Synthesis of enantiomericaly pure γ-lactones from 2,3-*O*-isopropylidene-D- or L-erythrose

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Abstract
Conventional synthetic transformations such as Wittig olefination, catalytic hydrogenation and lactonization reactions were used to obtain enantiomerically pure (*R*)-γ-caprolactone and (*S*)-japonilure, pheromones of the beetle *Trogoderma* and the Osaka beetle *Anomala osakana*, respectively, as well as the hydroxylated γ-lactone L-factor from 2,3-*O*-isopropylidene-*D*- or *L*-erythrose.

Keywords: (*R*)-γ-Caprolactone, (*S*)-japonilure, L-factor, 2,3-*O*-isopropylidene-*D*- or *L*-erythrose, Wittig olefination

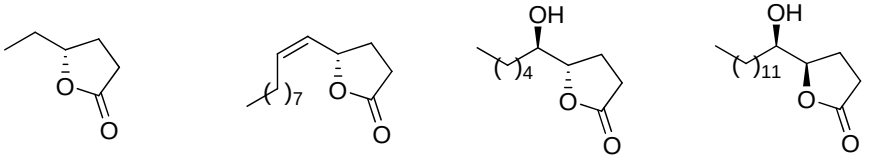
Introduction

Many natural products with important biological activities have the structure of a chiral γ-lactone.[1] A number of such lactones have been isolated from insects and are part of their intriguing communication systems. (*R*)-γ-Caprolactone **1** is a component of the pheromone secreted by the female dermestid beetle *Trogoderma glabrum* and *Trogoderma granarium*[2] (Figure 1). These beetles are among the worst insect pests infecting nearly all forms of stored products, including grain, meat, dairy products, carpets and clothing. (4*R*,5*Z*)-4-Hydroxy-5-tetradecenoic acid γ-lactone[3] **ent-2**[4] or (*R*)-japonilure is a pheromone of the Japanese beetle *Popillia japonica*, a notorious pest of a variety of trees, grasses, ornamentals and cultivated crops, whereas (*S*)-japonilure[5] **2** is the pheromone of the Osaka beetle *Anomala osakana*. These two pheromones act as strong behavioral antagonists for the allospecific receiver,[6] a fact that increases the demand for enantiomerically pure (*R*)- or (*S*)-japonilure.

(4*S*,5*R*)-4,5-Dihydroxydecanoic acid γ-lactone or L-factor[7] **3** and (4*R*,5*R*)-4,5-dihydroxyheptadecanoic acid γ-lactone or (–)-muricatacin[8] **4** have closely related structures possessing an additional hydroxyl group with respective erythro- and threo- relative configurations differing also in the length of the carbon chains. The first of them, produced by

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Streptomyces griseus, was initially proposed to be an autoregulator of anthracycline biosynthesis, whereas muricatacin isolated from the tropical fruit, *Annona muricata* is an anticancer agent.



(*R*)-γ-Caprolactone **1** (*S*)-Japonilure **2** L-(+)-Factor **3** (-)-Muricatacin **4**

Figure 1

The synthesis of the above γ-lactones and related compounds has became the subject of intensive work and a number of publications towards their enantioselective syntheses have been reported in the literature,[9-12] including both asymmetric synthesis and chiral pool. In addition, enantiomerically pure γ-lactones are valuable chiral synthetic intermediates, useful for further transformations.[13] Our continuing interest in the synthesis of pheromones and natural products with a lactonic structure using inexpensive commercially available carbohydrates,[14] prompted us to investigate the synthesis of enantiomerically pure γ-lactones, such as those depicted in Figure 1.

