Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 827–833

TETRAHEDRON: *ASYMMETRY*

Transformation of D-glucose to 1-deoxy-1-[4′-methoxyphenyl]-2*R*,3*R*,4*R*-pentitol template: synthesis of Karalicin analogues

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Received 5 January 1998; accepted 13 January 1998

Abstract

Transformation of D-glucose to Karalicin isomers **1–1b** is reported via the key chiron 5,6-anhydro-D-glucofuranose **2**. Crucial protection and deprotection strategies of pentitol chiral template **6** are described.

The increasing occurrence of the life threatening herpes virus infection in children with inherited T-cell deficiencies and in patients who are immunosuppressed because of AIDS infection, transplantation or cancer therapy has given great importance to the rapid development of chemotherapeutic agents.[1] Chemotherapeutic agents that act specifically on viral rather than on host macromolecular synthesis are being developed. Thus, acyclovir, vidarabine, cytovene, famvir and cidofovir have been the present drugs of choice for oral and genital herpes.[1] Recently Karalicin **1** a p-methoxyphenyl pentitol derivative whose absolute stereochemical structure has not been determined was isolated from *Pseudomonas fluorescens/putida* strains collected from sewer channels.[2] Earlier, other bioactive compounds pyrrolnitrin[3] pyoluteorin,[4] and pyoverdine siderophore[5] had been isolated from these strains. Karalicin **1** has been shown to possess antiviral activity against herpes viruses, whilst polio and vaccinia viruses were found to be less sensitive.[6] Karalicin **1** has shown inhibitory effects on the multiplication of the herpes virus *in vitro*. Due to these interesting antiviral properties the synthesis of **1** and its analogues were taken up as a part of our programme to obtain selective and effective antiviral compounds. In order to establish the absolute stereochemical structure of **1** synthesis by chiron approach starting from D-glucose was considered.

Retrosynthetic analysis (Scheme 1) to derive the 1-deoxy-pentitol template of **1** suggested carbon–carbon bond formation by regioselective nucleophilic opening of 5,6-anhydro-D-glucofuranose derivative **2** by p-methoxy phenylmagnesium bromide followed by one carbon degradation of the terminal diol (by periodate cleavage). This general strategy in principle would allow synthesis of all the eight possible isomers of Karalicin **1** to establish unambiguously the absolute stereochemistry by choice of monosaccharides that are available in appropriate chiral forms.

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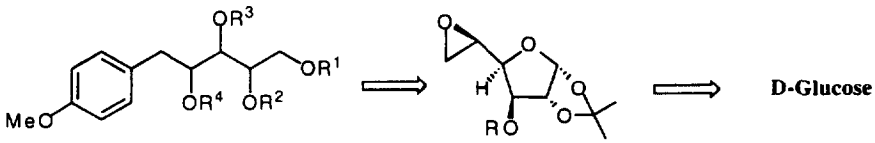
0957-4166/98/$19.00
PII: S0957-4166(98)00017-2

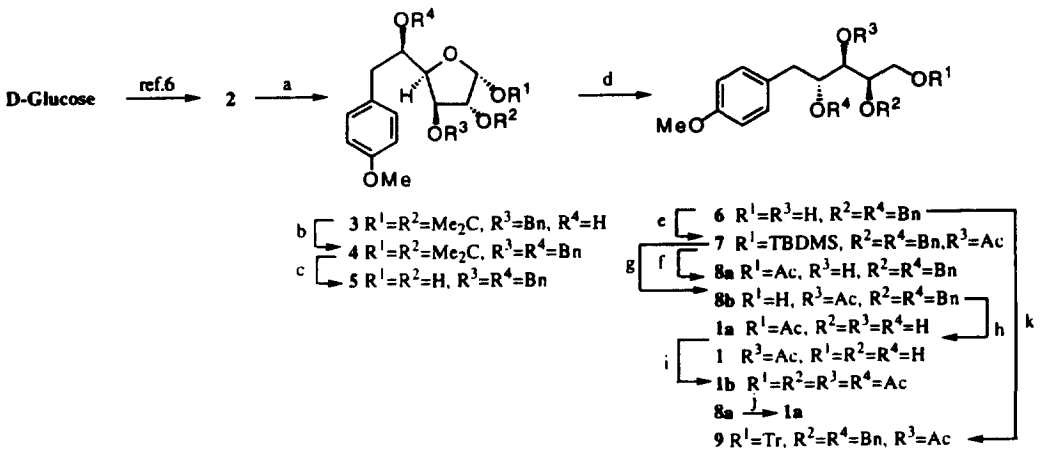


1 R^1= R^2= R^4= H; R^3= Ac
1a R^1=Ac; R^2=R^3=R^4=H
1b R^1=R^2=R^3=R^4=Ac

2, R=Bn

Scheme 1.

