

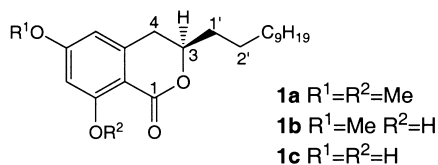
Stereoselective Synthesis of (3*R*)-3,4-Dihydro-6,8-dimethoxy-3-undecyl-1*H*-[2]benzopyran-1-one and Derivatives, Metabolites from *Ononis natrix*

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A short stereoselective synthesis of (3*R*)-3,4-dihydro-6,8-dimethoxy-3-undecyl-1*H*-[2]benzopyran-1-one and derivatives isolated from *Ononis natrix* has been described. Condensation of dodecanoyl chloride with 3,5-dimethoxyhomophthalic acid afforded 6,8-dimethoxy-3-undecylisocoumarin **3**, which, on sequential saponification and esterification, yielded the keto ester **5**. Enantioselective reduction of **5** with TarB-NO₂/LiBH₄ directly furnished the title dihydroisocoumarin **1a** in 80% ee (82% yield). Partial as well as complete demethylation of the latter provided the dihydroisocoumarins **1b** and **1c**, respectively. Diastereotopy of the CH₂ H-atoms on either side of the stereogenic center (C(3)) and the mass-fragmentation pattern of the dihydroisocoumarins have also been described. All of the compounds synthesized were examined *in vitro* for antifungal activity.

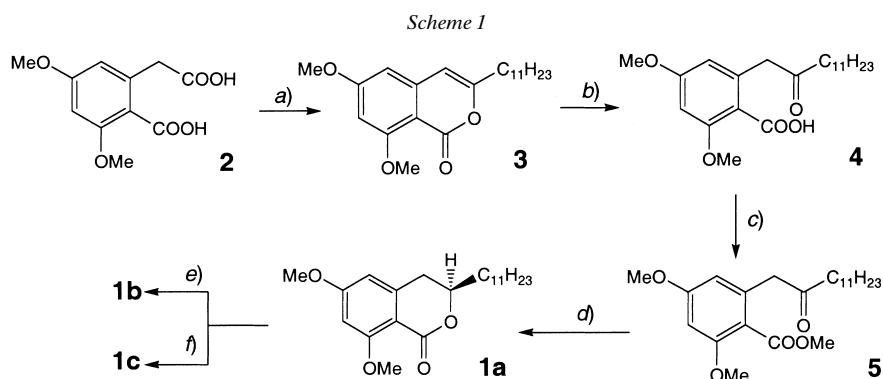
Introduction. – *Ononis natrix* is a small flowering plant belonging to family Leguminosae. The infusion of its roots has diuretic, antirheumatic properties, and has been used for certain disturbances of the urinary tract. During phytochemical studies of this plant, *Feliciano et al.* had isolated 3,4-dihydro-6,8-dimethoxy-3-undecylisocoumarin (**1a**; R¹ = R² = Me; isocoumarin = 1*H*-[2]benzopyran-1-one), its 8-hydroxy- (**1b**; R¹ = Me, R² = H) and 6,8-dihydroxy- (**1c**; R¹ = R² = H) derivatives as (*R*)-antipodes, from the hexane extract along with some related compounds [1][2]. *Kazlauskas et al.* had isolated earlier the related (3*R*)-3,4-dihydro-8-hydroxy-3-undecylisocoumarin from the brown alga *Caulocystis cephalornithos* [3].



We have already reported on the total synthesis of the title dihydroisocoumarins as racemates [4] by the multistep strategy developed during the synthesis of 6-methoxymellein, a phytoalexin, and metabolite of several fungi and peniolactol, the metabolite of the wood attacking fungus *Peniophora sanguinea* [5]. Title dihydroisocoumarins, besides their diuretic, antirheumatic, and antibacterial activities, are potential antifungal agents, and a detailed study of their biological profile required a short synthetic route. Condensation of acid chlorides with homophthalic acids has been useful for the construction of 3-substituted isocoumarin skeleton, which could easily be converted into corresponding 3,4-dihydroisocoumarins [6]. Herein, a facile stereo-

selective synthesis of title dihydroisocoumarins involving TarB-NO₂ as chiral *Lewis* acid for enantioselective reduction as a key step, and their antifungal activities are described.

