), 1.39 (d, J_{HH} = 7.2 Hz, 3 H, 24-H), 1.21 (d, J_{HH} = 7.2 Hz, 3 H, 30-H), 1.19 (d, J_{HH} = 6.8 Hz, 3 H, 29-H), 1.07 (t, J_{HH} = 8.0 Hz, 3 H, 23-H), 1.06 (d, J_{HH} = 7.2 Hz, 3 H, 27-H), 1.06 (t, J_{HH} = 6.8 Hz, 3 H, 1-H), 0.95 (d, J_{HH} = 7.2 Hz, 3 H, 28-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.6 (C-3), 179.5 (C-19), 179.0 (C-7), 165.8 (C-9), 164.9 (C-21), 160.3 (C-17), 158.5 (C-5), 121.8 (C-18), 118.8 (C-6), 118.2 (C-8), 117.0 (C-20), 102.4 (C-15), 76.3 (C-13), 66.8 (C-11), 47.2 (C-4), 42.8 (C-16), 36.8 (C-10), 36.0 (C-2), 35.7 (C-12), 32.1 (C-14), 24.7 (C-22), 14.5 (C-27), 14.4 (C-24), 12.9 (C-28), 12.1 (C-30), 11.3 (C-31), 10.7 (C-23), 10.0 (C-29), 9.5 (C-25), 9.3 (C-26), 9.2 (C-32), 7.6 (C-1) ppm. MS (ESI): m/z = 559.4 $[M + H]^+$, 581.4 $[M + Na]^+$, 1139.6 $[2M + Na]^+$. HRMS (ESI): calcd. for $C_{32}H_{46}O_8Na$ $[M + Na]^+$ 581.3090; found 581.3093.

4-*epi*-Onchidiol (3): Colorless crystals; m.p. 173–175 °C. $[\alpha]_D^{20}$ = +34 (c = 0.07, MeOH). UV (MeOH): λ_{max} (logε) = 260 (4.5) nm. ECD (MeOH, $c = 1.33 \times 10^{-3}$) λ_{max} ($\Delta\varepsilon$) = 287 (+4.58), 272 (–6.79), 257 (+9.09), 237 (–26.01), 228 (–24.18), 193 (+48.48) nm. IR (KBr): $\tilde{\nu}$ = 3432, 2980, 2939, 2885, 1727, 1654, 1593, 1461, 1425, 1383, 1186, 1059, 977 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.36 (dd, J_{HH} = 10.6, 2.0 Hz, 1 H, 11-H), 4.32 (s, 1 H, OH), 3.79 (dd, J_{HH} = 2.5, 2.5 Hz, 1 H, 13-H), 3.73 (q, J_{HH} = 7.0 Hz, 1 H, 4-H), 3.24 (q, J_{HH} = 7.0 Hz, 1 H, 16-H), 3.06 (m, 1 H, 10-H), 2.53 (m, 1 H, 2a-H), 2.32 (m, 2 H, 2b-H and 22a-H), 2.12 (m, 1 H, 22b-H), 2.10 (m, 1 H, 14-H), 2.01 (m, 1 H, 12-H), 1.97 (s, 3 H, 31-H), 1.93 (s, 3 H, 26-H), 1.91 (m, 3 H, 25-H), 1.82 (s, 3 H, 32-H), 1.74 (d, J_{HH} = 7.0 Hz, 3 H, 24-H), 1.16 (t, J_{HH} = 7.5 Hz, 3 H, 23-H), 1.15 (d, J_{HH} = 7.0 Hz, 3 H, 30-H), 1.05 (t, J_{HH} = 7.6 Hz, 3 H, 1-H), 0.99 (d, J_{HH} = 7.2 Hz, 3 H, 29-H), 0.98 (d, J_{HH} = 7.2 Hz, 3 H, 27-H), 0.97 (d, J_{HH} = 7.0 Hz, 3 H, 28-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.6 (C-3), 179.9 (C-19), 179.6 (C-7), 166.1 (C-21), 165.4 (C-9), 162.0 (C-5), 161.0 (C-17), 121.5 (C-18), 119.6 (C-6), 118.4 (C-8), 117.6 (C-20), 102.7 (C-15), 77.0 (C-13), 66.5 (C-11), 48.5 (C-4), 42.5 (C-16), 37.1 (C-10), 36.4 (C-12), 34.6 (C-2), 32.4 (C-14), 25.0 (C-22), 14.9 (C-27), 13.4 (C-24), 13.0 (C-28), 12.3 (C-30), 11.4 (C-31), 11.3 (C-23), 10.3 (C-29), 10.0 (C-25), 9.64 (C-26), 9.61 (C-32), 8.1 (C-1) ppm. MS (ESI): m/z = 559.5 $[M + H]^+$, 581.5 $[M + Na]^+$, 597.3 $[M + K]^+$, 1139.6 $[2M + Na]^+$. HRMS (ESI): calcd. for $C_{32}H_{46}O_8Na$ $[M + Na]^+$ 581.3090; found 581.3105.

X-ray Crystallographic Analysis of 2 and 3: The data collection of **2** was performed with a Bruker Smart Apex CCD diffractometer with graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å) at 293 K. The data collection of **3** was performed with a Bruker Apex II CCD diffractometer by using Cu-K_α radiation (λ = 1.54178 Å) at 133 K. The structures were solved by direct methods and refined with full-matrix least-squares calculations on F^2 using SHELXL.[17] CCDC-824267 (for **2**) and -824268 (for **3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Computational Details: Geometry optimizations [B3LYP/6-31G(d) level of theory] and TDDFT calculations were performed with Gaussian 03[18] by using various functionals (B3LYP, BH&HLYP, PBE0) and TZVP basis set. ECD spectra were generated as the sum of Gaussians[19] with 2700 and 2100 cm^{-1} half-height width (corresponding to ca. 17 and 13 at 250 nm, respectively) by using dipole-velocity computed rotational strengths.