Thus D-glucose was transformed to the 5,6-anhydroepoxyglucofuranose derivative **2** by established[7] procedures (Scheme 2). Regioselective nucleophilic opening of epoxide **2** by p-methoxy phenylmagnesium bromide[8] in THF at 0°C for 2 h gave **3** in 81% yield, which as characterised from the ^{1}H-NMR spectrum from the appearance of benzylic protons H-6 (2H) at δ 2.7 (1H, dd, J_{gem} 13.6 Hz, $J_{5,6}$ 7.7 Hz) and δ 2.96 (1H, dd, $J_{5,6'}$ 2.8 Hz), aromatic OCH_3 at δ 3.78 and anomeric proton H-1 at δ 5.9 (1H, d, $J_{1,2}$ 4.1 Hz). Benzylation BnBr–NaH/DMF of **3** gave **4** which on subsequent deprotection of acetonide ($TFA/H_2O/CH_2Cl_2$) gave **5** in high yield, which on oxidative cleavage with $NaIO_4$ followed by reduction with $NaBH_4$ gave the diol **6** as a crystalline compound m.p. 65–67°C. A one pot regioselective silylation of **6** with tert-butyldimethylsilyl chloride followed by acetylation (Ac_2O/Py/1 h) gave the 3-O-acetyl-5-O-silyl derivative **7** which was characterised by the ^{1}H-NMR spectrum from the appearance of the acetyl group at δ 2.03 (3H, s, $OCOCH_3$) and H-3 at δ 5.27 (1H, t, $J_{2,3}$=$J_{3,4}$ 4.8 Hz) shifted downfield due to acetylation.



Scheme 2. (a) p-OMePhMgBr/CuI/THF/0°C/2 h, 81%; (b) BnBr/NaH/DMF/O°C–RT/1 h, 94%; (c) $TFA:H_2O:CH_2Cl_2$ (2:1:2)/35°C/6 h, 80%; (d) $NaIO_4$/MeOH:H_2O (2:1)/0°C–RT/1 h; $NaBH_4$/isopropyl alcohol/ RT/1 h, 83%; (e) TBDMSCl/Py/RT/3 h; Ac_2O/Py/1 h, 90%; (f) TBAF/THF/0°C/30 min. 98%; (g) 1% p-TsOH in MeOH:CH_2Cl_2 (1:3)/−20°C/18 h, 87% (h) PdO/H_2/1atm/EtOAc/2 h, 90%; (i) Ac_2O/Py/1 h, 95%; (j) 10% Pd–$BaSO_4$/H_2/1atm/ MeOH/4 h, 93%; (k) Ph_3CCl/Py/RT/6 h; Ac_2O/RT/1 h, 92% yield

Desilylation of **7** with tetrabutylammonium fluoride resulted in the exclusive isolation of the unwanted **8a** due to migration of the C-3-O acetyl group to the C-5 hydroxyl group, formation of **8b** was not observed. In order to prevent isomerisation of the acetyl group during base catalysed desilylation a recently reported method[9] of desilylation by use of I_2, MeOH at reflux temperature was also tried unsuccessfully resulting in the isolation of a mixture of **8a:8b** in a ratio of 4:1. After trying several methods of desilylation the best procedure established was by use of 1% p-TsOH in MeOH–CH_2Cl_2 strictly at −20°C for 18 h, quenching the reaction mixture with triethylamine and evaporation of solvent