Results and Discussion. – 3,5-Dimethoxyhomophthalic acid **2** was prepared from 3,5-dimethoxybenzyl bromide *via* Rh-catalyzed direct carbonylation to corresponding phenylacetic acid as a key step [7]. Direct condensation of 3,5-dimethoxyhomophthalic acid with dodecanoyl chloride at elevated temperature afforded the 6,8-dimethoxy-3-undecylisocoumarin **3** in 65% yield [8] (*Scheme 1*). It showed the characteristic 1-H *singlet* of isocoumarin moiety at δ 6.07 for H–C(4) in the ¹H-NMR and signals at δ 103.1 (C(4)) and 160.0 (C(3)) in the ¹³C-NMR spectrum. DEPT 90° and DEPT 135° experiments confirmed these assignments. Mass spectrum showed the characteristic isocoumarin fragments at *m/z* 220, 205, and 177, in addition to the molecular ion, and IR spectrum showed the lactone C=O absorption at 1685 cm^{–1}.



a) C₁₁H₂₃COCl, 200°, 4 h; 65%. b) 5% KOH, EtOH, 4 h reflux; 72%. c) MeI, K₂CO₃, dry acetone, 3 h; 95%. d) LiBH₄, TarB-NO₂, 2 h, r.t.; 82%. e) BBr₃, CH₂Cl₂, –78°, 10 min; 78%. f) BBr₃, CH₂Cl₂, –78° → r.t. overnight; 72%.

Alkaline hydrolysis of the isocoumarin **3** to furnish the 4,6-dimethoxy-2-(2-oxotridecyl)benzoic acid (**4**) was accomplished in 78% yield. The keto acid existed in equilibrium with its cyclic tautomeric lactol form *viz.* 3,4-dihydro-3-hydroxy-6,8-dimethoxy-3-undecylisocoumarin as evidenced by the ¹H-NMR. Thus, in addition to the 2-H *singlet* at δ 4.04 for benzylic H-atoms, (H–C(1'), open-chain form) each of the H-atoms showed a *triplet* at δ 2.57–2.61 (*J* = 4.2) and at 2.29–2.40 (*J* = 4.5) most probably by ⁴*J* coupling in ¹H-NMR and signal for benzylic C-atom at δ 77.7 in ¹³C-NMR spectrum was observed.

The keto acid was converted into the corresponding ester, as such keto esters are known to afford better enantioselectivities in stereoselective reductions. Esterification with absolute MeOH in presence of a catalytic amount of acid was unsuccessful and resulted in dehydration back to the parent isocoumarin. The esterification was successfully achieved by treatment with MeI in presence of anhydrous K₂CO₃ in dry acetone to afford the keto ester **5**. Keto ester **5** showed the 3-H *singlet* at 3.66 (COOMe) and 2-H *singlet* at 3.95 (ArCH₂) in ¹H-NMR, [M – MeOH]⁺ ion at *m/z* 360

in MS, and ester and ketone C=O absorptions at 1716 and 1694 cm⁻¹, respectively, in IR spectrum.

