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Δ-Keto-acid/hydroxy-lactone isomerization in some lichen depsides, depsidones and diphenyl ethers†

Philippe Uriac,*[a] Solenn Ferron,[a] Philippe Jehan,[b] Thierry Roisnel[a] and Sophie Tomasi[a]

In some compounds in lichens, the carboxylic acid is *ortho*-substituted by an 2-oxoalkyl chain. This particular structure induces the existence of δ-keto-acid **ka** or hydroxy-lactone **hl** isomers, clearly identified by their NMR data and chemical properties, such as dehydration, methylation and behaviour in thermal conditions. Internal hydrogen bonding between the carboxylic acid and substituent in the *ortho*′ position is proposed as an isomerization modulator: an H-bond acceptor (OCH_3) leads to **ka** isomers, whereas **hl** isomers are obtained with an H-bond donor (OH).

Introduction

Depsides, depsidones and diphenyl ethers are naturally occurring polyfunctionalized aromatic compounds produced by lichens[1,2] or, more rarely, by fungi.[3] In some depsides, the C-6 position of the B ring (more commonly referred to as C-6′) is substituted by a 2-oxoalkyl chain, as shown in Fig. 1 for seven specialized metabolites selected for this study. This unusual chain was introduced as a linear acyl-CoA precursor involved in the polyenzymatic system of polyketide synthase (PKS).[4,5] The presence of a free carboxylic acid on C-1′, in the *ortho* position to the 2-oxoalkyl chain induces the δ-keto-acid (**ka**)/hydroxy-lactone (**hl**) isomerization (Scheme 1). The factors influencing the position of this equilibrium are not well understood although this phenomenon, wrongly termed "tautomerism", has been reported.[6–11] Hence, the occurrence of **ka** and/or **hl** isomers should be explored further.

In the present study, new results are presented allowing the establishment of the structure and stability of compounds depicted in Fig. 1. Thus, the first observation of the hydroxy-lactone isomers (**hl**) of 2′-*O*-methylmicrophyllinic **2** and of 2′-*O*-methylsuperphyllinic **3** acids, as well as the obtention of α-collatollic **5** and α-alectoronic **6** acids as δ-keto-acid open form (**ka**), is reported, and their ^1H NMR data analyzed. Then, to validate **hl** and **ka** structures, the synthesis of some new derivatives is described. Finally, the hydrogen bonding between the carboxylic acid and vicinal $O\text{-}R_{2'}$ ($R_{2'}$ = H or CH_3) is proposed as the main isomerization modulator.

Results

The structures of compounds **1–4** [6] and **5–7** [7–11] (Fig. 1), isolated after acetone extraction and purification by column

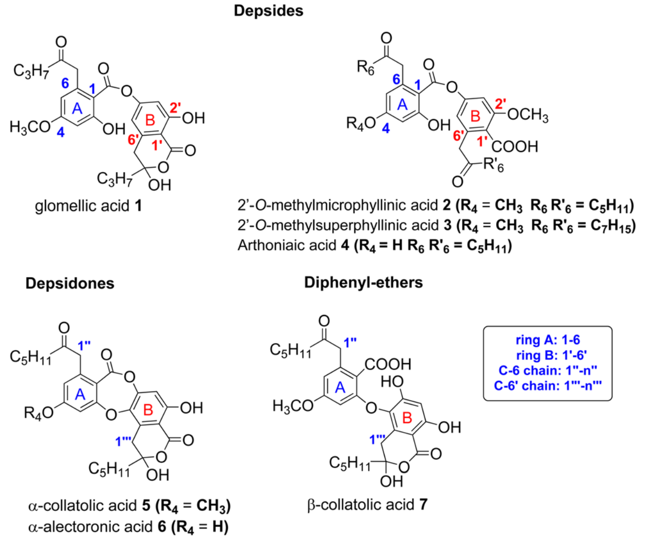

Fig. 1 Structure of depsides, depsidones and diphenyl-ethers bearing a 2-oxoalkyl chain considered in this study. Other metabolites are listed in S1.†

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[a] Univ Rennes, CNRS, ISCR (Institut des Sciences Chimiques de Rennes)-UMR 6226, Rennes, France. E-mail: sophie.tomasi@univ-rennes.fr

[b] Univ Rennes, CNRS, ScanMAT UAR 2025, CRMPO (Centre Régional de Mesures Physiques de l'Ouest), F-35000 Rennes, France. E-mail: philippe.uriac@univ-rennes. fr

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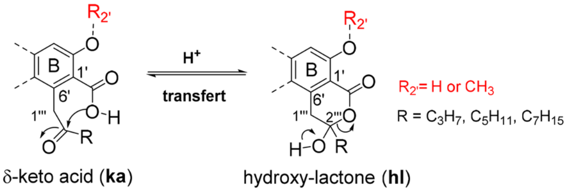


Scheme 1 Δ-Keto-acid/hydroxy-lactone (**ka**/**hl**) isomerism.

chromatography and/or preparative thin-layer chromatography, were confirmed by NMR analyses and matched values stated in the literature.