in high vacuum (0.01 Torr) gave **8a:8b** in a ratio of 1:6 (by ^{1}H-NMR). Formation of **8a** was evident from the ^{1}H-NMR spectrum from the appearance of an acetyl group at δ 2.02 (3H, s) and H-5 (2H) shifted downfield to δ 4.1–4.3 (m, 3H, merged with H-4) and also from the upfield shift of H-3 proton to δ 3.4 due to deacetylation. Compound **8b** was characterised by the ^{1}H-NMR spectrum from the appearance of an acetyl group at δ 2.10 (s, 3H), and H-3 at δ 5.15 (1H, dd, $J_{2,3}$ 4.2 Hz, $J_{3,4}$ 4.0 Hz). However, the problem of isomerisation continued even during hydrogenolysis. Thus when, **8a:8b** was hydrogenated in ethyl acetate at 1 atm pressure at 0°C using PdO as a catalyst resulted in the isolation of **1:1a** in a ratio of 1:1 (by ^{1}H-NMR). Attempts to isolate **1** by preparative thin layer chromatography also met with failure because of rapid isomerisation of **1** to **1a** (1:1 ratio) while removing the solvent. Hydrogenolysis by change of solvents (MeOH, cyclohexane) and catalysts (Pd/C, $Pd/BaSO_4$) also did not prevent isomerisation. Thus, hydrogenolysis of **8a** at 1 atm pressure with $Pd/BaSO_4$ in MeOH gave a crystalline Karalicin analogue **1a**, m.p. 103–105°C, in quantitative yield and was characterised from the ^{1}H-NMR spectrum. In order to synthesise Karalicin **1** an alternative route devoid of alkaline and acidic reaction conditions was considered. Diol **6** was converted in a one pot reaction to the trityl derivative **9** by reaction with Ph_3CCl/Py followed by acetylation. Compound **9** was hydrogenated with Pd–$BaSO_4$ catalyst in EtOAc to isolate **1:1a** in a ratio of 1:4 due to migration of the acetyl group. In order to characterise **1/1a** and other isomeric monoacetylated derivatives **7, 8a** and **8b**, **1/1a** was converted to the tetra-acetate **1b** by acetylation. The ^{1}H-NMR spectrum of **1b** exhibited four acetyl group singlets at δ 1.90 (2/4 –OAc), δ 2.01 (5 –OAc), δ 2.03 (3 –OAc), 2.04 (2/4 –OAc), 3.89 (dd, 1H, $J_{5,5'}$ 11.2, $J_{4,5}$ 6.4 Hz, H-5), 4.25 (dd, 1H, $J_{4,5'}$ 4.5 Hz, H-5′), 5.24 (ddd, 1H, $J_{2,3}$ 6.7 Hz, H-2), 5.28 (dd, 1H, $J_{3,4}$ 5.6 Hz, H-3) and 5.37 (ddd, 1H, H-4).

In conclusion, a simple, high yielding method based on a protection–deprotection strategy to prepare Karalicin anologues from D-glucose has been described by a chiron approach. Synthesis of Karalicin **1** could not be achieved due to facile migration of the acetyl group from secondary to the terminal primary alcohol.

1. Experimental section

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 and 400 MHz) spectrometer, with tetramethylsilane as an internal standard for solutions in deuteriochloroform. J values are given in hertz. 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*.

1.1. 3-O-Benzyl-1,2-O-isopropylidine-6-C-(4′-methoxyphenyl)-α-D-glucopentofuranose 3

To a solution of 5,6-anhydro-3-O-benzyl-1,2-O-isopropylidine-α-D-glucopentofuranose **2** (3.5 g, 11.9 mmol) in dry THF (30 cm^3) was added copper(I) iodide (0.03 g) and the reaction mixture was cooled to 0°C. Freshly prepared 4-methoxyphenylmagnesium bromide (4.45 g of fresh 4-bromoanisole and 0.57 g of magnesium in 20 ml of dry THF, 23.95 mmol) was added dropwise over 30 min. to the reaction mixture and stirred for 2 h at 0°C. After completion of the reaction (monitored by TLC) it was quenched by addition of saturated aqueous ammonium chloride solution (20 cm^3) and then filtered through a bed of Celite and washed with ethyl acetate. The filtrate was concentrated to a syrupy residue and was extracted

