Synthesis of (±)-Nephromopsinic, (−)-Phaseolinic, and (−)-Dihydropertusaric Acids

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Dedicated to Professor *Dieter Seebach* for his formidable and communicative enthusiasm for chemistry

The formal syntheses of (±)-nephromopsinic acid, (−)-phaseolinic acid, and the first total synthesis of (−)-dihydropertusaric acid from (±)- and (−)-7-oxabicyclo[2.2.1]hept-5-en-2-one are described. These syntheses take advantage of a previously reported radical rearrangement (1,2-acyl migration). A remarkable iodide-mediated cleavage of a bicyclic system, followed by the introduction of the γ-chains *via* a mixed *Kolbe* electrolysis, are the key steps of these syntheses. This approach is general and could be applied for the preparation of all kinds of paraconic acids with excellent control of the stereochemistry.

Introduction. – Paraconic acids are a class of trisubstituted γ-butyrolactones, bearing a COOH group in the β-position, which are isolated from lichens, moss, and fungus. Many of them possess an attractive biological profile ranging from antitumor antibiotic, antifungal, and antibacterial activities [2][3]. They have attracted considerable attention of synthetic chemists, and several different strategies toward their syntheses have been elaborated. Efficient methods for the preparation of β,γ-*trans*-γ-butyrolactones have been reported, and a few syntheses of enantiomerically pure material have appeared (for leading references, see [4–10]). However, β,γ-*cis* disubstituted systems such as (−)-nephromopsinic acid (**1**) [11–13], (−)-dihydropertusaric acid (**2**) [14–16], and (−)-phaseolinic acid (**3**) [17] are more difficult to prepare. Interestingly, these three compounds possess a very similar substitution pattern, they differ only by the C residue in the γ-position. Therefore, it would be highly attractive to elaborate a synthesis that allows the introduction of the γ-substituent at a late stage of the synthesis. In this paper, we describe the formal syntheses of (±)-nephromopsinic acid [18] and (−)-phaseolinic acid [3][19–22] as well as the first total synthesis of (−)-dihydropertusaric acid[3]). The syntheses use 7-oxanorbornenone as starting material [23], a chiral building block avaiblable in both enantiomeric forms [24], and are characterized by the late introduction of the γ-chain. A preliminary account of this work has already been published [25]. This approach is expected to be general for any type of paraconic acids.

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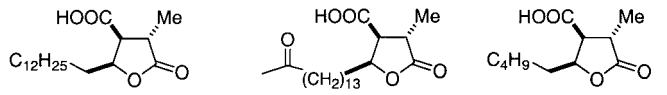
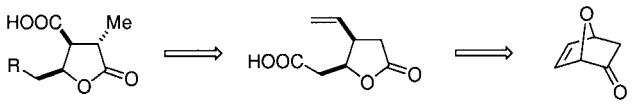
[3]) The relative configuration of (−)-dihydropertusaric acid has been incorrectly assigned as β,γ-*trans* by *Huneck et al.* [14]. Recently, *Maier et al.* revised this structure and showed that (−)-dihydropertusaric acid has the relative configuration depicted in formula **2** corresponding to *Huneck*'s dihydropertusaric acid [16].



1 (–)-Nephromopsinic acid **2** (–)-Dihydropertusaric acid **3** (–)-Phaseolinic acid

Results and Discussion. – The retrosynthetic analysis is highlighted in *Scheme 1*. The paraconic acids **1**–**3** should be obtained from the carboxylactone **4** *via* lactone-enolate alkylation for the introduction of the α-Me group, and mixed *Kolbe* electrolysis for the introduction of the desired γ-chain. The lactone **4** should be available from 7-oxanorbornenone **5** *via* a radical addition-rearrangement process [26], followed by a *Baeyer–Villiger* oxidation and a *Lewis* acid-induced rearrangement of a bicyclic lactone.

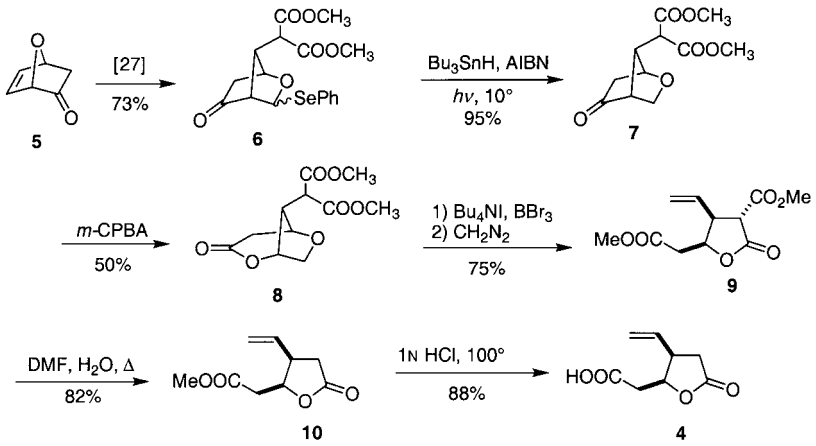
Scheme 1



1-3 **4** **5**

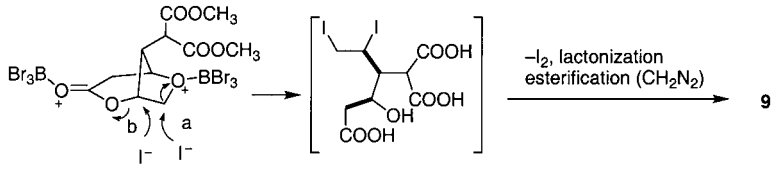
The bicyclic seleno-acetal **6** is a highly versatile building block that has already been used for the synthesis of 12-epiprostaglandins and all-*cis*-thromboxanes [27][28]. It is easily obtained *via* radical addition of dimethyl phenylselenomalonate to (±)- or (–)-7-oxabicyclo[2.2.1]hept-5-en-2-one (**5**; *Scheme 2*) [23]. Reductive deselanylation (Bu_3SnH, AIBN) of **6** furnished the bicyclic compound **7** in 95% yield. *Baeyer–Villiger* oxidation with 4-chloroperbenzoic acid (*m*-CPBA) gave the desired lactone **8** (50%) together with its regioisomer. Treatment of the bicyclic lactone **8** with Bu_4NI and BBr_3, followed by esterification of the carboxy group with CH_2N_2 furnished the γ-lactone **9** in 75% yield. A tentative mechanism of this remarkable rearrangement is depicted in *Scheme 3*. It consists of the simultaneous acid catalyzed opening of the bicyclic ether (*a*)

Scheme 2



5 **6** **7** **8** **9** **10** **4**

Scheme 3



and of the lactone (*b*). The methyl ester moieties are also presumably hydrolyzed under these conditions. Elimination of I_2 from the vicinal diodide affords the vinyl group. The final product **9** results from lactonization and esterification of the carboxy residues with CH_2N_2. Decarboxylation of **9** in refluxing DMF/H_2O afforded lactone **10**, which was treated with refluxing 1M HCl to provide the free acid **4** in good yield. No β-fragmentation of the β-acyloxy ester was observed under these relatively harsh conditions. Moreover, the stereochemical integrity of the lactone was kept; a reversible fragmentation–cyclization process could have led to epimerization of the γ-center.

