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Synthesis of harzialactone A and its isomers from D-glucose and assignment of absolute stereochemistry

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Abstract

The synthesis of the marine metabolite (3*R*,5*R*)-harzialactone A **1** from D-glucose is described. Syntheses of all the isomers (3*S*,5*R*)-**2**, (3*R*,5*S*)-**3** and (3*S*,5*S*)-**4** of **1** are also described and the absolute stereochemistry for the natural product **1** is assigned unambiguously. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

Marine microorganisms have been a rich source of bioactive metabolites, especially those with novel structural features that might represent possible leads in the new drug discovery process.[1] Numata et al. have previously isolated antitumour and cytotoxic compounds from microorganisms living in the marine environment.[2] *Trichoderma harzianum* OUPS-N115 strain that was initially isolated from the sponge *Halichondria okadai* collected in the Tanabe Bay of Japan and crude metabolites extracted were shown to exhibit cytotoxic activity against the P388 lymphocytic leukaemia test system in cell cultures.[2] Fractionation of the crude culture filtrate resulted in the isolation of harzialactone A **1** among other lactones. The absolute stereochemistry for **1** was established using ^{1}H NMR spectra by comparison of the observed coupling constants and NOE data with those of related compounds.[2]

Due to our interest in the design and synthesis of oxygenated lactones[3] as cytotoxic agents, we targeted the synthesis of harzialactone A **1** and its isomers for studying structure–activity relationships. We have earlier reported the synthesis of harzialactone A **1** by a chiron approach and revised the absolute stereochemistry as 3*R* and 5*R* configurations.[4] Now, we report the synthesis of all possible stereoisomers of harzialactone A **1**, viz. (3*S*,5*R*)-**2**, (3*R*,5*S*)-**3** and (3*S*,5*S*)-**4**, respectively, by a similar chiron approach and unambiguously assign the absolute configuration for the natural harzialactone A **1** as 3*R* and 5*R*.

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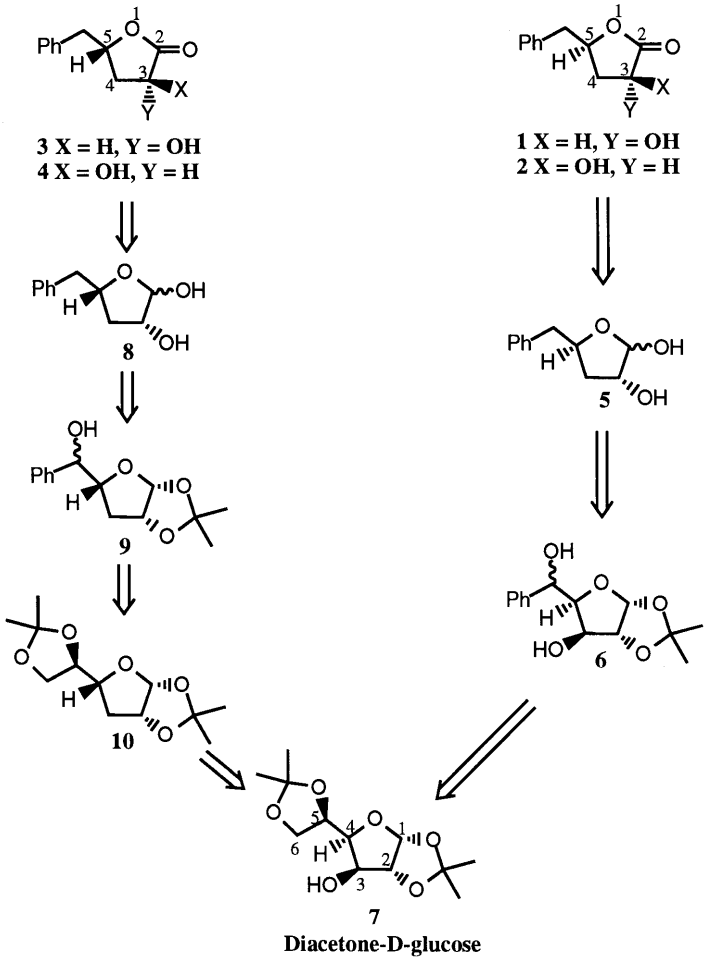
2. Results and discussion

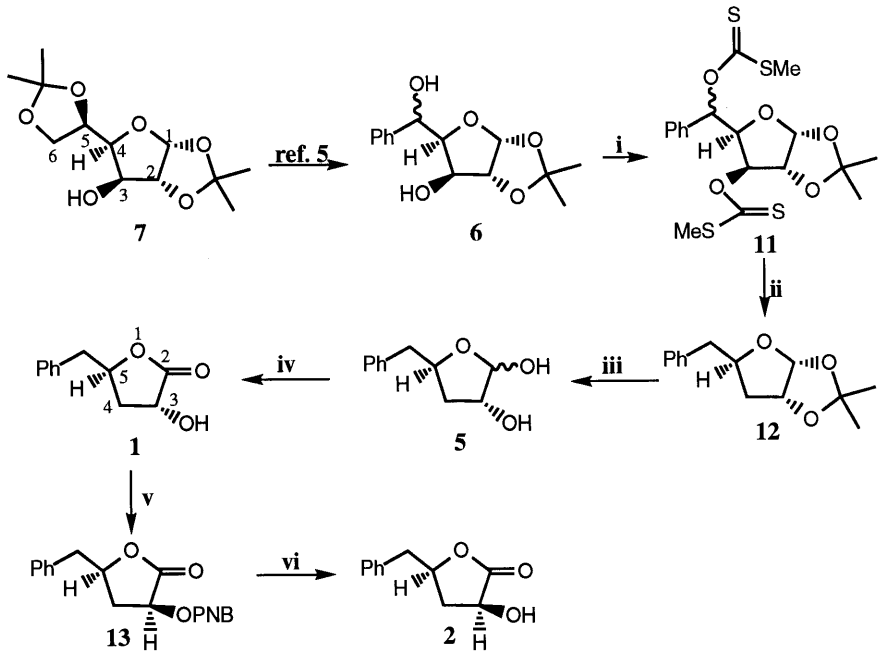
Retrosynthetic analysis of (3*R*,5*R*)-**1** indicates that it could be derived from diol **5** by regioselective oxidation of the lactol (Scheme 1). Diol **5** in turn could be derived from diacetone-D-glucose **7** having the appropriate stereogenic centres at C-2 and C-4. The isomeric hydroxyfuranolactone (3*R*,5*S*)-**3**, which is an antipode of **2**, could be derived from diol **8** by a similar sequence of reactions via intermediates **9** and **10** derived from D-glucose by inverting the configuration at C-4. The hydroxylactones (3*S*,5*R*)-**2** and (3*S*,5*S*)-**4** could be derived by inverting the configuration at C-3 of **1** and **3**, respectively.



