The Enantioselective Formal Synthesis of (+)-Avenaciolide and (+)-Isoavenaciolide from Tri-*O*-acetyl-D-glucal Using a Ring Contraction Reaction as the Key Step

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We describe a formal synthesis of (+)-avenaciolide and (+)-isoavenaciolide starting from methyl tri-*O*-acetyl-D-glucal. The key steps are a ring-contraction reaction of compound **8** to give the bicyclo **6**, and the oxidation of the diol **9** to give the bis-lactone framework.

Introduction

Carbohydrates are appropriate starting materials and intermediates for the synthesis of enantiomerically pure compounds (chiron approach).[1] With this purpose, the elaboration of efficient reactions allowing the fast functionalization and transformation of the sugar backbone avoiding long protecting-deprotecting sequences is an important goal. Recently we showed that 3-*O*-triflyl-pyranosyl derivatives could be converted into branched furanosides in high yields through a ring contraction reaction;[2] these furanosides were found to be appropriate intermediates for the synthesis of branched and bicyclonucleosides.[3]

Avenaciolide [(−)-**1**],[4] isoavenaciolide [(−)-**2**],[5] and ethisolide [(−)-**3**][5] (Figure 1) are secondary metabolites, isolated from *Aspergillus* and *Penicillium* fermentation broths, which inhibit fungal growth.

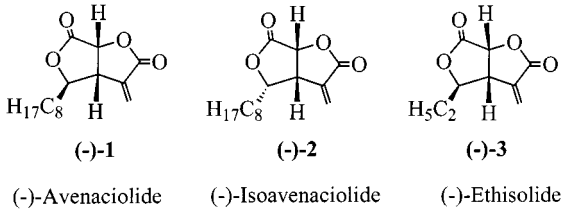


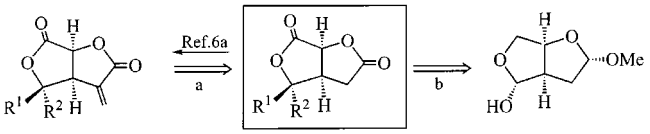
Figure 1. Metabolites isolated from *Aspergillus* and *Penicillium* fermentation broths

Strategies for the synthesis of avenaciolide[6] reported so far include Nielsen or Fittig condensations,[6a] carbohydrate modifications,[6b−6d] nucleophilic addition to butenolides,[6e−6h] furan [4+2] cycloadditions,[6i,6j] furan−aldehyde [2+2] cycloaddition,[6k] glycolate Claisen rearrangement,[6l,6m] epoxy alcohol rearrangements,[6n] radical cyclizations,[6d,6q,6r] carbonyl ene reactions,[6o] trisilanyl ether cyclizations,[6p] selective enolate hydroxylations,[6t] and intramolecular alkoxycarbonylation of tungsten-π-allyl complexes.[6v]

In this report we show that the furanoside **6**, obtained through a ring contraction reaction from the pyranosyl triflate **8**, is a useful intermediate for synthesizing (+)-avenaciolide, the enantiomer of the natural product, which has a unique bis-lactone skeleton, and other related products.

Results and Discussion

Considering that the last step in most syntheses introduces the exocyclic double bond (Scheme 1, a), which is generally made by Johnson's method,[6a] our targets are compounds **4** and **5**. We thought that the bis-lactones could be synthesized from product **6**.[2] In fact, the structure of **6** resembles the basic skeleton of avenaciolide, although the configuration of the bridging carbons is reversed. On the other hand, this product contains two masked carbonyl-groups: the hemiacetal group enables the chain to be introduced by reaction with an organometallic reagent (Scheme 1, b).