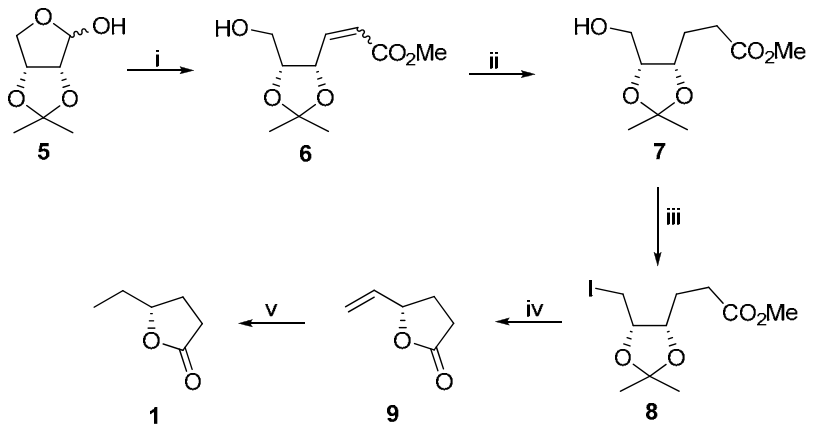
Results and Discussion

Protected *D*- or *L*-erythrose were the starting material of choice, since both enantiomers are easily prepared either from the respective inexpensive commercial *D*- or *L*-arabinose,[15] or from *D*-ribose[16] or isoascorbic acid.[17] This fact has the advantage of allowing the possibility to prepare both enantiomers of the target molecule, simply by selecting the other starting enantiomer of erythrose. In our hands, protected *D*- and *L*-erythrose (**5** and **ent-5**, respectively) were repeatedly prepared from the respective *D*- and *L*-arabinose,[15] in 90% yield.

A 2:5 mixture of E-/Z-**6** (Scheme 1) in 90% yield was prepared by Wittig olefination of **5** with the stable ylide $Ph_3P{=}CHCO_2Me$. It has been reported,[17a] that this reaction yields exclusively the E-**6**. However, the given ^1H and ^{13}C NMR data[17a] were consistent to those of Z-**6** we obtained (J_{cis} = 11.6 Hz, J_{trans} = 16.1 Hz). It is also well known that the presence of a 4-OH at an aldehyde (open form of **5**) favors the formation of *Z*-alkenes in Wittig reactions with stable ylides.[18] Subsequent catalytic hydrogenation over Raney Ni of this mixture gave 70% yield of the saturated ester **7**.[14b] After some experimentation,[19] the desired iodide **8** was prepared in 90% yield from **7** by careful balancing the ratio of reactants (1.1 equiv. I_2, 1.0 equiv. imidazole, 2.0 equiv. Ph_3P, toluene, reflux, 2h).

Treatment of **8** with activated Zn in refluxing methanol[20] for 2 h, afforded the known unsaturated γ-lactone **9** in 95% yield. Apparently, the organozinc compound intermediate formed by zinc insertion into the C-I bond, led to elimination of the β-alkoxy group and the hydroxyl-

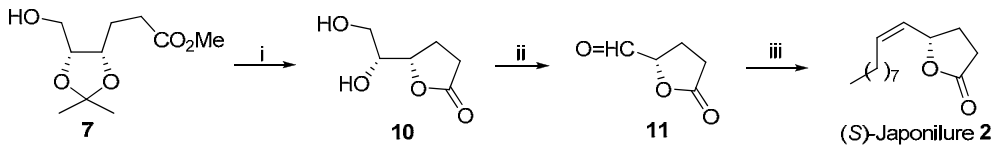
ester generated was spontaneously cyclized to give lactone **9**. It has been reported in the literature,[21] that catalytic hydrogenation of this lactone in the racemic form under pressure in the presence of platinum led to the formation of γ-caprolactone **1** in 78% yield. In our hands, (*R*)-γ-caprolactone **1** was prepared in 80% yield by hydrogenation of **9** at atmospheric pressure with Raney Ni as a catalyst. Its $[\alpha]_D$ value, spectroscopic and analytical data were in excellent agreement with those reported in the literature.[9]



Scheme 1. Reagents and conditions: (i) $Ph_3P{=}CHCO_2Me$, $PhCO_2H$, THF, reflux, 24 h, 90%, (E/Z = 2:5); (ii) Raney Ni, H_2, MeOH, 20 ºC, 2 h, 70%; (iii) I_2 (1.1 equiv.), imidazole (1.0 equiv.), Ph_3P (2.0 equiv.), toluene, reflux, 2 h, 90%; (iv) Zn, MeOH, reflux, 2 h, 95%; (v) Raney Ni, H_2, MeOH, 20 ºC, 2 h, 80%.

