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$Pd(II)Cl_2$ Mediated Oxidative Cyclisation of Hydroxy-Vinylfurans to Lactols: Synthesis of Hagen's Gland Lactones

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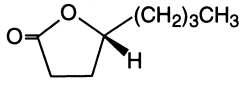
Abstract—A concise synthesis of Hagen's gland lactones **3**–**6** by a chiron approach starting from D-mannose is described. Transformation of D-mannose to dihydroxy-vinylfuran **8** followed by $Pd(II)Cl_2$ mediated oxidative cyclisation to obtain the tetrahydrofurofuran diol **7** constituted the key reaction in the total synthesis of **3**–**6**.

Introduction

Hagen's glands located near the abdominal tips of the Braconid wasps, *Diachasmimorpha longicaudata* (Ashmead), *Diachasmimorpha tryoni* (Cameron) and *fopius* (*Biosteres*) *arisanus* contain fragrant volatile biological control agents that are rich in lactones. There has been considerable interest in the study of their biological role.[1,2] Williams and coworkers have tentatively characterised these lactones as octan-4-olide **1**, dodecan-4-olide **2**, bicyclic lactones (3aα, 5β, 6aα)-5-*n*-butyl tetrahydrofuro-[3,2-b]furan-2(3H)-one **3** and the 5-*n*-hexyl derivative **4** respectively based on NMR considerations.[3] Kitching et al.[4] have established the absolute stereochemistry of **1**–**4** by efficient synthesis and enantioselective gas chromatography. **1** and **2** were synthesized starting from (*S*)-glutamic acid and assigned (*R*)-configuration at C-5; bicyclic lactones 5(*R*) *cis*-**3** and 5(*R*) *cis*-**4** were synthesized by palladium(II) catalysed oxycarbonylation–lactonization reaction with an unsaturated 1,3-diol to obtain by flash chromatography separable diastereomers of **3** and **4**. The relative stereochemistry of *cis* and *trans* **3** and **4** was determined by NOE measurements and MM3 calculations.



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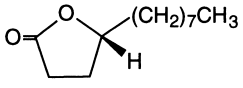

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As part of our long term program in the fabrication of bicyclic lactones as bioactive agents we have recently described the first enantiospecific synthesis of 5(*R*)-Hagen's gland lactones **3** and **4** from D-glucose by Wittig-olefination-cyclisation protocol.[5]

Now we report synthesis of bicyclic lactones **3**–**6** by Pd(II) catalysed oxidative cyclisation of hydroxy-vinylfurans[6] by the method that was earlier developed by us for the construction of tetrahydrofurofurans and demonstrated for the synthesis of goniofufurone analogues[7,8] and (+)-*trans* kumausyne.[9]

Results and Discussion

Herein we report a concise synthesis of Hagen's gland lactones **3**–**6** by the chiron approach starting from D-mannose. From retrosynthetic analysis (Scheme 1) lactones **3**–**6** could be formed from lactol **7** by sequential reactions such as homologation and oxidation. Lactol **7** could be derived from dihydroxy-vinylfuran **8** by means of the $Pd(II)Cl_2$ mediated oxidative cyclisation protocol developed earlier in our laboratory.[6–8] Hydroxy-vinylfuran **8** in turn could be obtained from diacetone-D-mannose[10] (**9**) by well established reactions.

9 Was reacted with carboethoxymethylene triphenylphosphorane in acetonitrile at reflux temperature for 6 h to obtain a diastereomeric mixture of C-glycosides **10** (α/β 1:1 by ^1H NMR)[11,12] which on subsequent reduction with lithium aluminium hydride in dry ether gave alcohol **11** (Scheme 2). Alcohol **11** was protected as benzyl ether **12**. Regioselective hydrolysis of the 5,6-*O*-isopropylidene group of **12** was effected smoothly in 60% aqueous acetic acid over 7 h at room temperature to obtain the diol **13** in 85% yield. **13** Was reacted with I_2, Ph_3P, imidazole (4 mol equiv. each) in THF at reflux temperature for 6 h to