(+)-1 R^1 = H, R^2 = n-C_8H_{17} **(+)-4** R^1 = H, R^2 = n-C_8H_{17} **6**

(+)-2 R^1 = n-C_8H_{17}, R^2 = H **(+)-5** R^1 = n-C_8H_{17}, R^2 = H

Scheme 1. Retrosynthesis of avenaciolide

Thus, tri-*O*-acetyl-D-glucal was converted into the 2-deoxy-glucose derivative **7** in accordance with reported procedures.[7] The reaction of **7** with triflic anhydride provides **8**[2] which was immediately heated to reflux in the presence of pyridine and water with hexafluoro-2-propanol as the solvent to afford compound **6** in excellent yield through a ring contraction reaction.[2]

In order to introduce the aliphatic chain, we first tried adding Grignard or organolithium reagents to hemiacetal carbonyl groups. This led to *anti* or *syn* compounds depending on the organometallic reagent used. We found that the inverse addition (compound **6** to recently synthesized

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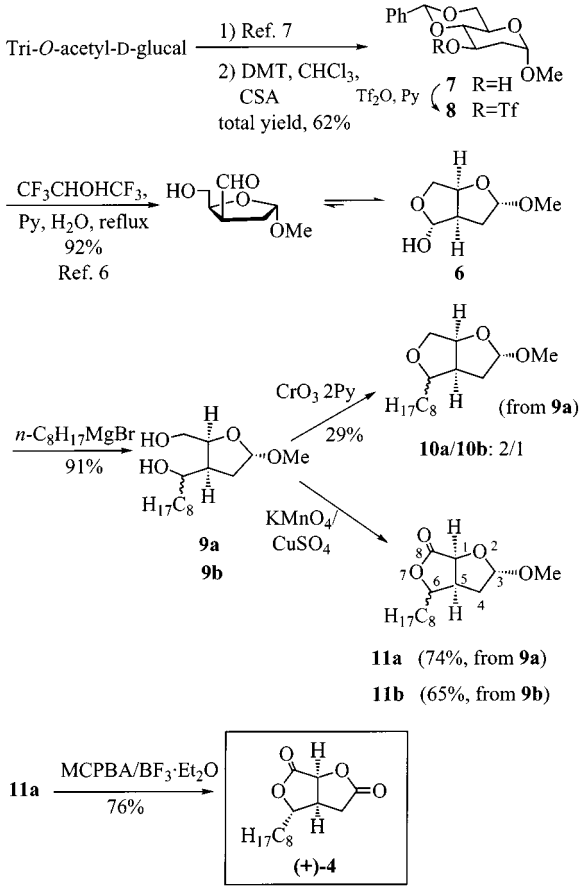
Grignard reagent) prevented salts from forming and favoured the hemiacetal reaction. The results were best when benzene was the solvent and diethyl ether was the coordinating ligand. The expected diol **9** was obtained in a 91% yield with a **9a/9b** ratio of 3:1 (Scheme 2).



Scheme 2. Synthesis of (+)-avenaciolide from tri-*O*-acetyl-D-glucal

Next, we considered the possibility of converting diol **9** into the bis-butyrolactone in one synthetic step, by simultaneously oxidizing the diol and the methyl acetal. The Jones reagent, because of its acid nature, seemed suitable for this objective since the methyl acetal hydrolysis can take place simultaneously. However, when compound **9** was treated with the Jones reagent at 25 °C the result was a complex mixture of compounds and we were unable to isolate any product. We therefore decided to oxidize the diol first. When **9a** was oxidized with PCC[8] (4 equiv.) or PDC (4 equiv.) the product was the result of the oxidative degradation of the C_8-chain. Mashood Ali et al.[9] showed that such an oxidation was favoured if there were higher amounts of oxidant. However, when the amount of oxidant (PCC or PDC) was reduced (1.8 equiv.) or other oxidant reagents used (e.g. CrO_3·2Py[10] or PDC-*t*BuOOH[11]) an inseparable mixture of tetrahydrofurans **10a** and **10b** (2:1 ratio) was mainly obtained (29%), together with a small amount of the desired lactone **11a** (4%). When QCC (quinolinium chlorochromate)[12] was used TLC monitoring showed the formation of different products, but in the IR spectrum no carbonyl band was detected.

The ^{1}H NMR spectrum of bicyclic **10a** showed two signals at δ = 4.12 and 3.86 with a geminal coupling of 10.2 Hz which were assigned to the H-8 and H-8′ protons, respectively. This means that position 8 had not been oxidized. Likewise, in the IR spectrum of the mixture no carbonyl or hydroxyl band appeared. The formation of **10a** can be explained by the protonation of a secondary alcohol and subsequent intramolecular attack of the primary hydroxyl on the generated carbocation, to give the tetrahydrofuran ring.