Hydroxylactones isomers 2hl and 3hl

The isomers **2hl** and **3hl** were observed only in their ^{1}H NMR spectra in a 15/85% mixture with their corresponding keto-acid isomers **2ka** and **3ka**, whereas **4hl** has never been observed. The occurrence of these **hl** forms could be assessed by the downfield shifting of H-1‴ and H-3‴ signals in relation to the transformation of the ketone on C-2‴ into a hemi-acetal. The C-2‴ chirality resulted in an AB system for the diastereotopic CH$_2$-1‴, whereas these protons were enantiotopic in the **ka** form, leading to a singlet. As an example, the spectrum of **3ka** + **3hl** mixture is shown on Fig. 2.

On the spectra of the 3‴-*O*-methyl derivatives of **1**, **5** and **6** (*vide infra*), an AB system was observed for CH$_2$-1‴ and CH$_2$-3‴.

Keto-acid isomers 5ka and 6ka

If pure depsidones **5hl** and **6hl** were dissolved in Culberson's solvent G (toluene, EtOAc, HCOOH: 70/40/4),[1] they were obtained as δ-keto-acid isomers **5ka** and **6ka** after evaporation of the solvent under reduced pressure. Likewise, only keto-acid forms could be observed when **5** and **6** were purified from acetone extracts of lichens using the same solvent system (respectively from *Tephrolema atra* and *Ochrolecchia parella*). For example, an enlarged version of the 2–4 ppm range of the ^{1}H NMR spectra of **5hl** and **5ka** is depicted in Fig. 3. The recovery of **5ka** and **6ka** after G solvent evaporation was observed when $(CD_3)_2CO$ was used as an NMR solvent. Interestingly, in the case of depside **1**, open isomers **1ka** have never been obtained. The open structures **5ka** and **6ka** were clearly attested in ^{1}H NMR by the signal deshielding of 2H-1‴ and 2H-3‴ induced by the carbonyl in position 2‴.

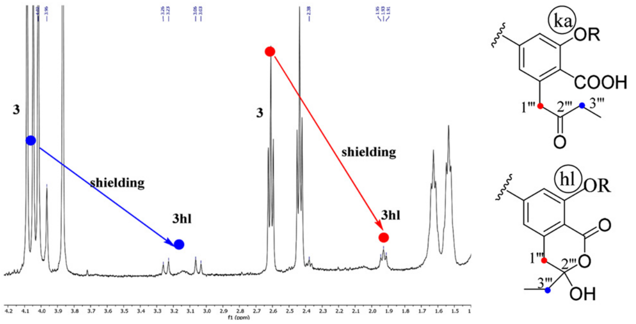


Fig. 2 Expansion of the ^{1}H NMR spectrum (2–4 ppm, 500 MHz, CDCl$_3$) of the mixture **3ka** + **3hl**.

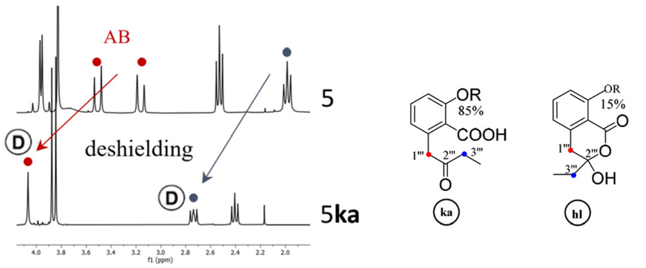


Fig. 3 Expansion of the ^{1}H NMR data (300 MHz) of **5** (**5hl**) and **5ka** (CDCl$_3$). Ⓓ: partial H/D exchange.

Finally, the hybridization change of C-1‴ resulting in significant differences in ^{1}H NMR data allowed the unequivocal attribution of **hl** or **ka** isomers, as illustrated for CH$_2$-1‴ and CH$_2$-3‴, in Table 1. To explain the coalescence (noted ^{a} in Table 1) occurring in the spectra of **hl** isomers, a "tautomerism equilibrium" has been previously proposed. Nevertheless, this phenomenon is the result of inversion of the hydroxy-lactone ring. This explanation was clearly attested with **6**[7], **7**[8] and **1** (see S4†) by the transformation at low temperature of the coalescent CH$_2$-1‴ signal into an AB system. The spectra of the **ka** isomers of **5** and **6** were recorded in *d6*-acetone, and the disappearance and/or intensity reduction of CH$_2$-1‴ and CH$_2$-3‴ signals were observed (Fig. 3). A keto–enol tautomerism, which induced a H/D exchange (noted Ⓓ in Table 1 and Fig. 3) and discussed below, could be proposed (see S4†). On ^{13}C NMR spectra, ring inversion and tautomerism resulted in the disappearance of signals but in some cases C-2‴ was observed near 206 ppm (**ka**) or 105 ppm (**hl**).

Reactivity in relation to the hydroxy-lactone structure (see S6†)

Most reactions were performed with collatolic acids **5** and **7** taken as examples, but new derivatives of α-alectoronic acid **6** and of glomellic acid **1** were also prepared.

Dehydration and *O*-methylation of the hydroxy-lactone ring

First, dehydration and *O*-methylation of the hydroxy-lactone isomers of **1**, **5** and **6** were performed to confirm the stability of the six-membered ring.

