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A Protecting-Group-Free Synthesis of Hagen's Gland Lactones

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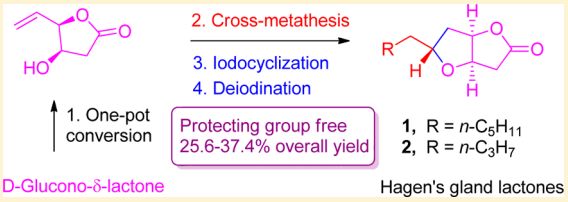
Supporting Information

ABSTRACT: A practical protecting group free synthesis of Hagen's gland lactones **1** and **2** is accomplished in four steps and 25.6 and 37.4% overall yields, respectively. The strategy relies on a one-pot conversion of D-glucono-δ-lactone to β-hydroxy-γ-vinyl-γ-lactone, cross-metathesis, and iodocyclization−deiodinization as key steps.



The morphology and chemical contents of Hagen's glands of the braconid wasps *Diachasmimorpha longicaudata* (Ashmead), *Diachasmimorpha tryoni* (Cameron), and *Diachasmimorpha arisanus* were shown to be taxonomic markers.[1] These glands, located near the abdominal tips of the wasps, contain lactones and are fragrance rich. Williams et al.[1c] suggested the presence of two bicyclic lactones **1** and **2** (Figure 1), which are now known as Hagen's gland lactones. The

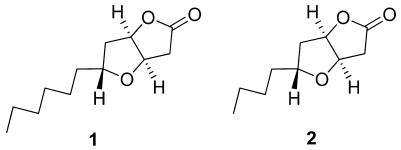
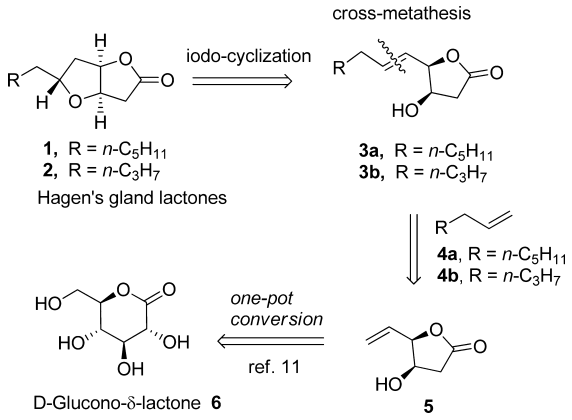


Figure 1. Structures of Hagen's gland lactones.

structures and relative stereochemistry of these lactones was based on NMR studies using Karplus-based calculation of vicinal ^{1}H−^{1}H couplings constants.[1c] The absolute stereochemistry of these lactones was later determined by Kitching and co-workers[1d] through synthesis. Considering the potential of Hagen's gland lactones as biocontrols of the fruit fly population in Hawaii and Queensland and with a hope that they can be assessed for a possible role in integrated pest management strategies, there have been considerable efforts in their synthesis.[1d,2−8]

Utilizing the readily available material, (*R*)-(+)-ricinoleic acid, Kitching and co-workers[1d] achieved the synthesis of two of the diastereomers of Hagen's gland lactones and by employing Sharpless asymmetric epoxidation, two other diastereomers were synthesized. The lactone construction strategy was based on a $PdCl_2$-catalyzed oxycarbonylation−lactonization reaction.[9] With the help of enantioselective gas chromatography, the absolute stereochemistry of **1** and **2** was established.[1d] Mereyala et al.[2] reported two syntheses of **1** and **2**. The first approach started from D-glucose and used a Wittig olefination cyclization strategy.[2a,b] In the second approach from D-mannose, a $PdCl_2$-catalyzed oxycarbonylation−lactonization with an unsaturated 1,3-diol was involved.[2c] Kitching[3] latter reported a detailed version of his earlier work of $PdCl_2$-catalyzed oxycarbonylation−lactonization strategy. A divergent approach to the formal synthesis of **1** and **2** was reported by Yadav and co-workers[4] employing a base-mediated rearrangement of oxepanone epoxide. In other chiron approaches, Banda and Chakravarthy[5] used the bis-acetonide of mannofuranolactone and Sartillo-Piscil and co-workers[6] started from 1,2-*O*-isopropylidene-α-D-xylofuranose derivative. Kapitán and Gracza[7] developed a asymmetric version of the oxycarbonylation−lactonization strategy using chiral bis(oxazoline) ligands. However, both the yield and ee were very poor. A recent synthesis by Gharpure et al.[8] relied on a diastereoselective intramolecular cyclopropanation of vinylogous carbonates, ring-opening of cyclopropanes, and iodolactonization. The literature reports depict lengthy sequences, and many of them employed protection−deprotection strategies resulting in lower overall yields. In our previous work, we have demonstrated a modified version of a one-pot conversion of D-glucono-δ-lactone to the γ-lactone building block **5**[10] (Scheme 1) from which a short