The reaction of **9a** and **9b** in the conditions reported by Jefford[13] gave a mixture of two compounds. In the case of **9a**, this mixture consisted of lactone **11a** in 74% yield and tetrahydrofuran derivative **10a** in 3% yield, whereas for **9b** it consisted of lactone **11b** in 65% yield and tetrahydrofuran derivative **10b** in 3% yield (Scheme 2).

The formation of lactone **11** involves the following sequence of events: oxidation of the primary hydroxyl group to the aldehyde, hemiacetal formation and oxidation to the lactone; or, oxidation to the acid and subsequent lactone formation. The lower yield of **11b** may be due to steric restrictions in the *endo* configuration.

The presence of the lactone group in **11** was inferred from: (i) the appearance of a typical butyrolactone carbonyl signal at 1788 cm^{-1} in the IR spectrum, (ii) the appearance of signals from the carbonyl group at δ = 174 in the ^{13}C NMR spectrum and signals from the acetal group at δ = 107 (C-3) and δ = 55 (OMe). The configuration of the chain was assigned by NOE and NOESY experiments. In **11a** a NOE effect was observed between H-4a and H-6, while in lactone **11b** it was observed between H-1 and H-5, and H-6 (Figure 2).

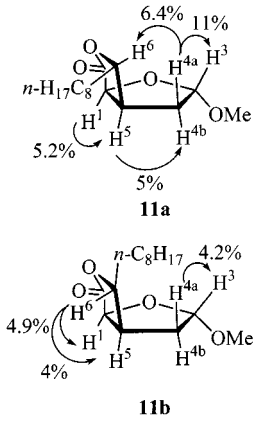
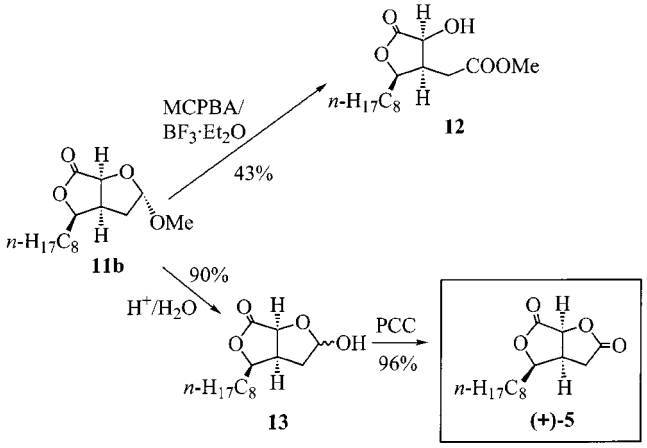


Figure 2. Results of the NOE experiments of compounds **11a** and **11b**

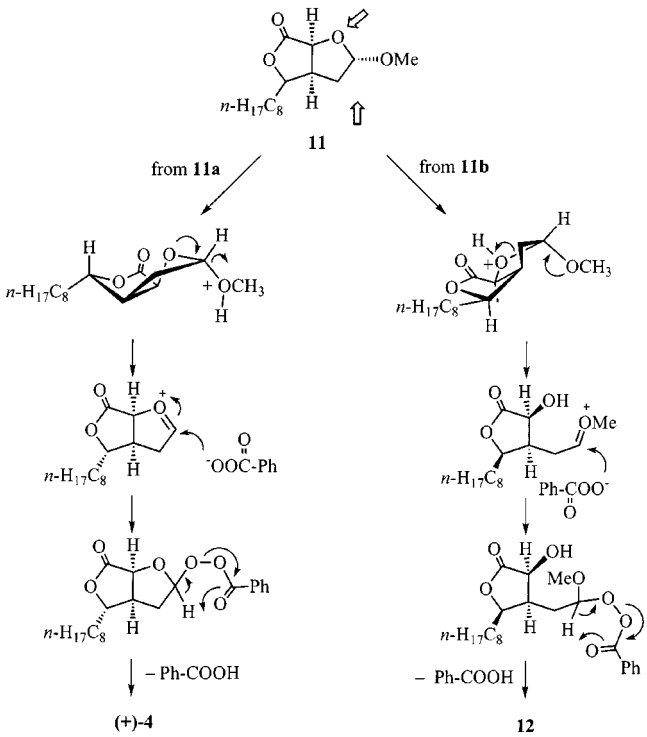
The last step oxidizes the acetal group in **11a**. Initially we tested two acidic oxidants, *m*-chloroperbenzoic acid (MCPBA) and the Jones reagent. The oxidation of lactone **11a** with the Jones reagent led to the bis-lactone compound (+)-**4** in a 48% yield. This yield was improved by using MCPBA and BF_3·Et_2O (Grieco oxidation[14]), and the desired bis-lactone (+)-**4** was obtained in a 76% yield (Scheme 2), thus completing the formal synthesis of (+)-Avenaciolide. Nevertheless, when lactone **11b** was oxidized