The next step in the synthesis is the introduction of the γ-chain by a mixed *Kolbe* electrolysis [29]. The *Kolbe* electrolysis approach, even if it is not generally high-yielding, presents some advantages over classical chemical methods, since it furnishes the desired coupling compounds in a single step with many different alkanoic acids. Moreover, the reaction conditions are very mild so that the lactone and the vinyl group are preserved during the electrolysis. To efficiently apply the mixed-*Kolbe*-electrolysis approach, a large excess of the side-chain acid is necessary. This is not a problem for the preparation of the precursors of nephromopsinic acid and phaseolinic acid, since tridecanoic acid **13a** and pentanoic acid **13c** are both commercially available. For the preparation of dihydropertusaric acid, it was necessary to synthesize the protected acid **13b**. For this purpose, we decided to use a recently developed, radical-mediated, one-pot reductive conjugate addition of alkenes to enones (*Scheme 4*) [30]. Unprotected undec-10-en-1-ol was hydroborated with catecholborane using *N*,*N*-dimethylacetamide as catalyst. *In situ* generated *B*-alkylcatecholborane was then used as radical precursor for conjugate addition to methyl vinyl ketone. This procedure proved to be much more practical on a large scale (50 mmol) than the one used by *Gerlach* and *Voss*, which is based on conjugate addition of organocuprate [31]. Oxidation of the primary alcohol **11** to the keto acid **12**, followed by protection of the oxo group as a dioxolane afforded the desired acid **13b**. The γ-chains were then introduced by mixed *Kolbe* electrolyses between the carboxylic acid **4** and 8 equiv. of **13a**–**13c**. The three desired mixed coupling products **14a**–**14c** were obtained in 40% yield[4]).

The final steps for the conversion of intermediates **14a**–**14c** to nephromopsinic, dihydropertusaric, and phaseolinic acids (**1**, **2**, and **3**, resp.) are depicted in *Scheme 5*. Lactones (±)-**14a** and (−)-**14b** were methylated with LDA/MeI in 85 and 62% yields, respectively. As anticipated, the alkylation is diastereoselective, and the Me groups in (±)-**15a** and (−)-**15b** are *trans* to the β- and γ-substituents. The lactone (±)-**15a** shows spectroscopical data identical with those reported by *Mulzer et al.* [18]. Conversion of

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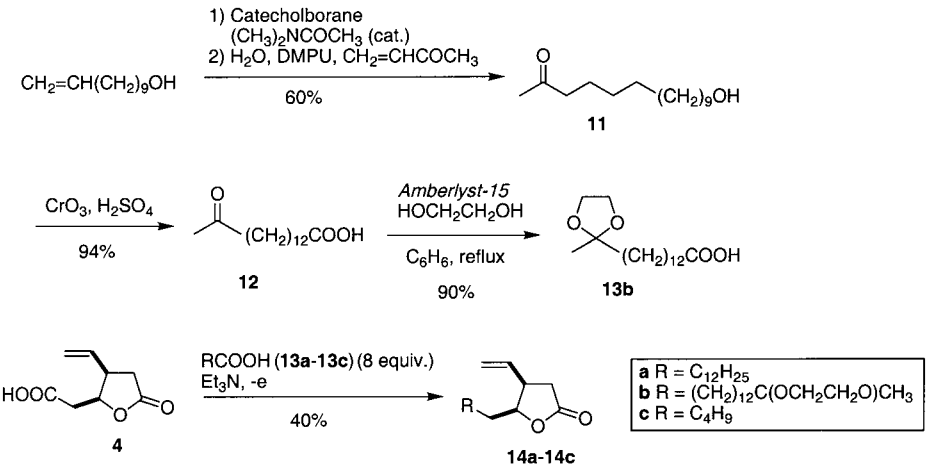
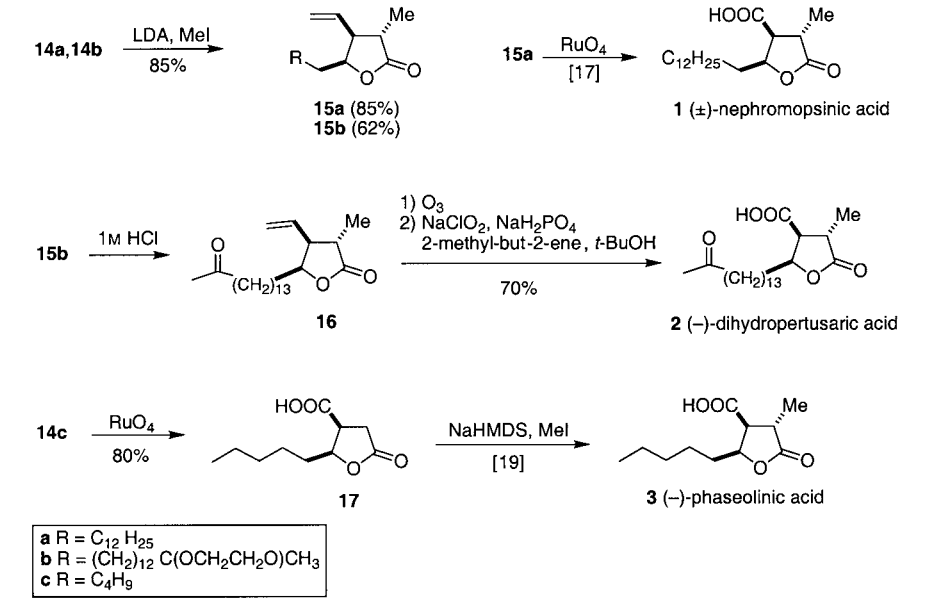
[4]) Mixed *Kolbe* electrolysis gives a statistical mixture of the three coupling products. By using 8 equiv. of the side-chain acid, it is possible to efficiently suppress the decarboxylative dimerization of **4**.

Scheme 4



Scheme 5



(±)-**15a** to nephromopsinic acid ((±)-**1**) by treatment with RuO_4 was reported in the literature [18]. The preparation of (−)-dihydropertusaric acid (**2**) was achieved by acidic hydrolysis of the acetal (−)-**15b**, followed by oxidation of the vinyl group of (−)-**16**. RuO_4 failed to give the desired carboxylic acid; therefore, the conversion of the vinyl lactone (−)-**16** to **2** was achieved in two steps by ozonolysis, followed by further oxidation of the intermediate aldehyde with $NaClO_2$. The physical and spectral data of

2 are identical to those reported for the (−)-dihydropertusaric acid isolated from the lychen *Punctelia microsticta* [15] and *Punctelia albescens* [14]. This total synthesis confirms the recently revised relative and absolute configurations of (−)-dihydropertusaric acid [16]. For the synthesis of (−)-phaseolinic acid (**3**), the reaction sequence had to be reversed due to problem to purify the methylated lactone. Therefore, the vinyl lactone (−)-**14c** was first oxidized with RuO_4 to the carboxylic acid (−)-**17**. This compound possesses spectroscopical and physical data identical to the synthetic intermediate of Valentin and co-workers, which was methylated with sodium hexamethyldisilazide and MeI to afford (−)-phaseolinic acid (**3**) [20].