Scheme 1. Retrosynthesis of Hagen's Gland Lactones 1 and 2



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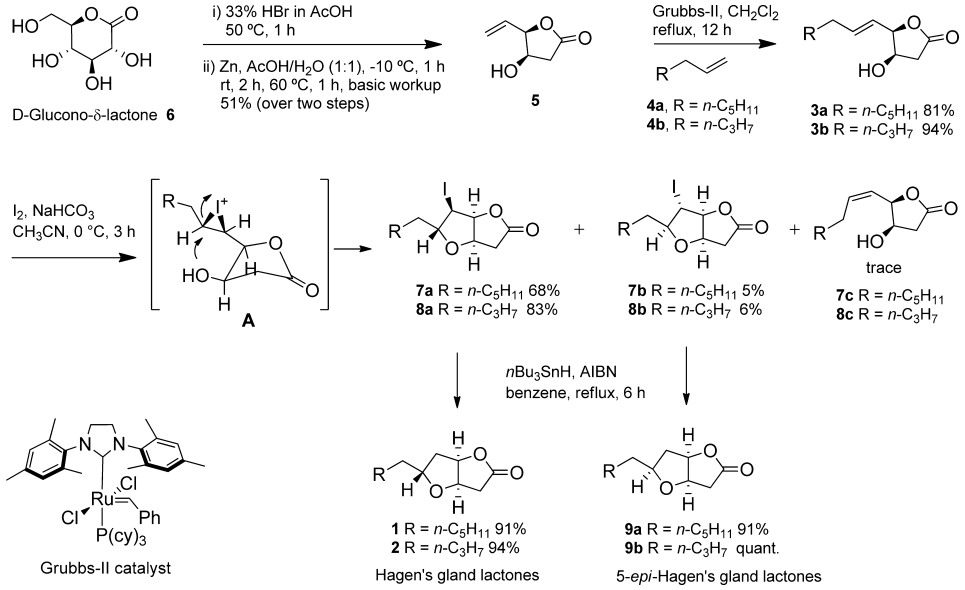
Scheme 2. Synthesis of Hagen's Gland Lactones 1 and 2



protecting group free synthesis of (+)-cardiobutanolide was achieved.[11] In continuation to this work, we visualized a short protecting group free synthesis of Hagen's gland lactones as shown in our retrosynthetic strategy (Scheme 1). Cross-metathesis of lactone **5** with a suitable olefin partner **4** would give **3**. We anticipated a diastereoselective iodocyclization would occur on **3** to give a *trans*-tetrahydrofuran ring. Subsequent deiodination would produce the Hagen's gland lactones **1** or **2**.

The forward synthesis is shown in Scheme 2. The γ-lactone **5** was prepared in 51% yield following our earlier report from D-glucono-δ-lactone in a one-pot conversion.[11] The cross-metathesis[12] reaction of **5** with **4a** went smoothly catalyzed by Grubbs second-generation (Grubbs-II) catalyst providing the lactone **3a** in 81% yield. Similarly, reaction of **5** with **4b** delivered **3b** in excellent yield of 94%. ^{1}H NMR analysis indicated approximately <10% formation of *Z*-olefin isomers. Although these could not be separated at this stage, they remained unreacted in the next reaction and hence were separated. The cycloetherification was accomplished through iodocyclization[13] of **3a** using molecular iodine and $NaHCO_3$ in CH_3CN solvent yielding **7a** and **7b** in a high diastereoselectivity of 14:1[14] through a plausible iodonium ion intermediate **A**. The bicyclic compounds were efficiently separated by flash column chromatography providing **7a** and **7b** in 68 and 5% yields, respectively.[15] Here, a trace amount of unreacted *Z*-olefin isomer **7c** from previous cross-metathesis reaction was also obtained. This could easily be characterized by comparing its NMR data with the *E*-isomer **3a**. Similarly, the iodocyclization of **3b** delivered **8a** and **8b** in a 14:1 ratio.[14] These were efficiently separated by flash column chromatography to give **8a** and **8b** in 83 and 6% yields, respectively.[15] Similar to the prior reaction, a trace amount of unreacted *Z*-isomer **8c** was isolated. Reductive radical-mediated removal of iodine from **7a** and **8a** using *n*-Bu_3SnH and AIBN in refluxing benzene provided the Hagen's gland lactones **1** and **2** in 91 and 94% yields, respectively. The bicyclic lactones were fully characterized by spectroscopic and analytical data which matched well with that reported.[3,8] Similarly, **7b** and **8b** on reductive removal of iodine furnished 5-*epi*-Hagen's gland lactones **9a** and **9b** in 91% and quantitative yields, respectively. The spectroscopic and analytical data of **9a** and **9b** matched well with that reported in literature.[3]

