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A general strategy for the formal synthesis of (−)-*trans*-kumausyne and total synthesis of (5*R*)-Hagen's gland lactones from diacetone-D-glucose

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Abstract

A general strategy for the formal synthesis of (−)-*trans*-kumausyne **1** via the bicyclic lactone (3a*R*,5*R*,6a*R*)-**4** and total synthesis of (5*R*)-Hagen's gland lactones **2** and **3** via bicyclic lactone (3a*R*,5*S*,6a*R*)-**5** starting from diacetone-D-glucose **6** is described. Syntheses of **4** and **5** were achieved by Wittig olefination–lactonization–Michael addition of the corresponding lactols **16** and **17**, respectively.

1. Introduction

Natural products containing tetrahydrofurans have been of special interest due to their widespread occurrence and their varied biological activities.[1,2] Notable among them are (−)-*trans*-kumausyne **1** and Hagen's gland lactones **2** and **3**. Compound **1** was isolated from the red alga *Laurencia nipponica yamada* by Kurosawa and co-workers.[3] Due to its unusual all *cis*-3-oxygenated-2,5-dialkyltetrahydrofuran core and rich functionality it has been the subject of considerable synthetic efforts. Overman's group accomplished the landmark total synthesis of (±)-**1** from 2-cyclopentylidenecyclopentanone using a novel Prins cyclization–pinacol rearrangement.[4] Sugimura et al. have reported a total synthesis of **1** by stereoselective formation of substituted tetrahydrofurans in the BF_3-promoted reaction of 2,3-*O*-isopropylidene derivatives of aldehydes with allylsilanes.[5] Martin et al. have disclosed a synthesis of **1** from propargyl alcohol that employed brominative cyclization as a key step to obtain the tetrahydrofuran.[6] Lee et al. have reported the synthesis of **1** by use of radical cyclization of β-alkoxy acrylate as a key step to form the tetrahydrofuran template.[7] Boukouvalas et al. have reported an elegant synthesis of **1** by Pd(II) mediated intramolecular alkoxycarbonylation–lactonization of an ene diol to generate tetrahydrofurofurone.[8] More recently, Fernandez de la Pradilla et al. have reported a formal synthesis of (+)-**1** using a highly

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stereoselective remote nucleophilic epoxidation of a sulfinyl diene moiety[9] and Pd(II) mediated oxidative cyclization of hydroxy(vinyl) furans to tetrahydrofurofurans, a methodology that was first developed by us.[10] Williams and co-workers have shown by chemical analysis that the glands of braconid wasps *Diachasmimorpha longicaudata* contain two bicyclic lactones which were tentatively identified as (3aα,5β,6aα)-5-butyl tetrahydrofuro-[3,2-*b*]fura-2-(3*H*)-one **2** and its corresponding 5-hexyl derivative **3** based on ^{1}H NMR considerations.[11] The absolute stereochemistry of these lactones was established by Kitching et a1.[12] based on the synthesis of a diastereomeric mixture by a Pd(II) mediated alkoxycarbonylation–lactonization protocol. We have recently reported a simple and general synthesis of Hagen's gland lactones **2** and **3** starting from D-glucose by a Wittig olefination–lactonization–Michael addition protocol.[13]

2. Results and discussion

Earlier, several authors have reported the synthesis of (−)-*trans*-kumausyne **1** via the advanced intermediate, bicyclic lactone **4**.[5,6,8] We have considered the preparation of bicyclic lactone (3a*R*,5*R*,6a*R*)-**4** and also its diastereomer (3a*R*,5*S*,6a*R*)-**5** for the synthesis of **1**, **2** and **3**, respectively, by a chiron approach starting from diacetone-D-glucose **6**, a general route which has potential for the synthesis of several other C-15 lipid metabolites (Fig. 1).