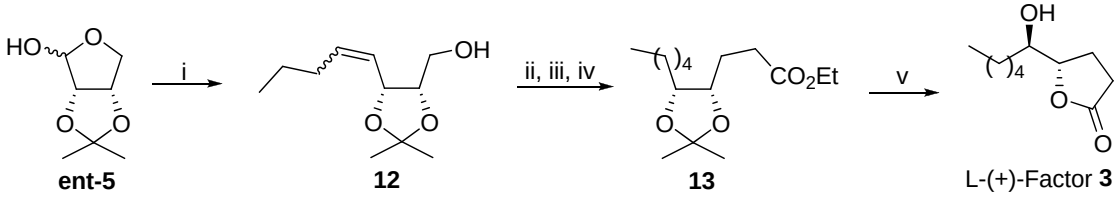
The overall yield was 43% from 2,3-*O*-isopropylidene-*D*-erythrose **5** in five steps or 39% from *D*-arabinose in seven steps. Compared to other syntheses of (*R*)-γ-caprolactone **1** from chiral pool components,[9] our method is the most highly yielding and one of the shortest synthetic approaches.

Methyl (4*S*,5*R*)-4,5-*O*-isopropylidene-4,5,6-trihydroxy-hexanoate **7**, intermediately prepared in the synthesis of (*R*)-γ-caprolactone **1**, could also be used for the easy access to (*S*)-japonilure **2** (Scheme 2). Treatment of **7** with a catalytic amount of *p*-toluenesulfonic acid afforded the known dihydroxy γ-caprolactone **10**[10g,22] in 45% yield, which upon periodate cleavage can afford aldehyde **11**, a reaction already applied for the preparation of **ent-11** from **ent-10**.[22b] The final step of its conversion to the desired (*S*)-japonilure **2** is known in the literature to proceed by a simple Wittig reaction.[10h]



Scheme 2. Reagents and conditions: (i) $TsOH{\cdot}H_2O$ (cat.), MeOH, 20 ºC, 2 h, 45%; (ii) Ref. 21b; (iii) Ref. 9h.

The last natural product we pursued was L-Factor **3** (Scheme 3). This compound has the structure of (*S*)-γ-decanolactone possessing an additional hydroxyl group at α-position relative to the lactone moiety with erythro- stereochemistry. *L*-Erythrose **ent-5** was the starting material and the terminal aliphatic chain was introduced by a Wittig reaction with the proper phosphorus ylide in 94% yield. (*Z*)-**12** was thus produced contaminated by 9% (*E*)-**12**, as shown by integration of the easily discerned H-3 proton signals in their ^{1}H NMR spectra. The primary hydroxyl group was then subjected to Swern oxidation following by a second Wittig olefination with the stable ylide $Ph_3P{=}CHCO_2Et$. The ratio of geometric isomers obtained was of no importance and the product was hydrogenated over catalytic Raney Ni to give the known ester **13** in 37% yield (three steps). The data of this compound were generally in agreement with those reported in the literature, except for the $[\alpha]_D$ values.[11c] For this reason, we proceeded in the next step and treatment of **13** with catalytic *p*-toluenesulfonic acid[11c] led to the formation of L-Factor **3** in 59% yield, whose analytical data was in good agreement with the reported data.[11]



Scheme 3. Reagents and conditions: (i) $Ph_3P^+CH_2CH_2CH_2CH_3Br^-$, *n*-BuLi, THF, -60 ºC, 24 h, 94%, (E/Z = 9:91); (ii) $(COCl)_2$, DMSO, Et_3N, DCM, 20 ºC, -60 ºC, 12 h; (iii) $Ph_3P{=}CHCO_2Et$, EtOH, 24 h; (iv) Raney Ni, H_2, MeOH, 20 ºC, 2 h, 37% from **12**; (v) $TsOH{\cdot}H_2O$ (cat.), MeOH, 20 ºC, 3 h, 59%.