into ethyl acetate (2×75 ml). Combined organic phases 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 (3.81 g, 81%) as a syrup. $[\alpha]_D$ −39.2 (c 1.32, $CHCl_3$): υ_{max}/cm^{-1} 3430 (OH): ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.35, 1.45 (2s, 6H, 2×C*H*$_3$), 2.7 (dd, 1H, J_{gem} 13.6 Hz, $J_{5,6}$ 7.7 Hz, H-6), 2.96 (dd, 1H, $J_{5,6'}$ 2.8 Hz, H-6′), 3.78 (s, 3H, OC*H*$_3$), 3.85–4.15 (m, 3H, H-3,4 and H-5), 4.45–4.65 (m, 2H, H-2 and $C_6H_5CH_2$), 4.70 (d, 1H, J_{gem} 12.7 Hz, $C_6H_5CH_2$), 5.9 (d, 1H, $J_{1,2}$ 4.1 Hz, H-1), 6.8 (d, 2H, J 8.5 Hz, Ar*H*), 7.15 (d, 2H, Ar*H*), 7.2–7.4 (m, 5H, Ar*H*). Anal. calcd for $C_{23}H_{28}O_6$: C=68.98; H, 7.05. Found: C, 68.92; H, 7.02.

1.2. 3,5-Di-O-benzyl-1,2-O-isopropylidine-6-C-(4′-methoxyphenyl)-α-D-glucopentofuranose **4**

To a slurry of hexane washed sodium hydride (0.25 g, 10.45 mmol) in dry DMF (3 cm^3) a solution of **3** (3.5 g, 8.7 mmol) in DMF (4 cm^3) was added at 0°C followed by benzyl bromide (1.78 g, 10.45 mmol). The reaction mixture was stirred for 30 min. at room temperature and then poured into cold water (50 cm^3) and extracted into diethyl ether (2×75 cm^3). 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 (5:1)] to obtain the title compound (4.06 g, 94%) as a syrup. $[\alpha]_D$ −59 (c 2.2, $CHCl_3$): ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.3, 1.42 (2s, 6H, 2×C*H*$_3$), 2.81 (dd, 1H, J_{gem} 13.2 Hz, $J_{5,6}$ 7.6 Hz, H-6), 3.12 (dd, 1H, $J_{5,6'}$ 2.8 Hz, H-6′), 3.78 (s, 3H, OC*H*$_3$), 3.95–4.09 (m, 3H, H-3,4 and H-5), 4.3–4.7 (m, 5H, H-2 and 2×$C_6H_5CH_2$), 5.9 (d, 1H, $J_{1,2}$ 4.2 Hz, H-1), 6.8 (d, 2H, J 8.5 Hz, Ar*H*), 7.1–7.45 (m, 12H, Ar*H*). Anal. calcd for $C_{30}H_{34}O_6$: C, 73.45; H, 6.99. Found: C, 73.42; H, 6.89.

1.3. 3,5-Di-O-benzyl-6-C-(4′-methoxyphenyl)-α/β-D-glucopentofuranose **5**

To a solution of **4** (3.1 g, 6.3 mmol) in dichloromethane (20 cm^3), 60% aqueous trifluoro acetic acid (15 cm^3) was added and stirred for 6 h at 35°C. After completion of the reaction, it was cooled to 10°C and neutralised with saturated aqueous sodium hydrogen carbonate solution (10 cm^3). The organic phase was separated and the aqueous layer extracted into dichloromethane (2×50 cm^3). The combined organic phases were dried (Na_2SO_4), filtered and concentrated to obtain the title compound **5** (2.3 g, 80%) as a syrup. υ_{max}/cm^{-1} 3500 (OH): ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.69–2.88 (m, 1H, H-6), 3.05–3.25 (m, 1H, H-6′), 3.78 (s, 3H, OC*H*$_3$), 3.88–4.09 (m, 2H, H-2 and H-4), 4.12–4.20 (m, 2H, H-3 and H-5) 4.3–4.65 (m, 4H, 2×$C_6H_5CH_2$), 5.1 (s, 0.4H, H-1), 5.49–5.55 (m, 0.6H, H-1), 6.8 (d, 2H, J 8.5 Hz, Ar*H*), 7.09–7.4 (m, 12H, Ar*H*). Anal. calcd for $C_{27}H_{30}O_6$: C, 71.98; H, 6.71. Found: C, 71.93; H, 6.66.