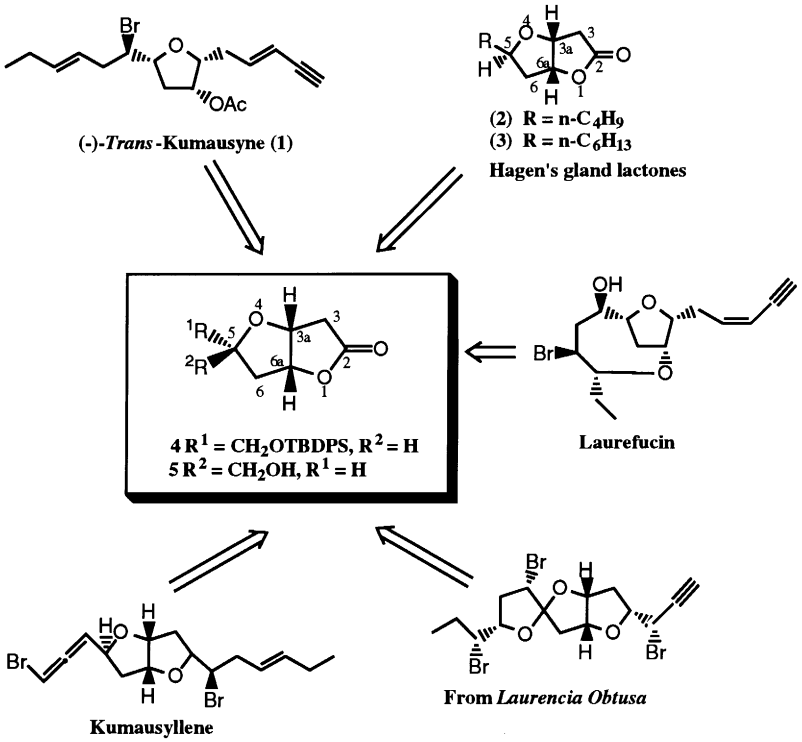
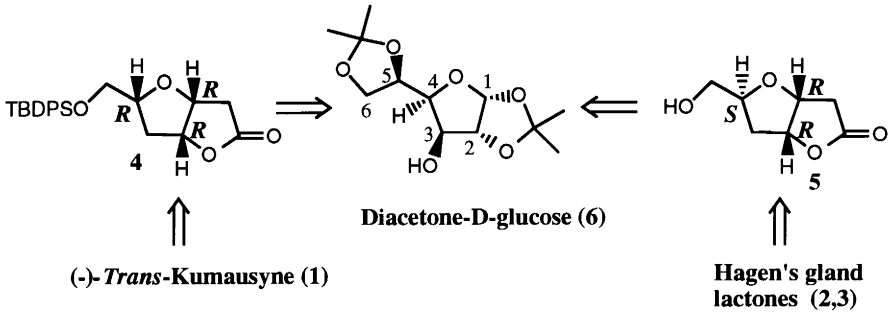


Fig. 1.

Retrosynthetic analysis (Scheme 1), derived by consideration of stereochemical flexibility, suggested that bicyclic lactones **4** and **5** could be derived from diacetone-D-glucose **6**. It required the configuration at C-4 to be inverted, deoxygenation of the C-3 hydroxyl group and Wittig olefination–lactonization–Michael addition at C1–C2 to obtain the advanced key intermediate **4**. Retrosynthetic

analysis of **2** and **3** indicated that they could be derived from **6** which has appropriate stereogenic centres at C-2, C-4 and requires deoxygenation of the C-3 hydroxyl group.

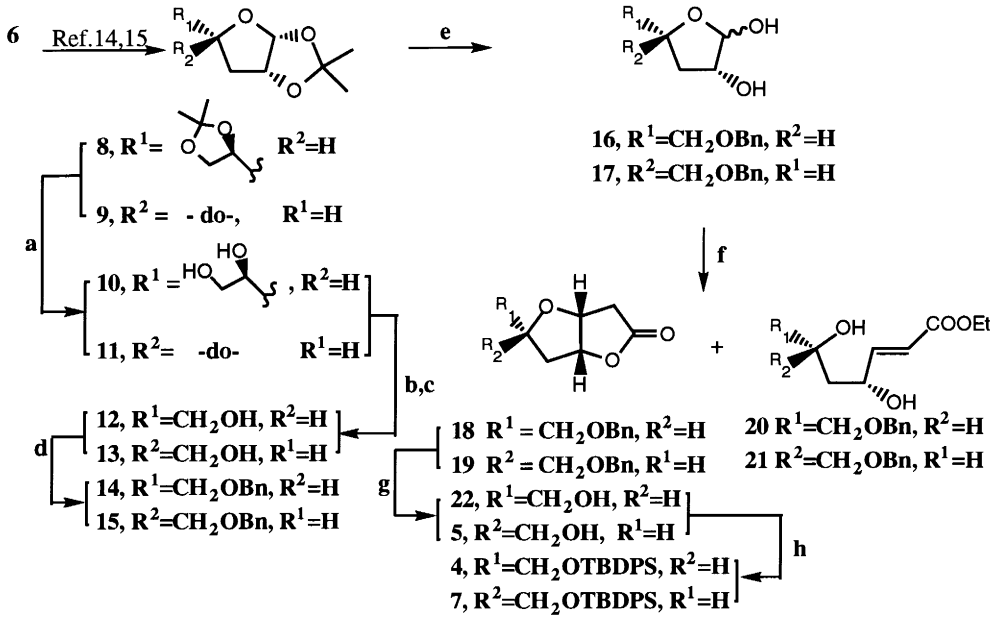


Scheme 1.