In conclusion, we have demonstrated a highly efficient and practical synthesis of Hagen's gland lactones **1** and **2** from cheaply available chiral pool material, D-glucono-δ-lactone, in four steps and 25.6 and 37.4% overall yields, respectively, without involvement of protecting groups.[16] The short synthesis capitalizes on a one-pot conversion of D-glucono-δ-lactone into the β-hydoxy-γ-lactone **5**, cross-metathesis, and iodocyclization−deiodinization as key steps. The synthesis can be completed in less than 4 days.

EXPERIMENTAL SECTION

General Information. Flasks were oven- or flame-dried and cooled in a desiccator. Dry reactions were carried out under an atmosphere of Ar or N_2. Solvents and reagents were purified by standard methods. Thin-layer chromatography was performed on EM 250 Kieselgel 60 F254 silica gel plates. The spots were visualized by staining with $KMnO_4$ or by UV lamp. ^{1}H NMR and ^{13}C NMR were recorded at 400 and 100 MHz, respectively, and chemical shifts are based on TMS peak at δ = 0.00 pm for proton NMR and $CDCl_3$ peak at δ = 77.00 ppm (t) in carbon NMR. IR samples were prepared by evaporation from $CHCl_3$ on CsBr plates. High-resolution mass spectra were obtained using positive electrospray ionization by TOF method.

(4*R*,5*R*)-4-Hydroxy-5-vinyldihydrofuran-2(3*H*)-one (5).[11] To D-glucono-δ-lactone **6** (4.0 g, 22.45 mmol) was added 33% hydrogen bromide in acetic acid (HBA, 16 mL) and the reaction mixture stirred at 50 °C for 1 h. It was then cooled to room temperature, and excess HBA was removed under reduced pressure. The resultant syrupy liquid was dissolved in 50% aqueous acetic acid (40 mL) and then cooled to −10 °C, and zinc powder (8.07 g, 123.49 mmol, 5.5 equiv) was added in portions over 1 h at −10 °C. The mixture was stirred and warmed to room temperature over 2 h and then heated at 60 °C for an additional 1 h. It was then filtered and the filtrate concentrated under reduced pressure. The residue was dissolved in water (30 mL) and cooled to 0 °C and the pH adjusted to 10 by slow addition of KOH pellets to precipitate the remaining zinc as the insoluble hydroxide and to affect C-3 deacetylation. After filtration, the basic filtrate was acidified to pH 5 using concentrated hydrochloric acid at 0 °C. Water was removed under reduced pressure and the residue dissolved in cold ethanol. Precipitated potassium chloride was removed by filtration and the filtrate concentrated. The residue was purified by silica gel column

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chromatography using petroleum ether/EtOAc (1:1) as eluent to give **5** (1.46 g, 51%): $[\alpha]^{25}_{D}$ = +45.3 (*c* = 0.8, $CHCl_3$) [lit.[10a] $[\alpha]_D$ = +43 (*c* = 1.15, $CHCl_3$)]; IR ($CHCl_3$) ν_{max} 3447, 2934, 1771, 1639, 1432, 1413, 1333, 1309, 1203, 1158, 1080, 1017, 990, 962, 901, 884, 833, 796 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 6.01−5.92 (m, 1H), 5.59−5.49 (m, 2H), 4.94−4.91 (m, 1H), 4.56−4.53 (m, 1H), 2.80 (dd, *J* = 17.7, 5.4 Hz, 1H), 2.63 (dd, *J* = 17.7, 1.3 Hz, 1H), 2.27 (brs, 1H, *OH*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 130.2, 120.6, 84.9, 69.4, 38.6; HRMS *m*/*z* calcd for $[C_6H_8O_3 + H]^+$ 129.0552, found 129.0551.