1.4. 2,4-Di(benzyloxy)-5-(4-methoxyphenyl)-(2R,3R,4R)-pentane-1,3-diol **6**

To a solution of **5** (1.9 g, 4.2 mmol) at 0°C in 50% aqueous methanol (25 cm^3) was added in one portion sodium metaperiodate (1.35 g, 6.32 mmol) and stirred at 0°C for 1 h. After completion of the reaction, solvent was removed on a rotary evaporator to obtain a residue which was dissolved in dichloromethane and filtered through Celite and bed washed with dichloromethane (2×25 cm^3). Combined organic phases were dried (Na_2SO_4), filtered and concentrated to a syrup, which was dissolved in isopropanol (10 cm^3), cooled to 0°C and sodium borohydride (0.26 g, 6.8 mmol) was added. The reaction mixture was stirred for 1 h and then quenched with a few drops of acetic acid and was gradually brought to room temperature. Isopropyl alcohol was removed under reduced pressure to obtain a residue which was extracted into ethyl acetate (2×75 cm^3). The combined organic 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 (3:1)] to obtain

the title compound (1.48 g, 83%) as a colorless crystalline solid, m.p. 65–67°C. $[\alpha]_D$ −44.5 (c 1.12, $CHCl_3$): υ_{max}/cm^{-1} 3450 (OH): ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.16 (br. s, OH), 2.65 (d, 1H, J 7.2 Hz, OH), 2.85 (dd, 1H, J_{gem} 13.2 Hz, $J_{1,2}$ 6.2 Hz, H-1), 3.04 (dd, 1H, $J_{1',2}$ 3.5 Hz, H-1′), 3.5–3.90 (m, 5H, H-2,3,4 and H-5), 3.78 (s, 3H, OCH_3), 4.20–4.7 (m, 4H, $2\times C_6H_5CH_2$), 6.8 (d, 2H, J 8.4 Hz, Ar*H*), 7.10–7.4 (m, 12H, Ar*H*). Anal. calcd for $C_{26}H_{30}O_5$: C, 73.91; H, 7.16. Found: C, 73.86; H, 7.09.

1.5. 2,4-Benzyloxy-1-[1-benzyloxy-4-tert-butyldimethylsilyloxy-(1R)-ethyl]-3-(4-methoxyphenyl)-(1R, 2R)-propylacetate 7

To a solution of diol **6** (1.0 g, 2.36 mmol) in pyridine (1.0 cm^3) at 0°C was added tert-butyldimethylsilyl chloride (0.426 g, 2.84 mmol) and stirred for 3 h at room temperature. When silylation was complete, acetic anhydride (0.3 cm^3) was added and stirred for 1 h. The reaction mixture was diluted with water and extracted into diethyl ether (2×25 cm^3). The combined ethereal layer was washed with 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 (6:1)] to obtain the title compound **7** (1.23 g, 90%) as a colorless syrup. $[\alpha]_D$ 20.45 (c 1.44, $CHCl_3$): υ_{max}/cm^{-1} 1742 (C=O): ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.3 (s, 6H, 2×Me), 0.88 (s, 9H, CMe_3), 2.03 (s, 3H, $OCOCH_3$), 2.7–2.8 (m, 2H, H-1,1′), 3.6–3.9 (m, 4H, H-2,4 and H-5,5′), 3.75 (s, 3H, OCH_3), 4.1–4.8 (m, 4H, $2\times C_6H_5CH_2$), 6.8 (d, 2H, J 8.0 Hz, Ar*H*), 7.0–7.38 (m, 12H, Ar*H*). Anal. calcd for $C_{34}H_{46}O_6Si$: C, 70.55; H, 8.01. Found: C, 70.41; H, 7.99.

1.6. 2,4-Di(benzyloxy)-3-hydroxy-5(4-methoxyphenyl)-(2R,3R,4R)-pentylacetate ***8a***

