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Chiron approach for the synthesis of (5*RS*)-Hagen's gland lactones from diacetone-D-mannose

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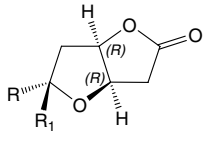
Abstract—A new and convergent synthetic route for (5*RS*)-Hagen's lactones **1**–**4** is described, starting from bisacetonide mannofuranolactone **5**. The key transformations in the synthesis are SmI_2 mediated α-deoxygenation of a aldonolactone to 2-deoxy lactone, Pd(II) mediated oxidative cyclization and an oxidation of tetrahydrofuran to a furanone.

1. Introduction

Williams and co-workers have shown by chemical analysis that the glands of braconid wasps *Diachasmimorpha longicaudata* contain two bicyclic lactones,[1] which were tentatively identified as (3aα,5β,6aα)-5-butyl tetrahydro-[2,2-*b*]fura-2-(3*H*)-one **1** and **3** (Fig. 1) and their corresponding 5-hexyl derivatives **2** and **4**. There has been considerable interest in the syntheses of these natural products and their analogues for studying structure–activity relationship. The absolute stereochemistry of these lactones was established by Kitching et al.[2] based on synthesis by a Pd(II) mediated alkoxycarbonylation. An enantiospecific synthesis of these lactones was reported by Mereyala et al. starting from D-glucose and D-mannose.[3] We report here a new and convergent route to Hagen's gland lactones **1**–**4** utilizing bisacetonide mannofuranolactone as chiral source. The key transformations in the synthesis are (i) SmI_2 mediated α-deoxygenation of a aldonolactone to 2-deoxy lactone, (ii) Pd(II) oxidative cyclization of a hydroxy alkene to lactol, and (iii) oxidation of a tetrahydrofuran to a furanone.



1 R=n-C_4H_9, R_1=H
2 R=n-C_6H_{13}, R_1=H
3 R=H, R_1=n-C_4H_9
4 R=H, R_1=n-C_6H_{13}

Figure 1.

2. Results and discussion

As shown in Scheme 1, the syntheses of Hagen's gland lactones **1**–**4** starts from bisacetonide mannofuranolactone **5**, which was prepared from diacetone-D-mannose.[4] Thus, regioselective hydrolysis of the terminal isopropylidene moiety of **5** with 60% aq HOAc at room temperature for 12 h gave lactone diol **6** in 86% yield. Glycol **6** was subjected to reductive elimination[5] with iodine–PPh_3–imidazole at reflux temperature for 3 h to give olefin **7** in high yield. Facile deoxygenation occurred to give 2-deoxy vinyl lactone **8**, when **7** was treated with SmI_2–ethylene glycol.[6] The lactone was reduced using LAH to give triol **9** in 76% yield. Triol **9** was reacted with 1.0 equiv of Tos-Cl, DMAP in pyridine at rt and the resulting primary tosylate was treated with NaH in THF to give the cyclized furan compound **10** in 79% yield. Hydroxyl olefin **10** was subjected to intramolecular $PdCl_2$ mediated oxidative cyclization[7] (anti-Wacker process) with a catalytic amount of $PdCl_2$, CuCl, and water–MeCN (4:1), while oxygen was bubbled for 8 h at room temperature to give a diastereomeric mixture of lactols **11** in 82% yield.

The furofuran rings with alkyl chains (*n*-butyl and *n*-hexyl) at C-5 were introduced via Grignard reagent addition to