Scheme 1.

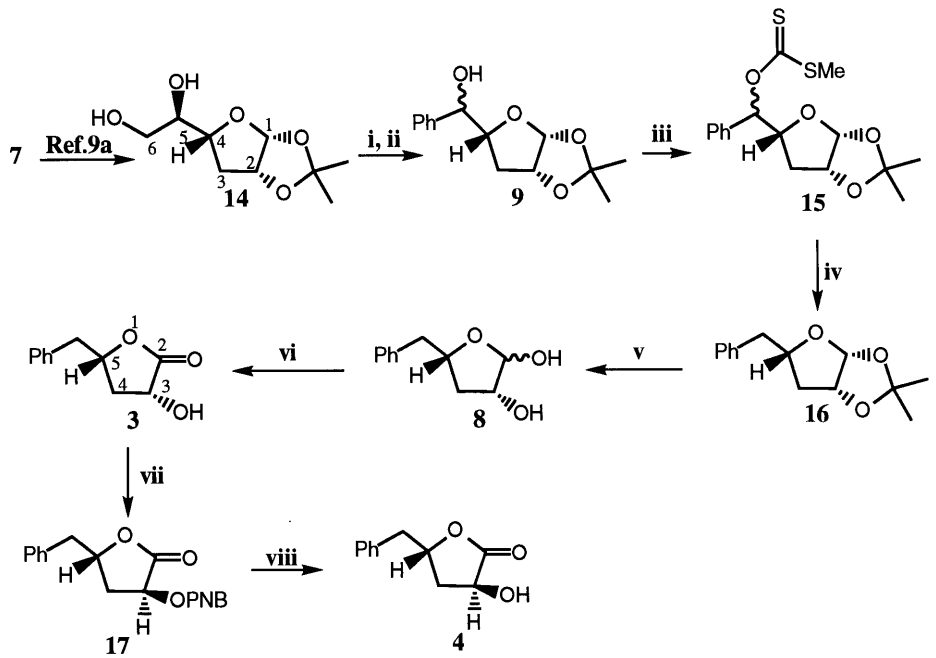
Thus, for the synthesis of **1**, diacetone-D-glucose **7** was transformed into the diol **6** in good yield by well established methods[5] (Scheme 2). Compound **6** was converted to the methyl xanthate derivative **11** by reaction with NaH–CS_2–MeI in THF and subjected to radical deoxygenation (BU_3SnH/cat. AIBN)[6] in refluxing toluene to obtain the dideoxy derivative **12** in an overall yield of 25% from D-glucose. Compound **12** was characterised from the ^1H NMR spectrum by the appearance of H-3 protons (2H) between δ 1.40 and 1.60 (m, 1H, overlapped)

and at δ 2.00 (ddd, 1H, $J_{3,3'}$ 13.0 Hz, $J_{3,2}$ 3.5 Hz, $J_{4,3'}$ 4.5 Hz) and benzylic protons at δ 2.80 (dd, 1H, J_{gem} 13.0 Hz, $J_{1',4}$ 6.0 Hz) and δ 3.02 (dd, 1H, $J_{1'',4}$ 5.0 Hz). Compound **12** was subjected to deprotection of the acetonide with aqueous acetic acid containing a catalytic amount of conc. H_2SO_4 to obtain the diol **5** as a crystalline solid, mp 91–93°C. Regioselective oxidation of the diol **5** with pyridinium dichromate in CH_2Cl_2 at reflux temperature gave the required lactone **1** in 10% yield. However, oxidation of **5** by use of Ag_2CO_3/Celite[7] in benzene:*N*,*N*-dimethylformamide (DMF) (8:1) at reflux temperature resulted in the isolation of the lactone **1** in 71% yield. Compound **1** was characterised from the ^{1}H NMR spectrum by the appearance of an H-3 proton at δ 3.95 (td, 1H, $J_{3,4}$ 8.3 Hz, $J_{3,4'}$ 8.3 Hz, J_{OH} 1.9 Hz) and from the characteristic IR absorption of γ-lactone at 1769 cm^{-1} and hydroxyl at 3500 cm^{-1}. Compound **1** exhibited a specific rotation of +38.0 (*c* 0.3, $CHCl_3$). ^{13}C, ^{1}H NMR and specific rotation data of (3*R*,5*R*)-**1** were in complete agreement with the data reported for the natural product that was earlier assigned (3*S*,5*S*)-configuration.[2] In order to assign unambiguously the absolute stereochemistry of **1**, syntheses of its antipode (3*S*,5*S*)-**4**[2] and the other two isomers **2** and **3** were also considered. Synthesis of (3*S*,5*R*)-hydroxylactone **2** was planned from **1** involving the inversion of configuration at C-3 by Mitsunobu reaction[8] of **1**. Thus, reaction of **1** with DEAD/*p*-$NO_2C_6H_4CO_2H/Ph_3P$ in THF gave the *p*-nitrobenzoate **13**. Formation of **13** was evident from the ^{1}H NMR spectrum by the appearance of H-3 at δ 5.73 (dd, $J_{3,4}$ 6.5 Hz, $J_{3,4'}$ 9.0 Hz) shifted downfield due to esterification. Compound **13** on reaction with a catalytic amount of NaOMe in methanol:dichloromethane (1:1) strictly at −20°C resulted in the isolation of (3*S*,5*R*)-**2** as a crystalline solid, mp 94–97°C, $[\alpha]_D$ −8.5 (*c* 1.1, $CHCl_3$). Compound **2** was characterised from ^{1}H NMR by the appearance of H-3 at δ 4.40–4.70 (m, 1H) merged with H-5 and the IR spectrum from the characteristic γ-lactone absorption at 1772 cm^{-1}.