(4*R*,5*R*)-4-Hydroxy-5-[(*E*)-oct-1-enyl]dihydrofuran-2(3*H*)-one (3a). To a stirred and degassed solution of **5** (170 mg, 1.33 mmol) and 1-octene **4a** (740 mg, 6.63 mmol, 5.0 equiv) in dry CH_2Cl_2 (15 mL) was added Grubbs second-generation catalyst (23 mg, 0.027 mmol, 2.0 mol %) at room temperature and the mixture refluxed for 12 h. The mixture was cooled and filtered through a small pad of silica gel and the filtrate concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (3:2) to give **3a** (228 mg, 81%) as a colorless oil: $[\alpha]^{25}_{D}$ = +29.2 (*c* = 0.9, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3431, 2930, 2857, 1774, 1665, 1325, 1163, 1076, 1012, 968 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 6.03−5.96 (m, 1H), 5.58 (dd, *J* = 15.6, 6.8 Hz, 1H), 4.88 (dd, *J* = 6.6, 3.7 Hz, 1H), 4.48−4.47 (m, 1H), 2.77 (dd, *J* = 17.6, 5.3 Hz, 1H), 2.62 (dd, *J* = 17.6, 0.9 Hz, 1H), 2.17−2.11 (m, 2H), 2.02 (brd, *J* = 2.7 Hz, 1H, *OH*), 1.44−1.26 (m, 8H), 0.88 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 138.9, 121.3, 85.0, 69.7, 38.7, 32.4, 31.6, 28.8, 28.6, 22.5, 14.0; HRMS *m*/*z* calcd for $[C_{12}H_{20}O_3 + H]^+$ 213.1491, found 213.1491.

(4*R*,5*R*)-4-Hydroxy-5-[(*E*)-hex-1-enyl]dihydrofuran-2(3*H*)-one (3b). The title compound was prepared from **5** (100 mg, 0.78 mmol) and 1-hexene **4b** (330 mg, 3.90 mmol, 5.0 equiv) by a procedure similar to that described for the preparation of **3a** to give **3b** (135 mg, 94%) as a colorless oil: $[\alpha]^{25}_{D}$ = +32.2 (*c* = 0.8, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3444, 2958, 2930, 2873, 1773, 1671, 1467, 1328, 1168, 1076, 1012, 967, 906 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 6.04−5.96 (m, 1H), 5.58 (dd, *J* = 15.6, 6.8 Hz, 1H), 4.88 (dd, *J* = 6.7, 3.7 Hz, 1H), 4.48−4.47 (m, 1H), 2.78 (dd, *J* = 17.6, 5.4 Hz, 1H), 2.62 (dd, *J* = 17.6, 1.2 Hz, 1H), 2.17−2.11 (m, 2H), 1.95 (brs, 1H, *OH*), 1.45−1.31 (m, 4H), 0.91 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 138.8, 121.4, 85.2, 69.6, 38.7, 32.0, 30.7, 22.1, 13.8; HRMS *m*/*z* calcd for $[C_{10}H_{16}O_3 + Na]^+$ 207.0997, found 207.1006.

(3a*R*,5*R*,6*R*,6a*S*)-5-Hexyl-6-iodotetrahydrofuro[3,2-*b*]furan-2(5*H*)-one (7a), (3a*R*,5*S*,6*S*,6a*S*)-5-Hexyl-6-iodotetrahydrofuro-[3,2-*b*]furan-2(5*H*)-one (7b), and (4*R*,5*R*)-4-Hydroxy-5-[(*Z*)-oct-1-enyl]dihydrofuran-2(3*H*)-one (7c). To a solution of **3a** (100 mg, 0.47 mmol) in MeCN (3 mL) were added sequentially $NaHCO_3$ (120 mg, 1.41 mmol, 3.0 equiv) and iodine (358 mg, 1.41 mmol, 3.0 equiv) at 0 °C and the mixture stirred for 3 h. The reaction was quenched with aqueous $Na_2S_2O_3$, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4:1) to give **7b** (8.0 mg, 5%) as a colorless solid. Further elution with petroleum ether/EtOAc (7:3) gave **7a** (108 mg, 68%) as a colorless solid and then **7c** (8 mg) as a colorless oil.