Thus, **6** was transformed to 3-deoxy-galacto-**8**[14] and glucofuranose **9**[15] derivatives by well established procedures (Scheme 2). Regioselective hydrolysis of the terminal isopropylidene groups of **8** and **9** with 60% aq. HOAc at room temperature for 4–6 h gave the corresponding diols **10** and **11**, respectively, in good yield. Oxidative cleavage of diols **10** and **11** with sodium metaperiodate followed by reduction with sodium borohydride gave the corresponding alcohols **12** and **13**, respectively. Benzylation of **12** and **13** with NaH–BnBr–DMF at 0°C gave the corresponding benzyl ethers **14** and **15**, respectively, in 90–95% yield. Acid catalyzed reaction of **14** and **15** with 40% aq. HOAc and cat. H_2SO_4 at 45°C gave the corresponding lactols **16** and **17**, respectively. Compounds **16** and **17** were characterized from the ^{1}H NMR spectrum by the appearance of anomeric protons at δ 5.08–5.5 (1H, α/β, mixture). In order to build the required tetrahydrofurofuran moiety, lactols **16** and **17** were severally reacted with carboethoxymethylene triphenylphosphorane in methanol at 10°C to afford the corresponding bicyclic lactones **18** (58%) and **19** (66%) and *trans*-olefins **20** (18%) and **21** (15%), respectively. Due to spontaneous lactonization and Michael ring closure[16c] formation of *cis*-olefins and corresponding butenolides was not observed.[16] Lactone **18** was characterized from the ^{1}H NMR spectrum by the appearance of characteristic H-3,3′ protons at δ 2.60–2.80 (m, 2H) and H-6a proton at δ 4.98–5.10 (m, 1H) and **19** by the appearance of H-3,3′ protons at δ 2.69–2.91 (m, 2H) and H-6a proton at δ 5.12 (dd, 1H, J=6.0, 4.7 Hz). Compounds **18** and **19** were also characterized from the IR spectra from the C=O absorption at 1768–1770 cm^{-1}. *trans*-Olefins **20** and **21** were characterized by the appearance of olefinic protons at δ 6.10 (d, 1H, J=16.2 Hz) and δ 6.95 (dd, 1H, J=16.2, 3.8 Hz) and ethoxycarbonyl protons at δ 1.30 (t, 3H) and δ 4.15 (q, 2H).

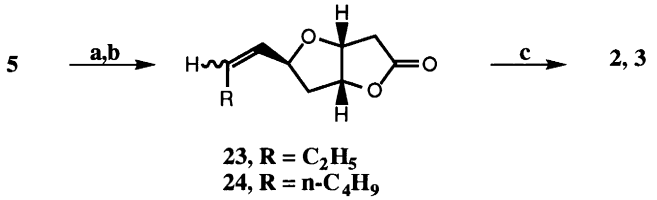
Hydrogenolysis of **18** and **19** with Pd/C and H_2 (1 atm) gave the corresponding hydroxy lactones **22** and **5**, respectively, in good yield. Silylation of **22** and **5** with *tert*-butyldiphenylsilyl chloride gave the corresponding lactones **4**[5,6,8] {$[\alpha]_D$ 25.4 (c 0.8, $CHCl_3$)} and **7** {$[\alpha]_D$ 25.0 (c 0.84, $CHCl_3$)},[17] respectively. Lactone **4** was characterized from the ^{1}H NMR and ^{13}C NMR spectra which were in complete agreement with the reported data.[8,17] Since elaboration of **4** to (−)-*trans*-kumausyne **1** has been earlier reported,[5,6,8] a formal synthesis of **1** has thus been achieved. Compound **7** was characterized by the appearance of protons at δ 1.11 (s, 9H), δ 2.55–2.80 (m, 2H, H-3,3′) and δ 5.10 (dd, 1H, J=4.9, 4.5 Hz, H-6a) in the ^{1}H NMR spectrum.

To achieve the total synthesis of (5*R*)-Hagen's gland lactones **2** and **3**, alcohol **5** was subjected to Swern oxidation to obtain the corresponding aldehyde which was immediately severally treated with alkylidene triphenylphosphoranes ($Ph_3P^+CH_2CH_2CH_3Br^-$/$Ph_3P^+CH_2(CH_2)_3CH_3Br^-$/$NaNH_2$, THF) to obtain the corresponding olefins (*E*/*Z*) **23** and **24** which were characterized from the ^{1}H NMR spectrum by the appearance of olefinic protons at δ 5.40–5.65 (m, 2H) (Scheme 3). Hydrogenation (Raney-Ni, H_2,



Scheme 2. (a) 60% aq. HOAc, rt, 4–6 h; (b) $NaIO_4$, CH_2Cl_2, satd $NaHCO_3$ soln, rt, 1 h; (c) $NaBH_4$, MeOH, 0°C–rt, 30 min; (d) NaH, BnBr, DMF, 0°C, 30 min; (e) 40% aq. HOAc, H_2SO_4, 45°C, 6–8 h; (f) $Ph_3P{=}CHCOOEt$, MeOH, 10°C, 8–12 h; (g) Pd/C, MeOH, H_2 (1 atm), rt, 3–5 h; (h) TBDPSCl, Py, 0°C, 2 h

EtOH) of olefins **23** and **24** gave the desired (5*R*)-Hagen's gland lactones **2** and **3**, respectively, in good yield. Lactone **3** was characterized from the ^{1}H NMR spectrum by the H-3,3′ protons at δ 2.64 (dd, 1H, J=19.1, 0.7 Hz), δ 2.75 (1H, dd, J=19.1, 6.4 Hz), H-3a proton at δ 4.80 (ddd, 1H, J=6.4, 4.5, 0.7 Hz) and H-6a proton at δ 5.11 (dd, 1H, J=4.9, 4.5 Hz). ^{1}H and ^{13}C NMR data[11,13] of **2** and **3** were consistent with those reported in the literature.