The enantiomer of L-Factor **ent-3** can also be prepared by the same route starting from protected *D*-erythrose **5**. In addition, their diastereoisomers with threo relative configuration could also be prepared by a Mitsunobu inversion of the free secondary hydroxyl group.[12] Furthermore, this method could be used for the synthesis of any analogous γ-lactone stereoisomer, differing also in the length of the carbon chains. In fact, the synthesis of *epi*-muricatacin by this procedure from protected *D*-erythrose **5** was reported by Scharf and coworkers.[17a]

Conclusions

In conclusion, easily accessible protected *D*- or *L*-erythrose obtained from the respective enantiomer of inexpensive commercial arabinose was used for the synthesis of enantiomerically pure γ-lactones, applying conventional synthetic transformations such as Wittig olefination, catalytic hydrogenation and lactonization reactions. The possibility of using either *D*- or *L*-erythrose is a great advantage, since both enantiomers of a chiral γ-lactone could be prepared. This was exemplified by the synthesis of pheromones (*R*)-γ-caprolactone and (*S*)-japonilure, as

well as the natural γ-lactone L-factor in enantiomerically pure form, reported here. In addition, several compounds prepared, such as **7**-**13**, could prove valuable chiral synthetic intermediates.

Experimental Section

General Procedures. All reagents are commercially available and were used without further purification. Solvents were dried by standard methods. Raney Ni was purchased from Aldrich. The reactions' progress was checked by thin layer chromatography (TLC) on Merck silica gel $60F_{254}$ glass plates (0.25 mm). The spots were visualised by heat staining with anisaldehyde in ethanol/sulfuric acid. Column chromatography was performed with Merck silica gel 60 (0.063-0.200 mm). Melting points were determined on a Kofler hot-stage microscope and are uncorrected. Optical rotations were determined at room temperature on an A. Krüss P3000 Automatic Digital Polarimeter. The ^{1}H- and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Bruker 300 AM spectrometer, with tetramethylsilane (TMS) as internal standard. IR spectra were recorded on a Perkin Elmer FT-IR 1650 instrument as indicated. High-resolution mass spectra (HRMS) were obtained on a 7 T APEX II mass spectrometer by electro spray technique, positive mode.

Methyl (4*S*,5*R*,2*E*)-4,5-*O*-isopropylidene-4,5,6-trihydroxyhex-2-enoate and **methyl (4*S*,5*R*,2*Z*)-4,5-*O*-isopropylidene-4,5,6-trihydroxyhex-2-enoate (6).** To a solution of protected *D*-erythrose (2.0 g, 12.5 mmol) in dry THF (60 mL), $Ph_3P{=}CHCO_2Me$ (5 g, 15 mmol) and $PhCO_2H$ (250 mg, 2 mmol) were added. The mixture was refluxed for 2 days and then the solvent was evaporated and the residue chromatographed on a silica gel column with hexane/EtOAc (4:1) as the eluent to give firstly ***Z*-6** (1.736 g) followed by ***E*-6** (0.494 g, combined yield 90%, E/Z ratio: 2/5) as thick oils. For *Z*-isomer: $[\alpha]_D^{25}$ +136.2 (*c* 1.2, $CHCl_3$) [for **ent-*Z*-6**, lit.[16c] $[\alpha]_D^{25}$ -140 (*c* 1.2, $CHCl_3$)]; FTIR (neat film) 3479, 2989, 2952, 2855, 1716, 1646, 1440, 1407, 1382, 1201, 1164, 1048, 1001, 934, 906, 876, 857, 824, 520 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (dd, *J* = 11.6, 7.1 Hz, 1H, H-3), 5.93 (d, *J* = 11.6 Hz, 1H, H-2), 5.59 (t, *J* = 7.1 Hz, 1H, H-4), 4.55 (m, 1H, H-5), 3.72 (s, 3H, MeO), 3.56 (m, 1H, H-6a), 3.42 (m, 1H, H-6b), 3.06 (t, *J* = 5.8 Hz, 1H, OH), 1.52 (s, 3H, Me), 1.39 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7 (C-1), 147.0 (C-3), 120.0 (C-2), 108.4 (*C*Me_2), 78.5 (C-5), 74.1 (C-4), 60.9 (C-6), 51.1 (MeO), 26.9 (Me), 24.2 (Me); HRMS *m/z* 239.0892 [$C_{10}H_{16}O_5Na$ $(M+Na)^+$ requires 239.0895]. For *E*-isomer: $[\alpha]_D^{25}$ +34.7 (*c* 3.0, $CHCl_3$); FTIR (neat film) 3469, 2989, 2938, 1725, 1662, 1438, 1382, 1310, 1260, 1217, 1165, 1119, 1049, 985, 931, 875, 857, 792, 724, 695, 542, 519 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (dd, *J* = 16.1, 5.8 Hz, 1H, H-3), 6.13 (dd, *J* = 16.1 Hz, 1.9, 1H, H-2), 4.81 (dt, *J* = 5.8, 1.3 Hz, 1H, H-4), 4.37 (q, *J* = 5.8 Hz, 1H, H-5), 3.79 (s, 3H, MeO), 3.56 (d, *J* = 5.8 Hz, 2H, H-6), 3.03 (br s, 1H, OH), 1.52 (s, 3H, Me), 1.39 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3 (C-1), 142.7 (C-3), 122.1 (C-2), 109.2 (*C*Me_2), 78.1 (C-5), 75.7 (C-4), 61.3 (C-6), 51.5 (MeO), 27.4 (Me), 24.9 (Me); HRMS *m/z* 239.0892 [$C_{10}H_{16}O_5Na$ $(M+Na)^+$ requires 239.0895].