with MCPBA the bis-lactone objective (+)-**5** was not obtained. Instead, compound **12** was produced because of the opening of the hemiacetal. So, we hydrolyzed the OMe group with sulfuric acid and water in acetone, and obtained compound **13**. Then we oxidized this compound with PCC to obtain the bislactone (+)-**5** with a global yield of 86% (Scheme 3). This completed the formal synthesis of (+)-Isoavenaciolide.



Scheme 3. Synthesis of (+)-isoavenaciolide

The different behaviour of hemiacetals **11a** and **11b** when they react with MCPBA to give compounds (+)-**4** and (+)-**12**, respectively, can be explained by the different activation of exocyclic or endocyclic oxygen, which is determined by the conformational restrictions in each case (Scheme 4).



Scheme 4. Proposed mechanism for oxidation of **11a** and **11b**

Conclusion

In conclusion, we have described here a short formal synthesis of (+)-avenaciolide and (+)-isoavenaciolide starting from tri-*O*-acetyl-D-glucal from a ring contraction reaction of methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-triflyl-α-D-*arabino*-pyranoside **(8)**.

Experimental Section

General Remarks: Melting points were measured on a Büchi 510 apparatus and are uncorrected. Optical rotations were measured at room temperature in 10 cm cells in a Perkin−Elmer 241 polarimeter. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 MHz apparatus (300 and 75.4 MHz, respectively), with $CDCl_3$ as solvent and using Me_4Si ($\delta = 0$) or the central solvent peak at $\delta_C = 77.0$ as internal reference. Infrared spectra were recorded in $CHCl_3$ solutions on an FT-spectrometer. Elemental analyses were determined by our university's Scientific Service using a Carlo−Erba Microanalyser. Flash column chromatography was performed with silica gel 60 A CC (230−400 mesh). Preparative thin layer chromatography was performed on silica gel 60. Solvents were distilled at atmospheric pressure before use. Benzene was dried by distillation from Na ribbon and stored over 4Å molecular sieves and under argon. Dry ether was obtained by distillation, under nitrogen, from sodium benzophenone ketyl. Other solvents were purified and dried by standard procedures. All the reactions were carried out under an argon atmosphere using standard syringe techniques.

Methyl 2,3-Dideoxy-3-*C*-[(1*RS*)-1-hydroxynonyl]-α-D-*threo*-pentofuranoside (9): Octylmagnesium bromide was prepared from *n*-octyl bromide (5.40 mL, 31.0 mmol) and magnesium (0.8 g, 32.8 mmol) in diethyl ether (6 mL) and benzene (50 mL) by maintaining the temperature at 30 °C during the addition of the reagents and then heating at 40 °C for one hour. Compound **6** (870 mg, 5.43 mmol) in 16 mL of anhydrous benzene was then added at room temperature to 43 mL of the Grignard solution under argon. After 2 hours at 40 °C the reaction mixture was cooled to 0 °C and poured into a saturated aqueous NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted several times with diethyl ether. The combined layers were dried ($MgSO_4$) and the solvent evaporated. The crude oil remaining was purified by flash chromatography (ethyl acetate/hexane 1:1) to obtain the diol **9** (1.35 g, 91%) as an epimeric mixture (ratio **9a/9b** = 3:1) which was purified by MPLC (from CH_2Cl_2 to CH_2Cl_2/MeOH 2%).