To a solution of **7** (0.75 g, 1.3 mmol) in dry THF (10 cm^3) was added tetrabutylammonium fluoride (0.4 g, 1.5 mmol) at 0°C and was stirred for 30 min. After completion of the reaction, solvent was removed under reduced pressure to obtain a residue which was extracted into ethyl acetate (50 cm^3). The organic layer was washed with water (2×25 cm^3), 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 (6:4)] to obtain the title compound **8a** (0.59 g, 98%) as a thick syrup. $[\alpha]_D$ 37.3 (c 1.0, $CHCl_3$): υ_{max}/cm^{-1} 1744 (C=O): ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.02 (s, 3H, $OCOCH_3$), 2.31 (d, 1H, J 8.4 Hz, OH), 2.82 (dd, 1H, J_{gem} 13.0 Hz, $J_{1,2}$ 6.0 Hz, H-1), 3.10 (dd, 1H, $J_{1',2}$ 2.7 Hz, H-1′), 3.4 (dd, 1H, $J_{2,3}$ 7.9 Hz, $J_{3,4}$ 6.2 Hz, H-3), 3.55–3.70 (m, 1H, H-2), 3.78 (s, 3H, OCH_3), 4.1–4.5 (m, 5H, H-5,5′, $1.5\times C_6H_5CH_2$), 4.65 (d, 1H, J_{gem} 12.5 Hz, $C_6H_5CH_2$), 6.8 (d, 2H, J 8.0 Hz, Ar*H*), 7.1–7.4 (m, 12H, Ar*H*). Anal. calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.33; H, 6.89.

1.7. 2-Benzyloxy-1-[1-benzyloxy-2-hydroxy-(1R)-ethyl]-3-(4-methoxyphenyl)-(1R,2R)-propylacetate ***8b***

To a solution of **7** (0.3 g, 0.51 mmol) in dichloromethane (10 cm^3) was added 1% p-TsOH solution in methanol (3.0 cm^3) at −20°C. Reaction was monitered by TLC and when complete (18 h) triethylamine (0.3 cm^3) was added and solvent was removed under high vacuum (0.01 Torr) to obtain a residue which was filtered on a short bed of silica gel to obtain the title compound **8b** (0.21 g, 87%) as a syrup. **8b**: $[\alpha]_D$ 14.2 (c 2.0, $CHCl_3$): υ_{max}/cm^{-1} 1740 (C=O): ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.10 (s, 3H, $OCOCH_3$), 2.5 (br. s, 1H, OH), 2.81 (dd, 1H, J_{gem} 12.8 Hz, $J_{1,2}$ 7.2 Hz, H-1), 2.98 (dd, 1H, $J_{1',2}$ 2.2 Hz, H-1′), 3.55–3.95 (m, 4H, H-2, H-4 and H-5), 3.80 (s, 3H, OCH_3), 4.35 (s, 2H, $C_6H_5CH_2$), 4.6 (d, 2H, J_{gem} 13.8 Hz, $C_6H_5CH_2$), 5.15 (dd, 1H, $J_{2,3}$ 4.2 Hz, $J_{3,4}$ 4.0 Hz, H-3), 6.8 (d, 2H, J 8.0 Hz, Ar*H*), 7.1–7.38 (m, 12H, Ar*H*). Anal. calcd for $C_{28}H_{32}O_6$: C, 72.29; H, 6.94. Found: C, 72.35; H, 6.89.

1.8. 2-Benzyloxy-1-[1-benzyloxy-2-(4-methoxyphenyl)-(1R)-ethyl]-3-trityloxy-(1R,2R)-propylacetate ***9***

To a solution of diol **6** (0.3 g, 0.71 mmol) in pyridine (1.0 cm^3) was added trityl chloride (0.25 g, 0.92 mmol) at 0°C and the reaction mixture was stirred for 6 h at room temperature. After completion of the reaction, acetic anhydride (0.3 cm^3) was added and stirred for 1 h. The reaction mixture was diluted with water and extracted into diethyl ether (2×30 cm^3). The combined ethereal layer was washed with 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 (5:1)] to obtain the title compound **9** (0.46 g, 92%) as a thick syrup. $[\alpha]_D$ 11.19 (c 1.06, $CHCl_3$): υ_{max}/cm^{-1} 1744 (C=O): ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.05 (s, 3H, OCOCH_3), 2.40–2.95 (m, 2H, H-1,1′), 3.35–3.68 (m, 4H, H-2, H-4 and H-5,5′), 3.80 (s, 3H, OCH_3), 4.12–4.78 (m, 4H, 2×$C_6H_5CH_2$), 5.8 (dd, 1H, $J_{2,3}$ 4.3 Hz, $J_{3,4}$ 4.2 Hz, H-3), 6.6–7.5 (m, 29H, Ar*H*). Anal. calcd for $C_{47}H_{46}O_6$: C, 79.86; H, 6.56. Found: C, 79.81; H, 6.53.