In conclusion, we have developed a new synthetic route that is expected to be general for all kinds of β,γ-*cis*-paraconic acids. Since the epimerization in the β-position has already been reported [3], access to the *trans*-substituted paraconic acids should also be possible. Moreover, the starting chiral building block **5** is easily prepared in both enantiomeric forms to offer a flexible entry for the preparation of enantiomerically pure paraconic acids with any desired absolute configuration.

We are very grateful to the *Swiss National Science Foundation* and to the *Federal Office for Science and Education (OFES/BBW)* for financial support.

Experimental Part

General. Enantiomerically pure *(−)-7-oxabicyclo[2.2.1]hept-5-en-2-one* ((−)-**5**) was obtained by resolution of the racemic ketone [24]. THF was freshly distilled from K under N_2; CH_2Cl_2, DMF, and benzene from CaH_2 under N_2, and toluene from Na under N_2. Gas chromatography (GC): *Fisons HRGC Mega 2* on *SE-54* column. For flash column chromatography (FC) and filtration, *Baker* silica-gel (0.63–0.200 mm) was used with AcOEt and hexane as solvent for elution. TLC were run on *Merck* silica-gel *60 F254* anal. plates; detection either with UV, I_2, or spraying with a soln. of 25 g phosphomolybdic acid, 10 g $Ce(SO_4)_2 \cdot 4H_2O$, 60 ml conc. H_2SO_4, and 940 ml H_2O, and subsequent heating. M.p.: not corrected; *Büchi Tottoli* apparatus. IR: *Mattson Unicam-5000*; in cm^{-1}. NMR: *Varian Gemini-200* (^1H: 200 MHz and ^{13}C: 50.3 MHz), *Bruker AM-360* (^1H: 360 MHz), *Bruker Avance-DRX-500* (^1H: 500 MHz, ^{13}C: 125.76 MHz); for ^1H, δ in ppm relative to $CDCl_3$ (= 7.26 ppm), ^{13}C multiplicities were determined by APT sequence; coupling constants *J* in Hz. MS: *Vacuum Generators Micromass VG 70/70E DS 11-250*; EI (70 eV), CI (CH_4 gas); *m*/*z* (%). Elemental analysis: *Ilse Beetz*, Microanalytisches Laboratorium, D-96301 Kronach, and *Ciba Geigy* Mikrolabor, CH-1726 Marly.

*Dimethyl (1*SR,*3*RS,*4*SR*)-2-[5-Oxo-3-(phenylselanyl)-2-oxabicyclo[2.2.1]hept-7-yl]malonate* ((±)-**6**). A soln. of (±)-**5** (2.04 g, 18.5 mmol) [32] and dimethyl 2-(phenylselanyl)propanedioate [33] (8.00 g, 27.8 mmol) in anh. and degassed benzene (100 ml) was irradiated with a sun lamp (300 W) overnight under N_2 at 30°. After evaporation of the solvent, FC (AcOEt/hexane 1:4) gave crude (±)-**6** (5.93 g, 81%), which was used without further purification for the next step. Recrystallization (AcOEt/hexane) furnished pure (±)-**6** with spectroscopical and physical data identical with those reported in [27].

*Dimethyl (1*S,*3*RS,*4*R*)-2-[5-Oxo-3-(phenylselanyl)-2-oxabicyclo[2.2.1]hept-7-yl]malonate* ((−)-**6**). The radical addition was carried out with (−)-(1*S*,4*S*)-**5** (4.88 g, 44.3 mmol) and dimethyl (phenylselanyl)propanedioate (21.6 g, 75.3 mmol) and gave crude (−)-**6** (14.60 g, 83%), which was used without further purification for the next step.

*Dimethyl (1*SR,*4*SR,*7*SR*)-2-(5-Oxo-2-oxabicyclo[2.2.1]hept-7-yl)malonate* ((±)-**7**). A soln. of crude (±)-**6** (1.91 g, 4.79 mmol), Bu_3SnH (1.5 ml, 5.6 mmol), and a cat. amount of AIBN in dry benzene (25 ml) was irradiated at 10° with a 300-W sun lamp during 3 h. The solvent was evaporated and the crude product was chromatographed (AcOEt/hexane 1:20). Recrystallization in Et_2O (or AcOEt/hexane) gave (±)-**7** (1.10 g, 95%). M.p. 71–72°. IR (KBr): 3020, 2980, 2960, 2900, 1760, 1735, 1490, 1430, 1400, 1380, 1320, 1310, 1290, 1275, 1250, 1240, 1230, 1200, 1190, 1150, 1090, 1030, 1005. ^1H-NMR (200 MHz, $CDCl_3$): 4.58 (br. *s*, H–C(1)); 4.03 (*dd*, *J* = 4.0, *J* = 9.0, H_{exo}–C(3)); 3.83 (*d*, *J* = 9.0, H_{endo}–C(3)); 3.78, 3.74 (2*s*, 2 COOMe); 3.62 (*d*, *J* = 11.5, C*H*(COOMe)$_2$); 2.8 (*dm*, *J* = 11.5, H–C(7)); 2.78 (br. *s*, H–C(4)); 2.48 (*d*, *J* = 18.0, H_{endo}–C(6)); 2.31 (*dm*, *J* = 18.0, H_{exo}–C(6)). ^{13}C-NMR (50.3 MHz, $CDCl_3$): 209.99 (*s*); 168.23 (*s*); 77.71 (*d*); 64.56 (*t*); 53.27 (*q*); 52.9 (*d*);

47.99 (*d*); 46.41 (*d*); 45.56 (*d*). CI-MS (CH_4): 244 (1.27, $[M+2]^{+\cdot}$), 243 (19.46, $[M+1]^{+\cdot}$), 242 (3.38, $M^{+\cdot}$) 225 (4), 214 (14), 213 (9), 211 (30), 210 (30), 200 (21), 193 (3), 183 (8), 181 (5), 178 (8), 172 (4), 171 (4), 169 (4), 168 (10), 153 (4), 149 (4), 141 (34), 140 (12), 139 (4), 137 (6), 136 (16), 135 (4), 134 (6), 133 (77), 132 (22), 125 (12), 123 (10), 113 (63), 112 (79), 111 (52), 110 (10), 109 (24), 108 (26), 100 (12), 98 (25), 95 (21), 85 (13), 82 (16), 81 (100), 78 (18), 77 (8), 71 (46), 70 (3). Anal. calc. for $C_{11}H_{14}O_6$ (242.23): C 54.54, H 5.83; found: C 54.58, H 5.82.