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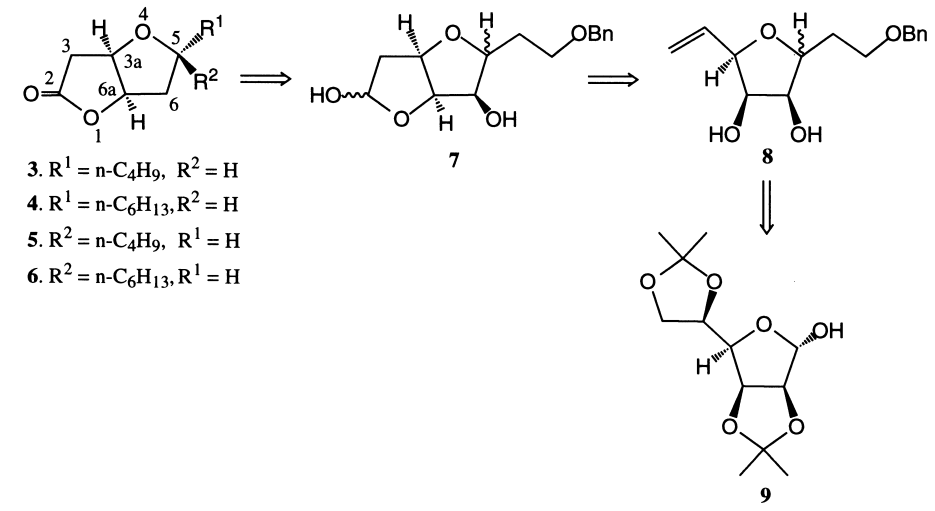
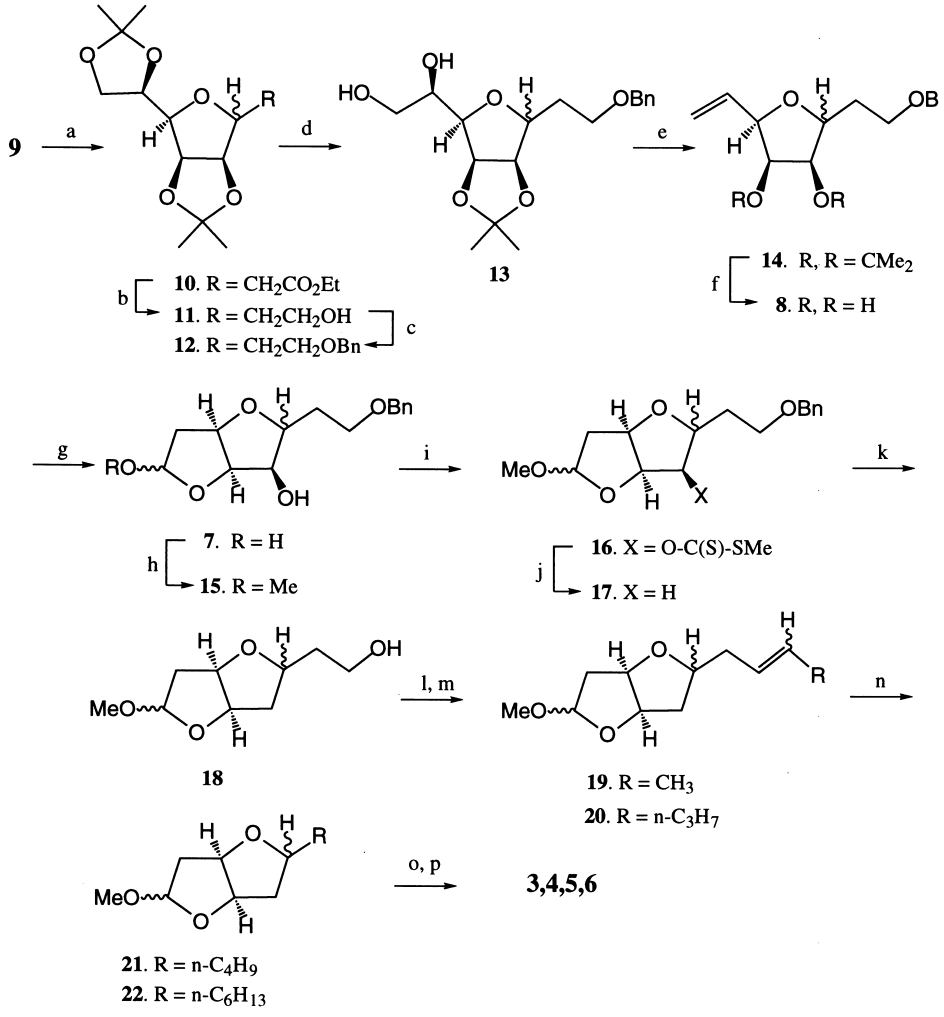


Scheme 1.