Data for ***7a:*** mp 69−71 °C; $[\alpha]^{25}_{D}$ = +129.8 (*c* = 0.4, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2951, 2929, 2858, 1795, 1778, 1619, 1523, 1459, 1389, 1268, 1183, 1156, 1067, 1032, 908, 849, 759, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 5.00 (t, *J* = 4.5 Hz, 1H), 4.91−4.87 (m, 1H), 3.98−3.93 (m, 1H), 3.72 (dd, *J* = 10.5, 4.3 Hz, 1H), 2.85−2.83 (m, 2H), 1.95−1.88 (m, 1H), 1.47−1.25 (m, 9H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 84.3, 83.1, 75.8, 37.2, 31.6, 31.1, 29.1, 25.6, 24.0, 22.5, 14.0; HRMS *m*/*z* calcd for $[C_{12}H_{19}O_3I + H]^+$ 339.0457, found 339.0462.

Data for ***7b:*** mp 63−65 °C; $[\alpha]^{25}_{D}$ = +78.2 (*c* = 0.25, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2930, 2856, 1791, 1775, 1618, 1523, 1459, 1162, 1060, 1034, 910, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 5.18 (dd, *J* = 4.5, 2.1 Hz, 1H), 4.76 (dd, *J* = 7.6, 3.3 Hz, 1H), 4.17 (td, *J* = 7.8, 4.1 Hz, 1H), 3.89 (dd, *J* = 7.4, 2.1 Hz, 1H), 2.76 (d, *J* = 3.3 Hz, 2H), 1.78−1.70 (m, 1H), 1.58−1.25 (m, 9H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 92.5, 89.9, 77.2, 35.9, 32.9, 31.6, 29.0, 25.9, 25.5, 22.5, 14.0; HRMS *m*/*z* calcd for $[C_{12}H_{19}O_3I + H]^+$ 339.0457, found 339.0465.

Data for ***7c:*** $[\alpha]^{25}_{D}$ = +8.8 (*c* = 0.75, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3446, 2962, 2929, 2857, 1771, 1657, 1465, 1331, 1163, 1072, 1017, 970, 904, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 5.92−5.85 (m, 1H), 5.58 (ddt, *J* = 10.9, 8.2, 1.6 Hz, 1H), 5.21 (ddd, *J* = 6.0, 3.8, 1.3 Hz, 1H), 4.49−4.48 (m, 1H), 2.80 (dd, *J* = 17.7, 5.5 Hz, 1H), 2.63 (dd, *J* = 17.7, 1.1 Hz, 1H), 2.18−2.05 (m, 2H), 1.92 (brs, 1H, *OH*), 1.42−1.25 (m, 8H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 138.1, 121.6, 80.6, 69.9, 38.5, 31.6, 29.3, 28.9, 28.4, 22.5, 14.0; HRMS *m*/*z* calcd for $[C_{12}H_{20}O_3 + H]^+$ 213.1491, found 213.1495.

(3a*R*,5*R*,6*R*,6a*S*)-5-Butyl-6-iodotetrahydrofuro[3,2-*b*]furan-2(5*H*)-one (8a), (3a*R*,5*S*,6*S*,6a*S*)-5-Butyl-6-iodotetrahydrofuro-[3,2-*b*]furan-2(5*H*)-one (8b), and (4*R*,5*R*)-5-[(*Z*)-Hex-1-enyl]-4-hydroxydihydrofuran-2(3*H*)-one (8c). The title compounds were obtained from **3b** (135 mg, 0.73 mmol) by a similar procedure as described for **7a** to give **8a** (188 mg, 83%) and **8b** (14 mg, 6%) as colorless solids and **8c** (10 mg) as a colorless oil.

Data for ***8a:*** mp 89−91 °C; $[\alpha]^{25}_{D}$ = +149.0 (*c* = 0.4, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3021, 2958, 2931, 2860, 1781, 1646, 1466, 1397, 1217, 1189, 1155, 1080, 1058, 1030, 902, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 5.00 (t, *J* = 4.5 Hz, 1H), 4.91−4.88 (m, 1H), 3.96 (td, *J* = 13.2, 2.6 Hz, 1H), 3.72 (dd, *J* = 10.5, 4.3 Hz, 1H), 2.86−2.84 (m, 2H), 1.95−1.89 (m, 1H), 1.48−1.34 (m, 5H), 0.92 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 84.3, 83.1, 75.8, 37.2, 30.8, 27.8, 24.0, 22.5, 13.9; HRMS *m*/*z* calcd for $[C_{10}H_{15}O_3I + Na]^+$ 332.9964, found 332.9976.

