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Note

A short and practical synthesis of two Hagen's gland lactones

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ABSTRACT

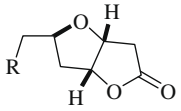
A seven-step total synthesis of Hagen's gland lactones **1** and **2** starting from 1,2-*O*-isopropylidene-α-D-xylofuranose **3** is reported. The success of this short and practical synthesis depends on the use of two key reactions: a stereoselective nucleophilic substitution at the anomeric position of **5** and **6**, which allowed the construction of the γ-lactone ring, and an alkyl substitution reaction on tosylated compound **4**, which permitted the carbon chain elongation of the tetrahydrofuran ring appendage at C-6.

It has been postulated that some species of wasps within the family of Braconidae are biocontrol agents for fruit fly populations in Hawaii and Queensland.[1] These Bracanoid wasps release fragrant volatile compounds that are rich in lactones, and presumably are responsible for the biological role.[2] Among the biologically active compounds isolated and characterized are bicyclic lactones **1** and **2** (Fig. 1).[3] Due to the apparent biological activity of **1** and **2** as possible insect-derived organic molecules, a number of total syntheses have been reported.[4]

As part of an ongoing project on the synthesis of nucleoside analogs,[5] as well as unnatural[6] and natural goniofufurones[7] starting form the chiral pool, we have developed an accessible procedure that allows the stereoselective nucleophilic substitution at the anomeric position of 1,2-*O*-isopropylidene-α-D-furanose derivatives.[5–8] We now present a rapid and practical synthesis of Hagen's lactones featuring the above reaction.

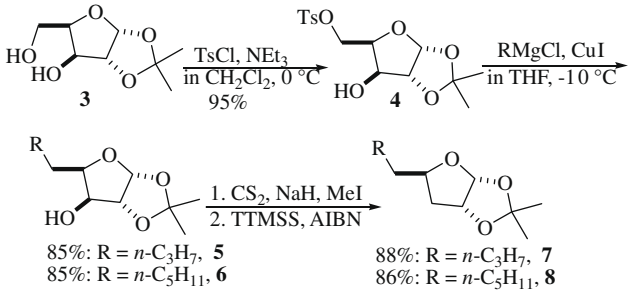
As shown in Scheme 1, the synthesis of Hagen's lactones **1** and **2** begins with the elaboration of deoxygenated compounds **7**[9] and **8** from 1,2-*O*-isopropylidene-α-D-xylofuranose derivative **3**. Thus, selective tosylation of the primary hydroxyl group of **3** with tosyl chloride and triethylamine gave tosylated compound **4**[10] in 95% yield. The tosyl group was substituted by Grignard reagents in the presence of CuI,[11] and the secondary hydroxyl groups of **5**[10] and **6** were removed by the use of the Barton–McCombie deoxygenation method[12] affording **7** and **8**, also in high yields (Scheme 1). It is important to mention that by employing tris(trimethylsilyl)silane (TTMSS),[12,13] instead of the traditional and toxic nBu$_3$SnH, the yields of the Barton–McCombie deoxygenation were improved: from 60–62% to 86–88% yields for **7** and **8**, respectively.

Compounds **7** and **8** were submitted to a C-glycosylation reaction with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$, giving a distereoisomeric mixture of tetrahydrofurans in a ratio of 78:22 and 80:20, respectively, in which the 1,4-trans stereoisomers (**9a** and **10a**) resulted as the major products (Scheme 2).



R = *n*-C_3H_7, **1**
R = *n*-C_5H_{11}, **2**

Figure 1. Hagen's gland lactones.



85%: R = *n*-C_3H_7, **5**
85%: R = *n*-C_5H_{11}, **6**

88%: R = *n*-C_3H_7, **7**
86%: R = *n*-C_5H_{11}, **8**

Scheme 1. Preparation of the deoxygenated compounds **7** and **8**.