*Dimethyl 2-[(1*S*,4*R*)-5-Oxo-2-oxabicyclo[2.2.1]hept-7-yl)]malonate* ((−)-**7**). The reduction of crude (−)-**6** (4.00 g, 10.06 mmol) gave (−)-**7** (2.19 g, 90%). The desired isomer was isolated *via* crystallization in Et_2O. M.p. 68–70°. $[\alpha]_{589}^{25} = -87$ ($c = 1.3$, $CHCl_3$).

Dimethyl 2-(3-Oxo-2,7-dioxabicyclo[3.2.1]oct-8-yl)malonate ((±)-**8**). Compound (±)-**7** (5.2 g, 21.467 mmol) in dry CH_2Cl_2 was oxidized with *m*-CPBA (5.5 g, 32.201 mmol) and $NaHCO_3$ (2.7 g, 32.2 mmol) as a buffer. The mixture was stirred for 10 min at r.t., and CH_2Cl_2 (50 ml) was added. The soln. was washed with H_2O, and the org. phase was dried (Na_2SO_4) and evaporated. The crude product was purified by FC to give a mixture of **8** and its regioisomer. Recrystallization from AcOEt/hexane provided pure (±)-**8** (2.7 g, 50%). IR (KBr): 3014, 2990, 2958, 2900, 2854, 1760, 1734, 1464, 1400, 1230, 1156. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.81–4.77 (*m*, H−C(1)); 4.41–4.37 (*m*, H−C(5)); 4.23 (*d*, $J = 11.3$, H−C(7)); 4.10 (*dd*, $J = 11.3$, 3.4, H−C(7)); 3.83, 3.81 (2*s*, 2 COOMe); 3.30 (*d*, $J = 11.5$, C*H*(COOMe)$_2$); 3.00 (*d*, $J = 11.5$, H−C(8)); 2.92–2.74 (*AB* of *ABX*, $J_{AB} = 18.9$, $J_{AX} = 2.1$, $J_{BX} = 3.1$, 2 H−C(4)). ^{13}C-NMR (50.3 MHz, $CDCl_3$): 167.52 (*s*); 79.71 (*d*); 74.82 (*d*); 72.53 (*t*); 53.08 (*q*); 50.14 (*d*); 46.14 (*d*); 40.02 (*t*). CI-MS (CH_4): 259 ($M^{+\cdot}$), 227 (5), 213 (5), 199 (16), 133 (13), 127 (9), 81 (5). Anal. calc. for $C_{11}H_{14}O_7$ (258.23): C 51.16, H 5.46; found: C 50.88, H 5.55.

*Methyl (3*RS*,4*SR*,5*SR*)-4-Ethenyl-2,3,4,5-tetrahydro-5-[(methoxycarbonyl)methyl]-2-oxofuran-3-carboxylate* ((±)-**9**). Compound (±)-**8** (1.75 g, 6.5 mmol) and Bu_4NI (12.1 g, 32.6 mmol) were dissolved in dry CH_2Cl_2 under N_2. The soln. was cooled to −30°, and Br_3B (3.1 ml, 33 mmol) was added *via* syringe. The mixture was stirred at −30° during 15 min and then allowed to warm to r.t. H_2O was added, and the phases were separated. The aq. phase was extracted with CH_2Cl_2. The org. layers were washed with a sat. $Na_2S_2O_3$ soln. and dried (Na_2SO_4), and the solvent was evaporated. The residue was dissolved in Et_2O, cooled with an ice bath, and CH_2N_2 was added, until the soln. remained pale yellow. The solvent was removed, and the crude product was purified by FC (AcOEt/hexane 1:2) to give (±)-**9** (1.58 g, 75%). Colorless oil. IR (film): 2957, 2360, 2342, 1787, 1742, 1439, 1355, 1317, 1287, 1199, 1166, 1126. ^{1}H-NMR (360 MHz, $CDCl_3$): 5.70 (*ddd*, $J = 18.6$, 16.8, 10.2, CH_2=C*H*); 5.31 (*dd*, $J = 6.4$, 0.8, 1 H, C*H*$_2$=CH); 5.26 (*dd*, $J = 13.1$, 0.8, 1 H, C*H*$_2$=CH); 5.16 (*m*, H−C(5)); 3.82 (*s*, COOMe); 3.75–3.70 (*m*, H−C(4)); 3.71 (*s*, COOMe); 3.58 (*d*, $J = 7.5$, H−C(3)); 2.66 (*dd*, $J = 16.6$, 7.3, C*H*$_2$COOMe). ^{13}C-NMR (50.3 MHz, $CDCl_3$): 170.20 (*s*); 169.74 (*s*); 167.17 (*s*); 131.36 (*d*); 120.57 (*t*); 77.64 (*d*); 53.26 (*q*); 52.13 (*q*); 51.20 (*d*); 46.29 (*d*); 35.74 (*t*). CI-MS (CH_4): 243 ($M^{+\cdot}$, 100), 211 (80); 193 (32), 165 (36), 138 (11), 112 (20), 81 (8). Anal. calc. for $C_{11}H_{14}O_6$ (242.23): C 54.54, H 5.83; found: C 54.44, H 5.64.

*Methyl (3*R*,4*S*,5*S*)-4-Ethenyl-2,3,4,5-tetrahydro-5-[(methoxycarbonyl)methyl]-2-oxofurancarboxylate* ((−)-**9**). The *Baeyer-Villiger* oxidation of (−)-**7** (2.19 g, 9.04 mmol) was carried out as described for the preparation of (±)-**8**. The regioisomers were not separated, and the mixture was used for the reaction with Br_3B/Bu_4NI to afford (−)-**9** (767 mg, 35%). Colorless oil. $[\alpha]_{589}^{23} = -52°$ ($c = 1$, $CHCl_3$).