Scheme 2. Reagents and conditions: (a) $Ph_3P{=}CHCOOEt$, ACN, reflux, 6 h, 84%; (b) LAH, Ether, reflux, 3 h, 82%; (c) NaH, BnBr, DMF, 0°C→RT, 1 h, 94%; (d) 60% aq. HOAc, RT, 7 h, 85%; (e) I_2, TPP, Imidazole, THF, reflux, 6 h, 86%; (f) 5% aq. H_2SO_4, Dioxane, reflux, 3 h, 81%; (g) $PdCl_2$, CuCl, DMF:H_2O (4:1), O_2, RT, 24 h, 84%; (h) Methanolic HCl, RT, 4 h, 88%; (i) CS_2–NaH–MeI, THF, 0°C→RT, 1 h, 92%; (j) $n$$Bu_3SnH$, AIBN, Toluene, reflux, 6 h, 69%; (k) Li, liq. NH_3, −20°C, 30 min, 73%; (l) Oxalyl chloride, DMSO, TEA, CH_2Cl_2, −78°C, 1 h; (m) $Ph_3P{=}CH{-}CH_3$ and $Ph_3P{=}CHCH_2CH_2CH_3$, THF, 0°C→RT, 2 h, 76%; (n) Raney Ni, H_2, EtOH, 4 h, 98%; (o) Aq. HCl, THF, 50°C, 1 h, 76%; (p) PDC, CH_2Cl_2, reflux, 1 h, 33–38%.

obtain vinylfuran **14** in 86% yield.[13,14] **14** Was characterised from the ^{1}H NMR spectrum by the appearance of vinylic protons at δ 5.2–5.45 (2H, m) and 5.85–6.1 (1H, m). The 2,3-*O*-isopropylidene protecting group of **14** was removed by refluxing for 3 h in dioxane containing 5% of H_2SO_4 to obtain hydroxy-vinylfuran **8**. **8** was subjected to intramolecular Pd(II)Cl_2 mediated oxidative cyclisation[8–10] with a catalytic amount of $PdCl_2$, CuCl, water:DMF (1:4) while oxygen was continuously bubbled for 24 h at room temperature to give a diastereomeric mixture of lactol **7** (1:1 by ^{1}H NMR) as a thick syrup in 84% yield. **7** was characterised from the ^{1}H NMR spectrum by the appearance of H-2 protons at δ 1.79–2.3 (m) and H-1 at δ 5.44–5.78 (m).

Lactol **7** was treated with methanolic hydrochloric acid to obtain the corresponding methylfuranoside **15** as a syrup in 88% yield. **15** was reacted with NaH–CS_2–MeI to obtain xanthate **16** which on further reaction with *n*-Bu_3SnH at reflux temperature in toluene containing a catalytic amount of AIBN gave the deoxy derivative **17** in 69% yield. **17** Was characterised from the appearance of H-3, H-6 protons between δ 1.15–2.4. Debenzylation of **17** was effected in Li, liq. NH_3 at −20°C for 30 min to obtain alcohol **18** as a syrup in 73% yield. Swern oxidation ($COCl_2$/DMSO/Et_3N) of alcohol **18** gave an aldehyde which was immediately reacted with alkylidene triphenylphosphoranes ($C_2H_5P^+Ph_3Br^-$ and *n*-$C_4H_9P^+Ph_3Br^-$, $NaNH_2$, THF) to obtain olefins **19** and **20** respectively, which were characterised from the ^{1}H NMR spectrum by the appearance of olefinic protons at δ 5.38–5.75 (m, 2H). **19** and **20** were hydrogenated [Raney Ni, EtOH, H_2 (1 atm)] to yield **21** and **22**, respectively, in quantitative yield. **21** and **22** were treated with aq. HCl in THF at 50°C for 1 h to obtain the corresponding lactols which were oxidised with PDC to obtain the desired Hagen's gland lactones **3**–**6** which were separated by column chromatography. **3** Was characterised from the ^{1}H NMR spectrum by the appearance of H-3a at δ 4.80 (ddd, 1H, J=6.4, 4.5, 0.7 Hz) and H-6a at δ 5.11 (dd, 1H, J=4.9, 4.5 Hz). Compound **5** was characterised from the ^{1}H NMR spectrum by the appearance of H-3a at δ 4.45 (ddd, 1H, J=4.0, 6.0, 1.0 Hz) and H-6a at δ 4.9 (dd, 1H, J=6.0, 3.8 Hz). **3**,**4** and **5**,**6** were virtually identical in ^{1}H NMR spectra; they differ only in the integration of aliphatic protons between δ 0.8–1.8. ^{1}H and ^{13}C NMR data of **3** and **4** were in agreement with that reported in the literature.[3,5]

In conclusion, enantiospecific syntheses of **3**–**6** have been achieved by the chiron approach starting from D-mannose involving Pd(II)Cl_2 mediated oxidative cyclisation of hydroxy-vinylfuran **8** to lactol **7** as a key step. Determination of the biological roles of **3**–**6** is in progress due to their availability in multigram amounts and will be reported elsewhere.