Methyl (4*S*,5*R*)-4,5-*O*-isopropylidene-4,5,6-trihydroxyhexanoate (7). To solution of **(*E*,*Z*)-6** (2.43 g, 11.2 mmol) in methanol (20 mL) catalytic amount of Raney Ni was added and the mixture was stirred under hydrogen atmosphere (1 atm) for 2 h at room temperature. Then, the solids were removed by filtration through Celite®, the solvent was evaporated and the residue chromatographed on a silica gel column with hexane/EtOAc (6:1) as the eluent to give **7** (1.71 g, 70%) as a thick oil: $[\alpha]_D^{25}$ -4.3 (*c* 2.6, $CHCl_3$); FTIR (neat film) 3464, 2987, 2937, 2876, 1739, 1439, 1371, 1248, 1219, 1164, 1044, 995, 871, 516 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.19 (m, 2H, H-4, H-5), 3.68 (s, 3H, MeO), 3.67 (d, *J* = 5.8 Hz, 2H, H-6), 2.56 (dt, *J* = 16.6, 7.1 Hz, 1H, H-2a), 2.40 (dt, *J* = 16.6, 7.7 Hz, 1H, H-2b), 1.93 (br s, 1H, OH), 1.84 (q, *J* = 7.1 Hz, 2H, H-3), 1.46 (s, 3H, Me), 1.36 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6 (C-1), 108.3 (*C*Me_2), 77.7 (C-5), 75.9 (C-4), 61.5 (C-6), 51.7 (MeO), 30.9 (C-2), 28.1 (Me), 25.4 (Me), 24.6 (C-3); HRMS *m/z* 241.1054 [$C_{10}H_{18}O_5Na$ $(M+Na)^+$ requires 241.1052].