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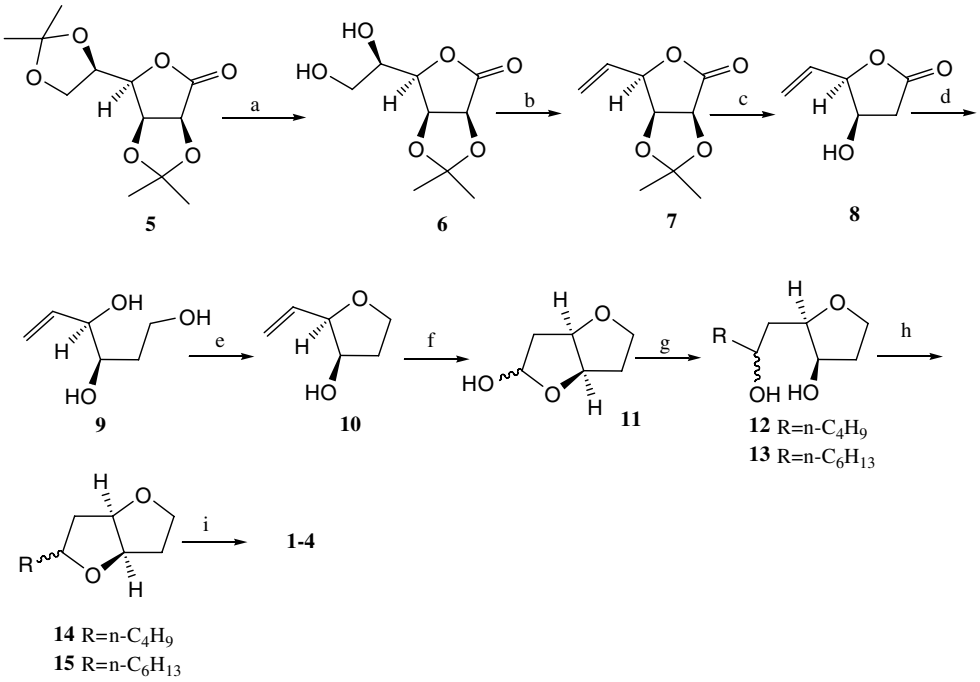

Scheme 1. Reagents and conditions: (a) 60% aq HOAc, rt, 12 h, 86%; (b) I_2, Ph_3P, imidazole, THF, reflux, 3 h, 90%; (c) SmI_2, ethylene glycol, THF, rt, 15 min, 87%; (d) LAH, THF, 0 °C, 2 h, 76%; (e) i. Tos-Cl, py, rt, 4 h; ii. NaH, THF, 0 °C, 2 h, 79%; (f) $PdCl_2$ (cat), CuCl, O_2, MeCN–water (4:1), rt, 8 h, 82%; (g) *n*-BuMgBr/*n*-HexMgBr, THF, THF, −10 °C, 2–3 h, 86–84%; (h) DIAD, TPP, THF, −5 °C, 2 h, 75–77%; (i) $NaBrO_3$, $KHSO_4$, water, 16 h, 52–49%.

lactol **11** followed by Mitsunobu cyclization. Thus, lactol **11** was treated with *n*-butylmagnesium bromide and *n*-hexylmagnesium bromide in THF at 0 °C for 2 h to give a diastereomeric mixture (2:1 ratio) of alcohols **12** and **13**. Treatment of the diastereomeric mixture of **12** and **13** with DIAD, TPP at 0 °C in THF for 6 h gave an inseparable mixture of the corresponding 5*R*/*S* furofurans (2:1 ratio) **14** and **15** in 75–77% yield. Finally, oxidation of CH_2 of the tetrahydrofuran ring[8] of **14** and **15** to lactones with sodium bromate gave the required Hagen's gland lactones **1**–**4**, which were separated by column chromatography. The spectral data for **1**–**4** are consistent with those reported in the literature.[1–3]

3. Conclusion

In conclusion, a new and novel synthetic route based on the chiron approach for Hagen's lactones **1**–**4** has been developed starting from bisacetonide mannofuranolactone. The key transformations in the synthesis are SmI_2 mediated reductive cleavage of isopropylidene moiety, Pd(II) mediated oxidative cyclization and an oxidation of a tetrahydrofuran to furanone.

4. Experimental

The solvents were distilled from the appropriate drying agents before use. Unless stated otherwise, all reactions were carried out under a positive pressure of nitrogen and were monitored by TLC on silica gel. Spots were detected under UV light or by charring with 10% H_2SO_4 in ethanol. The solvents were evaporated under reduced pressure and below 40 °C (bath). Organic solutions of crude products were dried over anhydrous Na_2SO_4. Column chromatography was performed on silica gel 60 (60–120 mesh). The ratio between silica gel and crude product ranged from 50 to 25:1 (w/w). Optical rotations were measured at 25 ± 2 °C. Melting points are uncorrected. ^1H NMR spectra were recorded at 250, 400 MHz, and chemical shifts are referenced to either TMS (0.0, $CDCl_3$). ^{13}C NMR spectra were recorded at 62.5, 100 MHz, and ^{13}C chemical shifts are referenced to $CDCl_3$ (77.00, $CDCl_3$).