*Methyl 2-[(2*SR*,3*RS*)-3-Ethenyl-2,3,4,5-tetrahydro-5-oxofuran-2-yl]acetate* ((±)-**10**). H_2O (0.24 ml, 13 mmol) was added to (±)-**9** (1.83 g, 0.41 mmol), which was dissolved in DMF (50 ml). After heating under reflux for 2 h, the solvent was evaporated. FC (AcOEt/hexane 1:2) of the crude product afforded (±)-**10** (1.32 g, 82%). Colorless oil. IR (film): 3002, 2956, 2360, 2342, 1784, 1740, 1439, 1387, 1350, 1317, 1283, 1222, 1199, 1173, 1162. ^{1}H-NMR (360 MHz, $CDCl_3$): 5.72 (*ddd*, $J = 16.7$, 10.2, 8.5, CH_2=C*H*), 5.25 (*dd*, $J = 10.2$, 0.9, 1 H, C*H*$_2$=CH); 5.20 (*dd*, $J = 16.7$, 0.9, 1 H, C*H*$_2$=CH); 5.05 (*q*, $J = 6.5$, H−C(2)); 3.72 (*s*, COOMe); 3.37–3.26 (*m*, H−C(3)); 2.79 (*dd*, $J = 17.4$, 8.2, H−C(4)); 2.73 (*dd*, $J = 16.8$, 7.6, 1 H, C*H*$_2$COOMe); 2.60 (*dd*, $J = 16.8$, 6.6, 1 H, C*H*$_2$COOMe); 2.48 (*dd*, $J = 17.4$, 4.9, H−C(4)). ^{13}C-NMR (50.3 MHz, $CDCl_3$): 175.38 (*s*); 170.11 (*s*); 133.16 (*d*); 119.21 (*t*); 78.46 (*d*); 52.02 (*q*); 42.31 (*d*); 35.63 (*t*); 34.26 (*t*). CI-MS (CH_4): 184 (100), 167 (30), 153 (37), 139 (17), 135 (31), 107 (54). Anal. calc. for $C_9H_{12}O_4$ (184.19): C 57.05, H 6.34; found: C 57.03, H 6.32.

*Methyl 2-[(2*S*,3*R*)-3-Ethenyl-2,3,4,5-tetrahydro-5-oxofuran-2-yl]acetate* ((−)-**10**). The decarboxylation was performed with (−)-**9** (1.5 g, 6.2 mmol) in DMF and 1.5 equiv. H_2O to give (−)-**10** (970 mg, 85%). Colorless oil. $[\alpha]_{589}^{25} = -36°$ ($c = 1.26$, $CHCl_3$).

*2-[(2*SR*,3*RS*)-3-Ethenyl-2,3,4,5-tetrahydro-5-oxofuran-2-yl]acetic Acid* ((±)-**4**). The ester (±)-**10** (1.32 g, 7.2 mmol) was dissolved in 1M HCl soln. (30 ml) and heated under reflux for 3 h. The soln. was cooled to r.t., extracted with CH_2Cl_2, and dried (Na_2SO_4). The solvent was evaporated to give (±)-**4** (1.07 g, 88%). Colorless oil. IR (film): 2928, 2261, 1783, 1718, 1422, 1313, 1286, 1197, 1161, 1033, 1020. ^{1}H-NMR (360 MHz, $CDCl_3$): 9.30 (br. *s*, COOH); 5.73 (*ddd*, $J = 17.0$, 10.3, 8.7, CH_2=C*H*); 5.27 (*dt*, $J = 10.3$, 0.9, 1 H, C*H*$_2$=CH); 5.22 (*dt*, $J = 17.0$,

0.9, 1 H, CH_2=CH); 4.98 (*td*, *J* = 7.5, 6.4, H–C(2)); 3.36–3.28 (*m*, H–C(3)); 2.78 (*dd*, *J* = 17.5, 8.2, H–C(4)); 2.76 (*dd*, *J* = 17.0, 7.7, 1 H, CH_2COOMe); 2.66 (*dd*, *J* = 17.0, 6.3, 1 H, CH_2COOMe); 2.48 (*dd*, *J* = 17.5, 4.8, H–C(4)). ^{13}C-NMR (125.76 MHz, $CDCl_3$): 175.34 (*s*); 174.56 (*s*); 132.95 (*d*); 119.56 (*t*); 78.06 (*d*); 42.26 (*d*); 35.44 (*t*); 34.25 (*t*). CI-MS (CH_4): 170 (55, $M^{+\cdot}$), 169 (19), 154 (19), 153 (100), 135 (16), 127 (13), 125 (28), 111 (17), 109 (12), 107 (26), 83 (15). Anal. calc. for $C_8H_{10}O_4$ (170.17): C 56.47, H 5.92; found: C 56.36, H 5.98.

2-[(2S,3R)-3-Ethenyl-2,3,4,5-tetrahydro-5-oxofuran-2-yl]acetic Acid ((–)-**4**). The saponification of (–)-**10** (810 mg, 4.4 mmol) gave (–)-**4** (607 mg, 81%). Colorless oil. $[\alpha]_{589}^{25} = -27^\circ$ (*c* = 0.5, $CHCl_3$).

14-Oxopentadecanoic Acid (**12**) [31]. To a soln. of undec-10-en-1-ol (6.00 ml, 30.0 mmol) and *N*,*N*-dimethylacetamide (0.25 ml, 0.3 mmol) in dry CH_2Cl_2 (20 ml) was added dropwise at 0° catecholborane (9.6 ml, 90.0 mmol). The mixture was then heated under reflux for 3 h, H_2O (2.16 ml, 120.0 mmol) was added dropwise at 0°, and the mixture was stirred at r.t. for 30 min. DMPU (3.6 ml, 30.0 mmol) and dry CH_2Cl_2 (60 ml) were added. O_2 (120 ml) was added over a period of 2 h, and the mixture was stirred during 2.5 h. Sat. NH_4Cl soln. (100 ml) was added, and the phases were separated. The aq. phase was extracted with CH_2Cl_2, and the combined org. phases were dried ($MgSO_4$) and evaporated. FC (Et_2O/hexane 4:6) gave *15-hydroxypentadecan-2-one* (**11**) (4.4 g, 59%). Ketone **11** (100 mg, 0.41 mmol) was dissolved in acetone (3 ml), and *Jones* reagent (77 µl; prepared from 26.7 g of CrO_3, 40 ml of H_2O, 23 ml of conc. H_2SO_4 and H_2O up to 100 ml) was added at 0°. After stirring at r.t. for 1 h, sat. $NaHCO_3$ soln. was added. The solvent was evaporated, and conc. HCl was added. The aq. phase was extracted with CH_2Cl_2, and the org. phase was dried ($MgSO_4$) and evaporated. FC (AcOEt/hexane 1:1) gave **12** (95 mg, 90%). IR (KBr): 2930, 2916, 2851, 1715, 1702, 1684, 1469, 1445. ^{1}H-NMR (360 MHz, $CDCl_3$): 2.41 (*t*, *J* = 7.3, CH_2(13)); 2.34 (*t*, *J* = 7.3, CH_2(2)); 2.13 (*s*, Me); 1.68–1.50 (*m*, 2 CH_2); 1.38–1.22 (*m*, 8 CH_2). ^{13}C-NMR (50.3 MHz, $CDCl_3$): 209.59 (*s*); 179.91 (*s*); 43.73 (*t*); 34.02 (*t*); 29.75 (*q*); 29.45–28.96 (8*t*; 29.45, 29.34, 29.13, 28.96, 4 signals missing); 24.62 (*t*); 23.79 (*t*). CI-MS (CH_4): 257 (7, $M^{+\cdot}$), 240 (17), 239 (100), 237 (19), 58 (16). Anal. calc. for $C_{15}H_{28}O_3$ (256.38): C 70.27, H 11.01; found: C 70.22, H 11.04.