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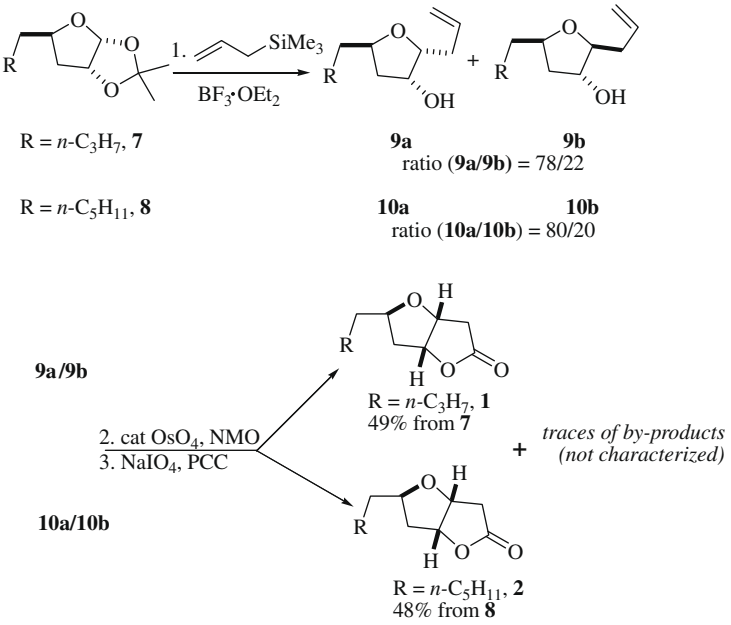
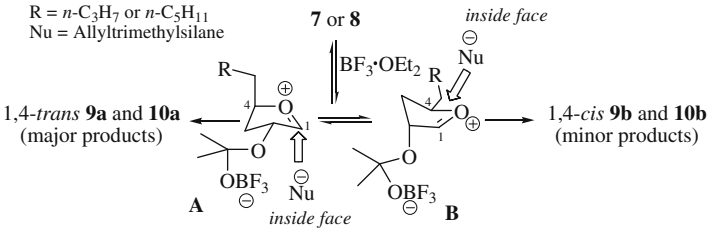


Scheme 2. Completion of Hagen's lactones **1** and **2**.



Scheme 3. Proposed model for the stereoselective nucleophilic substitution at the anomeric position of **7** and **8**.

Initially, we made efforts to separate the major diastereoisomers (**9a** and **10a**) from the reaction mixture by chromatography; however, because only one spot is observed by tlc, the separation turned out to be very difficult. Therefore, we decided to complete the synthesis of Hagen's gland lactones **1** and **2** using the diastereoisomeric mixture of tetrahydrofurans (**9a/9b)** and (**10a/10b**) as starting materials, by applying a sequential dihydroxylation–dehomologation–oxidation procedure (Scheme 2). The minor and undesired 1,4-cis stereoisomers **9b** and **10b** were transformed, in small quantities, to side products that were not isolated and did not interfere with the chromatography purification of the Hagen's gland lactones **1** and **2**, which the NMR and optical data matched those reported in the literature.[3,4]

It is noteworthy to mention that the good stereoselectivity for the nucleophilic substitution of **7** and **8** can be better explained by considering Woerpel's stereoelectronic model,[14] rather than the Reissig steric model.[15] In this regard, five-membered ring oxocarbenium ions **A** and **B** are invoked (Scheme 3). Therefore, in accordance with Woerpel's model, the electronic nature of C-2 alkoxy group contributes to the stereoselectivity, where the oxocarbenium ion **A** prefers to orient the alkoxy group in a pseudoequatorial position,[14c] then approach of the nucleophile occurs on the inside face leading to 1,4-trans-products **9a** and **10a** as the major diastereoisomers. Although Woerpel's group has exhaustively studied the factors that control the high stereoselectively on a number of ribose derivatives, they have not had examined the 3,5-dideoxyfuranoside system.[14] Therefore, the stereoselective *C*-glycosylation of **7** and **8** represents an interesting example where the key role of the electronic nature of C-2 alkoxy group in the preferred inside attack on the five-membered ring oxocarbenium ions is shown.