4.1. 2,3-*O*-Isopropylidene-D-mannofuranose lactone 6

A solution of **5** (10.0 g, 38.7 mmol) in 60% aq HOAc (100 ml) was stirred at rt for 12 h. The reaction was monitored by TLC and when complete, acetic acid was removed by azeotropic distillation with toluene in vacuo to obtain a syrupy residue, which was filtered on a bed of silica gel (60–120 mesh, hexane–EtOAc, 2:1) to obtain the title compound **6** (7.26 g, 86%) as a syrup. ^1H NMR (400 MHz, $CDCl_3$): δ 1.36, 1.45 (6H, 2s, $2\times CH_3$), 2.15 (1H, br s, OH), 2.75 (1H, br d, OH), 3.75 (1H, dd, $J = 11.0$, 3.8 Hz, H-6), 3.92 (1H, dd, $J = 11.0$, 3.5 Hz, H-6′), 4.01 (1H, m, H-5), 4.44 (1H, dd, $J = 3.5$, 4.1 Hz, H-3), 4.81 (1H, d, $J = 4.1$ Hz, H-2), 4.88 (1H, dd, $J = 3.5$, 3.3 Hz, H-4). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.32, 27.16 ($2\times CH_3$), 63.65 (C-6), 69.80 (C-5), 76.35 (C-3), 76.55 (C-2), 77.33 (C-4), 114.92 (CMe_2), 173.79 (C=O). Anal. Calcd for $C_9H_{14}O_6$: C, 49.54; H, 6.47. Found: C, 49.51; H, 6.42.

4.2. 2,3-*O*-Isopropylidene-5,6-dideoxy-D-mannofuranose lactone 7

To a solution of diol **6** (7.1 g, 32.5 mmol) in THF (100 ml) containing triphenylphosphine (25.54 g, 97.5 mmol) and imidazole (13.26 g, 195 mmol) at 45 °C was added iodine (24.74 g, 97.5 mmol), and the reaction refluxed for 3 h. When TLC indicated completion of the reaction, the THF was removed under vacuum to obtain a thick syrup. It was dissolved in *t*-BME (400 ml), 5% aqueous NaOH solution (250 ml) was added, and the organic layer was separated, washed with water (100 ml), saturated sodium thiosulfate (100 ml) and again water (100 ml). The organic phase was separated, dried (Na_2SO_4), and concentrated to obtain a residue, which was filtered on a bed of silica gel (60–120 mesh, hexane–EtOAc, 5:1) to obtain the title compound **7** (5.4 g, 90%) as a syrup. $[\alpha]_D^{21} = +31.9$ (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40, 1.48 (6H, 2s, $2 \times CH_3$), 4.82–4.87 (2H, m, H-2, 3), 4.94 (1H, dd, $J = 3.8$, 1.5 Hz, H-4), 5.45 (1H, dd, $J = 9.9$, 1.0 Hz, H-6), 5.52 (1H, dd, $J = 16.6$, 1.5 Hz, H-6′), 5.96–6.03 (1H, m, H-5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.23, 27.16 ($2 \times CH_3$), 76.62 (C-3), 78.19 (C-2), 80.52 (C-4), 114.49 (*C*Me$_2$), 121.44 (C-6), 130.58 (C-5), 174.37 (C=O). Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.62; H, 6.51.