Experimental

^{1}H NMR spectra were measured with a Varian Gemini (200 and 400 MHz) spectrometer, with tetramethylsilane as internal standard for solutions in deuteriochloroform. ^{13}C NMR spectra were taken with a Varian Gemini (50 MHz) spectrometer with $CDCl_3$ as internal standard (δ_c 77.0) for solutions in deuteriochloroform. Optical rotations were measured with a JASCO DIP-370 instrument and $[\alpha]_D$ values are in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were taken with a Perkin–Elmer 1310 spectrometer. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40°C in vacuo. All moisture sensitive reactions were performed under a nitrogen atmosphere using flame dried glassware. Solvents were dried over standard drying agents and freshly distilled prior to use.

3,6-Anhydro-2-deoxy-4,5:7,8-di-*O*-isopropylidene-D-glycero-D-talo/galacto octitol (11). A solution of ester **10**[11] (30.0 g, 90.6 mmol) in dry diethyl ether (400 ml) was added to an ice cooled and stirred suspension of lithium aluminium hydride (5.16 g, 135.6 mmol) in dry diethyl ether (300 ml) under nitrogen atmosphere. The reaction mixture was refluxed for 3 h and quenched with successive addition of EtOAc (30 ml), water (30 ml) and 20% NaOH solution (30 ml). The reaction mixture was filtered through celite and the filter cake was washed with diethyl ether (2×300 ml). The combined ethereal layers were dried (Na_2SO_4), concentrated to a syrupy residue and filtered on a bed of silica gel (60–120 mesh, hexane:EtOAc, 2:1) to obtain the title compound **11** (21.6 g, 82%) as a thick syrup. $[\alpha]_D$=−7.04 (*c* 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.36, 1.42, 1.45, 1.50, 1.52 (12H, 5s, 4×CH_3), 1.6–2.15 (2H, m, H-2), 3.5–4.82 (9H, m, H-1,3-8). Anal. Calcd for $C_{14}H_{24}O_6$: C, 58.30; H, 8.39. Found: C, 58.48; H, 8.45.

3,6-Anhydro-1-*O*-benzyl-2-deoxy-4,5:7,8-di-*O*-isopropylidene-D-glycero-D-talo/galacto octitol (12). To a slurry of hexane washed sodium hydride (2.1 g, 87.0 mmol) in dry *N*,*N*-dimethylformamide (40 ml) was added a solution of **11** (21.0 g, 72.6 mmol) in DMF (45 ml) at 0°C. To this suspension was added dropwise benzyl bromide (13.8 g, 81.0 mmol) and the mixture was stirred for 1 h at room temperature. When reaction was complete, excess of sodium hydride was quenched by addition of methanol (10 ml), the reaction mixture was poured into ice-cold water (500 ml) and extracted into diethyl ether (2×300 ml). The combined ethereal extracts were dried (Na_2SO_4), filtered and concentrated to obtain a residue which was filtered on a bed of silica gel (60–120 mesh, hexane:EtOAc, 4:1) to obtain the title compound **12** (25.8 g, 94%) as a syrup. $[\alpha]_D$=−2.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.3, 1.42, 1.48, 1.50, 1.53 (12H, 5s, 4×CH_3), 1.72 (1H, dd, J_{gem}=14.1, 4.6 Hz, H-2), 2.0 (1H, dd, H-2′), 3.39–4.75 (11H, m, H-1,3–8 and OCH_2Ph), 7.18–7.41 (5H, m, ArH). Anal. Calcd for $C_{21}H_{30}O_6$: C, 66.63; H, 7.99. Found: C, 66.87; H, 8.15.

3,6-Anhydro-1-*O*-benzyl-2-deoxy-4,5-*O*-isopropylidene-D-glycero-D-talo/galacto octitol (13). A mixture of compound **12** (25.2 g, 66.6 mmol) and 60% aq. acetic acid (250 ml) was stirred at room temperature for 7 h. 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, 3:1) to obtain the title compound **13** (19.2 g, 85%) as a thick syrup. $[\alpha]_D$=−3.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32, 1.48,

1.51 (6H, 3s, 2×CH_3), 1.68–2.2 (2H, m, H-2,2′), 3.5–2.75 (2H, br s, OH), 3.41–4.89 (11H, m, H-1,3–8 and OCH_2Ph), 7.21–7.42 (5H, m, ArH). Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.87; H, 7.75. Found: C, 64.12; H, 7.83.