Scheme 2. *Reagents and conditions:* i, NaH, CS_2, MeI, THF, 0°C→rt; ii, nBu_3SnH, AIBN, toluene, reflux; iii, 60% aq. CH_3COOH, cat. H_2SO_4, 45°C; iv, Ag_2CO_3–Celite, C_6H_6:DMF (8:1), reflux; v, *p*-NB acid, Ph_3P, DEAD, THF, 0°C→rt; vi, $NaOCH_3$, MeOH:CH_2Cl_2 (1:1), −20°C

Synthesis of hydroxylactone (3*R*,5*S*)-**3** was achieved starting from diacetone-D-glucose **7**. Compound **7** was converted to the 3-deoxy diol derivative **14** by literature methods[9a] and reacted with sodium metaperiodate to obtain the corresponding aldehyde that was immediately reacted with phenylmagnesium bromide to isolate the alcohol **9** (Scheme 3). Compound **9** was converted to the methyl xanthate ester **15** and deoxygenated to obtain the dideoxyfuranose derivative **16** in good yield. Reaction of **16** with aq. acetic acid containing a catalytic amount of conc. H_2SO_4 resulted in the isolation of diol **8**, that on further regioselective oxidation with Ag_2CO_3/Celite in benzene:DMF (8:1) at reflux temperature gave the hydroxylactone (3*R*,5*S*)-**3** as a crystalline solid in good yield, mp 101–103°C, $[\alpha]_D$ +8.7 (*c* 1.1, $CHCl_3$). Compound **3** was characterised by ^1H NMR spectrum from the appearance of H-3 at δ 4.40–4.70 (m, 1H) merged along with H-5. (3*R*,5*S*)-**3** was identical to (3*S*,5*R*)-**2** in the ^1H and ^{13}C NMR spectra, except it exhibited the opposite sign of the specific rotation. Thus, **3** is an enantiomer of **2**.

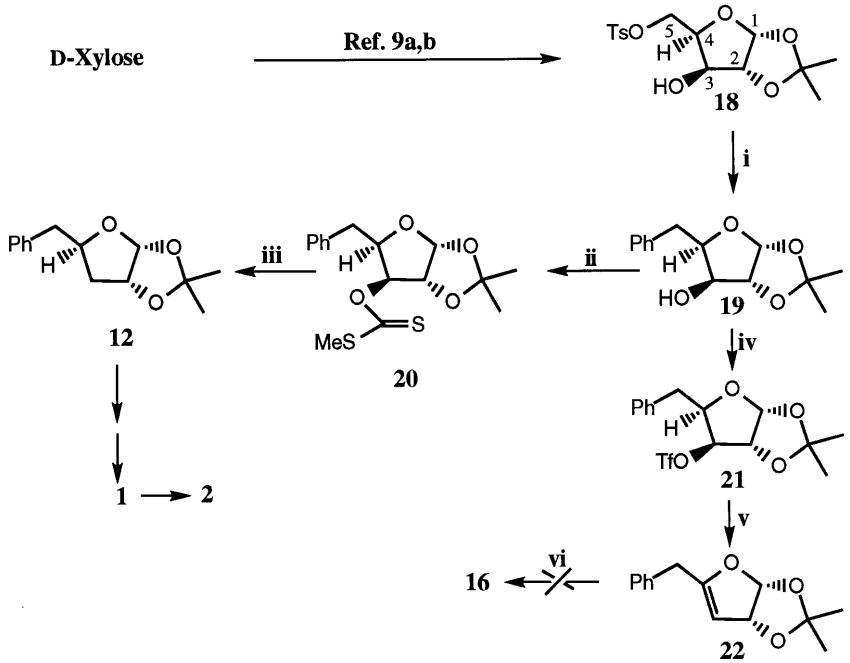


Scheme 3. *Reagents and conditions*: i, $NaIO_4$, CH_2Cl_2:MeOH:sat. aq. $NaHCO_3$, 0°C→rt; ii, phenylmagnesium bromide, THF, 0°C; iii, NaH, CS_2, MeI, THF, 0°C→rt; iv, Bu_3SnH, AIBN, toluene, reflux; v, 60% aq. CH_3COOH, cat. H_2SO_4, 45°C; vi, Ag_2CO_3–Celite, C_6H_6:DMF (8:1), reflux; vii, *p*-NB acid, Ph_3P, DEAD, THF, 0°C→rt; viii, $NaOCH_3$, MeOH:CH_2Cl_2 (1:1), −20°C

The synthesis of hydroxylactone (3*S*,5*S*)-**4** was achieved from **3** by inverting the configuration at the C-3 hydroxyl. Thus, the Mitsunobu reaction of **3** (DEAD/*p*-$NO_2C_6H_4CO_2H$/Ph_3P) gave the *p*-nitrobenzoyl ester derivative **17** that on further reaction with a catalytic amount of NaOMe in MeOH and dichloromethane (1:1) at −20°C gave (3*S*,5*S*)-**4** in good yield, as a crystalline solid, mp 71–74°C, $[\alpha]_D$ −38.0 (*c* 0.3, $CHCl_3$). (3*S*,5*S*)-**4** was characterised as the enantiomer of (3*R*,5*R*)-**1** due to the negative sign of specific rotation and superimposable ^1H and ^{13}C NMR spectra. Thus, natural harzialactone A was unambiguously assigned the structure (3*R*,5*R*)-**1** and not (3*S*,5*S*) as was assigned earlier.[2]

In order to prepare a large number of structural analogues of **1** for studying structure–activity relationships, we have developed an alternative, high yielding and concise synthetic route

starting from D-xylose. Thus, reaction of 1,2-*O*-isopropylidene-α-D-xylofuranose with *p*-toluenesulphonyl chloride gave the mono tosylate **18** in good yield[9a,b] (Scheme 4). Compound **18** on Grignard reaction with phenylmagnesium bromide gave **19**. Compound **19** was converted to the methyl xanthate ester **20** and then deoxygenated (Bu_3SnH/AIBN) to obtain the advanced intermediate **12** in an overall yield of 40% from D-xylose. Syntheses of **1** and **2** from **12** have been carried out as described in Scheme 2. In order to synthesise **3** and **4** from the intermediate **19** it was required to deoxygenate the C-3 hydroxyl group and invert the configuration at C-2 (Scheme 4). Compound **19** was converted to the 3-*O*-triflate **21** and reacted with DBU in benzene to obtain unsaturated furan derivative **22** in good yield. Compound **22** was characterised from the ^1H NMR spectrum by the appearance of a double bond proton H-3 at δ 5.95–6.18 merged with H-1. However, hydrogenation of **22** with Raney Ni in ethanol at 1 atm pressure of H_2 to obtain **16** resulted in decomposition of **22**. Hence, it was not possible to prepare hydroxylactones **3** and **4** by this route.