- In a study dedicated to the lichenochemical investigation of *Tephromela atra*,[7] the presence of the α-deoxycollatolic acid (= α-collatone) was reported. In the present study, such water removal from acids **5** and **7** was achieved by heating these compounds in a CHCl$_3$ or CDCl$_3$/CF$_3$COOH 80/20 mixture at 55 °C, thereby yielding α-collatone **8** and β-collatone **9**. The latter was obtained as crystals suitable for X-ray analysis (Fig. 4) clearly disclosing the hydrogen bonding between OH-2′ and C═O-1′.
- Using the *O*-methylation method previously undertaken,[9] in the structural determination of α-alecteronic acid **6**

Table 1 Selected ^{1}H NMR data of **hl** or **ka** isomers (detailed spectra in S2 and S3†)

CH_2	**1**	**2hl**	**3hl**	**5hl**	**6hl**	**7hl**
1‴	3.07–3.25 AB^a	3.03–3.22 AB, *J* = 16	3.04–3.24 AB, *J* = 16	3.18–3.52 AB, *J* = 16.2	3.55 (s^a)	3.06–3.20 AB^a, *J* = 16
3‴	1.98 (t^a)	1.91 (t, *J* = 8)	1.93 (t, *J* = 8.2)	2 (t, *J* = 8.2)	1.99 (t^a)	1.96 (t, *J* = 8)

CH_2	**2ka**	**3ka**	**4**	**5ka** Ⓓ	**6ka**
1‴	4.00 (s)	4.02 (s)	3.85 (s)	4.04 (s)	4.28 (s^a)
3‴	2.42 t, *J* = 7.5	2.44 t, *J* = 7.5	2.51 t, *J* = 7.5	2.36 s^a	2.44 t^a, *J* = 7.5

δ_H in ppm, *J* in Hz. ^{a} Coalescent. Ⓓ: partial H/D exchange.

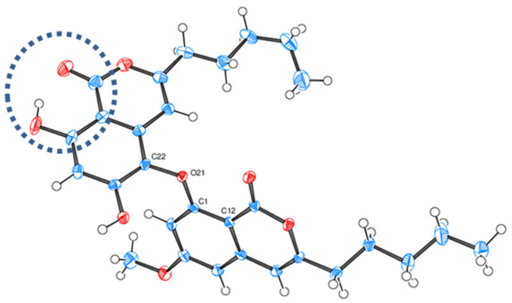
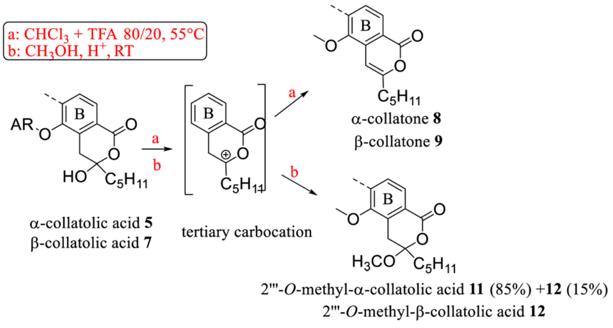


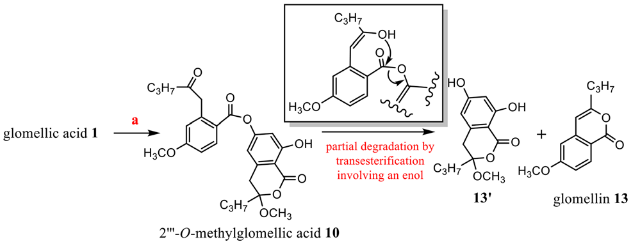
Fig. 4 ORTEP diagram of β-collatone **9** (drawn with ellipsoids at 50% probability). H-bonding site is emphasized in the dashed blue circle.

(CH_3OH, H^+ catalytic at room temperature), 2‴-*O*-methyl derivatives **10**, **11** and **12** from **1**, **5** and **7** (Schemes 2 and 3) could be obtained, respectively, in fair yields using CF_3COOH as a catalyst. As previously reported, diastereotopic CH_2 appeared as an AB system. Interestingly, the same tertiary carbocation intermediate could be postulated in the dehydration and nucleophilic attack of CH_3OH.

In these conditions (CH_3OH, H^+), chemical evolution occurred with **10** and **11**. Regarding the specific example of **10**, the rapid cleavage of the ester bond led to glomellin[6] **13** and to the analogous structure of penidiolactol[12] **13′** (Scheme 3). In the case of **11**, analogous transesterification partially led to **12** (Schemes 2 and 5).



Scheme 2 Reactivity of the hydroxy-lactone ring of **5** and **7**.

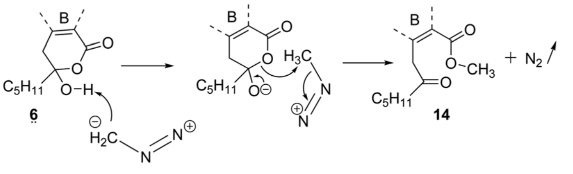


Scheme 3 *O*-Methylation of **1** and degradation of **10**.