Methyl (4*S*,5*S*)-4,5-isopropylidenedioxy-6-iodohexanoate (8). A solution of **7** (685 mg, 3.14 mmol), Ph_3P (1.64 g, 6.28 mmol), imidazole (214 mg, 3.14 mmol) and I_2 (880 mg, 3.45 mmol) in toluene (40 mL) was refluxed for 2 h, then saturated aqueous $NaHCO_3$ (30 mL) was added and the resulting mixture was stirred at room temperature for 30 min. The organic layer was decolorized by treatment with saturated aqueous $Na_2S_2O_3$, washed with H_2O (30 mL) and dried over Na_2SO_4. The solvent was then evaporated and the residue chromatographed on a silica gel column with hexane/EtOAc (15:1) as the eluent to give **8 (**927 mg, 90%) as a thick oil: R_f = 0.48 (hexane/EtOAc, 3:1); $[\alpha]_D^{25}$ -7.7 (*c* 9.4, $CHCl_3$); FTIR (neat film) 2986, 2934, 2863, 1738, 1437, 1380, 1369, 1246, 1219, 1160, 1068, 867, 514 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.38 (dt, *J* = 6.4, 5.8 Hz, 1H, H-5), 4.15 (ddd, *J* = 10.3, 5.8, 3.2 Hz, 1H, H-4), 3.68 (s, 3H, MeO), 3.20 (dd, *J* = 17.3, 7.1 Hz, 1H, H-6a), 3.13 (dd, *J* = 17.3, 5.8 Hz, 1H, H-6a), 2.58 (ddd, *J* = 16.7, 9.0, 5.8 Hz, 1H, H-2a), 2.45 (dt, *J* = 16.7, 7.7 Hz, 1H, H-2b), 1.85 (m, 2H, H-3), 1.46 (s, 3H, Me), 1.36 (s, 3H, Me). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1 (C-1), 108.3 (*C*Me_2), 77.7 (C-5), 76.1 (C-4), 51.3 (MeO), 30.1 (C-2), 28.0 (Me), 25.3 (Me), 24.2 (C-3), 2.1 (C-6). HRMS *m/z* 351.0071 [$C_{10}H_{17}IO_4Na$ $(M+Na)^+$ requires 371.0069].

(*S*)-5-Vinyldihydrofuran-2(3*H*)-one (9). To a solution of **8** (588 mg, 1.80 mmol) in MeOH (20 mL), was added activated Zn[20a] (580 mg, 9 mmol) and the mixture was refluxed for 2 h with stirring. Then, the solids were removed by filtration through Celite®, the solvent was evaporated and the residue chromatographed on a silica gel column with hexane/EtOAc (3:1) as the eluent to give **9** (245 mg, 95%) as a thick oil with ^1H and ^{13}C NMR were identical to those reported in the literature.[22] R_f = 0.25 (hexane/EtOAc, 3:1); $[\alpha]_D^{25}$ +25.0 (*c* 1.0, $CHCl_3$) [lit.[23] $[\alpha]_D$ +28 (*c* 1.48, $CHCl_3$)]; HRMS *m/z* 135.0424 [$C_6H_8O_2Na$ $(M+Na)^+$ requires 135.0422].

(*R*)-5-Ethyldihydrofuran-2(3*H*)-one (1). To a solution of **9** (258 mg, 1.8 mmol) in methanol (8 mL) catalytic amount of Raney Ni was added and the mixture was stirred under hydrogen atmosphere (1 atm) for 2 h at room temperature. Then, the solids were removed by filtration through Celite®, the solvent was evaporated and the residue chromatographed on a silica gel column with hexane/EtOAc (4:1) as the eluent to give **1** (209 mg, 80%) as a thick oil with ^1H and

^{13}C NMR were identical to those reported in the literature.[9] $[\alpha]_D^{25}$ +50.8 (*c* 1.3, MeOH) [lit.[9i] $[\alpha]_D^{21}$ +53.1 (*c* 1.005, MeOH)]; HRMS *m/z* 137.0580 [$C_6H_{10}O_2Na$ $(M+Na)^+$ requires 137.0578].

(*S*)-5-((*R*)-1,2-Dihydroxyethyl)dihydrofuran-2(3*H*)-one (10). A solution of **7** (272 mg, 1.24 mmol) and $TsOH{\cdot}H_2O$ (15 mg) in MeOH (30 mL) was stirred at room temperature for 2 h. Saturated aqueous $NaHCO_3$ (10 mL) was added, the mixture was extracted with ethyl acetate (3x60 mL) and the organic phase was washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on a silica gel column with hexane/EtOAc (1:1) as the eluent to give **10** (82 mg, 45%). $[\alpha]_D^{25}$ +14.6 (*c* 1.3, $CHCl_3$) [lit.[22a] $[\alpha]_D^{20}$ +4.3 (*c* 2, MeOH); for **ent-10**, lit.[22b] $[\alpha]_D^{20}$ -15.1 (*c* 1.2, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.52 (dt, *J* = 7.1, 5.0 Hz, 1H, H-4), 3.92 (dt, *J* = 5.0, 4.1 Hz, 1H, H-5), 3.79 (dd, *J* = 11.1, 4.1 Hz, 1H, H-6a), 3.69 (dd, *J* = 11.1, 6.1 Hz, 1H, H-6b), 2.57 (t, *J* = 8.1 Hz, 2H, H-2), 2.29 (q, *J* = 8.1 Hz, 2H, H-3).