3,6-Anhydro-1-*O*-benzyl-2,7,8-trideoxy-4,5-*O*-isopropylidene-D-talo/galacto-oct-7-enitol (14). To a solution of diol **13** (18 g, 52.8 mmol) in toluene (500 ml) containing triphenylphosphine (55.8 g, 213.0 mmol) and imidazole (14.46 g, 213.0 mmol) at 50°C was added iodine (53.4 g, 213.0 mmol) and refluxed for 6 h. Progress of the reaction was monitored by TLC, when the reaction was complete solvent was removed under vacuum, to obtain a thick syrup. It was dissolved in EtOAc (500 ml), 5% aqueous NaOH solution (150 ml) was added, organic layer was separated and aqueous layer was extracted into EtOAc (300 ml). The pooled organic phase was washed with water (150 ml), saturated sodium thiosulphate (150 ml) and water (150 ml). The organic phase was separated, concentrated to a residue and filtered on a bed of silica gel (60–120 mesh, hexane: EtOAc, 6:1) to obtain the title compound **14** (13.92 g, 86%) as a colourless oil. $[\alpha]_D=-27.3$ (*c* 1.5, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 1.29, 1.48, 1.49 (6H, 3s, 2×CH_3), 1.76 (1H, dd, $J_{gem}=14.0$, 4.2 Hz, H-2), 2.05 (1H, dd, H-2′), 3.52–4.38 (4H, m, H-1,1′, 3 and H-6), 4.5 (2H, s, OCH_2Ph), 4.51–4.70 (2H, m, H-4 and H-5), 5.2–5.45 (2H, m, H-8, 8′), 5.85–6.10 (1H, m, H-7), 7.15–7.45 (5H, m, ArH). Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.01; H, 7.95. Found: C, 71.17; H, 8.18.

3,6-Anhydro-1-*O*-benzyl-2,7,8-trideoxy-D-talo/galacto oct-7-enitol (8). To a solution of **14** (13.2 g, 43.38 mmol) in dioxane (60 ml) was added 5% aq. H_2SO_4 (10 ml) and the reaction mixture was refluxed for 3 h. After completion of the reaction, solvent was removed under vacuum and extracted into EtOAc (450 ml). Organic phase was washed with saturated $NaHCO_3$ solution (150 ml), water (150 ml), dried (Na_2SO_4) and concentrated to obtain a residue, which was filtered on a bed of silica gel (60–120 mesh, hexane: EtOAc, 3:1) to obtain the title compound **8** (9.24 g, 81%) as a syrup. $[\alpha]_D=1.4$ (*c* 0.9, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 1.89–2.3 (2H, m, H-2,2′), 3.48–4.6 (6H, m, H-1,3–6), 4.51 (2H, s, OCH_2Ph), 5.2–5.4 (2H, m, H-8,8′), 5.80–6.10 (1H, m, H-7), 7.2–7.40 (5H, m, ArH). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.15; H, 7.63. Found: C, 68.28; H, 7.74.

(2*R*/*S*, 3*R*,3a*S*,5*R*/*S*,6a*R*)-2-Benzyloxy ethyl[3,2-b]furan-3,5-diol (7). To a solution of diol **8** (9.0 g, 34.0 mmol) in 20% aq. DMF (60 ml) was added Pd(II)Cl_2 (0.12 g, 0.68 mmol), CuCl (3.37 g, 34.0 mmol) and oxygen was bubbled for 24 h at room temperature. Progress of the reaction was monitored by TLC, when the reaction was complete the reaction mixture was diluted with diethyl ether (450 ml), filtered through a bed of silica gel and eluted with diethyl ether (300 ml). The combined ethereal layers were washed with 2% aq. HCl (200 ml) and water (2×100 ml). Organic phase was separated, dried (Na_2SO_4), concentrated to obtain a residue, which was filtered on a bed of silica gel (60–120 mesh, hexane:EtOAc, 2:1) to obtain the title compound **7** (8.04 g, 84%) as a thick syrup. $[\alpha]_D=12.1$ (*c* 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 1.79–2.3 (4H, m, H-6,6′ and CH_2CH_2OBn), 3.48–4.85 (8H, m, H-2,3,3a,6a, CH_2CH_2OBn and OCH_2Ph), 5.44–5.78 (1H, m, H-1), 7.18–7.41 (5H, m, ArH). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.26; H, 7.20. Found: C, 64.39; H, 7.27.