The crucial step of the present synthesis was the enantioselective reduction of the prochiral keto acid **4** or keto ester **5**, for which the choice of a chiral reducing agent was important. The only precedence in literature of the stereoselective reduction of such keto acids or keto esters is by *Krohen et al.* [9]. Thus, reduction with *Midland's* Alpine-boranes and enzymes like horse liver dehydrogenase were not successful, whereas more reactive diisopinocampheyl boranes reduced the acid or ester to dihydroisocoumarin in 41 and 62% ee, respectively. Higher enantioselectivities were achieved with baker's yeast (>99% ee) but with the opposite (*S*)-configuration. Other related examples include the CBS reduction of keto amides to amide alcohols in 15–45% ee (95% ee in one case), followed by basic hydrolysis to dihydroisocoumarins [10] and the DIBAL-H reduction of the chiral tricarbonyl complexes of prochiral ketones to homobenzylic alcohols as intermediates in the synthesis of dihydroisocoumarins, which gave good diastereoselection (75% de) [11]. We decided to use the recently reported tartaric acid derived boronate ester chiral *Lewis* acid, TarB-NO₂ in combination with LiBH₄ for enantioselective reduction of aryl ketones [12]. Thus, with 2 equiv. of TarB-NO₂ and 1 equiv. of LiBH₄ for 1 equiv. of keto ester **5**, the dihydroisocoumarin **1a** was obtained in 80% ee (82% yield) [13][14]. The enantiomeric excesses (ee) were determined by NMR with chiral shift reagents, and the absolute configuration was checked by the sign of optical rotation. The H-atoms of CH₂ groups on either side of the newly created stereogenic center (C(3)) exhibited the diastereotopic effect [15]. The CH₂(4) with restricted motion owing to its incorporation in the heterocyclic ring, and CH₂(1') and CH₂(2') groups with free rotation correspond to *ABX*, *ABMNX*, and *ABMNX*₂ systems, respectively. The *AB* H-atoms (CH₂(4)) at δ 2.73–2.88 showed that the H-atom *cis* to side chain located slightly downfield shows a double *doublet* at δ 2.81–2.88 ppm ($J_{\text{gem}} = 16.4$, $J_{\text{cis}} = 3.5$ Hz), and the *trans*-H-atom resonates slightly upfield at 2.73–2.78 ppm ($J_{\text{gem}} = 16.2$, $J_{\text{trans}} = 11.9$ Hz), with a chemical shift difference of *ca.* 0.07 ppm, which corresponds to the extent of diastereotopy. The H–C(3) showed a *dddd* pattern at δ 4.31, indicating the presence of diastereotopic CH₂ groups on either side. Thus, each of the H-atoms of CH₂(1') (H_A–C(1') and H_B–C(1')) also showed a *dddd* at δ 1.61 and 1.80 with a chemical shift difference of 0.19 ppm, an almost double extent of diastereotopy compared to that between H_A–C(4) and H_B–C(4). The diastereotopic effect extends up to the H-atoms of CH₂(2') with two sets of *multiplets* at δ 1.45 and 1.54 ppm, respectively; in this case $\Delta\nu$ is reduced to *ca.* 0.1 ppm due to larger separation from the stereogenic center. There is no indication of diastereotopy beyond C(2'), and the rest of H-atoms (CH₂(3')–CH₂(10')) show an 18-H, br. *singlet* at δ 1.23 ppm. ¹³C-NMR Spectrum showed signals at δ 77.6 and 35.0 for C(3) and C(4), respectively. The lactone C=O absorption appeared at 1720 cm⁻¹ in IR spectrum.

Selective demethylation of the (3*R*)-3,4-dihydro-6,8-dimethoxy-3-undecylisocoumarin (**1a**) was carried out using BBr₃ under mild conditions (–78°, 10 min) to furnish the (3*R*)-3,4-dihydro-8-hydroxy-6-methoxy-3-undecylisocoumarin (**1b**). ¹³C-NMR Spectrum showed signals at δ 79.4 and 34.9 for C(3) and C(4), respectively. IR Spectrum showed the lactone C=O absorption at 1665 cm⁻¹ due to internal chelation.

Complete demethylation of **1a** was achieved with BBr₃ at –78° and allowing it to warm to 4° overnight to yield the (3*R*)-3,4-dihydro-6,8-dihydroxy-3-undecylisocou-

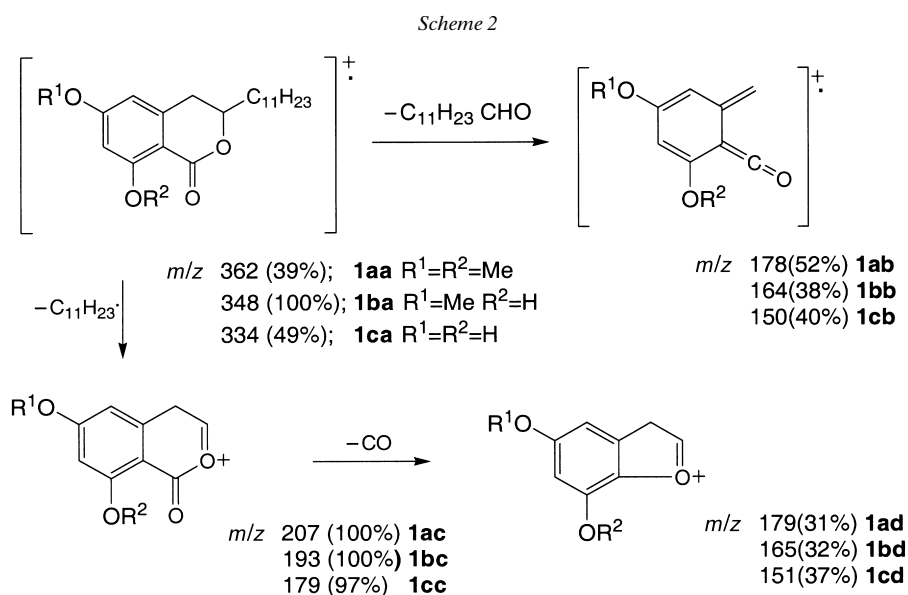
Table 1. NMR Data for the H-Atoms at and around the Stereogenic Center (C(3)) of Dihydroisocoumarins **1a–1c**