Scheme 4. *Reagents and conditions:* i, phenylmagnesium bromide, THF, 0°C→rt; ii, NaH, CS_2, MeI, THF, 0°C→rt; iii, Bu_3SnH, AIBN, toluene, reflux; iv, trifluoromethanesulphonic anhydride, pyridine, CH_2Cl_2, 0°C; v, DBU, THF, 60°C; vi, (W4)-Raney Ni, EtOH, 1 atm H_2

In conclusion syntheses of all four stereoisomers **1**–**4** of harzialactone A have been achieved by a chiron approach starting from D-glucose. The naturally occurring harzialactone A **1** was unambiguously assigned the correct absolute stereochemistry.

3. Experimental

^1H NMR spectra were measured with a Varian Gemini 200 MHz spectrometer with tetramethylsilane as internal standard for solutions in deuteriochloroform. *J* values are given in

Hertz. ^{13}C NMR spectra were recorded on a Varian Gemini 50 MHz spectrometer with $CDCl_3$ as the internal standard (δ_C 77.0) for solutions in deuteriochloroform. Optical rotations were measured with a JASCO DIP-370 instrument and $[\alpha]_D^{25}$ values are in units of 10^{-1} deg cm^2 g^{-1}. All melting points are uncorrected. IR spectra were recorded on a Perkin–Elmer 1310 spectrometer. All organic solvents were freshly distilled prior to use. Air sensitive reactions were generally performed under a positive pressure of nitrogen within the glassware, which had been flame-dried under vacuum.

*3.1. A mixture of 1-[2,2-dimethyl-(6*S*)-O-(*S*-methyl dithiocarbonyl)-(3a*R*,5*R*,6a*R*)perhydrofuro-[2,3-*d*][1,3]dioxol-5-yl]-phenylmethyl-(1*R/S*)-O-(*S*-methyl dithiocarbonate)* **11**

To a solution of compound **6**[5] (3.5 g, 13.2 mmol) in dry THF was added hexane washed sodium hydride (0.8 g, 33.0 mmol) at 0°C and the mixture was stirred for 15 min. To the above reaction mixture at 0°C was added carbon disulphide (2.0 mL, 33.0 mmol) and this was stirred for 15 min. This was followed by the addition of iodomethane (2.1 mL, 33.0 mmol) at 0°C and the reaction mixture was brought to room temperature and stirred. When the reaction was complete, excess sodium hydride was quenched with a few drops of acetic acid and concentrated to obtain a residue, which was dissolved in dichloromethane (100 mL), washed with water (2×40 mL), dried (Na_2SO_4), filtered and concentrated to a residue which was filtered on a bed of silica gel [60–120 mesh, hexane:ethyl acetate (4:1)] to obtain a diastereomeric mixture (3:1) of the title compound **11** (5.5 g, 94%) as a colourless syrup. δ_H (200 MHz; $CDCl_3$) 1.30, 1.50, 1.60 (6H, 3s, 2×Me), 2.50, 2.54, 2.60, 2.64 (6H, 4s, 2×SMe), 4.58, 4.64 (1H, 2d, J 4.7, H-6a), 4.75–4.92 (1H, m, H-5), 5.34, 5.90 (1H, 2d, J 2.3, 4.5, H-6), 6.00, 6.14 (1H, 2d, J 2.3 4.5 H-3a) 6.60, 6.71 (1H, 2d, J 10.0 $C_6H_5C\underline{H}$) and 7.25–7.50 (5H, m, ArH); found: C, 48.59; H, 4.82%; $C_{18}H_{22}O_5S_4$ requires: C, 48.41; H, 4.97%.

*3.2. 2,2-Dimethyl-5-phenylmethyl-(3a*R*,5*R*,6a*R*)-perhydrofuro[2,3-*d*][1,3]dioxole* **12**

To a solution of the dixanthate **11** (5.45 g, 12.2 mmol) in dry toluene (225 mL) were added tributyltin hydride (8.9 g, 30.5 mmol), AIBN (5 mg) and the mixture was refluxed under a nitrogen atmosphere for 6 h. After completion of the reaction, solvent was removed under reduced pressure to obtain a residue which was filtered on a bed of silica gel [60–120 mesh, hexane:ethyl acetate (6:1)] to obtain the title compound **12** (2.1 g, 74%) as a colourless syrup. $[\alpha]_D$ −18.0 (c 1.3, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 1.29, 1.49 (6H, 2s, 2×Me), 1.40–1.60 (1H, m, H-6, merged), 2.00 (1H, ddd, J_{gem} 13.0, $J_{6,6a}$ 3.5, $J_{5,6'}$ 4.5, H-6′), 2.80 (1H, dd, J_{gem} 13.0, $J_{1',5}$ 6.0, $C_6H_5C\underline{H}_2$), 3.02 (1H, dd, $J_{1'',5}$ 5.0, $C_6H_5C\underline{H}_2$), 4.40 (1H, dddd, H-5), 4.65 (1H, t, $J_{3a,6a}$ 4.0, $J_{6,6a}$ 4.0, H-6a), 5.80 (1H, d, H-3a), 7.10–7.35 (5H, m, ArH); δ_C (50 MHz, $CDCl_3$) 25.9, 26.5 (2×$\underline{C}H_3$), 38.3 (C-6), 40.2 ($C_6H_5\underline{C}H_2$), 78.1, 80.2 (C-5, 6a), 105.2 (C-3a), 110.6 (C-2) and 126.2–137.5 (aromatic); found: C, 71.94; H, 7.88%; $C_{14}H_{18}O_3$ requires: C, 71.77; H, 7.74%.