In summary, we have developed an accessible synthesis of Hagen's lactones **1** and **2** in overall yields of 35% and 33%, respectively, from 1,2-*O*-isopropyliden-α-D-xylofuranose using a stereoselective nucleophilic substitution at anomeric position.

1. Experimental

1.1. General

All reagents were commercially obtained (Aldrich, Fluka) at highest commercial quality and were used without further purification. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 45 °C at about 30 mmHg. All nonaqueous reactions were carried under an argon atmosphere, freshly distilled solvents under anhydrous conditions, unless otherwise noted. THF and benzene were distilled from sodium–benzophenone; CH_2Cl_2 was distilled from calcium hydride. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and ammonium molybdate solution and heat as the developing agent. NMR spectra were recorded on Varian Mercury 400 MHz and calibrated using TMS as an internal reference. Chemical shifts are reported in parts per million (ppm). The following abbreviations were used to explain the multiplicities: s = singlet; d = doublet, t = triplet, q = quartet, m = multiplet,

br = broad. IR spectra were recorded on a Nicolet 380 FT-IR spectrometer and values are reported in cm^{-1} units. Optical rotations were recorded on a Perkin Elmer 341 polarimeter.

1.2. General procedure for Grignard reaction[11]

To a solution of copper iodide (2.0 mmol) in dry THF (10 mL) under N_2 atmosphere at −10 °C was added the corresponding *n*-alkyl magnesium chloride (2.0 mmol). The reaction mixture was stirred for 30 min, and 1,2-*O*-isopropylidene-5-*O*-*p*-toluensulfonyl-α-D-xylofuranose **4**[10] (1.0 mmol dissolved in 5 mL of dry THF) was slowly added. The reaction mixture was allowed to react for 4 h at 0 °C. When the consumption of starting material was complete (monitored by TLC), the reaction mixture was quenched by the addition of ammonium chloride (5 mL of a saturated aqueous solution), and was extracted with diethyl ether (3 × 30 mL). The combined ethereal layers were washed with water (50 mL), dried with Na_2SO_4, filtered, and concentrated. The residue purified by flash silica gel chromatography (hexane–EtOAc 7:1) afforded **5** or **6** in high yields.

1.3. 1,2-*O*-Isopropylidene-5-deoxy-5-*C*-(*n*-propyl)-α-D-xylofuranose (5)[10]

Yield 85% as a crystalline solid; Mp = 72–73 °C; $[\alpha]_D$ −13.5 (*c* 1, $CHCl_3$); lit: −13.6 (*c* 1.0, $CHCl_3$); IR ν_{max} (CH_2Cl_2) 3403, 2917, 2851, 1458, 1372, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.81 (t, 3H, *J* = 6.8 Hz), 1.24 (s, 3H), 1.31 (m, 2H), 1.42 (s, 3H), 1.47–1.67 (m, 4H), 3.97 (b, 1H), 4.04 (td, 1H, *J* = 6.8, 2.4 Hz), 4.40 (d, 1H, *J* = 5.2 Hz), 5.82 (d, 1H, *J* = 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 22.7, 26.1, 26.5, 27.2, 28.1, 75.3, 80.2, 85.2, 104.1, 111.3; EI-MS *m/z* (rel intensity) 201 ($[M+H-CH_3]^+$, 23); FAB-HRMS *m/z* 217.1440 $[M+H]^+$. Calcd for $C_{11}H_{21}O_4$: 217.1442.