Scheme 3. (a) Oxalyl chloride, DMSO, TEA, CH_2Cl_2, −78°C, 1 h; (b) $Ph_3P{=}CHCH_2CH_3/Ph_3P{=}CH(CH_2)_3CH_3$, THF, −20°C, 1–2 h; (c) W-4 Raney-Ni, H_2 (1 atm), EtOH, rt, 2–4 h

In conclusion, this general strategy has been demonstrated to be serviceable for stereoselective construction of tetrahydrofuran and tetrahydrofurofuran core structure of several natural products by a chiron approach. Further investigations into the application of this strategy to other brominated tetrahydrofuran non-terpenoids isolated from the red alga of genus laurencia are under progress.

3. Experimental

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. ^{1}H NMR spectra were measured with a Varian Gemini (200 MHz) spectrometer, with tetramethylsilane as an

internal standard for solutions in deuteriochloroform. J values are given in hertz. ^{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.

3.1. 3-Deoxy-1,2-O-isopropylidene-L-arabinofuranose **12**

To a solution of **10** (1.8 g, 8.8 mmol) at 0°C in dichloromethane (50 ml) and satd aqueous $NaHCO_3$ (3 ml) was added in one portion sodium metaperiodate (3.6 g, 16 mmol) and the mixture stirred vigorously at room temperature for 1 h. After completion of the reaction anhydrous Na_2SO_4 (10 g) was added to the reaction mixture and filtered through a bed of Celite. The Celite bed was washed with dichloromethane (2×50 ml), the filtrate was concentrated to a thick syrup and dissolved in methanol (50 ml), cooled to 0°C and sodium borohydride (0.33 g, 8.8 mmol) was added. The reaction mixture was stirred for 30 min and then quenched with a few drops of acetic acid. The solvent was removed under reduced pressure to obtain a residue which was extracted into ethyl acetate (2×75 ml). The combined organic extracts were washed with brine (50 ml), water, 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, 1:1) to obtain the title compound **12** (1.29 g, 84%) as a colourless syrup. IR: ν_{max} 3450 cm^{-1} (OH); $[\alpha]_D^{25}$ −30.86 (c 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.30, 1.53 (2s, 6H, 2×CH_3), 1.9–2.3 (m, 2H, H-3), 3.58 (dd, 1H, J=4.1, J_{gem}=11.2 Hz, H-5), 3.75 (dd, J=4.2 Hz, 1H, H-5′), 4.3 (m, 1H, H-4), 4.72 (dd, 1H, J=3.9, 4.2 Hz, H-2), 5.8 (d, 1H, J=3.9 Hz, H-1). Anal. calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.08; H, 8.02.

3.2. 3-Deoxy-1,2-O-isopropylidene-α-D-ribofuranose **13**

Prepared from the diol **11** (2.0 g, 9.8 mmol) as described for compound **12** to obtain the title compound **13** (1.43 g, 84%) as a white solid. Mp 82–84°C; $[\alpha]_D^{25}$ −7.4 (c 0.7, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.32, 1.42 (2s, 6H, 2×CH_3), 1.8–2.1 (m, 2H, H-3,3′), 3.52 (dd, 1H, J_{gem}=11.0, 3.8 Hz, H-5), 3.88 (dd, 1H, J_{gem}=11.0, 3.2 Hz, H-5′), 4.22–4.4 (m, 1H, H-4), 4.72 (dd, 1H, J=4.4, 4.4, 4.6 Hz, H-2), 5.78 (d, 1H, H-1). Anal. calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.27; H, 8.19.

3.3. 5-O-Benzyl-3-deoxy-1,2-O-isopropylidene-L-arabinofuranose **14**

To a solution of **12** (1.2 g, 6.9 mmol) in dry *N*,*N*-dimethylformamide (3 ml) sodium hydride (0.24 g, 10 mmol) was added at 0°C followed by benzyl bromide (1.75 g, 10.3 mmol). The reaction mixture was stirred for 30 min at room temperature, poured into ice cold water and extracted into diethyl ether (2×100 ml). The combined ether extracts were washed with water (100 ml), 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 **14** (1.61 g, 88%) as a colourless syrup. $[\alpha]_D^{25}$ −7.64 (c 0.95, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.98–2.2 (m, 2H, H-3,3′), 3.48–3.70 (m, 2H, H-5,5′), 4.22–4.4 (m, 1H, H-4), 4.48–4.74 (m, 3H, H-2 and OCH_2Ph), 5.78 (d, 1H, J=4.0 Hz, H-1), 7.2–7.40 (m, 5H, ArH). Anal. calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.11; H, 7.57.

3.4. 5-O-Benzyl-3-deoxy-1,2-O-isopropylidene-α-D-ribofuranose **15**

Prepared from **13** (1.4 g, 8.0 mmol) as described for compound **14** to obtain the title compound **15** (1.92 g, 91%) as a syrup. $[\alpha]_D^{25}$ −11.9 (c 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.31, 1.50 (2s, 6H, 2×CH_3), 1.65–1.84 (m, 1H, H-3), 2.3 (dd, 1H, J_{gem}=12.5, 4.6 Hz, H-3′), 3.48–3.70 (m, 2H, H-5,5′), 4.28–4.45 (m, 1H, H-4), 4.6 (s, 2H, OCH_2Ph), 4.70 (dd, 1H, J=4.3, 4.6 Hz, H-2), 5.8 (d, 1H, H-1), 7.2–7.4 (m, 5H, ArH). Anal. calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.38; H, 7.69.