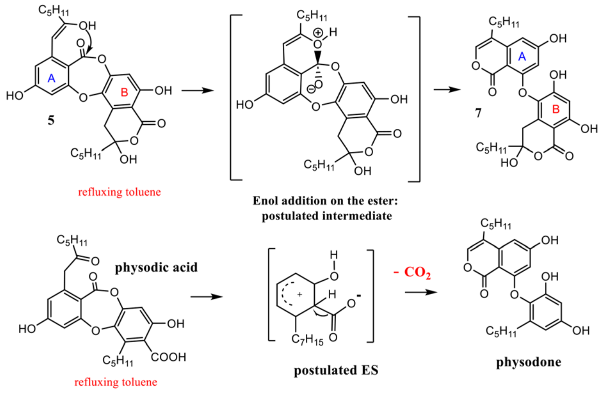
The methyl ester of **2** is the main metabolite of *Porpidia contraponenda*,[6] but those of **1**, **5** and **7** were never observed under our conditions. Moreover, the synthesis of methyl α-alectoronate **14** has been reported[9] if diazomethane is used with **6**. The authors suggested that the methylation occurred on the carboxylic acid of **6ka** after hydroxy-lactone ring opening. However, another mechanistic sequence in accordance with the **hl** structure (Scheme 4) can be envisaged in which the driving force would be the OH-lactone deprotonation of **6hl** leading to CH_3^+, which could methylate the alectoronate.

Thermal isomerization of hydroxy-lactones: examples of α-collatolic acid 5 and physodic acid

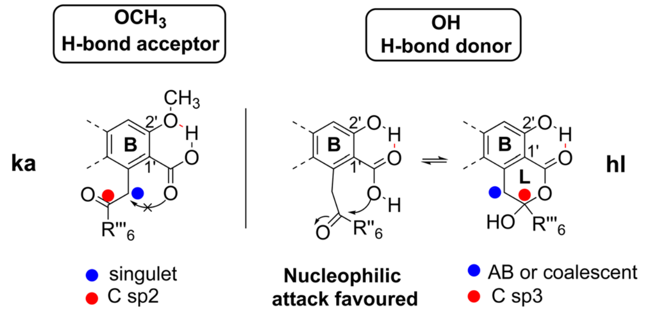
The behavior in thermal conditions of α-collatolic acid **5** and physodic acid were compared. The previously observed[7] isomerization of α-collatolic acid **5** into corresponding β-isomer **7** was confirmed herein by heating in refluxing toluene or *d8*-toluene (Scheme 5). With respect to the degradation of **10**, involvement of an enol intermediate, assisted by the eventual acidic catalysis of free COOH-1′, can be postulated. In contrast,



Scheme 4 Synthesis of methyl α-alectoronate **14** using CH_2N_2. Mechanistic proposition.



Scheme 5 Thermal isomerization of **5** and decarboxylation of physodic acid.



Scheme 6 Influence of hydrogen bonding on isomerization.

physodic acid was isomerized and decarboxylated to give physodone,‡ [15] in same thermal conditions. In this case, acid deprotonation, followed by a electrophilic substitution, has been proposed according to the literature.[13] Then, this decarboxylation absence with **5** and **6** is another strong argument in favor of the cyclic structure (Scheme 5 and S5†). Mixtures of **α** (depsidones) and **β** isomers (diphenyl-ethers) of **5** and **6** are also signaled in acetonic extracts of lichens (for example, in *Xanthoparmelia glabrans*[14]).

Reactivity in relation of the δ-keto-acid structure

^{1}H NMR spectra, recorded in *d6*-acetone, revealed a property in accordance with the open **ka** structure of **2**. Thus, disappearance of CH_2-1‴ and CH_2-3‴ signals was observed (see S4†). This phenomenon, also attested in ^{2}H NMR, can be explained by their deuteriation involving an enol. The NMR solvent would provide deuterium atoms and tautomerism would be catalysed by the close carboxylic acid. Thus, H/D exchange never occurred on the C-1″ and C-3″ of the A ring bearing an ester on C-1. The less easy enolization of CH_2-3‴ was slower and incomplete. Compounds **5ka** and **6ka** presented such an H/D exchange.

Discussion

The results concerning the preparation and characterization of **2hl**, **3hl**, **5ka** and **6ka**, as well as those devoted to the stability of the **hl** and **ka** isomers, must be explained. The occurrence of a hydroxy group, acting as an H-bond donor (**1**, **5–7**), is in relation to the hydroxy-lactone ring **hl**, whereas a methoxy substituent, acting as an H-bond acceptor (**2–4**), is instead associated with δ-keto-acid **ka** isomers, as clearly attested by NMR data (Scheme 2). Then, the stabilization energy due to the hydrogen bonding (Scheme 6) between *O*-$R_{2'}$ and COOH-1′ could be the main reason accounting for the isomerization control. If $R_{2'}$ = H (**1**, **5–7**), then the hydrogen bonding between OH-2′ and COOH-1′ promoted the nucleophilic attack of the hydroxy group of the carboxyl on the ketone to give hydroxy-lactone. In contrast, with $R_{2'}$ = CH_3 (**2–4**), this hydroxy group is bonded with the methoxy group, and δ-keto-acid remains untransformed. Such hydrogen bonding has been widely discussed[12,15] and attested through the X-ray structure of 5-methylmellein[16] and β-collatone **9** (Fig. 4).