	H–C(3)	H _A –C(4)	H _B –C(4)	H _A –C(1')	H _B –C(1')	H _A –C(2')	H _B –C(2')
1a	4.31 (dddd, <i>J</i> = 10.5, 7.6, 5.4, 4.6)	2.85 (dd, <i>J</i> = 16.4, 3.52)	2.75 (dd, <i>J</i> = 16.2, 11.92)	1.61 (dddd, <i>J</i> = 13.5, 10.2, 5.7, 5.3)	1.80 (dddd, <i>J</i> = 13.7, 10.2, 7.4, 5.2)	1.40 (m)	1.54 (m)
1b	4.50 (dddd, <i>J</i> = 11.0, 7.5, 5.0, 3.7)	2.90 (dd, <i>J</i> = 16.5, 11.1)	2.83 (dd, <i>J</i> = 16.0, 3.7)	1.71 (dddd, <i>J</i> = 14.1, 10.4, 5.4, 5.3)	1.85 (dddd, <i>J</i> = 13.5, 10.3, 7.6, 5.4)	1.45 (m)	1.54 (m)
1c	4.70 (dddd, <i>J</i> = 11.2, 7.4, 5.5, 3.6)	2.96 (dd, <i>J</i> = 16.3, 4.0)	2.85 (dd, <i>J</i> = 16.2, 10.80)	1.75 (dddd, <i>J</i> = 14.0, 10.1, 7.5, 5.0)	1.89 (dddd, <i>J</i> = 13.6, 10.1, 7.4, 5.0)	1.47 (m)	1.60 (m)

marin (**1c**). The latter was characterized by the complete absence of MeO–C(8) and MeO–C(6) *singlets* both in ¹H- and ¹³C-NMR spectra, and by the downfield shift of characteristic signals.

The NMR data for the H-atoms at and around the stereogenic center (C(3)) of the dihydroisocoumarins **1a–1c** are collected in Table 1. It is evident that the substituents R¹ and R² have no significant effect on splitting pattern and *J* values, except for slight variation of δ values. Thus, CH₂(4) H-atoms show a consistent *J*_{gem} value of 16.2 ± 0.3 Hz and two different *J*_{vic} values for *cis* and *trans* H-atoms with a ratio of *ca.* 1:3, the one resonating downfield and showing lower *J* value, but the order may be reversed. Similarly, the CH₂(1') H-atoms couple to different extent with their vicinal counterparts.

Scheme 2 delineates the mass fragmentation pattern of the EI mass spectra of dihydroisocoumarins **1a–1c**, which is consistent with the general mass-fragmentation mechanism for dihydroisocoumarins. The major peaks correspond to α -cleavage, loss of CO, and *retro-Diels–Alder* cleavage products.



The isocoumarin, keto acid, keto ester, and dihydroisocoumarin **3**, **4**, **5**, and **1a–1c**, respectively, were examined *in vitro* for antifungal activities against some human, animal, and plant pathogenic molds [16] (*Table 2*). It is evident from *Table 2* that **5** is more potent than **4**, and **1a** shows more antifungal activity compared to the corresponding isocoumarin **3**. Among dihydroisocoumarins **1a–1c**, 8-hydroxy and 6,8-dihydroxy derivatives, **1b** and **1c**, respectively, are more active compared to dimethoxy compound **1a**, possibly due to internal chelation between OH and lactone C=O groups [17].