1.4. 1,2-*O*-Isopropylidene-5-deoxy-5-C-(*n*-pentyl)-α-D-*xylo*furanose (6)

Yield 86% as crystalline solid; Mp = 75 °C; $[\alpha]_D$ −16.4 (*c* 1, $CHCl_3$); IR ν_{max} (CH_2Cl_2) 3399, 2925, 2851, 1380, 1160, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.81 (t, 3H, *J* = 6.8 Hz), 1.24 (s, 3H), 1.22-1.31 (m, 6H), 1.48–1.56 (m, 4H), 1.52 (m, 2H), 1.63 (m, 2H), 3.97 (d, 1H, *J* = 2.4 Hz), 4.04 (td, 1H, *J* = 6.8, 2.4 Hz), 4.4 (d, 1H, *J* = 4.0 Hz), 5.8 (d, 1H, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 22.5, 25.9, 26.1, 26.5, 27.5, 29.3, 31.6, 75.3, 80.2, 85.1, 104.1, 111.3; EI-MS *m/z* (rel intensity) 229 ($[M+H-CH_3]^+$, 35); FAB-HRMS *m/z* 245.1787 $[M+H]^+$. Calcd for $C_{13}H_{25}O_4$: 245.1753.

1.5. General procedure for Barton–McCombie reduction with silane

A suspension of the corresponding secondary alcohol **5** or **6** (1.0 mmol) and sodium hydride (3.0 mol) in dry THF (40 mL) under argon atmosphere was allowed to react for 30 min at room temperature. Then, CS_2 was added all at once, and the reaction mixture was stirred for 30 min before to add CH_3I (2.0 mol) in a single portion. The reaction mixture was stirred for another 25 min. When the consumption of starting material was complete (monitored by TLC), the reaction mixture was quenched by the addition of glacial acetic acid (0.5 mL). The solution was filtered and the filtrate was concentrated under reduced pressure. A combined mixture of H_2O–EtOAc (50 mL of a 1:1 mixture) was added, and organic phase was extracted with EtOAc (three 30 mL portions), dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purged with argon and dissolved in dry benzene (5 mL), and tris(trimethylsilyl)silane (1.8 mmol) and AIBN (0.1 mmol) were added. The reaction mixture was heated at reflux in an argon atmosphere until TLC analysis indicates the disappearance of starting material (approx 2 h). The benzene was removed on a rotary evaporator to obtain a residue which was filtered and evaporated. The residue purified by flash silica gel chromatography (first hexane then a mixture of hexane–EtOAc 4:1) afforded deoxygenated compounds **7** and **8** in high yields.

1.6. (3a*R*,5*R*,6a*R*)-5-Butyl-dihydro-2,2-dimethyl-5*H*-furo[2,3-*d*][1,3]dioxole (7)

Yield 88% as colorless syrup; $[\alpha]_D$ −12.6 (*c* 1, $CHCl_3$); IR ν_{max} (CH_2Cl_2) 2959, 2925, 2855, 1097, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.83 (t, 3H, *J* = 6.8 Hz) 1.18–1.39 (m, 6H), 1.24 (s, 3H), 1.44 (s, 3H), 1.59 (m, 1H), 2.02 (dd, 1H, *J* = 13.2, 4.0 Hz), 4.09 (m, 1H), 4.64 (t, 1H, *J* = 4.0 Hz), 5.73 (d, 1H, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 22.7, 26.0, 26.5, 28.1, 33.9, 38.9, 77.9, 80.5, 105.2, 110.6; EI-MS *m/z* (rel intensity) 185 ($[M-CH_3]^+$, 6); FAB-HRMS *m/z* 201.2829 $[M+H]^+$. Calcd for $C_{11}H_{21}0_3$: 201.2829.

1.7. (3a*R*,5*R*,6a*R*)-5-Hexyl-dihydro-2,2-dimethyl-5*H*-furo[2,3-*d*][1,3]dioxole (8)

Yield 86% as colorless syrup; $[\alpha]_D$ −15.5 (*c* 1, $CHCl_3$), IR ν_{max} (CH_2Cl_2) 2925, 2855, 1376, 1164, 1070, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, 3H, *J* = 6.8 Hz), 1.28 (m, 7H), 1.31 (s, 3H), 1.42 (m, 3H), 1.51 (s, 3H), 1.65 (m, 1H), 2.09 (dd, 1H, *J* = 13.2, 4.0 Hz), 4.16 (m, 1H), 4.71 (t, 1H, *J* = 4.4 Hz), 5.80 (d, 1H, *J* = 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 22.5, 26.0, 26.1, 26.5, 29.3, 31.7, 34.2, 38.9, 77.9, 80.5, 105.2, 110.6; EI-MS *m/z* (rel intensity) 213 ($[M-CH_3]^+$, 10); FAB-HRMS *m/z* 229.1796 $[M+H]^+$. Calcd for $C_{13}H_{25}0_3$: 229.1804.