To explain obtaining **5ka** and **6ka** during G solvent evaporation, one can propose that, in this solvent, HCOOH would induce breaking of H-bonds, whereas EtOAc would act as an H-bond acceptor. Finally, in depsidones **5** and **6**, the ether bridge would induce steric hinderance, disfavouring COOH-1′ attack on the ketone and preventing **5hl** and **6hl** obtention. On the contrary, the ether absence in depside **1hl** could explain why **1ka** has never been obtained.

Conclusions

In conclusion, it appears that the structure of specialized metabolites bearing a δ-keto-acid moiety on ring B is the result of isomerization controlled by internal hydrogen bonding. This latter involves the acid function and its *ortho* OH or OCH_3 substituent. If a methoxy is present in C-2′, they should be described as keto-acids (**ka**). If C-2′ is bearing an OH, they should be termed hydroxy-lactones **hl** according to their reactivity. Thus, in the latter case, we suggest to delete the frequent mention of tautomerism. To standardize the nomenclature of these compounds according to their reactivity, we propose to name unusual isomers using the prefix "**iso**" as follows: **5ka** = α-isocollatolic acid, **6ka** = α-isoalectoronic acid, **2hl** = 2′-*O*-methylisomicrophyllinic acid, and **3hl** = 2′-*O*-methylisosuperphyllinic acid. Finally, this study is another demonstration[6] of the interest of the extraction of natural products which allows original structural and/or mechanistic chemical studies.

Experimental

Reagents

All reagents were of high quality and purchased from commercial suppliers. They were used as received without further purification or purified/dried according to standard procedures.

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‡ Personal communication. See the NMR spectra in S5.†

Preparation of extracts and samples

Lichen thalli (often with minerals) were ground and extracted thrice with warm acetone. After drying, the solvent was evaporated under reduced pressure. Isolation of **1–4** has been previously reported. Depsidone **5** was obtained from *Tephromela atra* (Huds.) Hafellner, whereas depsidone **6** from *Ocholechia parella* (L.) Massal using the same procedure described previously.[7,8] Both were collected on coastal rocks at Lancieux (France, department 22). To perform the methylation of **2**, *Porpidia cinereoatra* was collected in Néant-sur-Yvel (France, department 56).

TLC analysis

Secondary metabolites were identified by thin-layer chromatography (TLC) using standards. Extracts and standards were loaded onto an aluminium sheet (10 × 20 cm) coated by silica gel 60F254 (Merck). Thereafter, plates were developed with solvent C (toluene/acetic acid: 85/15) or solvent G (toluene/ethyl acetate/formic acid: 139/83/8). All TLC plates were observed under UV light at 254 and 365 nm (12 W, 6 W at 365 nm, 6 W at 254 nm; Fischer Bioblock Scientific). TLC examples are given in ESI.†

Experimental R_f values in solvent C: **1** (0.30), **5** (0.35), **6** (0.16), **7** (0.22), **8** (0.40), **9** (0.51), **10** (0.51), **13** (0.55), **13′** (0.32), **11** (0.49), and **12** (0.39) (see TLC on ESI†).

Purifications using liquid chromatography

Silica gel 60 (Merck) and mainly solvent system C[1] were used for the purification of different extracts. Combined fractions with selected metabolites were washed once with water to eliminate acids, dried over $MgSO_4$ and evaporated under reduced pressure. Preparative TLC was also performed using the same solvent.

Tephromela atra: 19.4 g; extract: 1.35 g; **5** after chromatography using solvent C or G: 220 mg recrystallization. In toluol: 160 mg.

Ochrolecchia parella: 8.3 g; extract: 390 mg; **6** after chromatography in solvent C or G: 45 mg.

Porpidia cinereoatra: extract: 320 mg; after chromatography in solvent C. **2**: 34 mg and confluentic acid: 160 mg.

High resolution mass spectrometry (HRMS) and tandem mass spectrometry (MS-MS)

The mass spectra of standards were recorded at CRMPO-ScanMat (Rennes, France) on an Orbitrap Thermo Fisher Scientific Q-Exactive instrument with an ESI (electrospray Ionization) source in negative mode by direct introduction at 5–10 μg mL^{-1}. Samples were prepared in methanol at 10 μg mL^{-1}.

Synthesis procedures

Reactions were performed on a small amount of extraction products; hence, yields are not given. Only the quantities obtained after working up are indicated.

Isomerization of 5 and 6. The open form **5ka** and **6ka** were first obtained during chromatographic purifications performed using G solvent (twice for **5ka** and once for **6ka**). After evaporation of the solvent under reduced pressure, the residue was dissolved in *d6*-acetone and obtained NMR spectra corresponded to **5ka** and **6ka**. If $CDCl_3$ was used, the obtained NMR spectra corresponded to **5** and **6**. The same result was obtained if pure **5** and **6** were dissolved in G solvent.