(2*S*,3*R*,4*Z*)-2,3-*O*-Isopropylidenedioxyoct-4-en-1-ol (12). A solution of $Ph_3P^+CH_2CH_2CH_2CH_3Br^-$ (6.7 g, 16.75 mmol) in dry THF (10 mL) containing catalytic amount of 12-crown-4 was cooled at –60 ºC and *n*-BuLi 2.34 M in hexanes (7 mL, 16.42 mmol) was added dropwise under argon atmosphere. The solution became orange-reddish, then protected *L*-erythrose **ent-5** (536 mg, 3.35 mmol) in THF (5 mL) was added at the same temperature and the mixture was allowed overnight to warm at room temperature before being quenched with saturated aqueous NH_4Cl. The mixture was subsequently extracted with CH_2Cl_2 (3x60 mL), the organic layer was washed with H_2O (60 mL) and dried over Na_2SO_4. The solvent was then evaporated and the residue chromatographed on a silica gel column with hexane/EtOAc (5:1) as the eluent to give **12 (**628 mg, 94%, *Z*/*E* = 91:9) as a thick oil: $[\alpha]_D^{25}$ -48.2 (*c* 4.2, $CHCl_3$); FTIR (neat film) 3456, 2986, 2960, 2932, 2873, 1457, 1380, 1244, 1216, 1165, 1044, 882 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) (*Z*-isomer) δ 5. 77 (m, 1H, H-5), 5.47 (dd, *J* = 9.8, 7.7 Hz, 1H, H-4), 5.01 (dd, *J* = 7.7, 6.2 Hz, 1H, H-3), 4.23 (dt, *J* = 6.2, 5.7 Hz, 1H, H-2), 3.57 (d, *J* = 5.7 Hz, 2H, H-1), 2.06 (m, 3H, OH, 6-H), 1.51 (s, 3H, Me), 1.45 (m, 2H, 7-H), 1.40 (s, 3H, Me), 0.92 (t, *J* = 7.5 Hz, 3H, H-8). ^{13}C NMR (75 MHz, $CDCl_3$) (*Z*-isomer) δ 135.3 (C-5), 124.4 (C-4), 108.5 (*C*Me_2), 78.3 (C-3), 72.9 (C-2), 62.2 (C-1), 29.9 (C-6), 27.9 (Me), 25.2 (Me), 22.6 (C-7), 13.7 (C-8); HRMS *m/z* 223.1305 [$C_{11}H_{20}O_3Na$ $(M+Na)^+$ requires 223.1305].

Ethyl (4*S*,5*R*)-4,5-isopropylidenedioxydecanoate (13). A solution of $(COCl)_2$ (0.95 mL, 10.9 mmol) in dry CH_2Cl_2 (12.5 ml) was cooled to –60 ºC and DMSO (1.5 mL, 20.0 mmol) in dry CH_2Cl_2 (7.5 ml) was added dropwise. Alcohol **12** (500 mg, 2.5 mmol) dissolved in dry CH_2Cl_2 (30 ml) was subsequently added, dropwise as well. After stirring for 20 min at the same temperature, Et_3N (5.95 mL, 40 mmol) was added and stirring was continued for 30 min. Then, the mixture was allowed to warm to room temperature, poured into water and the organic phase was washed with brine (3×30 ml). The aqueous layer was extracted with CH_2Cl_2 (3×50 ml). The combined organic phases were dried and concentrated in vacuum. The resulting aldehyde was dissolved in EtOH (50 mL), $Ph_3P{=}CHCO_2Et$ (1.305 g, 3.75 mmol) was added and the mixture was allowed to stir overnight. The solvent was subsequently evaporated and the residue chromatographed on a silica gel column with hexane/EtOAc (10:1) as the eluent to give a thick