Prepared from compound **20** (1.15 g, 3.40 mmol), by reaction with tributyltin hydride (1.2 g, 4.1 mmol) and AIBN (5 mg) as described for the preparation of compound **12** from **11**, to obtain the title compound **12** (0.61 g, 77%) as a colourless syrup. Analytical data obtained were in complete agreement with the compound obtained from **11**.

3.3. A mixture of 5-phenylmethyl-(2S/R,3R,5R)-tetrahydrofuran-2,3-diol **5**

A solution of **12** (2.0 g, 8.5 mmol) in 60% aq. acetic acid (12 mL) and a catalytic amount of H_2SO_4 was stirred at 45°C for 6 h. After completion of the reaction, it was neutralised carefully with solid $NaHCO_3$ and extracted into ethyl acetate (40 mL). The organic phase was separated, washed with water (2×15 mL), dried (Na_2SO_4), filtered and concentrated to a residue which was purified on a bed of silica gel [60–120 mesh, hexane:ethyl acetate (1:2)] to obtain the title compound **5** (1.4 g, 85%) as a crystalline solid, mp 91–93°C. $[\alpha]_D$ +17.0 (*c* 0.6, $CHCl_3$). δ_H (200 MHz, $CDCl_3$) 1.80–2.10 (2H, m, H-4,4′), 2.63 (1H, br.s, OH), 2.70–3.20 (2H, m, $C_6H_5C\underline{H}_2$), 3.80 (1H, br.s, OH), 4.10–4.35 (1H, m, H-5), 4.50–4.75 (1H, m, H-3), 5.27 (0.4H, s, H-2), 5.38 (0.6H, d, $J_{2,3}$ 3.0, H-2) and 7.20–7.45 (5H, M, ArH); δ_C (50 MHz, $CDCl_3$) 37.2, 37.7 (C-4), 41.4, 43.3 ($C_6H_5\underline{C}H_2$), 70.5, 75.8, 76.3, 79.1 (C-3,5), 96.3, 102.6 (C-2) and 125.0–138.5 (aromatic); found: C, 68.25; H, 7.31%; $C_{11}H_{14}O_3$ requires: C, 68.02; H, 7.27%.

3.4. 3-Hydroxy-5-phenylmethyl-(3R,5R)-tetrahydrofuran-2-one **1**

To a solution of **5** (1.3 g, 6.7 mmol) in benzene:*N*,*N*-dimethylformamide (20 mL, 8:1) was added Ag_2CO_3–Celite (4.8 g, 8.0 mmol) and refluxed for 3 h. After completion of the reaction, the catalyst was filtered off and concentrated to a residue, which was chromatographed on silica gel [60–120 mesh, hexane:ethyl acetate (3:1)] to obtain the title compound **1** (0.91 g, 71%) as a white solid, mp 78–79°C (lit.,[2] 82–84°C). $[\alpha]_D$ +38.0 (*c* 0.3, $CHCl_3$). ^1H NMR, ^{13}C NMR and IR spectra of **1** were in complete agreement with the reported data.[2]

3.5. 3-(4-Nitrophenylcarbonyloxy)-5-phenylmethyl-(3S,5R)-tetrahydrofuran-2-one **13**

To a solution of compound **1** (0.8 g, 4.0 mmol) in dry THF (30 mL) were added 4-nitrobenzoic acid (1.9 g, 11.6 mmol) and triphenylphosphine (3.7 g, 14.2 mmol) followed by diethyl azodicarboxylate (2.7 g, 15.6 mmol) in dry THF (5 mL) at 0°C and then the reaction mixture was brought to room temperature and stirred under a nitrogen atmosphere for 8 h. After completion of the reaction, the solvent was removed in vacuo to obtain a residue which was purified by column chromatography [SiO_2, 60–120 mesh, hexane:ethyl acetate (9:1)] to obtain the title compound **13** (1.1 g, 79%) as a crystalline solid, mp 123–126°C. $[\alpha]_D$ −8.0 (*c* 1.2, $CHCl_3$); IR ν_{max} (neat) cm^{-1} 1733, 1796. δ_H (200 MHz, $CDCl_3$) 2.00–2.30 (1H, m, H-4), 2.70–2.96 (1H, m, H-4′), 3.05 (1H, dd, J_{gem} 14.0, $J_{1',5}$ 6.4, $C_6H_5C\underline{H}_2$), 3.22 (1H, dd, $J_{1'',5}$ 7.0, $C_6H_5C\underline{H}_2$), 4.62–4.88 (1H, m, H-5), 5.73 (1H, dd, $J_{3,4}$ 6.5, $J_{3,4'}$ 9.0, H-3), 7.12–7.50 (5H, m, ArH) and 8.12–8.49 (4H, m, ArH); found: C, 63.41; H, 4.49%; $C_{18}H_{15}NO_6$ requires: C, 63.34; H, 4.43%.

3.6. 3-Hydroxy-5-phenylmethyl-(3S,5R)-tetrahydrofuran-2-one **2**

To a solution of compound **13** (0.5 g, 1.5 mmol) in MeOH:CH_2Cl_2 (8 mL, 1:1) at −20°C was added a catalytic amount of sodium methoxide and the mixture was stirred for 15 min. After completion of the reaction, the reaction mixture was neutralised with carbon dioxide and the solvent was removed in vacuo to obtain a residue which was filtered on a bed of silica gel [60–120 mesh, hexane:ethyl acetate (4:2)] to obtain the title compound **2** (0.24 g, 83%) as a crystalline solid, mp 94–97°C. $[\alpha]_D$ −8.5 (*c* 1.1, $CHCl_3$); IR ν_{max} (neat) cm^{-1} 3400, 1772; δ_H (200

MHz, $CDCl_3$) 1.97 (H, dt, J_{gem} 12.0, $J_{3,4}$ 11.0, $J_{4,5}$ 11.0, H-4), 2.62 (1H, ddd, $J_{3,4'}$ 4.8, $J_{4',5}$ 7.1, H-4′), 2.80–3.00 (3H, m, $C_6H_5C\underline{H}_2$ and OH), 3.17 (1H, dd, J_{gem} 13.3, $J_{1',5}$ 6.2, $C_6H_5C\underline{H}_2$), 4.40–4.70 (2H, m, H-3,5) and 7.10–7.45 (5H, m, ArH); δ_C (50 MHz, $CDCl_3$) 36.5 (C-4), 41.1 ($C_6H_5\underline{C}H_2$), 68.4 (C-3), 77.2 (C-5), 126.9–135.5 (aromatic) and 177.5 (C=O); found: C, 68.70; H, 6.22%; $C_{11}H_{12}O_3$ requires: C, 68.74; H, 6.29%. HRMS: M^+ 192.0795 (requires M^+ 192.0786).