13-(2-Methyl-1,3-dioxolan-2-yl)tridecanoic Acid (**13b**). A soln. of **12** (1.2 g, 4.6 mmol), ethylene glycol (0.43 ml, 8.3 mmol), and *Amberlyst 15* (20 mg) in dry benzene (60 ml) was heated under reflux in a *Dean-Stark* apparatus overnight. The catalyst was filtered off, and the solvent was evaporated. FC (AcOEt/hexane 1:1) gave **13b** (1.3 g, 94%). ^{1}H-NMR (360 MHz, $CDCl_3$): 3.98–3.85 (*m*, OCH_2CH_2O); 2.33 (*t*, *J* = 7.5, CH_2COOH, 1.70–1.55 (*m*, 2 CH_2); 1.31 (*s*, Me); 1.40–1.15 (*m*, 18 CH_2). ^{13}C-NMR (50.3 MHz, $CDCl_3$): 179.38 (*s*); 110.23 (*s*); 64.55 (2*t*); 39.18–24.07 (12*t*, 39.18, 33.96, 29.83, 29.52, 29.38, 29.19, 29.03, 24.66, 24.08, 3 signals missing); 23.68 (*q*). IR (KBr): 3444, 2990, 2921, 2882, 2850, 1704, 1472. CI-MS(CH_4): 301 (69, $M^{+\cdot}$), 299 (16), 283 (50), 239 (21), 87 (100). Anal. calc. for $C_{15}H_{28}O_3$ (300.44): C 67.96, H 10.74; found: 67.72, H 11.01.

(4RS,5SR)-4-Ethenyl-2,3,4,5-tetrahydro-5-tridecylfuran-2-one ((±)-**14a**). A soln. of (±)-**4** (24 mg, 0.141 mmol) and *tridecanoic acid* (**13a**; 242 mg, 1.128 mmol) in MeOH (1.5 ml) was partially neutralized with Et_3N (10 µl, 0.07 mmol) and was electrolyzed in an undivided cell with a Pt-foil electrode (current density 100 mA/cm^2), until the current collapsed. The solvent was evaporated. The residue was dissolved in AcOEt and then washed with 1N NaOH soln. The org. layer was dried (Na_2SO_4) and purified by FC (AcOEt/hexane 1:3) to give (±)-**14a** (16 mg, 40%). Colorless oil. IR (film): 2990, 2974, 2928, 2856, 2361, 1774, 1295, 1237, 902. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.76 (*ddd*, *J* = 17.0, 10.3, 8.7, CH_2=C*H*); 5.19 (*dt*, *J* = 10.3, 1.2, 1 H, CH_2=CH); 5.15 (*dt*, *J* = 17.0, 1.2, 1 H, CH_2=CH); 4.49 (*ddd*, *J* = 9.2, 6.4, 4.2, H–C(5)); 3.19–3.11 (*m*, H–C(4)); 2.70 (*dd*, *J* = 17.3, 8.1, H–C(3)); 2.43 (*dd*, *J* = 17.3, 5.7, H–C(3)); 1.60–1.40 (*m*, CH_2); 1.25 (*m*, CH_2), 0.88 (*t*, *J* = 6.8, Me). ^{13}C-NMR (125.76 MHz, $CDCl_3$): 176.25 (*s*); 134.05 (*d*); 118.04 (*t*); 83.28 (*d*); 43.13 (*d*); 34.73 (*t*); 31.91 (*t*); 30.86 (*t*); 29.67–29.34 (9*t*, 29.67, 29.63, 29.60, 29.52, 29.43, 29.34, 3 signals missing); 25.68 (*t*); 22.68 (*t*); 14.10 (*q*). CI-MS (CH_4): 296 (16, $M^{+\cdot}$), 295 (59, $M^{+\cdot}$), 278 (19), 277 (41), 236 (28), 235 (100), 233 (28), 137 (17), 111 (16). HR-MS: calc.: 295.2659, found: 295.2631.

(4R,5S)-4-Ethenyl-2,3,4,5-tetrahydro-5-[13-(2-methyl-1,3-dioxolan-2-yl)tridecyl]furan-2-one ((–)-**14b**). A soln. of (–)-**4** (25 mg, 0.147 mmol) and **13b** (353 mg, 1.18 mmol) in MeOH (1.5 ml) was partially neutralized with Et_3N (11 µl, 0.074 mmol) and was electrolyzed in an undivided cell with a Pt-foil electrode (current density 100 mA/cm^2), until the current collapsed. The solvent was evaporated. The residue was dissolved in AcOEt and then washed with 1N NaOH soln. The org. layer was dried (Na_2SO_4) and purified by FC (AcOEt/hexane 1:3) to give (–)-**14b** (56 mg, 40%). Colorless oil. $[\alpha]_{589}^{23} = -13.1^\circ$ (*c* = 0.5, $CHCl_3$). IR (film): 2986, 2931, 1731, 1375. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.76 (*ddd*, *J* = 17.0, 10.3, 8.7, CH_2=C*H*); 5.19 (*dt*, *J* = 10.3, 1.3, 1 H, CH_2=CH); 5.16 (*dt*, *J* = 17.0, 1.3, 1 H, CH_2=CH); 4.57–4.48 (*m*, H–C(5)); 3.98–3.89 (*m*, OCH_2CH_2O); 3.19–3.11 (*m*, H–C(4)); 2.71 (*dd*, *J* = 17.3, 8.1, H–C(3)); 2.44 (*dd*, *J* = 17.3, 5.6, H–C(3)); 1.65–1.48 (*m*, CH_2); 1.31 (*s*, Me); 1.30–1.23 (*m*, CH_2). ^{13}C-NMR (125.76 MHz, $CDCl_3$): 176.65 (*s*); 134.36 (*d*); 118.40 (*t*); 110.55 (*s*); 83.64 (*d*); 64.94 (*t*); 43.47 (*d*); 39.58–24.05 (13*t*, 39.58, 35.08, 31.20, 30.22, 29.94, 29.91, 29.86, 29.77, 29.69, 26.02, 24.45,

24.05, 1 signal missing); 24.05 (*q*). ESI-HR-MS: 381 (M^+), 403 ($[M+Na]^+$). Anal. calc. for $C_{23}H_{40}O_4$ (380.57): C 72.59, H 10.59; found: C 72.45, H 10.40.