4.3. (4*R*,5*R*)-4-Hydroxy-5-vinyl-dihydro-furan-2-one 8

To a solution of **7** (5.3 g, 28.7 mmol) in anhydrous ethylene glycol (20.7 g, 344.3 mmol) and deoxygenated anhydrous THF (20 ml) was added dropwise a solution of 0.1 M SmI_2 in THF (86.1 ml, 86.1 mmol) at rt under an argon atmosphere. After stirring for 15 min, a satd aq $NaHCO_3$ solution was added and then the mixture was extracted with EtOAc. The organic layer was washed with a satd aq $Na_2S_2O_3$ solution, water, and brine before being dried, filtered, and evaporated to obtain a residue, which was purified by chromatography (silica gel 60–120 mesh, hexane–EtOAc, 7:1) to obtain the title compound **8** (3.2 g, 87%) as a colorless oil. $[\alpha]_D^{21} = +21.5$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.59 (1H, dd, $J = 19.0$, 0.7 Hz, H-3), 2.80 (1H, dd, $J = 19.0$, 6.1 Hz, H-3′), 3.01 (1H, br s, OH), 4.54–4.55 (1H, m, H-4), 4.89–4.91 (1H, m, H-5), 5.46–5.55 (2H, m, H-7, 7′, vinyl), 5.93–6.02 (1H, m, H-6, vinyl). ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.10 (C-3), 69.87 (C-4), 85.37 (C-5), 129.09 (C-7, vinyl), 130.73 (C-6, vinyl), 176.54 (C=O). Anal. Calcd for $C_6H_8O_3$: C, 56.24; H, 6.29. Found: C, 56.17; H, 6.23.

4.4. (3*R*,4*R*)-Hex-5-ene-1,3,4-triol 9

To an ice-chilled solution of $LiAlH_4$ (49.2 ml, 1 M in THF, 49.2 mmol) was added a solution of **8** (3.2 g, 24.6 mmol) in THF (50 ml) dropwise, and the reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched by slowly adding water (2.0 ml) and maintaining the temperature at <5 °C. Then 2 M NaOH (10.0 ml) and water (1.0 ml) was added, respectively, and the reaction mixture was warmed to room temperature and stirred for 1 h. The reaction was filtered through a plug of Celite and the filtrate was concentrated to give crude product. The crude product was purified by column chromatography (silica gel 60–120 mesh, hexane–EtOAc, 1:2) to give **9** (2.47 g, 76%) as a thick syrup. $[\alpha]_D^{21} = +9.1$ (*c* 0.5, D_2O); ^{1}H NMR (400 MHz, D_2O): δ 1.51–1.59 (1H, m, H-2), 1.71–1.77 (1H, m, H-2′), 3.55–3.62 (3H, m, H-1, 1′, 3), 3.92–3.96 (1H, m, H-4), 5.21–5.32 (2H, m, H-6, 6′), 5.81–5.90 (1H, m, H-5). ^{13}C NMR (100 MHz, D_2O): δ 34.67 (C-1), 58.90 (C-1), 71.20 (C-3), 76.12 (C-4), 118.10 (C-6), 136.92 (C-5). Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.47; H, 9.08.

4.5. (2*R*,3*R*)-2-Vinyl-tetrahydro-furan-3-ol 10

To a solution of **9** (2.45 g, 18.5 mmol) in pyridine (10 ml) was added *p*-toluenesulfonyl chloride (3.53 g, 18.5 mmol). The resulting solution was stirred at rt for 3 h. The reaction mixture was subsequently partitioned between H_2O (10 ml) and ethyl acetate (50 ml), and the organic layer was washed with water (3×10 ml), dried, filtered, and concentrated. The crude product was dissolved in THF (10 ml), followed by the addition of NaH (0.74 g, 18.5 mmol) at 0 °C and the mixture was allowed to stir for 2 h at rt. The reaction mixture was then neutralized with acetic acid (0.2 ml) and concentrated to an oily residue, which was purified by chromatography (4:1, hexanes–EtOAc) to afford the target compound **10** (1.67 g, 79% over two steps) as a colorless oil. $[\alpha]_D^{21} = +26.1$ (*c* 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 1.9 (1H, br s, OH), 2.02–2.31 (2H, m, H-4, 4′), 3.89–3.94 (1H, m, H-5), 4.11–4.19 (1H, m, H-5′), 4.2–4.5 (2H, m, H-2, 3), 5.42 (1H, dd, $J = 9.9$, 1.0 Hz, CH=CH_2), 5.55 (1H, dd, $J = 16.6$, 1.5 Hz, CH=CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.80 (C-4), 66.59 (C-5), 73.32 (C-3), 84.10 (C-2), 118.63 (CH=*C*H$_2$), 134.10 (*C*H=CH$_2$). Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.05; H, 8.76.