9a: $R_f = 0.30$ (CH_2Cl_2/methanol = 10:1). − $[\alpha]_D^{25} = +82.45$ (c = 1.10, $CHCl_3$). − ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.91$ (d, $J_{1,2a}$ = 5.1 Hz, 1 H, 1-H), 4.32 (td, $J_{4,3} = J_{4,6} = 7.5$ Hz, $J_{4,6'} = 4.2$ Hz, 1 H, 4-H), 4.10 (bs, 1 H, OH), 3.98 (bs, 1 H, OH), 3.64 (m, 3 H, 6-H, 6′-H, 5-H), 3.27 (s, 3 H, OMe), 2.58 (m, 1 H, H-3), 1.79 (dd, $J_{2b,3} = 7.2$ Hz, $J_{2b,2a} = 12.6$ Hz, 1 H, 2b-H), 1.60 (td, $J_{2a,3}$ = 12.6 Hz, 1 H, 2a-H), 1.21 (m, 14 H, *n*-octyl), 0.82 (t, $J = 6.9$ Hz, 3 H, *n*-octyl). − ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 103.8$ (C-1), 79.8 (C-4), 76.2 (C-6), 61.7 (C-5), 54.5 (OMe), 45.1 (C-3), 36.2 (C-2), 35.3, 31.7, 28.5, 29.4, 29.1, 25.0, 22.5, 13.9 (*n*-octyl). − $C_{15}H_{30}O_4$: C 65.66, H 11.02; found C 65.65, H 11.03.

9b: $R_f = 0.33$ (CH_2Cl_2/methanol = 10:1). − $[\alpha]_D^{25} = +97.30$ (c = 1.08, $CHCl_3$). − m.p. 39−41 °C. − ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.08$ (d, $J_{1,2a}$ = 5.1 Hz, 1 H, 1-H), 4.13 (dt, $J_{4,3}$ = 9.0 Hz,

$J_{4,6} = J_{4,6'} = 2.1$ Hz, 1 H, 4-H), 3.87 (m, 2 H, 6-H, 5-H), 3.76 (dd, $J_{6',6} = 12.6$ Hz, 1 H, 6′-H), 3.68 (bs, 1 H, OH), 3.35 (s, 3 H, OMe), 2.52 (qd, $J_{3,4} = J_{3,5} = J_{3,2a} = 9.0$ Hz, $J_{3,2b} = 1.3$ Hz, 1 H, 3-H), 2.36 (bs, 1 H, OH), 2.14 (ddd, $J_{2a,2b} = 12.9$ Hz, 1 H, 2a-H), 1.82 (dd, 1 H, 2b-H), 1.30 (m, 14 H, *n*-octyl), 0.88 (t, $J = 6.9$ Hz, 3 H, *n*-octyl). − ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 104.4 (C-1), 79.2 (C-4), 68.6 (C-6), 61.5 (C-5), 54.6 (OMe), 43.8 (C-3), 36.5 (C-2), 31.7, 31.7, 29.5, 29.4, 29.1, 26.1, 22.5, 13.9 (*n*-octyl). − $C_{15}H_{30}O_4$ (274): calcd. C 65.66, H 11.02; found C 65.82, H 11.09.

(1*S*,3*S*,5*S*,6*S*)-3-Methoxy-6-octyl-2,7-dioxabicyclo[3.3.0]octan-8-one (11a): An oxidating mixture was prepared by pounding $KMnO_4$ (2 g) and $CuSO_4{\cdot}5H_2O$ (0.2 g) in a mortar. The mixture $KMnO_4/CuSO_4{\cdot}5H_2O$ (1.60 g) was added to a solution of **9a** (200 mg, 0.73 mmol) in CH_2Cl_2 (4 mL). The reaction mixture was stirred for 90 minutes at room temperature protected from light, and then it was filtered through a Celite pad. Evaporation of the solvent gave the crude product mixture which was subjected to flash chromatography (ethyl acetate/hexane 2:5) to obtain **11a** (148 mg, 74%) as a white solid and the tetrahydrofuran derivative **10a** (5 mg, 3%).