Data for ***8b:*** mp 85−87 °C; $[\alpha]^{25}_{D}$ = +37.1 (*c* = 0.5, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3021, 2930, 2858, 1790, 1646, 1466, 1403, 1217, 1160, 1058, 995, 858, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 5.18 (dd, *J* = 4.5, 2.1 Hz, 1H), 4.76 (dd, *J* = 7.6, 3.3 Hz, 1H), 4.18 (td, *J* = 7.8, 4.1 Hz, 1H), 3.90 (dd, *J* = 7.4, 2.1 Hz, 1H), 2.77 (d, *J* = 3.3 Hz, 2H), 1.78−1.71 (m, 1H), 1.61−1.29 (m, 5H), 0.91 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 92.5, 89.8, 77.1, 35.8, 32.6, 28.0, 25.5, 22.4, 13.8; HRMS *m*/*z* calcd for $[C_{10}H_{15}O_3I + Na]^+$ 332.9964, found 332.9975.

Data for ***8c:*** $[\alpha]^{25}_{D}$ = +32.9 (*c* = 0.2, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3444, 3019, 2959, 2930, 2861, 1771, 1647, 1459, 1330, 1216, 1164, 1089, 1016, 970, 907, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 5.91−5.84 (m, 1H), 5.59 (ddt, *J* = 11.2, 8.0, 1.5 Hz, 1H), 5.20 (ddd, *J* = 8.0, 3.8, 1.2 Hz, 1H), 4.51−4.48 (m, 1H), 2.80 (dd, *J* = 17.7, 5.5 Hz, 1H), 2.62 (dd, *J* = 17.7, 1.0 Hz, 1H), 2.20−2.04 (m, 2H), 1.44−1.25 (m, 4H), 0.91 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 138.0, 121.6, 80.6, 69.9, 38.5, 31.4, 28.1, 22.2, 13.8; HRMS *m*/*z* calcd for $[C_{10}H_{16}O_3 + Na]^+$ 207.0997, found 207.1008.

(3a*R*,5*R*,6a*R*)-5-Hexyltetrahydrofuro[3,2-*b*]furan-2(5*H*)-one (1). To a stirred solution of iodolactone **7a** (100 mg, 0.296 mmol) in benzene (20 mL) were added *n*-Bu_3SnH (172 mg, 0.2 mL, 0.592 mmol, 2.0 equiv) and AIBN (20 mg, 0.12 mmol, 0.4 equiv). The reaction was refluxed for 6 h and then cooled to room temperature, and volatiles were evaporated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4:1) to give **1** (57.1 mg, 91%) as a colorless oil: $[\alpha]^{25}_{D}$ = +47.8 (*c* = 0.9, $CHCl_3$) [lit.[6] $[\alpha]_D$ = +50.6 (*c* = 1.0, $CHCl_3$)]; IR ($CHCl_3$) ν_{max} 3020, 2930, 2858, 1780, 1465, 1343, 1174, 1070, 908 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ = 5.11 (t, *J* = 4.7 Hz, 1H), 4.82 (t, *J* = 5.3 Hz, 1H), 4.10−4.03 (m, 1H), 2.76 (dd, *J* = 18.8, 6.5 Hz, 1H), 2.64 (d, *J* = 18.7 Hz, 1H), 2.37 (dd, *J* = 13.8, 4.6 Hz, 1H), 1.70−1.58 (m, 1H), 1.54−1.24 (m, 10H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.0, 84.9, 78.2, 77.3, 38.8, 36.6, 34.6, 31.7, 29.2, 26.0, 22.5, 14.0; HRMS *m*/*z* calcd for $[C_{12}H_{20}O_3 + H]^+$ 213.1491, found 213.1489.