Table 2. *Antifungal Activity* (antifungal activity determined by agar-dilution method and the results reported as linear-growth inhibition (LGI) [%] at 400 µg/ml [%] of media SDA; standard drugs: miconazole and ketoconazole)

Pathogens	3	4	5	1a	1b	1c	Standard drugs
<i>Trichophyton schoenleinii</i>	23	17.5	27	19.4	25.0	26.3	70
<i>Candida albicans</i>	–	–	–	–	–	–	79
<i>Aspergillus niger</i>	47.9	46.2	54	50	54	55	20
<i>Microsporium canis</i>	48.6	31	55	56	60	64	98.4
<i>Fusarium solani</i>	24.8	16.8	29.0	34	32	31	73.5
<i>Pseudallescheria boydii</i>	12.5	6.9	21	13.2	15	12.7	100

In summary, an efficient stereoselective synthesis of the principal dihydroisocoumarins of *Ononis natrix* has been accomplished. It involves three linear steps and proceeds with an overall yield of 40%.

Experimental Part

General. THF was dried over Na/benzophenone under N₂ and CH₂Cl₂ over CaH₂ under Ar and distilled fresh before use. Flash column chromatography (FC): *Merck Kieselgel 60* (230–400 mesh). Optical rotations: in CHCl₃ on a *Perkin-Elmer 341* polarimeter. IR Spectra were recorded on a *Bruker Vector 22*. ¹H- and the ¹³C-NMR spectra were determined in CDCl₃ solns. at 400 (*Bruker AM-400*) and 100 MHz (*Bruker AM-100*), resp. EI-MS (70 eV): *MAT 312* instrument. Elemental analyses: *CHN-Rapid Heraeus*. Enantiomeric excesses (ee) were determined by ¹H-NMR with (+)-[Eu(hfc)₃] as optically active shift reagent.

6,8-Dimethoxy-3-undecyl-1H-[2]benzopyran-1-one (3). A stirred mixture of *3,5-dimethoxyhomophthalic acid (2)*; 0.5 g, 2.08 mmol) and dodecanoyl chloride (1.82 g, 8.33 mmol) was heated on an oil bath at 200° for 4 h. FC of the residue (petroleum ether/AcOEt 9:2) afforded **3** (0.48 g, 1.35 mmol, 65%). Colorless prisms. IR (KBr): 2913, 2849, 1685, 1645, 1625, 1575, 1510, 860, 835, 810. ¹H-NMR (400 MHz, CDCl₃): 0.87 (*t*, *J* = 7.12, Me(11')); 1.25 (*br. s*, CH₂(3')–CH₂(10')); 1.65 (*q*, *J* = 8.4, CH₂(2')); 2.44 (*t*, *J* = 7.0, CH₂(1')); 3.87 (*s*, MeO–C(6)); 3.95 (*s*, MeO–C(8)); 6.07 (*s*, H–C(4)); 6.30 (*s*, H–C(5)); 6.41 (*s*, H–C(7)). ¹³C-NMR (100 MHz, CDCl₃): 165.5 (C(1)); 163.5 (C(8)); 160.0 (C(3)); 159.5 (C(6)); 142.6 (C(4a)); 103.1 (C(4)); 99.6 (C(5)); 98.3 (C(7)); 56.4 (MeO–C(8)); 55.7 (MeO–C(6)); 33.9 (C(1')); 32.0 (C(9')); 29.74, 29.72, 29.6, 29.55, 29.51, 29.4 (C(4')–C(8')); 26.9 (C(2')); 24.7 (C(3')); 22.8 (C(10')); 14.2 (C(1')). EI-MS (70 eV): 360 (63, *M*⁺), 220 (43), 206 (17), 205 (100), 177 (52), 149 (38). Anal. calc. for C₂₂H₃₂O₄: C 73.30, H 8.95; found: C 73.21, H 8.98.