11a: $R_f = 0.25$ (hexane/ethyl acetate = 5:2). − $[\alpha]_D^{25} = +79.36$ (c = 1.01, $CHCl_3$). − m.p. 53−54 °C. − IR: 1765 cm^{-1} (ν_{CO}). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.17 (d, $J_{3,4a} = 4.5$ Hz, 1 H, 3-H), 4.73 (d, $J_{1,5} = 8.4$ Hz, 1 H, 1-H), 4.29 (td, $J_{6,n\text{-octyl}} = J_{6,n\text{-octyl}} = 6.6$ Hz, $J_{6,5} = 2.4$ Hz, 1 H, 6-H), 3.36 (s, 3 H, OMe), 3.02 (qd, $J_{5,4a} = J_{5,4b} = 8.4$ Hz, 1 H, 5-H), 2.31 (dd, $J_{4b,4a} = 12.9$ Hz, 1 H, 4b-H), 1.92 (ddd, 1 H, 4a-H), 1.27 (m, 14 H, *n*-octyl), 0.88 (t, J = 6.9 Hz, 3 H, *n*-octyl). − ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 174.4 (CO), 106.9 (C-3), 84.0 (C-6), 77.4 (C-1), 55.0 (OMe), 43.2 (C-5), 38.2 (C-4), 36.3, 31.6, 29.2, 29.0, 28.9, 24.7, 22.5, 13.9 (*n*-octyl). − $C_{15}H_{26}O_4$ (270): C 66.64, H 11.18; found C 66.60, H 11.16.

(1*S*,3*S*,5*S*,6*R*)-3-Methoxy-6-octyl-2,7-dioxabicyclo[3.3.0]octan-8-one (11b): Using the procedure described above, the oxidating mixture (91.4 mg) was added to a solution of compound **9b** (113 mg, 0.27 mmol) in CH2Cl2 (3 mL) and the reaction mixture was stirred for 6 hours. After workup the crude product was subjected to flash chromatography (ethyl acetate/hexane 2:5) to obtain solid **11b** (72 mg, 65%) and tetrahydrofuran derivative **10b** (3 mg, 3%).

11b: $R_f = 0.3$ (hexane/ethyl acetate = 5:2). − $[\alpha]_D^{25} = +83.68$ (c = 1.51, $CHCl_3$). − m.p. 36−37 °C. − IR: 1788 cm^{-1} (ν_{CO}). − ^{1}H NMR (300 MHz, $CDCl_3$)): δ = 5.13 (d, $J_{3,4a} = 4.5$ Hz, 1 H, 3-H), 4.82 (d, $J_{1,5} = 8.1$ Hz, 1 H, 1-H), 4.56 (m, 1 H, 6-H), 3.36 (s, 3 H, OMe), 3.35 (m, 1 H, 5-H), 2.01 (dd, $J_{4b,4a} = 12.9$ Hz, $J_{4b,5} = 8.1$ Hz, 1 H, 4b-H), 1.91 (ddd, 1 H, 4a-H), 1.27 (m, 14 H, n-octyl), 0.88 (t, $J = 6.9$ Hz, 3 H, n-octyl). − ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 174.8 (CO), 106.7 (C-3), 78.6 (C-1), 78.2 (C-6), 55.0 (OMe), 41.7 (C-5), 31.6 (C-4), 31.5, 31.0, 29.2, 29.0, 25.5, 22.5, 13.9 (*n*-octyl). − $C_{15}H_{26}O_4$(270): C 66.64, H 11.18; found C 66.53, H 11.22.