(2*R*/*S*, 3*R*,3a*S*,5*R*/*S*,6a*R*)-2-Benzyloxy ethyl-5-methoxy-[3,2-b]furan-3-ol (15). A solution of lactol **7** (7.8 g, 27.6 mmol) in 2% methanolic hydrochloric acid (120 ml) was stirred for 4 h at room temperature. Progress of the reaction was monitored by TLC, when the reaction was complete, Ba_2CO_3 (5 g) was added and filtered. Filtrate was concentrated to a syrupy residue, which was filtered on a bed of silica gel (60–120 mesh, hexane:EtOAc, 4:1) to obtain the title compound **15** (7.2 g, 88%) as a thick syrup. $[\alpha]_D=36.1$ (*c* 0.7, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 1.8–2.38 (4H, m, H-6,6′ and CH_2CH_2OBn), 2.55 (br s, OH), 3.31–3.41 (3H, 2s, OMe), 3.46–5.3 (9H, m, H-2,3,3a,5,6a, CH_2CH_2OBn and OCH_2Ph), 7.18–7.41 (5H, m, ArH). Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.27; H, 7.54. Found: C, 65.32; H, 7.58.

(2*R*/*S*, 3*R*,3a*S*,5*R*/*S*,6a*R*)-2-Benzyloxy ethyl-5-methoxy-3-*O*-(S-methyldithio-carbonate)-[3,2-b]furan (16). To a solution of **15** (6.6 g, 22.5 mmol) in THF (150 ml) was added hexane washed sodium hydride (0.78 g, 33.6 mmol) and carbon disulfide (3.48 g, 44.4 mmol) at 0°C. After stirring for 15 min iodomethane (4.8 g, 33.9 mmol) was added and brought to room temperature. After completion of the reaction (30 min), excess sodium hydride was quenched by addition of glacial acetic acid. Solution was filtered, concentrated to a syrupy residue, which was extracted into diethyl ether (450 ml). The ethereal layer was washed with water, dried (Na_2SO_4), filtered and concentrated to obtain the title compound **16** (7.92 g, 92%) as an oil. $[\alpha]_D=51.4$ (*c* 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 1.82–2.32 (4H, m, H-6,6′ and CH_2CH_2OBn), 2.59, 2.61 (3H, 2s, SMe), 3.32, 3.36, 3.4 (3H, 3s, OCH_3), 3.48–5.22 (8H, m, H-2,3a,5,6a, CH_2CH_2OBn and OCH_2Ph), 5.8–6.0 (1H, m, H-3), 7.18–7.44 (5H, m, ArH). Anal. Calcd for $C_{18}H_{24}O_5S_2$: C, 56.23; H, 6.30. Found: C, 56.39; H, 6.42.

(2*R*/*S*,3a*S*,5*R*/*S*,6a*R*)-2-Benzyloxy ethyl-5-methoxy-[3,2-b]furan (17). A solution of xanthate **16** (7.8 g, 20.1 mmol) tri-*n*-butyltin hydride (9.0 g, 30.6 mmol) and AIBN (40 mg) in toluene (450 ml) was refluxed for 6 h. When reaction was complete, solvent was removed under reduced pressure to obtain a residue, which was filtered on a bed of silica gel (60–120 mesh, hexane:EtOAc, 7:1) to obtain the title compound **17** (3.9 g, 69%) as a colourless oil. $[\alpha]_D=68.3$ (*c* 1.1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 1.15–2.4 (6H, m, H-3,3′,6,6′ and CH_2CH_2OBn), 3.28,3.3,3.38 (3H, 3s, OCH_3), 3.5–3.7 (2H, m, CH_2CH_2OBn), 3.89–4.15 (1H, m, H-6a), 4.4–5.18 (5H, m, H-2,3a,5 and OCH_2Ph), 7.15–7.4 (5H, m, ArH). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.03; H, 7.97. Found: C, 69.09; H, 8.03.

(2*R*/*S*,3a*R*,5*R*/*S*,6a*R*)-2-Hydroxy ethyl-5-methoxy-[3,2-b]furan (18). To a solution of **17** (3.5 g, 12.6 mmol) in liq. ammonia (60 ml) at −20°C was added lithium (0.15 g, 25.0 mmol) and stirred for 30 min. After completion of the reaction, it was brought to room temperature and quenched with solid NH_4Cl. This residue was extracted into ethyl acetate (200 ml) and washed with water, dried (Na_2SO_4)

concentrated to a syrupy residue which was filtered on a bed of silica gel (60–120 mesh, hexane:EtOAc, 3:1) to obtain the title compound **18** (1.71 g, 73%) as a colourless oil. $[\alpha]_D$=86.5 (*c* 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 1.2–2.42 (6H, m, H-3,3′,6,6′ and CH_2CH_2OH), 3.35,3.37, 3.4 (3H, 3s, OMe), 3.65–3.9 (2H, m, CH_2CH_2OH), 4.05–5.2 (4H, m, H-2,3a,5 and 6a). Anal. Calcd for $C_9H_{16}O_4$: C, 57.41; H, 8.57. Found: C, 57.47; H, 8.62.