4,6-Dimethoxy-2-(2-oxotridecyl)benzoic Acid (or 3,4-Dihydro-3-hydroxy-6,8-dimethoxy-3-undecyl-1H-[2]benzopyran-1-one; 4). A stirred soln. of **3** (0.4 g, 1.11 mmol) in EtOH (15 ml) was treated with 5% KOH (30 ml), and the mixture was refluxed for 4 h. After cooling the mixture, most of the EtOH was evaporated. Cold H₂O (15 ml) was added, and the mixture was acidified with dil. HCl and extracted with AcOEt (2 × 30 ml). The org. phase was dried (MgSO₄), and the solvent was evaporated under vacuum to leave a solid.

Recrystallization from AcOEt/petroleum ether afforded **4** (0.30 g, 0.80 mmol, 72%). White scales. IR (KBr): 3011, 2949, 1716, 1683, 1601, 1202, 1162. ¹H-NMR (400 MHz, CDCl₃)¹⁾: 0.86 (*t*, *J* = 6.38, Me(11')); 1.23 (br. *s*, CH₂(2')–CH₂(10')); 1.53–1.62 (*m*, CH₂(1')); 2.29–2.40 (*t*, *J* = 4.5, 1 H–C(4)); 2.57–2.61 (*t*, *J* = 4.2, 1 H–C(4)); 3.84 (*s*, MeO); 3.98 (*s*, MeO); 6.39 (*d*, *J* = 2.0, H–C(7)); 6.47 (*d*, *J* = 2.2, H–C(5)); 11.22 (br. *s*, COOH). ¹³C-NMR (100 MHz, CDCl₃): 195.5 (C(3), C=O); 168.3 (COOH); 132.7 (C(5)); 131.8 (C(6)); 127.4 (C(7)); 77.7 (C(4)); 55.6 (2 MeO); 42.9 (C(1')); 32.1 (C(9')); 29.8, 29.79, 29.77, 29.71, 29.68, 29.65, 29.6 (C(2')–C(8')); 22.8 (C(10')); 14.2 (C(11')). EI-MS: 378 (27.8, *M*⁺), 360 (51), 220 (53), 195 (46), 178 (70), 150 (32). Anal. calc. for C₂₂H₃₄O₅: C 69.81, H 9.05; found: C 69.78, H 9.08.

Methyl 4,6-Dimethoxy-2-(2-oxotridecyl)benzoate (5). A mixture of **4** (0.25 g, 0.66 mmol) and anh. K₂CO₃ (0.5 g) in dry acetone (10 ml) was treated with MeI (56 mg, 24.7 ml, 0.78 mmol) and refluxed for 3 h. The mixture was filtered while hot, the filter cake was washed with warm dry acetone, and the solvent was evaporated to yield **5** (0.26 g, 0.66 mmol, 100%). Oil. IR (film): 3011, 2949, 1725, 1710, 1694, 1601, 1162. ¹H-NMR (400 MHz, CDCl₃; numbering according to cyclic form): 0.87 (*t*, *J* = 6.52, Me(11')); 1.26 (br. *s*, CH₂(2')–CH₂(10')); 1.68 (*m*, CH₂(1')); 2.27–2.35 (*t*, *J* = 4.2, 1 H–C(4)); 2.39–2.52 (*t*, *J* = 4.5, 1 H–C(4)); 3.66 (*s*, COOMe), 3.81 (*s*, MeO); 3.88 (*s*, MeO); 3.95 (*s*, ArCH₂); 6.30 (*d*, *J* = 2.0, H–C(7)); 6.41 (*d*, *J* = 2.24, H–C(5)). EI-MS: 392 (42.0, *M*⁺), 237 (17.80), 220 (53), 209 (43.8), 178 (70). Anal. calc. for C₂₃H₃₆O₅: C 70.38, H 9.24; found: C 70.33, H 9.21.