oil, which was dissolved in MeOH (50 mL), catalytic amount of Raney Ni was added and the mixture was stirred under a hydrogen atmosphere (1 atm) for 24 h at room temperature. Then, the solids were removed by filtration through Celite®, the solvent was evaporated and the residue chromatographed on a silica gel column with hexane/EtOAc (15:1) as the eluent to give **13** (252 mg, overall 37%) as a thick oil with ^{1}H and ^{13}C NMR identical to those reported in the literature:[11] $[\alpha]_D^{25}$ –20.45 (*c* 2.47, $CHCl_3$) {lit.[11c] $[\alpha]_D^{25}$ +4.1 (*c* 1.0, $CHCl_3$)}; FTIR (neat film) 2985, 2961, 2935, 2861, 1738, 1456, 1370, 1246, 1218, 1164, 1064, 870 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (q, *J* = 7.0 Hz, 2H, O*CH*$_2$CH$_3$), 4.11-3.99 (m, 2H, 4-H, 5-H), 2.52 (dt, *J* = 16.2, 7.5 Hz, 1H, H-2a), 2.38 (dt, *J* = 16.2, 7.9 Hz, 1H, H-2b), 1.77-1.69 (m, 2H, OH, 3-CH_2), 1.43 (s, 3H, Me), 1.58-1-47 (m, 2H, 6-CH_2), 1.45-1.35 (m, 2H, 6-CH_2), 1.33 (s overlaping with a m, 9H, 7-CH_2, 8-CH_2, 9-CH_2, Me), 1.26 (t, *J* = 7.0 Hz, 3H, OCH$_2$*CH*$_3$), 0.89 (t, *J* = 6.4 Hz, 3H, 10-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4 (C-1), 107.5 (*C*Me$_2$), 77.9 (C-4), 76.9 (C-5), 60.2 (O*CH*$_2$CH$_3$), 31.8, 30,8, 29.3, 28.4, 26.0, 25.8, 25.3, 22.5, 14.1, 13.9; HRMS *m/z* 295.1883 [$C_{15}H_{28}O_4Na$ $(M+Na)^+$ requires 295.1880].

(*S*)-5-((*R*)-1-Hydroxyhexyl)dihydrofuran-2(3*H*)-one (3). A solution of **13** (110 mg, 0.4 mmol) and TsOH·H_2O (5 mg) in MeOH (10 mL) was stirred at room temperature for 3 h. Saturated aqueous $NaHCO_3$ (5 mL) was added, the mixture was extracted with ethyl acetate (2x20 mL) and the organic phase was washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on a silica gel column with hexane/EtOAc (3:1) as the eluent to give L-factor **3** (44 mg, 59%) with ^{1}H and ^{13}C NMR identical to those reported in the literature.[11]: $[\alpha]_D^{25}$ +10.8 (*c* 0.5, $CHCl_3$) [lit.[11d] $[\alpha]_D$ +11.0 (*c* 1.37, CCl_4)]; FTIR (neat film) 3445, 2930, 2856, 1765, 1462, 1187, 1024, 927 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.46 (dt, *J* = 7.5, 3.1 Hz, 1H, 4-H), 3.93 (m, 1H, 5-H), 2.78 (br s, 1H, OH), 2.55 (m, 2H, 2-CH_2), 2.28 (m, 1H, 3-Ha), 2.15 (m, 1H, 3-Hb), 1.53 (m, 1H, 6-Ha), 1.42 (m, 3H, 6-Hb, 9-CH_2), 1.33 (br s, 4H, 7-CH_2, 8-CH_2), 0.90 (t, *J* = 6.6 Hz, 3H, 10-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8 (C-1), 83.0 (C-4), 71.2 (C-5), 31.8, 31,6, 28.6, 25.2, 22.4, 21.0, 13.9; HRMS *m/z* 209.1150 [$C_{10}H_{18}O_3Na$ $(M+Na)^+$ requires 209.1148].

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