*(4*R,5S*)-4-Ethenyl-2,3,4,5-tetrahydro-5-pentylfuran-2-one* ((−)-**14c**). A soln. of (−)-**4** (50 mg, 0.35 mmol) and *pentanoic acid* (**13c**; 284 mg, 2.8 mmol) in MeOH (1.7 ml) was partially neutralized with Et_3N (24 µl, 0.17 mmol) and electrolyzed in an undivided cell with a Pt-foil electrode (current density 100 mA/cm^2), until the current collapsed. The solvent was evaporated. The residue was dissolved in AcOEt and then washed with 1N NaOH soln. The org. layer was dried (Na_2SO_4) and purified by FC (AcOEt/hexane 1:3) to give (−)-**14c** (21 mg, 40%). Colorless oil. $[\alpha]_{589}^{23} = -28.5°$ ($c = 0.2$, $CHCl_3$). IR (film): 2955, 2934, 2862, 2349, 2325, 1782, 1466, 1422, 1170, 1141, 1002. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.76 (*ddd*, *J* = 16.9, 10.3, 8.9, CH_2=C*H*); 5.19 (*d*, *J* = 10.3, 1 H, C*H*$_2$=CH); 5.14 (*dt*, *J* = 16.9, 1.2, 1 H, C*H*$_2$=CH); 4.50 (*ddd*, *J* = 9.2, 6.1, 4.2, H−C(5)); 3.21–3.10 (*m*, H−C(4)); 2.71 (*dd*, *J* = 17.4, 8.2, H−C(3)); 2.44 (*dd*, *J* = 17.4, 5.8, H−C(3)); 1.66–1.44 (*m*, 2 CH_2); 1.43–1.23 (*m*, 3 CH_2), 0.89 (*t*, *J* = 6.7, Me). ^{13}C-NMR (125.76 MHz, $CDCl_3$): 175.46 (*s*); 134.06 (*d*); 117.98 (*t*); 83.26 (*d*); 43.18 (*d*); 34.78 (*t*); 31.55 (*t*); 30.87 (*t*); 25.39 (*t*); 22.48 (*t*); 13.96 (*q*). CI-MS (CH_4): 183 (44, M^+), 165 (24), 124 (17), 123 (100), 99 (10), 82 (13), 81 (12), 54 (23). Anal. calc. for $C_{11}H_{18}O_2$ (182.26): C 72.49, H 9.95; found: C 72.50, H 9.82.

*(3*RS,*4*RS,*5*RS*)-4-Ethenyl-2,3,4,5-tetrahydro-3-methyl-5-tridecylfuran-2-one* ((±)-**15a**). To a soln. of (±)-**14a** (9.0 mg, 32 µmol) in dry THF (2 ml) was added at −78° a 0.2M LDA soln. (0.24 ml, 48 µmol). The mixture was stirred at −78° for 1 h, and MeI (10 µl, 160 µmol) was added. The mixture was allowed to warm to −40° and stirred at this temp. for 4 h. H_2O was added, and the phases were separated. The aq. phase was extracted with Et_2O, and the combined org. phases were dried (Na_2SO_4). After evaporation of the solvents, FC (AcOEt/hexane 1:10) of the residue gave (±)-**15a** (8.4 mg, 85%). Colorless oil. Spectral data in accordance with literature data [18]. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.72 (*ddd*, *J* = 17.0, 10.2, 8.8, CH_2=C*H*); 5.24–5.17 (*m*, C*H*$_2$=CH); 4.48 (*m*, H−C(5)); 2.81 (*m*, H−C(4)); 2.49 (*dq*, *J* = 11, 7, H−C(3)); 1.45–1.55 (*m*, CH_2); 1.24 (*s*, 11 CH_2); 1.22 (*d*, *J* = 7.0, Me); 0.88 (*t*, *J* = 7, Me). ^{13}C-NMR (125.76 MHz, $CDCl_3$): 178.86 (*s*); 133.89 (*d*); 118.97 (*t*); 80.97 (*d*); 51.43 (*d*); 38.40 (*d*); 31.90 (t); 30.87 (t); 29.66–29.31 (9*t*); 25.79 (t); 22.68 (t); 14.12 (*q*); 13.46 (*q*).

*(3*S,*4*S,*5*S*)-4-Ethenyl-2,3,4,5-tetrahydro-3-methyl-5-[13-(2-methyl-1,3-dioxolan-2-yl)tridecyl]furan-2-one* ((−)-**15b**). To a soln. of (−)-**14b** (54 mg, 0.14 mmol) in dry THF (2 ml) was added at −78° 0.2M LDA (0.70 ml, 0.14 mmol). The mixture was stirred at −78° for 1 h, and MeI (0.02 ml, 0.28 mmol) was added. The mixture was allowed to warm to −40° and then stirred at this temp. for 4 h. H_2O was added, and the phases were separated. The aq. phase was extracted with Et_2O, and the combined org. phases were dried (Na_2SO_4). After evaporation of the solvents, FC (AcOEt/hexane 1:10) of the residue gave (−)-**15b** (35 mg, 62%). Colorless oil. $[\alpha]_{589}^{26} = -19.4$ ($c = 0.5$, $CHCl_3$). IR (film): 2929, 2855, 2383, 1767, 1731. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.72 (*ddd*, *J* = 17.0, 10.2, 8.8, CH_2=C*H*); 5.24–5.17 (*m*, C*H*$_2$=CH); 4.52–4.45 (*m*, H−C(5)); 3.98–3.89 (*m*, 2 CH_2); 2.85–2.77 (*m*, H−C(4)); 2.53–2.45 (*m*, H−C(3)); 1.31 (*s*, Me); 1.35–1.24 (*m*, CH_2); 1.22 (*d*, *J* = 7.0, Me). ^{13}C-NMR (125.76 MHz, $CDCl_3$): 179.18 (*s*); 134.27 (*d*); 119.30 (*t*); 110.55 (*s*); 81.32 (*d*); 64.96 (*t*); 64.94 (*t*); 51.79 (*d*); 39.58 (*t*); 38.77 (*d*); 31.23–24.45 (12 *t*, 31.23, 30.22, 29.98, 29.94, 29.91, 29.88, 29.80, 29.70, 26.14, 24.45, 2 signals missing); 24.05 (*q*); 13.82 (*q*). ESI-MS: 395 (M^+), 417 ($[M+Na]^+$). Anal. calc. for $C_{24}H_{42}O_4$ (394.59): C 73.05, H 10.73; found: C 73.01, H 10.69.