4.6. (2*RS*,3a*R*,6a*R*)-Hexahydrofuro-[3,2-*b*]furan-2-ol 11

To a solution of alkene **10** (1.66 g, 14.5 mmol) in 20% aq acetonitrile (30 ml) were added $PdCl_2$ (0.13 g, 0.7 mmol) and CuCl (1.43 g, 14.5 mmol) in one portion. Air was bubbled through the solution for 8 h at rt. The reaction mixture was then diluted with CH_2Cl_2 (100 ml), and the resulting mixture was filtered through a Celite and rinsed with CH_2Cl_2 (2×50 ml). The organic layers were combined and washed with 1 M aq HCl solution (100 ml) and water (2×100 ml). The organic phase was separated, dried, filtered, and concentrated. Purification of the resulting residue by chromatography (silica gel, 60–120 mesh, 3:1, hexanes–EtOAc) afforded the title compound **11** (1.55 g, 82%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.8–2.4 (2H, m, H-3, 3′, 6, 6′), 3.6–4.8 (4H, m, H-3a, 5, 5′, 6a), 5.42 (0.44H, dd, $J = 8.4$, 5.5 Hz, H-2), 5.59 (0.56H, ddd, $J = 5.4$, 5.3, 3.9 Hz, H-2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.11, 39.33 (C-6), 41.32, 41.80 (C-3), 65.09, 67.6 (C-5), 82.85, 83.60 (C-3a), 85.32, 86.13 (C-6a), 100.21, 100.30 (C-2). Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 55.30; H, 7.68.

4.7. (2*R*,2′*RS*,3*R*)-2-(2′-Hydroxyhexyl)-tetrahydro-3-furan-3-ol 12

To a solution of **11** (0.75 g, 5.8 mmol) in THF (10 ml) was added a solution of *n*-butylmagnesium bromide (11.5 ml,

1 M in THF, 11.5 mmol) at 0 °C and stirred for 2 h at this temperature. The reaction was quenched with aqueous ammonium chloride solution and extracted with ethyl acetate (2 × 50 ml). The combined organic phases were washed with water, dried, filtered, and concentrated to obtain the residue, which was purified by column chromatography (silica gel, 60–120 mesh, 4:1, hexanes–EtOAc) to obtain the title compound **12** (0.93 g, 86%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.8 (3H, m, CH_3), 1.3–1.5 (6H, m, *n*-butyl), 1.7–2.2 (4H, m, H-1′, 4), 3.5–4.6 (7H, m, H-2, 2′, 3, 5 and OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.36, 14.38, 22.97, 25.59, 25.75, 32.16, 32.24, 35.72, 37.56, 38.78 (*n*-C_4H_9, C-1′, 4), 66.18, 66.35 (C-5), 69.75, 70.84 (C-2′), 72.60, 72.86 (C-3), 82.32, 82.40 (C-2). Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.72; H, 10.66.

4.8. (2*R*,2′*RS*,3*R*)-2-(2′-Hydroxyoctyl)-tetrahydro-3-furan-3-ol 13

The title compound **13** was prepared from **11** (0.75 g, 5.8 mmol) as described for compound **12** using *n*-hexylmagnesium bromide. Colorless oil. Yield: 1.05 g, 84%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.8 (3H, m, CH_3), 1.3–1.5 (10H, m, *n*-butyl), 1.7–2.2 (4H, m, H-1′, 4), 3.5–4.6 (7H, m, H-2, 2′, 3, 5 and OH). Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.58; H, 11.16.

4.9. (2*RS*,3a*R*,6a*R*)-2-Butyl-hexahydrofuro-[3,2-*b*]furan 14

To a solution of **12** (0.80 g, 4.3 mmol) and TPP (1.14 g, 4.3 mmol) in anhydrous THF (15 ml) was added DIAD (0.91 g, 4.3 mmol) dropwise at 0 °C. The mixture was allowed to warm to rt and stirred for 6 h. Concentration of the reaction mixture in vacuo followed by chromatographic purification (silica gel, 60–120 mesh, 5:1, hexanes– EtOAc) gave the title compound **14** (0.54 g, 75%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.8 (3H, m, CH_3), 1.3–1.8 (6H, m, *n*-butyl), 1.8–2.4 (4H, m, H-1′, 4), 3.7–4.7 (5H, m, H-2, 3a, 5, 5′, 6a). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.38, 22.96, 26.24, 32.27, 33.98, 35.43, 37.58, 39.25, 40.00, 40.98 (*n*-C_4H_9, C-1′, 4), 68.02, 68.73 (C-5), 79.72, 80.54, 83.57, 84.22, 86.90 (C-2, 3a, 6a). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.49; H, 10.68.