*3.7. A mixture of 1-[2,2-dimethyl-(3a*R,*5*R,*6a*R*)-perhydrofuro[2,3-*d*][1,3]dioxol-5-yl]-phenyl-methan-(1*R/S*)-ol* ***9***

To a solution of **14** (3.5 g, 17.2 mmol) at 0°C in CH_2Cl_2:MeOH:satd aq. $NaHCO_3$ (1:1:0.1, 70 mL) was added in one portion $NaIO_4$ (9.2 g, 43.0 mmol) and the mixture was stirred for 2 h at room temperature. After completion of the reaction, the reaction mixture was diluted with dichloromethane (70 mL) and filtered through Celite. The filtrate was concentrated in vacuo to obtain the aldehyde (2.7 g, 90%) as a thick syrup. The aldehyde was dried under high vacuum for 1 h at room temperature and reacted with phenylmagnesium bromide [prepared from bromobenzene (3.6 g, 23.0 mmol) and magnesium (0.56 g, 23.0 mmol)] in dry THF (38 mL) under a nitrogen atmosphere at 0°C for 20 min. The reaction mixture was stirred for a further 4 h at 0°C and quenched with satd aq. ammonium chloride (7 mL) and filtered through Celite. The filtrate so obtained was concentrated to a residue and was chromatographed [SiO_2, 60–120 mesh, hexane:ethyl acetate (4:1)] to obtain a diastereomeric mixture (1:1 by ^1H NMR) of the title compound **9** (3.1 g, 80%) as a thick syrup. δ_H (200 MHz, $CDCl_3$) 1.32, 1.62 (6H, 2s, 2×CH_3), 1.80–2.35 (2H, m, H-6,6′), 2.80 (1H, br.s, OH), 4.00–4.35 (1H, m, H-5), 4.60–4.75 (1H, m, H-6a), 4.88 (0.5H, d, *J* 9.0, $C_6H_5C\underline{H}$), 4.98 (0.5H, d, *J* 4.5, $C_6H_5C\underline{H}$), 5.72 (0.5H, d, *J* 3.5, H-3a), 5.82 (0.5H, d, *J* 2.5, H-3a) and 7.20–7.50 (5H, m, ArH); found: C, 67.34; H, 7.32%; $C_{14}H_{18}O_4$ requires: C, 67.18; H, 7.25%.

*3.8. A mixture of 1-[2,2-dimethyl-(3a*R,*5*R,*6a*R*)-perhydrofuro[2,3-*d*][1,3]dioxol-5-yl]-phenyl-methyl-(1*R/S*)-O-(S-methyl dithiocarbonate)* ***15***

Prepared from the alcohol **9** (3.0 g, 12.0 mmol), sodium hydride (0.43 g, 18.0 mmol), carbon disulphide (1.1 mL, 18.0 mmol) and iodomethane (1.1 mL, 18.0 mmol) as described for compound **11** to obtain the title compound **15** (3.9 g, 95%) as a colourless syrup. δ_H (200 MHz, $CDCl_3$) 1.34, 1.70, 1.72 (6H, 3s, 2×Me), 1.80–2.40 (2H, m, H-6,6′), 2.56, 2.58 (3H, 2s, SMe), 4.40–4.82 (2H, m, H-5,6a), 5.80, 5.84 (1H, 2d, *J* 4.0, 3.5, H-3a), 6.68 (1H, d, *J* 9.0, C_6H_5–$C\underline{H}$) and 7.20–7.50 (5H, m, ArH); found: C, 56.66; H, 6.01%; $C_{16}H_{20}O_4S_2$ requires: C, 56.45; H, 5.92%.

*3.9. 2,2-Dimethyl-5-phenylmethyl-(3a*R,*5*S,*6a*R*)-perhydrofuro[2,3-*d*][1,3]dioxole* ***16***

Prepared from the xanthate derivative **15** (3.8 g, 11.2 mmol) by reaction with tributyltin-hydride (4.1 g, 14.0 mmol) and AIBN (5 mg) as described for compound **12**, to obtain the title compound **16** (2.1 g, 79%) as a colourless syrup. $[\alpha]_D$ −26.0 (*c* 1.1, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 1.36, 1.64 (6H, 2s, 2×Me), 1.90–2.10 (2H, m, H-6,6′), 2.90 (1H, dd, J_{gem} 14.0, $J_{1',5}$ 8.0, $C_6H_5C\underline{H}_2$), 3.18 (1H, dd, $J_{1'',5}$ 7.0, $C_6H_5C\underline{H}_2$), 4.20–4.40 (1H, m, H-5), 4.60–4.80 (1H, m, H-6a),

5.76 (1H, d, $J_{3a,6a}$ 4.0, H-3a) and 7.10–7.40 (5H, m, ArH). δ_C (50 MHz, $CDCl_3$) 25.9, 26.9 (2×CH_3) 35.5, 42.3 (C-1′, 6), 80.8, 81.6 (C-6a,5), 106.4 (C-3a), 111.9 ($\underline{C}Me_2$) and 126.0–138.4 (aromatic); found: C, 71.92; H, 7.79%; $C_{14}H_{18}O_3$ requires: C, 71.77; H, 7.74%.