1.9. 1-[1,2-Dihydroxy-(1R)-ethyl]-2-hydroxy-3-(4-methoxyphenyl)-(1R,2R)-propylacetate ***1*** *and 2,3,4-trihydroxy-5-(4-methoxyphenyl)-(2R,3R,4R)-pentylacetate* ***1a***

A solution of **8a:8b** (1:6 by NMR, 0.2 g, 0.43 mmol) and PdO (10 mg) in ethyl acetate (5.0 cm^3) was stirred under a hydrogen atmosphere (1 atm) for 2 h at room temperature. The catalyst was filtered off and solvent removed under reduced pressure to obtain an inseparable mixture of **1:1a** (1:1, 0.11 g, 90%) as a thick syrup. Anal. calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.06; H, 7.02.

Compound **1a:** To a solution of **8a** (0.5 g, 1.07 mmol) in methanol (10 cm^3) was added 10% Pd–$BaSO_4$ (10 mg) and stirred under a hydrogen atmosphere (1 atm) for 4 h at room temperature. The catalyst was filtered off and the solvent removed under reduced pressure to obtain the title compound **1a** (0.285 g, 93%) as a colorless crystalline solid, m.p. 103–105°C: υ_{max}/cm^{-1} 1744 (C=O): $[\alpha]_D$ 19.6 (c 1.0, $CHCl_3$): ^{1}H-NMR ($CDCl_3$, D_2O exchanged, 200 MHz): δ 2.12 (s, 3H, OCOCH_3), 2.72 (dd, 1H, J_{gem} 13.0 Hz, $J_{1,2}$ 9.0 Hz, H-1), 2.95 (dd, 1H, $J_{1',2}$ 3.8 Hz, H-1′), 3.41 (dd, 1H, $J_{2,3}$ 4.0 Hz, $J_{3,4}$ 4.5 Hz, H-3), 3.78 (s, 3H, OCH_3), 3.92 (ddd, 1H, H-2), 4.1–4.3 (m, 3H, H-4 and H-5,5′), 6.8 (d, 2H, J 8.0 Hz, Ar*H*), 7.15 (d, 1H, Ar*H*). Anal. calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.11; H, 7.01.

1.10. 1-[1,2-Di(methylcarbonyloxy)-(1R)-ethyl]-3-(4-methoxyphenyl)-2-methylcarbonyloxy-(1R, 2R)-propylacetate ***1b***

To a solution of **1/1a** (0.1 g, 0.35 mmol) in pyridine (1.0 cm^3) was added acetic anhydride (0.3 cm^3) at 0°C and stirred for 1 h at room temperature. After completion of the reaction, the reaction mixture was diluted with water (5 cm^3) and extracted into diethyl ether (2×10 cm^3). The combined organic phase was washed with 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 (3:1)] to obtain the title compound **1b** (0.137 g, 95%) as a thick syrup. **1b**: $[\alpha]_D$ 42.1 (c 0.75, $CHCl_3$): υ_{max}/cm^{-1} 1742 (C=O): ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.90 (2/4 –OAc), 2.01 (5 –OAc), 2.03 (3 –OAc), 2.04 (2/4 –OAc), 2.77 (dd, 1H, J_{gem} 14.4, $J_{1,2}$ 6.2 Hz, H-1), 2.82 (dd, 1H, $J_{1',2}$ 3.4 Hz, H-1′), 3.76 (s, 3H, OCH_3), 3.89 (dd, 1H, $J_{5,5'}$ 11.2 Hz, $J_{4,5}$ 6.4 Hz, H-5), 4.25 (dd, 1H, $J_{4,5'}$ 4.5 Hz, H-5′), 5.24 (ddd, 1H, $J_{2,3}$ 6.7 Hz, H-2), 5.28 (dd, 1H, $J_{3,4}$ 5.6 Hz, H-3), 5.37 (ddd, 1H, H-4). Anal. calcd for $C_{20}H_{26}O_9$: C, 58.33; H, 6.39. Found: C, 58.29; H, 6.32.

Acknowledgements

RRG thanks University Grants Commission, New Delhi for the financial assistance in the form of a Senior Research Fellowship.

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