(1*S*,5*S*,6*S*)-6-Octyl-2,7-dioxabicyclo[3.3.0]octan-3,8-dione [(+)-4]: MCPBA (358 mg, 0.64 mmol) and $BF_3{\cdot}Et_2O$ (2 μL, 0.016 mmol) were added to a solution of lactone **11a** (42.0 mg, 0.16 mmol) in CH_2Cl_2 (2 mL), and the resulting solution was stirred for 72 hours. The reaction mixture was washed with a saturated aqueous solution of $NaHCO_3$ and then extracted with ether (3 × 10 mL). The combined ether extracts were washed with brine and dried with $MgSO_4$. Removal of the solvent and flash chromatography (ethyl acetate/hexane 1:2) of the residue afforded 30 mg (76%) the desired bis-lactone (+)-**4** as an oil. The spectroscopic data[6c][6e] of this product were identical to those previously reported.

[(+)-4]: $R_f = 0.35$ (hexane/ethyl acetate = 2:1). − $[\alpha]_D^{25} = +2.70$ (c = 1.21, $CHCl_3$); [data found for enantiomer[6n] $[\alpha]_D^{25} = -3.5$ (c = 1.2, $CHCl_3$)]. − IR: 1785 cm^{-1} (ν_{CO}). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.02 (d, $J_{1,5} = 7.5$ Hz, 1 H, 1-H), 4.35 (dt, J = 7.2, 4.8 Hz, 1 H, 6-H), 3.05 (m, 1 H, 5-H), 2.95 (dd, $J_{4b,4a} = 17.7$ Hz, $J_{4b,5} = 9.3$ Hz, 1 H, 4b-H), 2.56 (d, $J_{4a,5} = 3.8$ Hz, 1 H, 4a-H), 1.74 (m, 2 H, *n*-octyl), 1.27 (m, 12 H, *n*-octyl), 0.88 (t, $J = 6.9$ Hz, 3 H, *n*-octyl). − ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 173.8, 170.0 (2CO), 84.8 (C-1), 77.0 (C-6), 30.1 (C-5), 35.4 (C-4), 32.7, 31.7, 29.6, 29.2, 29.0, 24.8, 22.5, 14.0 (*n*-octyl). − $C_{14}H_{22}O_4$ (254): C 66.10, H 8.70; found C 66.18, H 8.65.

Methyl (2′*R*,3′*S*,4′*S*)-2-[4′-Hydroxy-2′-octyltetrahydrofuran-5′-on-3′-yl] Acetate (12): The lactone **11b** (107 mg, 0.40 mmol) was dissolved in 5 mL of CH_2Cl_2. MCPBA (811 mg, 1.45 mmol) and $BF_3{\cdot}Et_2O$ (5 μL, 0.04 mmol) were added, and the mixture was stirred for 72 hours. The solution was then treated with saturated sodium bicarbonate solution. The solution was extracted with ether (3 × 10 mL) and the combined ether extracts were washed with brine and dried ($MgSO_4$). Removal of the solvent and flash chromatography (ethyl acetate/hexane 1:1) of the residue afforded the lactone **12** (49 mg, 43%) as an oil.

12: $R_f = 0.30$ (hexane/ethyl acetate = 1:1). − $[\alpha]_D^{25} = +24.17$ (c = 0.61, $CHCl_3$). − IR: 3441 cm^{-1} (ν_{OH}), 1776 (ν_{CO}), 1732 (ν_{CO}). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.43 (q, $J_{2',3'} = J_{2',octyl} = 6.2$ Hz, 1 H, 2′-H), 4.23 (t, $J_{4',3'} = J_{4',OH} = 4.8$ Hz, 1 H, 4′-H), 3.84 (s, 3 H, OCH_3), 3.04 (d, $J_{OH,4'} = 4.8$ Hz, 1 H, OH), 2.78−2.62 (m, 2 H, 2-H), 2.61−2.55 (m, 1 H, 3′-H), 1.57 (m, 2 H, *n*-octyl), 1.27 (m, 12 H, *n*-octyl), 0.88 (t, $J = 6.8$ Hz, 3 H, *n*-octyl). − ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 175.9, 173.7 (2CO), 80.9 (2′-C), 70.8 (4′-C), 53.0 (OCH_3), 43.1 (3′-C), 35.4 (2′-C), 31.7, 31.4, 29.3, 29.1, 29.1, 25.0, 22.5, 14.0 (*n*-octyl). − $C_{15}H_{26}O_5$ (286): C 62.91, H 9.15; found C 63.11, H 9.12.