*(3*S,*4*S,*5*S*)-4-Ethenyl-2,3,4,5-tetrahydro-3-methyl-5-(14-oxopentadecyl)furan-2-one* ((−)-**16**). A soln. of (−)-**15b** (27 mg, 0.07 mmol) in 1M HCl soln. (5 ml) was heated under reflux for 1 h. Extraction with CH_2Cl_2 afforded **16** (18 mg, 80%). Colorless oil. $[\alpha]_{589}^{26} = -26.2$ ($c = 0.2$, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$): 5.71 (*ddd*, *J* = 17.0, 10.3, 8.8, CH_2=C*H*); 5.24–5.20 (*m*, 1 H, C*H*$_2$=CH); 5.18 (*t*, *J* = 1.1, 1 H, C*H*$_2$=CH); 4.51–4.45 (*m*, H−C(5)); 2.85–2.77 (*m*, H−C(4)); 2.53–2.45 (*m*, H−C(3)); 2.41 (*t*, *J* = 7.5, CH_2CO); 2.03 (*s*, Me); 1.60–1.46 (*m*, CH_2); 1.35–1.20 (*m*, CH_2); 1.21 (*d*, *J* = 7.1, Me). ^{13}C-NMR (125.76 MHz, $CDCl_3$): 209.49 (*s*); 178.86 (*s*); 133.91 (*d*); 118.98 (*t*); 80.98 (*d*); 51.44 (*d*); 43.83 (*d*); 38.41 (*q*); 30.88–23.85 (10*t*, 30.89, 29.87, 29.59, 29.51, 29.45, 29.39, 29.34, 29.16, 25.80, 23.85); 13.47 (*q*). IR (film): 3685, 3024, 2433, 2400, 1523. ESI-HR-MS: 351 (M^+), 373 ($[M+Na]^+$). Anal. calc. for $C_{22}H_{38}O_3$ (350.54): C 75.38, H 10.93; found: C 75.45, H 10.75.

*(2*S,*3*S,*4*S*)-2,3,4,5-Tetrahydro-4-methyl-5-oxo-2-(14-oxopentadecyl)furan-3-carboxylic acid* (*=(−)-Dihydropertusaric Acid*; **2**). A flow of O_3 was passed through a soln. of (−)-**16** (7.0 mg, 20 µmol) in CH_2Cl_2 (5 ml) at −78°. After the appearance of a blue coloration, the O_3 flow was stopped and replaced by a flow of N_2 for 15 min. Me_2S (100 µl, 1.4 mmol) was added at −78°, and the soln. was stirred for 1 h at this temp., and then the mixture was allowed to warm to r.t. and stirred for 1 h. CH_2Cl_2 was added, and the org. phase was washed with H_2O. After removal of the solvent *in vacuo*, the residue was dissolved in a mixture of ^{t}BuOH (4 ml) and 2-methylbut-2-ene (1 ml) and stirred at r.t. A soln. of $NaClO_2$ (20 mg, 0.18 mmol) and $NaH_2PO_4 \cdot H_2O$ (25 mg, 0.18 mmol) in H_2O (2 ml) was added dropwise. The mixture was stirred at r.t. for 2 h, and the volatile

compounds were removed by evaporation under reduced pressure. H_2O (5 ml) was added, and the aqueous soln. was extracted with hexane. The aq. layer was acidified and extracted with Et_2O. The combined Et_2O extracts were dried (Na_2SO_4), and the solvent was evaporated to give crude **2** (7.0 mg). Recrystallization from AcOEt/hexane gave pure **2** (5.1 mg, 70%). Physical and spectral data are in accordance with data reported for the natural product [16]. M.p. 105–107° ([16]: 107–108°). $[\alpha]_{589}^{25} = -6.9$ ($c = 0.2$, $CHCl_3$). $[\alpha]_D^{25} = -64$ ($c = 0.2$, MeOH) ([16]: $[\alpha]_D^{25} = -72$ ($c = 1.45$, MeOH)). IR (film): 3685, 3156, 3021, 2434, 2401, 2254, 1795, 1524. ^{1}H-NMR (360 MHz, $CDCl_3$): 11.0 (br. *s*, COOH); 4.72–4.65 (*m*, H–C(2)); 3.23 (*dd*, $J = 10.0$, 8.3, H–C(3)); 3.05 (*dq*, $J = 10.1$, 7.0, H–C(4)); 2.44 (*t*, $J = 7.3$, CH_2CO); 2.17 (*s*, MeCO); 1.58–1.52 (*m*, CH_2); 1.33 (*d*, $J = 7.0$, Me); 1.30–1.24 (*m*, 11 CH_2). ^{13}C-NMR (125.76 MHz, $CDCl_3$): 209.7 (*s*); 177.5 (*s*); 173.5 (*s*); 77.6 (*d*); 51.8 (*d*); 44.1 (*t*); 36.8 (*d*); 31.4 (*t*); 29.5 (*q*); 29.2 (9*t*); 25.7 (*t*); 24.1 (*t*); 14.75 (*q*). ESI-MS: 369 (M^+), 391 ($[M + Na]^+$). Anal. calc. for $C_{21}H_{36}O_5$ (368.52): C 68.45, H 9.85; found: C 68.22, H 10.04.

*(2*S*,3*S*)-2,3,4,5-Tetrahydro-5-oxo-2-pentylfuran-3-carboxylic acid* ((−)-**17**). To a stirred soln. of (−)-**14c** (20 mg, 0.11 mmol) in a solvent mixture of CCl_4 (200 µl), MeCN (200 µl), and H_2O (300 µl) were added $NaIO_4$ (98 mg, 0.45 mmol) and $RuCl_3$ (3.0 mg, 11 µmol) at r.t. After 3 h at r.t., CH_2Cl_2 (2 ml) was added, and the aq. phase was separated and extracted with CH_2Cl_2. The combined org. layers were filtered through *Celite*. After evaporation of the volatiles, the residue was diluted with Et_2O (2 ml), and sat. $NaHCO_3$ soln. (2 ml) was added. The org. phase was separated, and the aq. one was acidified with 1M HCl soln. The product was extracted with CH_2Cl_2 and dried (Na_2SO_4). The solvent was evaporated to give (−)-**17** (17 mg, 80%). $[\alpha]_{589}^{23} = -28.5$ ($c = 0.3$, $CHCl_3$). IR (KBr): 3177, 3148, 3135, 2957, 2933, 2861, 2341, 1753, 1740, 1410. ^{1}H-NMR (500 MHz, $CDCl_3$): 4.66 (*dd*, $J = 13.4$, 7.3, H–C(2)); 3.52–3.42 (*m*, H–C(3)); 2.90 (*dd*, $J = 17.7$, 5.0, H–C(4)); 2.71 (*dd*, $J = 17.7$, 8.5, H–C(4)); 1.71–1.25 (*m*, 4 CH_2); 0.89 (*t*, $J = 7.0$, Me). ^{13}C-NMR (125.76 MHz, $CDCl_3$): 175.07 (*s*); 174.55 (*s*); 80.17 (*d*); 44.11 (*d*); 31.83 (*t*); 31.36 (*t*); 31.28 (*t*); 25.48 (*t*); 22.40 (*t*); 13.84 (*q*). CI-MS (CH_4): 200 (2, M^+), 154 (17), 139 (12), 1293 (86), 111 (15), 101 (100), 83 (40), 73 (28), 72 (10), 71 (12), 58 (2), 57 (18), 56 (13), 55 (71). Anal. calc. for $C_{10}H_{16}O_4$ (200.23): C 59.98, H 8.05; found: C 59.83, H 8.01. Physical and spectral data in accordance with data in [20].

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