Supporting Information (see footnote on the first page of this article): 1D NMR, 2D NMR, and HRMS spectra and crystallographic data of **2** and **3**.

Acknowledgments

This research work was financially supported by the National Marine "863" Project (No. 2011AA09070102), the National Natural Science Foundation of China (Nos. 21021063, 21072204), the Science and Technology Commission of Shanghai Municipality (STCSM) Project (10540702900), the State Key Laboratory of Drug Research/Shanghai Institute of Materia Medica (SKLDR/SIMM) Projects (SIMM1105 KF-04, SIMM1106 KF-11), and the Hungarian-Chinese Intergovernmental S&T Cooperation Programme (2011–2013). This work was also partially funded by a grant from the Chinese Academy of Sciences (CAS) (KSCX2-YW-R-18). The stereochemical studies were supported by the Hungarian Scientific Research Fund (OTKA, K-81701 and TÁMOP 4.2.1./B-09/1/KONV-2010-0007).

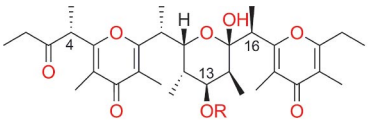
[1] M. T. Davies-Coleman, M. J. Garson, *Nat. Prod. Rep.* **1998**, *15*, 477–493.
[2] J. Darias, M. Cueto, A. R. Diaz-Marrero in *Progress in Molecular and Subcellular Biology Vol. 43: Molluscs: From Chemo-Ecological Study to Biotechnological Application* (Eds.: G. Cimino, M. Gavagnin), Springer, Berlin, **2006**, p. 105.
[3] J. W. Blunt, B. R. Copp, M. H. G. Munro, P. T. Northcote, M. R. Prinsep, *Nat. Prod. Rep.* **2011**, *28*, 196–268 and previous issues in this series.
[4] I. Paterson, C. J. Cowdwn, D. J. Wallace, in *Modern Carbonyl Chemistry* (Ed.: J. Otera), Wiley-VCH, Weinheim, **2000**, pp. 249–297.
[5] E. Fleury, M.-I. Lannou, O. Bistri, F. Sautel, G. Massiot, A. Pancrazi, J. Ardisson, *Eur. J. Org. Chem.* **2009**, 4992–5001.
[6] S. G. Smith, J. M. Goodman, *J. Am. Chem. Soc.* **2010**, *132*, 12946–12959.
[7] M. Carbone, M. Gavagnin, C. A. Mattia, C. Lotti, F. Castelluccio, B. Pagano, E. Mollo, Y. W. Guo, G. Cimino, *Tetrahedron* **2009**, *65*, 4404–4409.
[8] a) J. E. Hochlowsky, D. J. Faulkner, G. K. Matsumoto, J. Clardy, *J. Am. Chem. Soc.* **1983**, *105*, 7413–7415; b) J. D. Brabander, W. Oppolzer, *Tetrahedron* **1997**, *53*, 9169–9202.
[9] The ECD spectrum of the onchidione sample isolated the first time (ref.[7]) was recorded in MeOH and was identical with that recorded in this work.
[10] G. Pescitelli, T. Kurtán, U. Flörke, K. Krohn, *Chirality* **2009**, *21*, E181–E201.
[11] J. Dai, K. Krohn, U. Flörke, G. Pescitelli, G. Kerti, T. Papp, K. E. Kövér, A. C. Bényei, S. Draeger, B. Schulz, *Eur. J. Org. Chem.* **2010**, 6928–6937.

[12] G. Kerti, T. Kurtán, A. Borbás, Z. B. Szabó, A. Lipták, L. Szilágyi, Z. Illyés-Tünde, A. Bényei, S. Antus, M. Watanabe, *Tetrahedron* **2008**, *64*, 1676–1688.
[13] T. Kurtán, G. Pescitelli, P. Salvadori, Á. Kenéz, S. Antus, L. Szilágyi, T.-Z. Illyés, I. Szabó, *Chirality* **2008**, *20*, 379–385.
[14] The configuration at C-12 in **2** is opposite with respect to that of **1** due to a different priority order of substituents in **1** and **2**.
[15] H. Arimoto, J.-F. Cheng, S. Nishiyama, S. Yamamura, *Tetrahedron Lett.* **1993**, *34*, 5781–5784.
[16] H. Arimoto, S. Nishiyama, S. Yamamura, *Tetrahedron Lett.* **1994**, *35*, 9581–9584.
[17] G. M. Sheldrick, *SHELXS-97*: *Program for Crystal Structure Resolution*, University of Göttingen, Göttingen, Germany, **1997**.
[18] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman Jr., J. A. Montgomery, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03*, Revision C.02. **2004**, Gaussian, Inc., Wallingford, CT.
[19] P. J. Stephens, N. Harada, *Chirality* **2010**, *22*, 229–233.

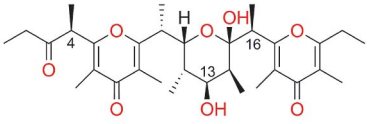
Received: October 31, 2011
Published Online: ■

Configuration Determination

The absolute configuration of three complex marine polypropionates was established by X-ray diffraction analysis and solid-state time-dependent density functional theory electronic circular dichroism.



(–)-onchidione (**1**) R = $CH_3(CH_3)CHCH_2CO$
(–)-onchidiol (**2**) R = H



(+)-4-*epi*-onchidiol (**3**)

Keywords: Natural products / Configuration determination / Polyketides / Circular dichroism