1.8. General procedure for the sequential allylation–dihydroxylation–dehomologation–oxidation reaction

To a solution of corresponding deoxygenated compounds **7** or **8** (1.0 mmol) and allyltrimethylsilane (6.0 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise $BF_3{\cdot}OEt_2$ (6.0 mmol) at 0 °C. The resulting solution was vigorously stirred for 4 h and then quenched by the addition of a satd aq $NaHCO_3$ (10 mL). The aqueous layer was extracted three times with CH_2Cl_2 (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give a diastereoisomeric mixture of tetrahydrofurans **9a** and **9b** in a ratio of 78:22, or **10a** and **10b** in a ratio of 80:20. The mixture of tetrahydrofurans (**9a**/**9b** or **10a**/**10b**) was dissolved in a mixture of acetone–H_2O 10:1 (10 mL), and *N*-methylmorpholine oxide (2.0 mmol) and OsO_4 (0.08 mmol) were added. The resulting solution was stirred at room temperature for 6 h, then an aqueous solution of $NaIO_4$ (2 mmol in 2 mL of water) was added dropwise and the resulting suspension was allowed to react at room temperature for 1 h. The solution was filtered to remove solids (washed with EtOAc) and the organic phase was extracted with EtOAc, and dried over Na_2SO_4. Then the solution is evaporated to dryness and redissolved in dry CH_2Cl_2 (10 mL), and PCC (2 mmol) was added. The resulting solution was allowed to react for 5 h at room temperature, and then the reaction was quenched by the addition of water (30 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 40 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue purified by flash chromatography (hexane–EtOAc 4:1) gave the corresponding Hagen's lactones **1** or **2** in good yields.

1.9. Hageńs gland lactones

1.9.1. (3a*R*,5*R*,6a*R*)-5-*n*-Butyl-tetrahydrofuro-[3,2*b*]furan-2(3*H*)-one (1)

Yield 49% as a colorless oil; $[\alpha]_D$ +50.9 (*c* 1, $CHCl_3$); lit:[3,4c] +49.9 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, 3H, *J* = 6.8 Hz),

1.25–1.68 (m, 7H), 2.38 (dd, 1H, J = 14.0, 4.8 Hz), 2.64 (d, 1H, J = 18.8 Hz), 2.77 (dd, 1H, J = 18.4, 6.8 Hz), 4.07 (m, 1H), 4.8 (t, 1H, J = 4.8 Hz), 5.1 (t, 1H, J = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 22.6, 28.1, 34.3, 36.6, 38.7, 77.3, 78.2, 84.9, 176.

1.9.2. (3a*R*,5*R*,6a*R*)-5-*n*-Hexyl-tetrahydrofuro-[3,2*b*]furan-2(3*H*)-one (2)

Yield 48% as colorless oil; $[\alpha]_D$ +50.6 (c 1, $CHCl_3$); lit:[3,4c] +50.01 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, 3H, J = 6.8 Hz), 1.29 (m, 8H), 1.52–1.68 (m, 3H), 2.38 (dd, 1H, J = 14, 4.8 Hz), 2.64 (d, 1H, J = 18.8 Hz), 2.77 (dd, 1H, J = 18.4, 6.8 Hz), 4.07 (m, 1H), 4.8 (t, 1H, J = 4.8 Hz), 5.1 (t, 1H, J = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 22.5, 25.9, 29.2, 31.6, 34.6, 36.6, 38.7, 77.3, 78.2, 84.9, 176.

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