(3a*R*,5*R*,6a*R*)-5-Butyltetrahydrofuro[3,2-*b*]furan-2(5*H*)-one (2). The title compound was prepared from **8a** (150 mg, 0.484 mmol) by a similar procedure as described for **1** to give **2** (83.8 mg, 94%) as a colorless oil: $[\alpha]^{25}_{D}$ = +49.2 (*c* = 1.0, $CHCl_3$) [lit.[6] $[\alpha]_D$ = +50.9 (*c* = 1.0, $CHCl_3$)]; IR ($CHCl_3$) ν_{max} 3020, 2859, 2933, 2861, 1784, 1653, 1467, 1345, 1178, 1065, 911 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 5.13 (t, *J* = 4.7 Hz, 1H), 4.82 (dt, *J* = 6.5, 4.9 Hz, 1H), 4.10−4.04 (m, 1H), 2.76 (dd, *J* = 18.7, 6.5 Hz, 1H), 2.64 (d, *J* = 18.7 Hz,

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1H), 2.38 (dd, J = 13.8, 4.5 Hz, 1H), 1.71−1.60 (m, 2H), 1.56−1.50 (m, 1H), 1.41−1.25 (m, 4H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 84.9, 78.1, 77.3, 38.7, 36.5, 34.3, 28.1, 22.5, 13.9; HRMS m/z calcd for $[C_{10}H_{16}O_3 + H]^+$ 185.1178, found 185.1182.

(3a*R*,5*S*,6a*R*)-5-Hexyltetrahydrofuro[3,2-*b*]furan-2(5*H*)-one (9a).[3] The title compound was prepared from **7b** (7 mg, 0.02 mmol) by a similar procedure as described for **1** to give **9a** (4.0 mg, 91%) as a colorless oil: $[\alpha]^{25}_D$ = +43.4 (c = 0.2, $CHCl_3$) [lit.[3] $[\alpha]_D$ = +45.6]; IR ($CHCl_3$) ν_{max} 3016, 2929, 2857, 1780, 1641, 1464, 1405, 1352, 1196, 1157, 1071, 897 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 5.02 (ddd, J = 6.9, 4.5, 2.3 Hz, 1H), 4.51 (dd, J = 7.1, 3.8 Hz, 1H), 3.97−3.90 (m, 1H), 2.73 (d, J = 3.3 Hz, 2H), 2.42 (ddd, m, J = 14.3, 7.2, 6.7 Hz, 1H), 1.88 (ddd, J = 14.3, 7.9, 2.2 Hz, 1H), 1.66−1.60 (m, 1H), 1.58−1.51 (m, 1H), 1.41−1.28 (m, 8H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 84.7, 80.3, 78.2, 38.3, 36.4, 35.5, 31.7, 29.2, 26.0, 22.6, 14.1; HRMS m/z calcd for $[C_{12}H_{20}O_3 + H]^+$ 213.1491, found 213.1487.

(3a*R*,5*S*,6a*R*)-5-Butyltetrahydrofuro[3,2-*b*]furan-2(5*H*)-one (9b).[3] The title compound was prepared from **8b** (25 mg, 0.08 mmol) by a similar procedure as described for **1** to give **9b** (14.8 mg, quantitative) as a colorless oil: $[\alpha]^{25}_D$ = +57.6 (c = 0.16, $CHCl_3$) [lit.[3] $[\alpha]_D$ = +55.8]; IR ($CHCl_3$) ν_{max} 3019, 2961, 2930, 2860, 1779, 1647, 1464, 1351, 1185, 1158, 1072, 962, 901, 848 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 5.02 (ddd, J = 6.9, 4.5, 2.3 Hz, 1H), 4.51 (dd, J = 7.3, 3.6 Hz, 1H), 3.97−3.92 (m, 1H), 2.73 (d, J = 3.3 Hz, 2H), 2.42 (ddd, J = 14.3, 7.8, 6.6 Hz, 1H), 1.89 (ddd, J = 14.3, 8.0, 2.2 Hz, 1H), 1.69−1.62 (m, 1H), 1.59−1.51 (m, 1H), 1.42−1.24 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 84.7, 80.3, 78.2, 38.2, 36.3, 35.2, 28.2, 22.5, 13.9; HRMS m/z calcd for $[C_{10}H_{16}O_3 + H]^+$ 185.1178, found 185.1185.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) Diastereomeric ratio was determined by ^{1}H NMR.

(15) The stereochemistry of **7a** and **8a** was unambiguously ascertained by their conversion into Hagen's gland lactones **1** and **2**, respectively.

(16) A provisional process patent on this work is filed, application no. 1908/MUM/2012.