3.10. A mixture of 5-phenylmethyl-(2S/R,3R,5S)-tetrahydrofuran-2,3-diol **8**

Prepared from compound **16** (2.0 g, 8.5 mmol) as described for compound **5** to obtain the title compound **8** (1.36 g, 82%) as a crystalline solid, mp 75–77°C (diastereomeric ratio 3:2). δ_H (200 MHz, $CDCl_3$) 1.45–1.90 (1H, m, H-4), 2.15–2.55 (1H, m, H-4′), 2.75–3.20 (2H, m, $C_6H_5C\underline{H}_2$), 3.60 (1H, br.s, OH), 4.00–4.70 (2H, m, H-3,5), 5.19 (0.6H, $J_{2,3}$ 4.5, H-2), 5.30 (0.4H, s, H-2) and 7.10–7.45 (5H, m, ArH); found: C, 68.19; H, 7.38%; $C_{11}H_{14}O_3$ requires: C, 68.02; H, 7.27%.

3.11. 3-Hydroxy-5-phenylmethyl-(3R,5S)-tetrahydrofuran-2-one **3**

Prepared from the lactol **8** (1.3 g, 6.7 mmol) and Ag_2CO_3–Celite (5.0 g, 8.4 mmol) in benzene: *N*,*N*-dimethylformamide (20 mL, 8:1) as described for compound **1** to obtain the title compound **3** (0.85 g, 66%) as a crystalline solid, mp 101–103°C. $[\alpha]_D$ +8.7 (*c* 1.1, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 1.97 (1H, dt, J_{gem} 12.0, $J_{3,4}$ 11.0, $J_{4,5}$ 11.0, H-4), 2.62 (1H, ddd, J_{gem} 12.0, $J_{3,4'}$ 4.8, $J_{4',5}$ 7.1, H-4′), 2.80–3.00 (2H, m, $C_6H_5C\underline{H}_2$ and OH merged), 3.17 (1H, dd, J_{gem} 13.3, $J_{1',5}$ 6.2, $C_6H_5C\underline{H}_2$), 4.40–4.70 (2H, m, H-3,5) and 7.10–7.45 (5H, m, ArH); δ_C (50 MHz, $CDCl_3$) 36.5 (C-4), 41.1 ($C_6H_5\underline{C}H_2$), 68.4 (C-3), 77.2 (C-5), 126.9–135.5 (aromatic) and 177.5 (C=O); found: C, 68.89; H, 6.37%; $C_{11}H_{12}O_3$ requires: C, 68.74; H, 6.29%. HRMS: M^+ 192.0788 (requires M^+ 192.0786).

3.12. 3-(4-Nitrophenylcarbonyloxy)-5-phenylmethyl-(3S,5S)-tetrahydrofuran-2-one **17**

Prepared from compound **3** (0.7 g, 3.6 mmol) by reaction with 4-nitrobenzoic acid (1.8 g, 10.9 mmol), triphenylphosphine (3.5 g, 13.3 mmol) and diethylazodicarboxylate (2.5 g, 14.5 mmol) as described for compound **13** to obtain the title compound **17** (0.99 g, 80%) as a crystalline solid, mp 84–87°C. $[\alpha]_D$ −17.0 (*c* 1.2, $CHCl_3$); IR ν_{max} (neat) cm^{-1} 1722, 1788; δ_H (200 MHz, $CDCl_3$) 2.40 (1H, ddd, J_{gem} 15.0, $J_{4,5}$ 12.0, $J_{3,4}$ 7.5, H-4), 2.62 (1H, ddd, $J_{4',5}$ 10.0, $J_{3,4'}$ 4.0, H-4′), 3.90 (2H, dd, *J* 12.0, $C_6H_5C\underline{H}_2$), 4.90–5.10 (2H, m, H-3,5), 7.15–7.50 (5H, m, ArH) and 8.10–8.40 (4H, m, ArH). δ_C (50 MHz, $CDCl_3$) 32.7 (C-4), 41.0 ($C_6H_5\underline{C}H_2$), 68.9, 78.1 (C-3,5), 123.4–139.8 (aromatic) and 163.4, 171.7 (C=O of ester, lactone); found: C, 63.51; H, 4.49%; $C_{18}H_{15}NO_6$ requires: C, 63.34; H, 4.43%.

3.13. 3-Hydroxy-5-phenylmethyl-(3S,5S)-tetrahydrofuran-2-one **4**

Prepared from compound **17** (0.5 g, 1.5 mmol) as described for compound **2**, to obtain the title compound **4** (0.2 g, 73%) as a crystalline solid, mp 71–74°C. $[\alpha]_D$ −38.0 (*c* 0. 3, $CHCl_3$); IR ν_{max} (neat) cm^{-1} 3420, 1771. δ_H (200 MHz, $CDCl_3$) 2.29 (1H, dt, J_{gem} 13.2, $J_{3,4}$ 8.3, $J_{4,5}$ 8.3, H-4), 2.38 (1H, ddd, $J_{4',5}$ 3.5, H-4′), 2.98 (1H, dd, J_{gem} 15.0, $J_{1',5}$ 5.50, $C_6H_5C\underline{H}_2$), 3.00 (1H, dd, $C_6H_5C\underline{H}_2$), 3.99 (1H, td, $J_{3,OH}$ 1.9, H-3), 4.92 (1H, dtd, H-5) and 7.20–7.40 (5H, m, ArH). δ_C (50 MHz, $CDCl_3$) 34.3 (C-4), 41.1 ($C_6H_5\underline{C}H_2$), 67.0 (C-3), 78.1 (C-5), 127.3–135.2 (aromatic) and 177.1 (C=O); found: C, 68.79; H, 6.33%; $C_{11}H_{12}O_3$ requires: C, 68.74; H, 6.29%. HRMS: M^+ 192.0792 (requires M^+ 192.0786).