3.5. 5-O-Benzyl-3-deoxy-L-arabinofuranose **16**

A solution of **14** (1.4 g, 5.3 mmol) in 40% aq. acetic acid (7 ml) and a drop of concd H_2SO_4 was stirred at 45°C for 6 h. After completion of the reaction, it was cooled to 10°C and neutralized with sodium hydrogen carbonate and extracted into ethyl acetate (2×100 ml). The organic phase was separated, washed with water (Na_2SO_4), filtered and concentrated to a residue which was purified on a bed of silica gel (60–120 mesh; hexane:EtOAc, 1:1) to obtain the title compound **16** (0.94 g, 80%) as a thick syrup. IR: ν_{max} 3450 cm^{-1} (OH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.72–2.6 (m, 2H, H-3,3′), 3.35–4.60 (m, 5H, H-2,4,5,5′ and OCH_2Ph), 4.7 (d, 1H, J=11.6 Hz, OCH_2Ph), 5.08–5.15 (br.s, 0.5H, H-1), 5.3 (s, 0.5H, H-1), 7.2–7.43 (m, 5H, ArH). Anal. calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.33; H, 7.16.

3.6. 5-O-Benzyl-3-deoxy-α/β-D-ribofuranose **17**

Prepared from **15** (1.8 g, 6.8 mmol) as described for compound **16** to obtain the title compound **17** (1.29 g, 85%) as a syrup. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.7–2.2 (m, 2H, H-3,3′), 2.7–3.0 (br.s, 1H, OH), 3.3–3.5 (m, 7H, H-1,2,4,5,5′ and OCH_2Ph), 7.08–7.41 (m, 5H, ArH). Anal. calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.22; H, 7.13.

3.7. (3aR,5R,6aR)-5-Benzyloxymethylperhydrofuro[3,2-b]furan-2-one **18** and [E,4R,6R]-ethyl-7-benzyloxy-4,6-dihydroxy-2-heptenoate **20**

To a solution of lactol **16** (0.3 g, 1.3 mmol) in methanol (10 ml) was added carboethoxymethylene triphenylphosphorane (0.91 g, 2.6 mmol) at 10°C and the reaction mixture was stirred for 8 h at 10°C. After completion of the reaction, solvent was removed under reduced pressure to obtain a residue which was chromatographed to elute first **20** (0.072 g, 18%) as a syrup. $[\alpha]_D^{25}$ −17.1 (c 0.3, $CHCl_3$); IR: ν_{max} 1718 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.3 (t, 3H, OCH_2CH_3), 1.4–1.8 (m, 2H, H-5,5′), 3.2–3.80 (m, 3H, H-6,7,7′) 4.02–4.1 (m, 1H, H-4), 4.15 (q, 2H, OC$H_2$$CH_3$), 4.55 (s, 2H, OC$H_2$Ph), 6.1 (d, 1H, J=16.5 Hz, H-2), 6.9 (dd, 1H, J=16.5, 6.2 Hz, H-3), 7.2–7.4 (m, 5H, ArH). Anal. calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.34; H, 7.58. This was followed by **18** (0.19 g, 57%) as a syrup. $[\alpha]_D^{25}$ +38.8 (c 0.39, $CHCl_3$); IR: ν_{max} 1770 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.12 (ddd, 1H, J=13.6, 7.8, 6.0 Hz, H-6), 2.4 (ddd, 1H, J=13.6, 6.0, 5.55 Hz, H-6′), 2.6–2.8 (m, 2H, H-3,3′), 3.38–3.6 (m, 2H, CH_2OBn), 4.22 (m, 1H, H-5), 4.48–4.7 (m, 3H, H-3a and OCH_2Ph), 4.98–5.1 (m, 1H, H-6a), 7.2–7.4 (m, 5H, ArH). Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.89; H, 6.58.

3.8. (3aR,5S,6aR)-5-Benzyloxymethylperhydrofuro[3,2-b]furan-2-one **19** and [E,4R,6S]-ethyl-7-benzyloxy-4,6-dihydroxy-2-heptenoate **21**