Isomerization of 2 and 3. The cyclic form **2hl** and **3hl** were observed as traces on NMR spectra recorded in $CDCl_3$ of **2** and **3** obtained after chromatographic purification using C solvent.

Dehydration of 5 and 7. The loss of water was performed in a mixture of $CHCl_3/CF_3COOH$ (2 mL/0.5 mL) at 50 °C. The reactions were monitored by TLC: after 5–7 days (no more conversion), the reaction was stopped. After water addition, the organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography using solvent C. NMR spectra of the transformation of **5** and **7** in $CDCl_3/CF_3COOH$ are shown in ESI.†

5 (20 mg) gave α-collatone = deoxycollatolic acid **8** (11 mg) with similar data to those previously reported.[7] Presence of residues of **5** and of **10** was noted on TLC.

7 (20 mg) gave β-collatone **9** (14 mg).

***O*-Methylations of 1, 5 and 7.** The methylation of OH-3‴ was performed in CH_3OH (2–3 mL) at room temperature with a catalytic amount of CF_3COOH. The reactions were monitored by TLC: for high conversion, 5 days were needed. Every day, one drop of CF_3COOH was added to enhance the reaction. Methanol was evaporated under reduced pressure, and the residue was purified by column chromatography using solvent C.

1 (15 mg) gave 2‴-*O*-methylglomellic acid **10** (12 mg). After 1 month, along with **10** (4 mg), hydrolysis compounds glomelline **13** (3 mg) and **13′** (3 mg) were obtained.

7 (30 mg) gave 2‴-*O*-methyl-β-collatolic acid **12** (24 mg) and **5** gave 2‴-*O*-methyl-α-collatolic acid **11** (14 mg) as a white precipitate after filtration. Isomerization of **11** into **12** was also observed by TLC.

Thermal isomerization of 5. The depsidone **5** was allowed to react in refluxing toluene for 1 week. After solvent evaporation under reduced pressure, the residue was purified by column chromatography using solvent C. Yield of **7**: 40–50%. Evolution in *d8*-toluene at 80 °C is shown in ESI.†

X-ray data

β-Collatone 9 CCDC 2241570.†

^{1}H, ^{2}H and ^{13}C NMR spectra

Spectra were recorded at 300/75 MHz or 500/100 MHz (cryoprobe) respectively, using $CDCl_3$ or d_6-acetone. Shifts (δ values) are given in parts per million (ppm) and coupling constants (J values) are given in Hertz (Hz). The multiplicity of signals was reported as follows: s (singlet), d (doublet), t (triplet), q (quadruplet), quint (quintet), sext (sextet), m (multiplet), * (broad or coalescent signal), dt (doublet of triplet), and td (triplet of doublet). The references were: $CDCl_3$/7.26 ppm and d_6-

acetone/2.05 ppm. In some compounds, coalescent signals were missing or badly resolved in ^{13}C NMR.

2hl and **3hl** in mixture with **2ka** and **3ka** (15/85%). Only some signals were visible.

2′-*O*-Methylisomicrophyllinic acid **2hl** $C_{30}H_{38}O_9$ M_W: 542.62 g mol^{-1}. 3-Hydroxy-8-methoxy-3-pentyl-3*H*-2-benzopyran-1(4*H*)-on-6-yl and 2-hydroxy-4-methoxy-6-(2-oxoheptyl) benzoate. **^{1}H NMR** (300 MHz, $CDCl_3$): 3.22 and 3.03 (AB, *J* = 16 Hz, 2H), 1.89 (t, 2H). In mixture with **2ka** (15/85%).

2′-*O*-Methylsuperphyllinic acid **3hl** $C_{34}H_{46}O_9$ M_W: 598.72 g mol^{-1}. 3-Heptyl-3-hydroxy-8-methoxy-3-3*H*-2-benzopyran-1(4*H*)-on-6-yl and 2-hydroxy-4-methoxy-6-(2-oxononyl)benzoate. **^{1}H NMR** (500 MHz, $CDCl_3$): 3.24 and 3.04 (AB, *J* = 16 Hz, 2H), 1.93 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$): 41.1 and 37.8. In mixture with **3ka** (15/85%).

In ^{13}C NMR of **5ka** and **6ka**, some signals of sp^2 carbons were not visible, particularly C‴-1 and C‴-2.

α-Isocollatolic acid **5ka**: [522-52-1] $C_{28}H_{32}O_9$ $C_{29}H_{34}O_9$ M_W: 526.58 g mol^{-1}. 8-Hydroxy-3-methoxy-11-oxo-1,6-bis(2-oxoheptyl)-11*H*-dibenzo[*b*,*e*][1,4]dioxepin-7-carboxylic acid. ^{1}H NMR (300 MHz, CD_3COCD_3): 6.87 (d, *J* = 2.4 Hz, 1H), 6.78 (d, *J* = 2.4 Hz, 1H), 6.70 (s, 1H), 4.08 (s, 2H), 4.04 (s*, 2H), 3.88 (s, 3H), 2.55 (t, *J* = 7.5 Hz, 2H), 2.36 (s*, 1.6H), 1.59 (m, 4H), 1.32 (m, 8H), and 0.89 (t, 6H). ^{13}C NMR (100 MHz, CD_3COCD_3): 163.5, 162.2, 162.1, 141.4, 141.0, 115.8, 114.2, 106.9, 104.2, 55.5, 54.6, 47.2, 42.0, 41.1, 31.5, 31.2, 23.1, 22.3, 22.2, 13.4, and 13.4.