3.14. 2,2-Dimethyl-5-phenylmethyl-(3aR,5R,6aR)-perhydrofuro[2,3-d][1,3]-dioxol-(6S)-ol **19**

To a solution of phenylmagnesium bromide [prepared from bromobenzene (6.5 g, 41.5 mmol) and magnesium (1.0 g, 41.5 mmol) in dry THF (70 mL)] at 0°C under a nitrogen atmosphere was added a solution of compound **18** (4.0 g, 11.6 mmol) in dry THF (20 mL) during a period of 10 min and the reaction mixture was brought to room temperature. The reaction mixture was stirred overnight at room temperature. After completion of the reaction, it was cooled to 0°C, quenched with satd aq. ammonium chloride (17 mL) and filtered through Celite. The Celite bed was washed with ethyl acetate (30 mL) and the combined filtrate was concentrated to a residue which was chromatographed [SiO_2, 60–120 mesh, hexane:ethyl acetate (4:1)] to obtain the title compound **19** (2.4 g, 83%) as a crystalline solid, mp 125–127°C. $[\alpha]_D$ −12.0 (*c* 1.1, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 1.26, 1.46 (6H, 2s, 2×Me), 1.61 (1H, d, $J_{6,OH}$ 6.0, OH), 2.90 (1H, dd, J_{gem} 18.0, $J_{1',5}$ 8.3, $C_6H_5C\underline{H}_2$), 3.02 (1H, dd, $J_{1'',5}$ 6.0, $C_6H_5C\underline{H}_2$), 3.90 (1H, dd, $J_{5,6}$ 2.3, H-6), 4.30 (1H, ddd, H-5), 4.43 (1H, d, $J_{3a,6a}$ 4.0, H-6a), 5.88 (1H, d, H-3a) and 7.10–7.35 (5H, m, ArH). δ_C (50 MHz, $CDCl_3$) 26.0, 26.5 (2×$\underline{C}H_3$) 33.8 ($C_6H_5\underline{C}H_2$), 74.6, 81.1, 85.2 (C-5,6,6a), 104.3 (C-3a), 111.4 ($\underline{C}Me_2$) and 126.4–137.5 (aromatic); found: C, 67.24; H, 7.27%; $C_{14}H_{18}O_4$ requires: C, 67.18; H, 7.25%.

3.15. 2,2-Dimethyl-5-phenylmethyl-(3aR,5R,6aR)-perhydrofuro[2,3-d][1,3]dioxol-(6S)-yl-O-(S-methyl dithiocarbonate) **20**

Prepared from the alcohol **19** (1.0 g, 4.0 mmol) by reaction with sodium hydride (0.15 g, 6.0 mmol), carbon disulphide (0.36 mL, 6.0 mmol) and iodomethane (0.37 mL, 6.0 mmol) as described for compound **11**. This gave the title compound **20** (1.26 g, 93%) as a colourless syrup. $[\alpha]_D$ −16.0 (*c* 1.1, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 1.34, 1.54 (6H, 2S, 2×CMe), 2.69 (3H, s, SMe), 3.00 (1H, dd, J_{gem} 15.0, $J_{1',5}$ 7.9, $C_6H_5C\underline{H}_2$), 3.10 (1H, dd, $J_{1'',5}$ 6.80, $C_6H_5C\underline{H}_2$), 4.55 (1H, ddd, $J_{5,6}$ 2.3, H-5), 4.64 (1H, d, $J_{3a,6a}$ 4.0, H-6a), 5.71 (1H, dd, H-6), 5.97 (1H, d, H-3a), 7.10–7.40 (5H, m, ArH); found: C, 56.59; H, 5.98%; $C_{16}H_{20}O_4S_2$ requires C, 56.45; H, 5.92%.

3.16. 2,2-Dimethyl-5-phenylmethyl-(3aR,5R,6aR)-perhydrofuro[2,3-d][1,3]dioxol-(6S)-yl-(trifluoromethanesulphonate) **21**

To a solution of **19** (1.0 g, 4.0 mmol) in dry dichloromethane (15 mL) at −10°C under a nitrogen atmosphere was added dry pyridine (1 mL, 12.0 mmol) followed by trifluoromethanesulphonic anhydride (1.4 g, 5.0 mmol). The reaction mixture was stirred at 0°C for 45 min and diluted with chilled dichloromethane (15 mL). The organic phase was separated and washed with chilled aq. 2% HCl (15 mL), water (2×25 mL), dried (Na_2SO_4) and concentrated at reduced pressure to obtain the title compound **21** (1.4 g, 92%) as a crystalline solid, mp 92–95°C. $[\alpha]_D$ −4.0 (*c* 1.1, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 1.38, 1.51 (6H, 2s, 2×Me), 2.92 (1H, dd, J_{gem} 13.6, $J_{1',5}$ 4.5, $C_6H_5C\underline{H}_2$), 3.12 (1H, dd, $J_{1'',5}$ 7.9, $C_6H_5C\underline{H}_2$), 4.55 (1H, ddd, $J_{5,6}$ 2.3, H-5), 4.75 (1H, dd, $J_{3a,6a}$ 4.0, H-6a), 5.10 (1H, d, $J_{5,6}$ 2.3, H-6), 6.20 (1H, d, H-3a) and 7.20–7.40 (5H, m, ArH); found: C, 47.31; H, 4.55%; $C_{15}H_{17}F_3O_6S$ requires: C, 47.12; H, 4.48%.

3.17. 2,2-Dimethyl-5-phenylmethyl-(3aR,6aR)-dihydrofuro[2,3-d][1,3]dioxole **22**

To a solution of compound **21** (1.35 g, 3.5 mmol) in dry THF (25 mL) was added 1,8-diazabicyclo-[5.4.0]undec-7-ene (0.8 g, 5.3 mmol) and the mixture was stirred at 60°C for 7

h. After completion of the reaction, the mixture was diluted with chilled water (10 mL) and diethyl ether (25 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether (2×10 mL). The combined organic phase was washed with water (2×10 mL), dried (Na_2SO_4) and concentrated to obtain the title compound **22** (0.6 g, 74%) as a crystalline solid, mp 62–64°C. $[\alpha]_D$ −95.0 (*c* 1.1, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 1.42, 1.50 (6H, 2s, 2×Me), 2.80–3.20 (2H, m, $C_6H_5C\underline{H}_2$), 4.80–5.00 (1H, m, H-6a), 5.95–6.18 (2H, m, H-3a,6) and 7.05–7.40 (5H, m, ArH); found: C, 72.47; H, 6.98%; $C_{14}H_{16}O_3$ requires: C, 72.39; H, 6.91%.

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