Prepared from **17** (0.9 g, 4 mmol) as described for compounds **18** and **20** to obtain the title compounds **19** (0.66 g, 66%) and **21** (0.18 g, 15%). Analytical data of **19**: mp 74–75°C; $[\alpha]_D^{25}$ +35.3 (c 1.35, $CHCl_3$); IR: ν_{max} 1769 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.02–2.2 (ddd, 1H, J=13.9, 9.0, 4.65 Hz, H-6), 2.35 (ddd, 1H, J_{gem}=13.9, 6.0, 1.5 Hz, H-6′), 2.68 (m, 2H, H-3,3′), 3.45 (dd, 1H, J_{gem}=11.6, 4.65 Hz, CH_2OBn), 3.60 (dd, 1H, J=4.1 Hz, CH_2OBn), 4.25–4.45 (m, 1H, H-5), 4.55 (s, 2H, OCH_2Ph), 4.81 (ddd, J=4.6, 0.7, 6.1 Hz, H-3a), 5.12 (dd, 1H, J=4.7 Hz, H-6a), 7.18–7.40 (m, 5H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 176.2 (C-2), 127.5–137.0 (aromatic), 84.7 (C-6a), 78.4 (C-3a), 77.8 (OCH_2Ph), 73.4 (C-5), 71.5 (CH_2OBn), 36.6 (C-3), 32.2 (C-6). Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.71; H, 6.48. Spectral data of **21**: $[\alpha]_D$ +6.1 (c 0.4, $CHCl_3$); IR: ν_{max} 1718 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, 3H, J=8.2 Hz, OCH_2CH_3), 1.5–2.2 (m, 2H, H-5,5′), 3.38–3.78 (m, 3H, H-6,7,7′), 4.25 (q, 2H, J=8.0 Hz, OC$H_2$$CH_3$), 4.5–4.7 (m, 3H, H-4 and OCH_2Ph), 6.15 (d, J=16.2 Hz, H-2), 6.95 (dd, 1H, J=16.0, 3.8 Hz, H-3), 7.2–7.4 (m, 5H, ArH). Anal. calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.38; H, 7.62.

3.9. (3aR,5R,6aR)-Hydroxymethylperhydrofuro[3,2-b]furan-2-one **22**

To a solution of **18** (0.18 g, 0.72 mmol) in methanol (10 ml) was added 10% Pd/C (10 mg) and the mixture was stirred under hydrogen atmosphere (1 atm) for 3 h at room temperature. The catalyst was filtered off and the solvent removed under reduced pressure to obtain the title compound **22** (0.11 g, 93%) as a thick syrup; $[\alpha]_D^{25}$ +34.2 (c 0.3, MeOH); IR: 1771 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.9–2.45 (m, 2H, H-6,6′), 2.65–2.9 (m, 2H, H-3,3′), 3.5–4.3 (m, 3H, H-5, CH_2OH), 4.5 (br.s, 1H, OH), 4.55–4.65 (m, 1H, H-3a), 4.95–5.1 (m, 1H, H-6a). Anal. calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.27; H, 6.32.

3.10. (3aR,5S,6aR)-Hydroxymethylperhydrofuro[3,2-b]furan-2-one **5**

Prepared from **19** (0.6 g, 2.4 mmol) as described for compound **22** to obtain the title compound **5** (0.36 g, 95%) as a syrup. $[\alpha]_D^{25}$ 41.7 (c 1.4, $CHCl_3$); IR: ν_{max} 1769 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.75 (br.s, 1H, OH), 2.02–2.24 (ddd, H, J=14.1, 4.2, 1.8 Hz, H-6), 2.38 (dd, 1H, J_{gem}=14.1, 4.85 Hz, H-6′), 2.6–2.9 (m, 2H, H-3,3′), 3.6 (dd, 1H, J_{gem}=14.0, 5.8 Hz, CH_2OH), 3.9 (dd, 1H, J=5.4 Hz, CH_2OH), 4.2–4.42 (m, 1H, H-5), 4.88 (ddd, 1H, J=6.1, 0.6, 4.7 Hz, H-3a), 5.16 (dd, 1H, J=6.1, 4.85 Hz, H-6a); ^{13}C NMR (50 MHz, $CDCl_3$): δ 33.8 (C-6), 38.7 (C-3), 63.3 (CH_2OH), 78.3 (C-5), 79.0 (C-3a) 85.0 (C-6a), 75.0 (C-2). Anal. calcd for $C_7H_{10}O_7$: C, 53.16; H, 6.37. Found: C, 53.12; H, 6.32.

3.11. (3aR,5R,6aR)-5-tert-Butyldiphenylsilyloxymethylperhydro[3,2-b]furan-2-one **4**

To a solution of **22** (0.24 g, 0.5 mmol) in pyridine (1 ml) at 0°C was added *tert*-butyldiphenylsilyl chloride (0.2 g, 0.76 mmol) and the mixture stirred for 2 h at room temperature. After completion of the reaction, it was diluted with water (50 ml) and extracted into diethyl ether (2×75 ml). 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 **4** (0.51 g, 85%) as a syrup. $[\alpha]_D^{25}$ +25.4 (c 0.8, $CHCl_3$); IR: ν_{max} 1771 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$):[8,16] δ 1.2 (s, 9H, CMe_3), 2.1–2.42 (m, 2H, H-6,6′), 2.65 (d, 2H, J=4.0 Hz, H-3,3′), 3.58–3.8 (m, 2H, CH_2OSiPh$_2$*t*-Bu), 4.0–4.2

(m, 1H, H-5), 4.55 (dd, 1H, J=3.6, 4.1 Hz, H-3a), 4.9–5.05 (m, 1H, H-6a), 7.3–7.8 (m, 10H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.0, 26.2 (CMe_3), 34.0 (C-6), 36.6 (C-3), 65.8 ($CH_2OTBDPS$), 78.8 (C-5), 80.7 (C-3a), 84.2 (C-6a), 127.0–136.0 (aromatic), 175.1 (C-2). Anal. calcd for $C_{23}H_{28}O_4Si$: C, 69.66; H, 7.12. Found: C, 69.78; H, 7.21.