2-[(*E*)-2-Butenyl]-5*R*/*S*-methoxy(2*R*/*S*,3a*R*,6a*R*)-perhydrofuro[3,2-b]furan (19). Dry dichloromethane (15 ml) containing dimethylsulfoxide (0.63 g, 6.6 mmol) was added to a solution of oxalyl chloride (0.84 g, 6.6 mmol) in dry dichloromethane (10 ml) at −78°C and stirred for 20 min under nitrogen atmosphere. A solution of alcohol **18** (0.78 g, 4.2 mmol) in dry dichloromethane (6 ml) was added to the above reaction mixture and stirred for 45 min followed by the addition of triethylamine (1.32 g, 13.2 mmol). The reaction mixture was brought gradually to room temperature and diluted with dichloromethane (90 ml). The organic phase was washed with brine (75 ml), dried (Na_2SO_4) and evaporated to obtain the aldehyde as a syrup which was immediately reacted with a solution of ethylidene triphenylphosphorane (generated in situ from n-C_2H_5P+Ph_3Br^- (3.0 g, 7.8 mmol), $NaNH_2$ (0.27 g, 7.2 mmol), THF (75 ml)) under nitrogen atmosphere for 1.5 h at −20°C. The reaction mixture was then quenched with saturated aq. NH_4Cl (75 ml) and was extracted into diethyl ether (2×75 ml). Combined ethereal layers were washed with water (75 ml), dried (Na_2SO_4) and concentrated to a syrupy residue which was filtered on a bed of silica gel (60–120 mesh, hexane:EtOAc, 6:1) to obtain the title compound **19** (0.63 g, 77%) as a colourless oil. $[\alpha]_D$ 82.5 (*c* 0.7, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 1.52–2.6 (9H, m, H-H-3,3′,6,6′ and n-C_4H_7), 3.38,3.4 (3H, 2s, OCH_3), 3.9–4.14 (1H, m, H-2), 4.51–5.29 (3H, m, H-3a,5,6a), 5.38–5.75 (2H, m, n-C_4H_7 olefinic). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.62; H, 9.16. Found: C, 66.68; H, 9.22.

2-[(*E*)-2-Hexenyl]-5*R*/*S*-methoxy(2*R*/*S*,3a*R*,6a*R*)-perhydrofuro[3,2-b]furan (20). Prepared from alcohol **18** (0.72 g, 3.81 mmol), n-C_4H_9P+Ph_3Br^- (3.0 g, 7.56 mmol) and $NaNH_2$ (0.27 g, 6.9 mmol) as described for compound **19** to obtain the title compound **20** (0.66 g, 76%) as a colourless oil. $[\alpha]_D$=76.1 (*c* 0.5, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 1.5–2.65 (9H, m, H-3,3′,6,6′ and n-C_6H_{11}), 3.39,3.41 (3H, 2s, OCH_3), 3.8–4.16 (1H, m, H-2), 4.48–5.3 (3H, m, H-3a,5,6a), 5.35–5.75 (2H, m, n-C_6H_{11} olefinic). Anal. Calcd for $C_{11}H_{18}O_3$: C, 68.98; H, 9.80. Found: C, 69.04; H, 9.87.

2-Butyl-(5*R*/*S*)-methoxy(2*R*/*S*,3a*R*,6a*R*)-perhydrofuro[3,2-b]furan (21). A solution of **19** (0.6 g, 3.0 mmol) was subjected to hydrogenation with Raney-Nickel catalyst (approximately 0.2 g) for 2 h under hydrogen atmosphere (1 atm). The catalyst was filtered off and the filtrate was concentrated to obtain the title compound **21** (0.594 g, 99%) as a syrup. $[\alpha]_D$=38.6 (*c* 1.03, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 0.8–2.4 (13H, m, H-3,3′,6,6′ and n-C_4H_9), 3.3,3.33 (3H, 2s, OCH_3), 3.6–5.2 (4H, m, H-2,3a,5,6a). Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.95; H, 10.07. Found: C, 66.11; H, 10.12.

2-Hexyl-(5*R*/*S*)-methoxy(2*R*/*S*,3a*R*,6a*R*)-perhydrofuro[3,2-b]furan (22). Prepared from olefin **20** (0.6 g, 2.64 mmol) as described for the compound **21** to obtain the title compound **22** (0.6 g, 98%) as a colourless oil. $[\alpha]_D$=42.6 (*c* 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 0.79–2.41 (17H, m, H-3,3′,6,6′ and n-C_6H_{13}), 3.31,3.34 (3H, 2s, OCH_3), 3.58–5.25 (4H, m, H-2,3a,5,6a). Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.37; H, 10.60. Found: C, 68.42; H, 10.66.