(3R)-3,4-Dihydro-6,8-dimethoxy-3-undecyl-1H-[2]benzopyran-1-one (1a). A soln. of **5** (0.23 g, 0.6 mmol) in dry THF (40 ml) was added slowly *via* syringe to a stirred soln. of TarB-NO₂ (30 ml of 0.4M in THF, 0.12 mmol) under Ar. The mixture was stirred for 30 min at r.t. LiBH₄ (3 ml, 2M in THF, 0.6 mmol) was added dropwise over 10 min, and the mixture was further stirred for 2 h (TLC). The mixture was quenched with H₂O (5 ml), acidified with 2N HCl, and extracted with Et₂O (3 × 50 ml). The combined org. layer was washed with brine (30 ml), dried (MgSO₄), and concentrated. FC (petroleum ether/AcOEt 7:1) afforded **1a** (0.178 g, 0.49 mmol, 82%). Colorless scales. [α]_D²⁵ = –59 (*c* = 0.96, CHCl₃). IR (film): 2924, 2853, 1720, 1710, 1604, 1583, 1572, 1464, 1198, 832. ¹H-NMR (400 MHz, CDCl₃): 0.86 (*t*, *J* = 6.0, Me(11')); 1.23 (br. *s*, CH₂(2')–CH₂(10')); 1.40 (*m*, 1 H–C(2')); 1.54 (*m*, 1 H–C(2')); 1.61 (*dddd*, *J* = 13.5, 10.2, 5.7, 5.3, 1 H–C(1')); 1.80 (*dddd*, *J* = 13.7, 10.2, 7.4, 5.2, 1 H–C(1')); 2.73–2.75 (*dd*, *J*_{gem} = 16.2, *J*_{trans} = 11.92, 1 H–C(4)); 2.88–2.96 (*dd*, *J*_{gem} = 16.4, *J*_{cis} = 3.52, 1 H–C(4)); 3.85 (*s*, MeO–C(6)); 3.91 (*s*, MeO–C(8)); 4.28–4.31 (*dddd*, *J* = 10.5, 7.6, 5.4, 4.6, H–C(3)); 6.28 (*d*, *J* = 2.12, H–C(7)); 6.37 (*d*, *J* = 2.4, H–C(5)). ¹³C-NMR (100 MHz, CDCl₃): 164.8 (C(1), CO); 163.0 (C(8)); 162.8 (C(6)); 144.0 (C(4a)); 107.2 (C(8a)); 103.9 (C(5)); 97.8 (C(7)); 77.6 (C(3)); 56.2 (MeO–C(8)); 55.6 (MeO–C(6)); 35.0 (C(4)); 34.8 (C(1')); 32.0 (C(9')); 29.74, 29.71, 29.68, 29.65, 29.6, 29.52, 29.5 (C(3')–C(8')); 25.0 (C(2')); 22.8 (C(10')); 14.2 (C(11')). EI-MS (70 eV): 362 (39, *M*⁺), 207 (100), 178 (52), 179 (31), 151 (42). Anal. calc. for C₂₂H₃₄O₄: C 72.85, H 9.45; found: C 72.81, H 9.44.

(3R)-3,4-Dihydro-8-hydroxy-6-methoxy-3-undecyl-1H-[2]benzopyran-1-one (1b). A 1M soln. of BBr₃ in CH₂Cl₂ (0.44 ml, 0.44 mmol) was injected to a stirred soln. of **1a** (80 mg, 0.22 mmol) in dry CH₂Cl₂ (3 ml) at –78°, under Ar. After stirring for 10 min, the mixture was poured into ice-water (20 ml) and stirred for 10 min. The layers were separated, and the aq. layer was extracted with CH₂Cl₂ (2 × 25 ml) and then with AcOEt (30 ml). The combined org. phases were dried (MgSO₄) and concentrated. FC (petroleum ether/AcOEt 8:2) afforded **1b** (60 mg, 0.17 mmol, 78%). Colorless prisms. [α]_D²⁵ = –18.2 (*c* = 0.31, CHCl₃). IR (film): 3435, 2956, 2924, 2855, 1727, 1665, 1627, 1461, 1461, 1271, 1249, 1121, 1072, 741. ¹H-NMR (400 MHz, CDCl₃): 0.87 (*t*, *J* = 7.0, Me(11')); 1.25 (br. *s*, CH₂(2')–CH₂(10')); 1.45 (*m*, 1 H–C(2')); 1.55 (*m*, 1 H–C(2')); 1.71 (*dddd*, *J* = 14.1, 10.4, 5.4, 5.3, 1 H–C(1')); 1.85 (*dddd*, *J* = 13.5, 10.3, 7.6, 5.4, 1 H–C(1')); 2.81–2.85 (*dd*, *J*_{gem} = 16.5, *J*_{cis} = 11.1, 1 H–C(4)); 2.84–2.96 (*dd*, *J*_{gem} = 16.0, *J*_{trans} = 3.7, 1 H–C(4)); 3.81 (*s*, MeO); 4.45–4.54 (*dddd*, *J* = 11.0, 7.5, 5.0, 3.7, H–C(3)); 6.24 (*d*, *J* = 2.76, H–C(7)); 6.36 (*d*, *J* = 2.64, H–C(5)); 11.25 (br., OH). ¹³C-NMR (100 MHz, CDCl₃): 170.0 (C(1), CO); 165.9 (C(6)); 164.7 (C(8)); 141.2 (C(4a)); 106.3 (C(5)); 103.9 (C(8a)); 99.5 (C(7)); 78.9 (C(3)); 55.6 (MeO); 34.9 (C(4)); 32.5 (C(1')); 32.0 (C(9')); 29.70, 29.69, 29.66, 29.64, 29.60, 29.54, 29.5 (C(3')–C(8')); 24.9 (C(2')); 22.8 (C(10')); 14.1 (C(11')). EI-MS (70 eV): 348 (39, *M*⁺), 207 (100), 178 (52), 179 (31), 151 (42). Anal. calc. for C₂₁H₃₂O₄: C 72.38, H 9.26; found: C 72.35, H 9.28.