*3.12. (3a*R*,5*S*,6a*R*)-5-*tert*-Butyldiphenylsilyloxymethylperhydro[3,2-*b*]furan-2-one **7***

Prepared from **5** (0.3 g, 1.9 mmol) as described for compound **4** to obtain the title compound **7** (0.66 g 88%) as a syrup. $[\alpha]_D^{25}$ +25.0 (c 0.8 $CHCl_3$); IR: ν_{max} 1771 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.1 (s, 9H, CMe_2), 2.1–2.45 (m, 2H, H-6,6′), 2.55–2.8 (m, 2H, H-3,3′), 3,7 (dd, 1H, J=9.2, 4.0 Hz, C*H*$_2$OSiPh$_2$*t*-Bu), 3.9 (dd, 1H, C*H*$_2$OSiPh$_2$*t*-Bu), 4.2–4.39 (m, 1H, H-5), 4.72–4.84 (m, 1H, H-3a), 5.1 (dd, 1H, J=4.5, 4.9 Hz, H-6a), 7.3–7.75 (m, 10H, ArH). Anal. calcd for $C_{23}H_{28}O_4Si$: C, 69.66; H, 7.12. Found: C, 69.71; H, 7.12.

*3.13. 5-[(*E/Z*)-1-Butenyl]-(3a*R*,5*S*,6a*R*)-perhydrofuro[3,2-*b*]furan-2-one **23***

Dry dichloromethane (5 ml) containing dimethylsulfoxide (0.25 g, 2.4 mmol) was added to solution of oxalyl chloride (0.26 g, 2.0 mmol) in dry dichloromethane (5 ml) at −78°C and the resulting solution was stirred for 20 min. A solution of lactone **5** (0.25 g, 1.6 mmol) in dry dichloromethane was added to the above reaction mixture and the whole was stirred for 45 min followed by the addition of triethylamine (0.48 g, 4.7 mmol). The reaction mixture was brought gradually to room temperature and diluted with dichloromethane (40 ml). The organic layer was washed with brine (2×25 ml), dried (Na_2SO_4) and evaporated to obtain the aldehyde as a thick syrup, which was immediately treated with a solution of propylidenetriphenylphosphorane [generated in situ from $nC_3H_7P^+Ph_3Br^-$ (1.13 g, 2.94 mmol), $NaNH_2$ (0.1 g, 2.6 mmol), THF (2.5 ml)] under a nitrogen atmosphere for 1.5 h at −20°C. The reaction mixture was then quenched with satd aq. ammonium chloride (25 ml) and extracted into diethyl ether (2×30 ml). The combined ethereal layers were washed with water, dried (Na_2SO_4) and concentrated to a residue which was chromatographed [SiO_2, 60–120 mesh, hexane:EtOAc, 4:1] to obtain the title compound **23** (0.13 g, 45%) as a colourless oil. $[\alpha]_D^{25}$ −21.2 (c 0.9, $CHCl_3$); IR: ν_{max} 1769 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.1 (t, 3H, J=8.0 Hz, C*H*$_3$CH$_2$), 1.6–2.5 (m, 4H, H-6,6′ and CH$_3$C*H*$_2$), 2.6–2.9 (m, 2H, H-3,3′), 4.40–4.52 (m, 1H, H-3a), 4.8–4.92 (m, 1H, H-5), 5.01–5.15 (m, 1H, 6a), 5.28–5.70 (m, 2H, *n*-C_4H_7 olefinic). Anal. calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.95; H, 7.81.

*3.14. 5[(*E/Z*)-1-Hexenyl]-(3a*R*,5*S*,6a*R*)-perhydrofuro[3,2-*b*]furan-2-one **24***

Prepared from **5** (0.2 g, 1.2 mmol) as described for compound **23** to obtain the title compound **24** (0.13 g, 49%) as a thick syrup. $[\alpha]_D^{25}$ −18.9 (c 0.6, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.1 (t, 3H, J=8.0 Hz, C*H*$_3$CH$_2$), 1.3–2.5 (m, 8H, H-6,6′ and CH$_3$(C*H*$_2$)$_3$), 2.6–2.9 (m, 2H, H-3,3′), 4.40–4.52 (m, 1H, H-3a), 4.8–4.92 (m, 1H, H-5), 5.01–5.15 (m, 1H, H-6a), 5.28–5.70 (m, 2H, *n*-C_4H_7 olefinic). Anal. calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.60; H, 8.69.