α-Isoalectoronic acid 6ka: [668-80-4] $C_{28}H_{32}O_9$ 55 g mol^{-1}. M_W: 512.55 g mol^{-1}. 3,8-Dihydroxy-11-oxo-1,6-bis(2-oxoheptyl)-11*H*-dibenzo[*b*,*e*][1,4]dioxepin-7-carboxylic acid. **^{1}H NMR** (300 MHz, CD_3COCD_3): 8.16 (s, 0.4H), 6.75 (d, *J* = 2.4 Hz, 1H), 6.63 (d, *J* = 2.4 Hz, 1H), 6.00 (s, 1H), 4.00 (s, 2H), 4.27 (s*, 2H), 3.97 (s, 2H), 2.52 (t, *J* = 7.5 Hz, 2H), 2.44 (t*, 1.8H), 1.55 (m, 4H), 1.29 (m, 8H), 0.88 (t, *J* = 7.4 Hz, 3H), and 0.82 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz, CD_3COCD_3): 162.6, 162.5, 162.1, 141.7, 141.1, 117.0, 112.9, 106.7, 105.8, 54.6, 47.3, 41.9, 41.5, 31.4, 31.2, 23.1, 22.3, 22.3, 13.4, and 13.4.

β-Collatone 9 [520-08-1] **^{1}H NMR** (300 MHz, $CDCl_3$): 11.04 (s, 1H), 9.21 (s, 1H), 6.57 (s, 1H), 6.51 (d, *J* = 2.3 Hz, 1H), 6.37 (d, *J* = 2.3 Hz, 1H), 6.36 (s, 1H), 6.24 (s, 1H), 3.80 (s, 3H), 2.53 (t, *J* = 7.5 Hz, 2H), 2.51 (t, *J* = 7.5 Hz, 2H), 1.70 (m, 4H), 1.37 (m, 4H), 1.33 (m, 4H), 0.93 (t, *J* = 6.9 Hz, 3H), and 0.91 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): 166.1, 165.9, 162.8, 161.7, 161.1, 159.8, 159.2, 157.8, 142.2, 132.0, 130.2, 104.6, 104.3, 103.5, 103.3, 102.9, 98.6, 98.4, 56.0, 33.7, 33.4, 31.3, 31.2, 26.6, 22.5, 22.5, 14.1, and 14.0. **HRMS** $[M - H]^-$ $C_{29}H_{31}O_8$ calc. 507.20244 found. 507.2024.

2‴-*O*-Methylglomellic acid 10 $C_{26}H_{30}O_9$ M_W: 486.51 g mol^{-1}. (8-Hydroxy-3-methoxy-3-propyl-3*H*-2-benzopyran-1(4*H*)-on-6-yl and 2-hydroxy-4-methoxy-6-(2-oxopentyl)benzoate). **^{1}H NMR** (300 MHz, $CDCl_3$): 11.21 (s, 1H), 11.19 (s, 1H), 6.62 (d, *J* = 2.4 Hz, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 1H), 6.3 (d, *J* = 2.4 Hz, 1H), 4.03 (s, 2H), 3.84 (s, 3H), 3.18 (m, J_{AB} = 16 Hz, 1H), 3.08 (m, J_{AB} = 16 Hz, 1H), 2.39 (m, 2H), 2.02 and 1.98 (2 m, 2H), 1.54 (m, 6H), 1.43 (m, 2H), 1.39 (m, 4H), 1.02 (t, 3H), and 1.02 (t, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): 207.2, 168.8, 168.6, 166.8, 165.2, 163.6, 160.0, 155.4, 139.9, 139.0, 113.6, 112.9, 109.5, 107.6, 106.6, 104.3, 100.2, 51.4, 50.1, 44.5, 37.3, 36.3, 17.2, 17.0, 14.2, and 13.8. **HRMS** $[M - H]^-$ $C_{26}H_{29}O_9$ calc. 485.18171 found. 485.1822.

Compound 13′ $C_{13}H_{16}O_5$ M_W: 252.27 g mol^{-1}. 3-Pentyl-3,6,8-trihydroxy-3*H*-2-benzopyrane-1(4*H*)-one **^{1}H NMR** (300 MHz, $CDCl_3$): 11.17 (s, 1H), 6.29 (d, *J* = 2.4 Hz, 1H), 6.20 (d, *J* = 2.4 Hz, 1H), 5.55 (s,1H), 3.35 (s, 3H), 3.11 (m, J_{AB} = 16 Hz, 1H), 3.00 (m, J_{AB} = 16 Hz, 1H), 1.44 (m, 6H), 1.44 (t, 3H), and 1.01 (t, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 168.8, 164.4, 162.5, 140.4, 107.4, 107.1, 101.9, 101.8, 50.1, 37.3, 36.3, 17.0, and 14.2. **HRMS** $[M - H]^-$ $C_{13}H_{15}O_5$ calc. 251.0925 found. 251.0924.