(3a*R*,5*R*,6a*R*)-5-Butylperhydrofuro[3,2-b]furan-2-one (3) and (3a*R*,5*S*,6a*R*)-5-butylperhydrofuro[3,2-b]furan-3-one (5). A solution of compound **21** (0.57 g, 2.85 mmol) in THF (15 ml) and 20% aqueous HCl (3 ml) was stirred for 1 h at 45°C. After completion of the reaction, reaction mixture was neutralised with sodium hydrogen carbonate and filtered. The filtrate was concentrated and extracted with ethyl acetate (75 ml), organic phase was washed with water, dried (Na_2SO_4), concentrated to obtain the lactol (0.39 g, 76%). Lactol was dissolved in dry dichloromethane (30 ml) and oxidised with pyridinium dichromate (0.87 g, 2.52 mmol) at reflux temperature for 45 min. When the reaction was complete, celite (3 g) and diethyl ether (75 ml) were added to the reaction mixture and filtered. The filtrate concentrated to a syrupy residue which was chromatographed (60–120 mesh, hexane:EtOAc, 4:1) to elute first **3** (0.174 g, 33%). $[\alpha]_D$=+49.9 (*c* 1.0, $CHCl_3$); IR (neat): ν 2930, 2825, 1770, 1190, 1050 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.8–1.9 (10H, m, H-6 and n-C_4H_9), 2.38 (dd, 1H, *J*=14.2, 4.2 Hz, H-6), 2.64 (dd, 1H, *J*=19.0, 0.7 Hz, H-3), 2.75 (dd, 1H, *J*=19.0, 6.4 Hz, H-3), 4.07 (dddd, 1H, *J*=10.0, 7.2, 5.1, 4.2 Hz, H-5), 4.80 (ddd, 1H, *J*=6.4, 4.5 0.7 Hz, H-3a) 5.11 (dd, 1H, *J*=4.9, 4.5 Hz, H-6a). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.25; H, 8.80.

Followed by **5** (0.183 g, 35%) as a colourless oil. $[\alpha]_D$=+24.9 (*c* 1.3, $CHCl_3$); IR (neat): ν 2931, 2820, 1771, 1193 and 1048 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.8–2.5 (11H, m, H-6,6′ and n-C_4H_9), 2.65 (dd, 2H, *J*=16.0, 4.0 Hz, H-3,3′), 3.8–3.98 (m, 1H, H-5), 4.45 (ddd, 1H, *J*=4.0, 6.0, 1.0 Hz, H-3a), 4.95 (dd, 1H, *J*=6.0, 3.8 Hz, H-6a). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.28; H, 8.82.

(3a*R*,5*R*,6a*R*)-5-Hexylperhydrofuro[3,2-b]furan-2-one (4) and (3a*R*,5*S*,6a*R*)-5-hexylperhydrofuro[3,2-b]furan-3-one (6). Prepared from compound **22** (0.54 g, 2.4 mmol) to obtain the title compounds **4** (0.174 g, 36%) and **6** (0.18 g, 38%) as colourless syrups.

Spectral data of **4** $[\alpha]_D$=+50.01 (*c* 1.0, $CHCl_3$); IR (neat): ν 2928, 2850, 1770, 1190, 1045 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.8–1.9 (14H, m, H-6 and n-C_6H_{13}), 2.38 (dd, 1H, *J*=14.2, 4.2 Hz, H-6), 2.64 (dd, 1H, *J*=19.0, 0.7 Hz, H-3), 2.75 (dd, 1H, *J*=19.0, 6.4 Hz, H-3), 4.07 (dddd, 1H, *J*=10.0, 7.2, 5.1, 4.2 Hz, H-5), 4.80 (ddd, 1H, *J*=6.4, 4.5, 0.7 Hz, H-3a), 5.11 (dd, 1H, *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, 67.99; H, 9.56.

Spectral data of **6** $[\alpha]_D$=+24.6 (*c* 1.3, $CHCl_3$); IR (neat): ν 2925, 2850, 1770, 1190, 1045 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.8–2.5 (15H, m, H-6,6′ and n-C_6H_{13}), 2.65 (dd,

2H, J=16.0, 4.0 Hz, H-3,3′), 3.8–3.98 (m, 1H, H-5), 4.45 (ddd, 1H, J=4.0, 6.0, 1.0 Hz, H-3a), 4.95 (dd, 1H, J=6.0, 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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