(1*S*,3*RS*,5*S*,6*R*)-3-Hydroxy-6-octyl-2,7-dioxabicyclo[3.3.0]octan-8-one (13): The lactone **11b** (99.0 mg, 0.37 mmol) was dissolved in acetone (3 mL). Then it was cooled to 0°C and water (1 mL) and conc. H_2SO_4 (0.5 mL) were added. The mixture was stirred for 72 hours at room temperature. The solution was treated with saturated sodium bicarbonate and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, concentrated and chromatographed on silica gel (hexane/ethyl acetate 1:1) to give 84 mg (90%) of a mixture of OH-*exo* and OH-*endo* isomers in a ratio of 1:1.

13: $R_f = 0.4$ (hexane/ethyl acetate = 1:1). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.63 (d, $J_{3,4} = 3.6$ Hz, 1 H, 3-H), 5.61 (d, $J_{3,4} = 3.6$ Hz, 1 H, 3-H), 4.85 (d, $J_{1,5} = 8.1$ Hz, 1 H, 1-H), 4.77 (d, $J_{1,5} = 8.7$ Hz, 1 H, 1-H), 4.60−4.40 (m, 2 H, 2 × 6-H), 4.40−4.20 (bs, 2 H, 2 × OH), 3.45−3.30 (m, 1 H, 5-H), 3.20−3.10 (m, 1 H, 5-H), 2.20−1.60 (2m, 4 H, 4 × 2-H), 1.73 (m, 4 H, *n*-octyl), 1.20 (m, 24 H, *n*-octyl), 0.81 (t, $J = 6.9$ Hz, 6 H, *n*-octyl). − ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 175.7 (2CO), 100.4, 99.5, 79.8, 78.8, 78.3, 41.5, 40.1, 33.2, 32.7, 32.1, 32.0, 31.7, 31.1, 29.6, 29.2, 29.1, 26.5, 25.7, 25.5, 24.7, 22.5, 13.9.

(1*S*,5*S*,6*R*)-6-Octyl-2,7-dioxabicyclo[3.3.0]octan-3,8-dione [(+)-5]: Pyridinium chlorochromate (283 mg, 1.3 mmol), anhydrous sodium acetate (108 mg, 1.3 mmol), 4Å molecular sieves (previously activated) (329 mg), and anhydrous CH_2Cl_2 (2 mL) were placed in a light-protected flask and stirred under argon for 10 min. A solution of compound **13** (884 mg, 0.33 mmol) in 1 mL of CH_2Cl_2 was added to the suspension obtained, and the stirring was maintained for 1 h at room temperature. The remaining solution was then diluted with diethyl ether (25 mL), filtered through a silica gel pad, and evaporated to dryness, to give compound (+)-**5** (80 mg, 96%) as white crystals.

[(+)-5]: R_f = 0.3 (hexane/ethyl acetate = 5:2). − $[\alpha]_D^{25}$ = +18.25 (c = 1.85, $CHCl_3$). − m.p. 109−111 °C (ref.[6d] 109−111 °C). − IR: 1788 cm^{-1} (ν_{CO}). − ^1H NMR (300 MHz, $CDCl_3$): δ = 5.18 (d, $J_{1,5}$ = 8.1 Hz, 1 H, 3-H), 4.63 (dt, $J_{6,CH2}$ = 8.4, $J_{6,5}$ = $J_{6,CH2}$ = 5.5 Hz, 1 H, 6-H), 3.50 (tdd, $J_{5,4}$ = 9.5, 9.5 Hz, 1 H, 5-H), 2.64 (d, 2 H, 4-H), 1.89−1.25 (m, 14 H, *n*-octyl), 0.89 (t, J = 6.9 Hz, 3 H, *n*-octyl). − ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 174.0, 170.8 (2 × CO), 78.8 (C-6), 77.0 (C-1), 39.3 (C-5), 25.3 (C-4), 31.7, 31.3, 29.6, 29.2, 29.1, 26.7, 22.5, 14.0 (*n*-octyl). − $C_{14}H_{22}O_4$ (254): C 66.10, H 8.70; found C 66.16, H 8.67.

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