2‴-*O*-Methyl-α-collatolic acid 11 $C_{30}H_{36}O_9$ M_W: 540.62 g mol^{-1}. (2,11-Dimethoxy-5-hydroxy-9-(2-oxoheptyl)-2-pentyl-4*H*,8*H*-[1,4]benzodioxepino[2,3-*f*][2]benzopyran-4(1*H*),8-dione). **^{1}H NMR** (300 MHz, $CDCl_3$): 11.01 (s, 1H), 6.79 (s, 1H), 6.58 and 6.59 (m, 2H), 3.99 and 3.97 (AB, J_{AB} = 17 Hz, 2H), 3.84 (s, 2H), 3.53 and 3.00 (AB, J_{AB} = 17 Hz, 2H), 3.34 (s, 3H), 2.54 (t, *J* = 7 Hz, 2H), 2.07–1.93 (mAB, 2H), 1.7–1.2 (m, 12H), 0.94, (t, *J* = 7 Hz, 3H), and 0.89 (t, *J* = 7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 168.1, 163.4, 161.7, 160.3, 150.5, 141.4, 129.7, 115.0 107.9, 107.5, 104.8, 55.8, 50.0, 48.0, 42.8, 35.0, 31.7, 31.3, 30.4, 23.3, 23.2, 22.5, 22.5, 14.0, and 14.0. **HRMS** $[M - H]^-$ $C_{30}H_{35}O_9$ calc. 539.22866 found. 539.2279.

2‴-*O*-Methyl-β-collatolic acid 12 $C_{30}H_{36}O_9$ M_W: 540.62 g mol^{-1}. (6,8-dihydroxy-3-methoxy-5-(6-methoxy-1-oxo-3-pentyl-1*H*-2-benzopyran-8-yl)oxy-3,6,8-trihydroxy-3-pentyl-1*H*-2-benzopyran-1(1*H*)-one). **^{1}H NMR** (500 MHz, $CDCl_3$): 11.12 (s, 1H), 6.58 (s*, 1H), 6.51 (d, *J* = 2.4 Hz), 6.50 (s, 1H), 6.21 (s, 1H), 3.79 (s, 3H), 3.35 (s, 3H), 3.24 (d, J_{AB} = 16 Hz, 1H), 2.99 (d, J_{AB} = 16 Hz, 1H), 2.51 (t, *J* = 7.4, 2H), 1.96 (m, 2H), 1.70 (m, 2H), 1.34 (m, 12H), 0.91 (t, *J* = 7.5, 3H), and 0.88 (t, *J* = 7.5, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 168.3, 166.0, 162.6, 162.2, 160.6, 159.4, 157.0, 141.7, 134.3, 131.2, 107.0, 103.8, 103.4, 103.2, 102.8, 99.9, 35.0, 33.3, 31.7, 31.5, 31.2, 29.7, 26.5, 23.1, 22.4, 22.4, and 14.0 **HRMS** $[M - H]^-$ $C_{30}H_{35}O_9$ calc. 539.22866 found. 539.2287.

Data concerning C-1‴2‴3‴ (Fig. 3)

Glomellic acid 1 [52589-14-7] **Proposed DCI**: 3,8-dihydroxy-3-propyl-3*H*-2-benzopyran-1(4*H*)-on-6-yl, and 2-hydroxy-4-methoxy-6-(2-oxopentyl)benzoate. **^{1}H NMR** (300 MHz, $CDCl_3$): 4.04 (s, 2H), 3.22*(s, 2H), 2.39 (t, *J* = 7.5 Hz, 2H), 1.98* (m, 2H). **^{13}C NMR** (80 MHz, CD_3COCD_3): 106.5, 43.5, and 37.2.[6]

2′-*O*-Methylmicrophyllinic acid 2 [79579-62-7] **^{1}H NMR** (300 MHz, $CDCl_3$): 4.07 (s, 2H), 4.03 (s, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), and 2.42 (t, *J* = 7.5 Hz, 2H).**^{13}C NMR** (80 MHz, $CDCl_3$): 51.2 and 42.7.[6]

2′-*O*-Methylsuperphyllinic acid 3 [108529-20-0] **^{1}H NMR** (300 MHz, $CDCl_3$): 4.06 (s, 2H), 4.02 (s, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), and 2.41 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): 207.3, 49.2, and 42.7.[6]

Arthoniaic acid 4 [25556-24-5] **^{1}H NMR** (300 MHz, $CDCl_3$): 4.17 (s, 2H), 3.85 (s, 2H), 2.51 (t, *J* = 7.5 Hz, 2H), and 2.48 (t, *J* = 7.5 Hz, 2H). **^{13}C NMR** (80 MHz, $CDCl_3$): 207.4, 47.7, and 42.5.[6]

Author contributions

Project design by P. Uriac. Synthesis by P. Uriac. Characterization by S. Ferron and P. Jehan. Crystallographic experiments and analyses by T. Roisnel. The manuscript was written by P. Uriac and S. Tomasi with edits from all authors.

Conflicts of interest

There are no conflicts of interest to declare.

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