(3R)-3,4-Dihydro-6,8-dihydroxy-3-undecyl-1H-[2]benzopyran-1-one (1c). A 1M soln. of BBr₃ in CH₂Cl₂ (0.88 ml, 0.88 mmol) was added dropwise to a stirred soln. of **1a** (80 mg, 0.22 mmol) in dry CH₂Cl₂ (3 ml) at –78° under Ar. The mixture was gradually allowed to warm to r.t. and stirred overnight. The mixture was poured into ice-cool H₂O, stirred for 10 min, and extracted with CH₂Cl₂ (3 × 30 ml) and then with AcOEt (30 ml). The combined org. phases were washed with H₂O, dried (MgSO₄), and concentrated. FC (petroleum

¹⁾ To avoid confusion and for direct comparison, C-atom numbering is considered same as in **3**.

ether/AcOEt 7:3) afforded **1c** (53 mg, 0.16 mmol, 72%). Colorless scales. $[\alpha]_D^{25} = -14.3$ ($c = 1.12$, CHCl_3). IR (film): 3435, 2956, 1727, 1669, 1627, 1461, 1461, 1271, 1249, 1121, 1072, 741. $^1\text{H-NMR}$ (400 MHz, CDCl_3): 0.88 (t , $J = 6.5$, Me($11'$)); 1.26 (br. s , $\text{CH}_2(2')\text{--CH}_2(10')$); 1.47 (m , 1 H–C($2'$)); 1.60 (m , 1 H–C($2'$)); 1.75 ($dddd$, $J = 14.0$, 10.1, 7.5, 5.0, 1 H–C($1'$)); 1.89 ($dddd$, $J = 13.6$, 10.1, 7.4, 5.0, 1 H–C($1'$)); 2.81–2.85 (dd , $J_{\text{gem}} = 16.2$, $J_{\text{trans}} = 10.8$, 1 H–C(4)); 2.84–2.96 (dd , $J_{\text{gem}} = 16.3$, $J_{\text{trans}} = 10.80$, 1 H–C(4)); 4.54–4.70 ($dddd$, $J = 10.5$, 7.6, 5.4, 4.6, H–C(3)); 6.24 (d , $J = 2.76$, H–C(7)); 6.36 (d , $J = 2.64$, H–C(5)). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): 170.3 (C(1), CO); 164.9 (C(6)); 162.6 (C(8)); 142.0 (C($4a$)); 106.9 (C(5)); 102.7 (C($8a$)); 102.2 (C(7)); 79.9 (C(3)); 34.9 (C(4)); 33.2 (C($1'$)); 32.0 (C($9'$)); 29.73, 29.71, 29.67, 29.65, 29.60, 29.55, 29.52 (C($3'$)–C($8'$)); 24.9 (C($2'$)); 22.6 (C($10'$)); 14.2 (C($11'$)). EI-MS (70 eV): 334 (49, M^+), 179 (97), 151 (37), 150 (40), 122 (34). Anal. calc. for $\text{C}_{20}\text{H}_{30}\text{O}_4$: C 71.82, H 9.04; found: C 71.86, H 9.01.

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