*3.15. (3a*R*,5*R*,6a*R*)-5-Butylperhydrofuro[3,2-*b*]furan-2-one **2***

A solution of ene **23** (0.12 g) in ethanol (10 ml) was subjected to hydrogenation with W-4 Raney-Ni catalyst (approximately 0.1 g) for 2 h. The catalyst was filtered off and the filtrate was concentrated to obtain the title compound **2** (0.11 g, 92%) as a syrup. $[\alpha]_D^{25}$ +51.1 (c 1.0, $CHCl_3$); IR: ν_{max} 1771 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.8–1.8 (m, 10H, H-6 and *n*-C_4H_9), 2.38 (dd, 1H, J=14.8, 4.2 Hz, H-6), 2.64 (dd, 1H, J=19.1, 0.7 Hz, H-3), 2.75 (dd, 1H, J=19.1, 6.4 Hz, H-3), 4.07 (4d, 1H, J=10.0, 7.2, 5.2, 4.2 Hz, H-5), 4.80 (ddd, 1H, J=6.4, 4.5, 0.7 Hz, H-3), 5.11 (dd, 1H, J=4.9, 4.5 Hz, H-6a); ^{13}C NMR 50 MHz, $CDCl_3$): δ 13.8, 12.5, 28.0, 34.2, 36.5, 38.6, 77.2, 78.1, 84.8, 175.9 (C=O). Anal. calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.27; H, 8.81.

*3.16. (3a*R*,5*R*,6a*R*)-5-Hexylperhydrofuro[3,2-*b*]furan-2-one **3***

Prepared from **24** as described for compound **2** in 94% yield. $[\alpha]_D^{25}$ +49.7 (c 1.0, $CHCl_3$); IR: ν_{max} 1771 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.8–1.8 (m, 14H, H-6 and *n*-C_6H_{13}), 2.38 (dd, 1H, J=14.8, 4.2 Hz, H-6), 2.64 (dd, 1H, J=19.1, 0.7 Hz, H-3), 2.75 (dd, 1H, J=19.1, 6.4 Hz, H-3), 4.07 (4d, 1H, J=10.0, 7.2, 5.2, 4.2 Hz, H-5), 4.80 (ddd, 1H, J=6.4, 4.5, 0.7 Hz, H-3), 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, 67.97; H, 9.58.

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References

1. Faulkner, D. *J. Nat. Prod. Rep.* **1992**, *9*, 323–364 and references cited therein.
2. For reviews on the subject, see: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309–3362; (b) Cardillo, G.; Orena, M. *ibid.* **1990**, *46*, 3321–3409 and references cited therein; (c) Barlett, P. A. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp. 411–454.
3. Suzuki, T.; Koizumi, K.; Suzuki, M.; Kurosawa, E. *Chem. Lett.* **1983**, 1643–1644.
4. Brown, M. J.; Harrison, T.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5378–5384.
5. Osumi, K.; Sugimura, H. *Tetrahedron Lett.* **1995**, *36*, 5789–5792.
6. Martin, T.; Soler, M. A.; Betancort, J. M.; Martin, V. S. *J. Org. Chem.* **1997**, *62*, 1570–1571.
7. Lee, E.; Yoo, S.-K.; Cho, Y.-S.; Cheon, H.-S.; Chong, Y. H. *Tetrahedron* **1997**, *38*, 7757–7758.
8. Boukouvalas, J.; Fortier, G.; Radu, I.-I. *J. Org. Chem.* **1998**, *62*, 916–917.
9. Fernandez de la Pradilla, R.; Montero, C.; Priego, J.; Martinez-Cruz, L. A. *J. Org. Chem.* **1998**, *63*, 9612–9613.
10. (a) Mereyala, H. B.; Gadikota, R. R.; Krishnan, R. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3567–3571; (b) Mereyala, H. B.; Gadikota, R. R.; Joe, M.; Arora, S. K.; Dastidar, S. G.; Agarwal, S. *Bioorg. Med. Chem.* **1999**, *7*, 2095–2103.
11. (a) Hagens, K. L. *Proc. Hawaii Entomol. Sc.* **1953**, *15*, 115–118; (b) Buckingham, G. R. *Ann. Entamol. Soc. Am.* **1968**, *61*, 233–234; (c) Williams, H. J.; Wong, M.; Wharton, R. A.; Vinson, S. B. *J. Chem. Ecol.* **1988**, *14*, 1727–1736.
12. Paddon-Jones, G. C.; More, C. J.; Brecknell, D. J.; Konig, W. A.; Kitching, W. *Tetrahedron Lett.* **1997**, *38*, 3479–3482.
13. Mereyala, H. B.; Gadikota, R. R. *Chem. Lett.* **1999**, 273–274.
14. Thomas, S. S.; Pleukiewicz, J.; Ison, E. R.; Bols, M.; Zou, W.; Szarek, W. A.; Kisilevsky, R. *Biochim. Biophys. Acta* **1995**, *1272*, 37–48.
15. (a) Iacono, S.; Rasmussen, J. R. *Org. Synth.* **1986**, *64*, 57–62; (b) Szabo, P.; Szabo, L. *J. Chem. Soc.* **1964**, 5139–5143.
16. (a) Corey, E. J.; Ruden, R. A. *Tetrahedron Lett.* **1973**, 1495–1499; (b) Herrera, F. J. L.; Conzalez, M. S. P.; Sampedro, M. N.; Aciego, R. M. D. *Tetrahedron* **1989**, *45*, 269–276; (c) Prakash, K. R. C.; Rao, S. P. *Tetrahedron* **1993**, *49*, 1505–1510.
17. Personal communication with Professor J. Boukouvalas.