4.10. (2*RS*,3a*R*,6a*R*)-2-Hexyl-hexahydrofuro-[3,2-*b*]furan 15

The title compound **15** was prepared from **13** (0.85 g, 3.9 mmol) as described for compound **14**. Colorless oil. Yield: 0.61 g, 77%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.8 (3H, m, CH_3), 1.3–1.8 (10H, m, *n*-hexyl), 1.8–2.4 (4H, m, H-1′, 4), 3.7–4.7 (5H, m, H-2, 3a, 5, 5′, 6a). Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.65; H, 11.13.

4.11. (3a*R*,5*R*,6a*R*)-5-Butylperhydrofuro-[3,2-*b*]furan-2-one 1 and (3a*R*,5*S*,6a*R*)-5-butylperhydrofuro-[3,2-*b*]furan-2-one 3

To a mixture of compound **14** (0.50 g, 2.9 mmol) and water (10 ml) were added sodium bromate (0.44 g, 2.9 mmol) and potassium hydrogen sulfate (0.44 g, 2.9 mmol). Stirring was continued at room temperature for 16 h. The reaction mixture was quenched with 10% aqueous solution of sodium sulfite (15 ml) and extracted with CH_2Cl_2 (2 × 25 ml), the combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated to obtain the residue which was purified by chromatography (hexane–EtOAc, 6:1) to elute first **1** (0.18 g, 34%) as a colorless oil: $[\alpha]_D^{21} = +52.1$ (*c* 0.5, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.81–1.85 (10H, m, H-6 and *n*-C_4H_9), 2.41 (1H, dd, $J = 14.0$, 3.9 Hz, H-6), 2.66 (1H, dd, $J = 19.1$, 0.7 Hz, H-3), 2.78 (dd, 1H, $J = 19.1$, 6.4 Hz, H-3), 4.07 (m, 1H, H-5), 4.80 (ddd, 1H, $J = 6.2$, 4.4, 0.7 Hz, H-3), 5.11 (dd, 1H, $J = 4.9$, 4.4 Hz, H-6a). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.24; H, 8.78.

Followed by **3** (0.097 g, 18%) as a colorless oil. $[\alpha]_D^{21} = +28.1$ (*c* 0.9, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.82–2.46 (11H, m, H-6, 6′ and *n*-C_4H_9), 2.65 (2H, dd, $J = 18.8$, 4.0 Hz, H-3, 3′), 3.84–3.98 (1H, m, H-5), 4.45 (1H, m, H-3a), 4.95 (dd, 1H, $J = 6.1$, 3.8 Hz, H-6a). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.25; H, 8.79.

4.12. (3a*R*,5*R*,6a*R*)-5-Hexylperhydrofuro-[3,2-*b*]furan-2-one 2 and (3a*R*,5*S*,6a*R*)-5-hexylperhydrofuro-[3,2-*b*]furan-2-one 4

The title compounds **2** (0.176 g, 30%) and **4** (0.111 g, 19%) were prepared from compound **15** (0.55 g, 2.77 mmol) as colorless oils. Spectral data of **2**: $[\alpha]_D^{21} = +50.6$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.8–1.9 (14H, m, H-6 and *n*-C_6H_{13}), 2.38 (1H, dd, $J = 14.2$, 4.2 Hz, H-6′), 2.64 (1H, dd, $J = 18.8$, 0.7 Hz, H-3), 2.75 (1H, dd, $J = 18.8$, 6.4 Hz, H-3), 4.07 (1H, m, H-5), 4.80 (1H, ddd, $J = 6.4$, 4.5, 0.7 Hz, H-3a), 5.11 (1H, dd, $J = 4.9$, 4.5 Hz, H-6a). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.97; H, 9.565. Spectral data of **4**: $[\alpha]_D^{21} = +25.9$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.83–2.5 (15H, m, H-6, 6′ and *n*-C_6H_{13}), 2.65 (2H, 2H, $J = 16.0$, 4.0 Hz, H-3, 3′), 3.84–3.98 (1H, m, H-5), 4.45 (1H, ddd, $J = 4.0$, 5.8, 1.0 Hz, H-3a), 4.95 (1H, dd, $J = 5.8$, 3.8 Hz, H-6a). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.95; H, 9.58.

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