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Synthesis and Antitumor Activity of Goniofufurone Analogues

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Abstract—Synthesis and antitumor activity of goniofufurone analogues **15**, **16**, **17**, **33**, and **46** is reported. Key step in the synthesis is Pd (II) mediated oxidative cyclisation of vinyl-(hydroxy) furans **18**, **19** to the corresponding lactols **32**, **43.** Cytotoxicities of **15**, **16**, **17**, **33**, and **46** tested against six human cancer cell lines are reported. Change of stereochemistry at C-5, C-6 and C-7 position of goniofufurone (**1**) did not enhance the cytotoxicities significantly.

Introduction

Bioactivity directed studies of the plant '*goniothalamus giganteus*' Hook.F.,Thomas (Annonaceae) from Thailand showed significant murine toxicity in the 3 ps lymphocytic leukaemia system.[1–5] Several bioactive compounds have been isolated and characterised, some representative styryl lactones goniofufurone (**1**), 7-epigoniofufurone (**2**), goniofupyrone (**3**), goniopypyrone (**4**), 9-deoxy-goniopypyrone (**5**), goniotriol (**6**), goniobutenolides A (**7**), B (**8**) and gonioheptolides A and B (**9**)[5] are shown in Figure 1. Among these **4** was the most bioactive showing non-selective ED_{50}-values in cytotoxicity of 6.7×10^{-1} mg/ml in the A-549 (human lung carcinoma), MCF-7 (human breast adeno-carcinoma), HT-29 (human colon adenocarcinoma), high toxicity to the brine shrimp (BS) and significant inhibition of the formation of the crown gall tumours on potato discs (PD). **1** Showed selective but moderate toxic activity in A 549 and moderate toxicity to the brine shrimp.[2] Absolute configuration of **1** and **2** has been established by synthesis.[6–23] Owing to their potential as antitumour agents several diastereomers **10–14** have been synthesised.[24–28] As a part of our long term programme in the fabrication of natural products as potential antitumour agents, we recently described stereoselective synthesis of (5-*R*)-diastereomer **14** of **1**.[27]

Results and Discussion

Synthesis

Herein, we report the synthesis of diastereomeric analogues of goniofufurone (**1**) for evaluation as selective antitumour agents. Synthesis of (5*R*,6*S*,7*S*)-diastereomer (**15**), (5*R*,6*R*,7*S*)-diastereomer (**16**) of **1** and also one carbon higher analogue (**17**) was targetted for evaluating them as antitumour agents. Retrosynthetic analyses of **15** and **16** (Scheme 1) indicated that the required [3.3.0] bicyclic frame could be derived from intramolecular $Pd(II)Cl_2$ mediated oxidative cyclisation[30] of the corresponding vinyl (hydroxy) furans **18** and **19**, respectively, by the well documented protocol[27,28] developed by us earlier. **18** and **19** in turn could be derived from the diacetone-D-mannose **20**.[29] **17** By retrosynthesis (Scheme 1) could be derived from **21** by Wittig olefination–cyclisation protocol. Synthesis of **21** itself is visualised from D-glucose by established chemical reactions.[31]

Thus synthesis of **15** was achieved (Scheme 2) by reaction of **20** with trimethylsulfoxonium iodide[32](TMSOI) to obtain an inseparable diastereomeric mixture of **22** and **23** (1:2.5 by ^{1}H NMR).[33]

However, their corresponding benzyl ethers **24** and **25** were separated by column chromatography and hydrogenated (Pd/C) to obtain **22** as a crystalline solid, mp 58–60°C. Compound **22** was characterised from the ^{1}H NMR by the appearance of H-7 protons at δ 3.45. **23** was earlier characterised by ^{1}H NMR and X-ray crystallography.[27] Swern oxidation of **22** gave the aldehyde which on immediate reaction with phenylmagnesium bromide at −20°C in tetrahydrofuran gave a diastereomeric

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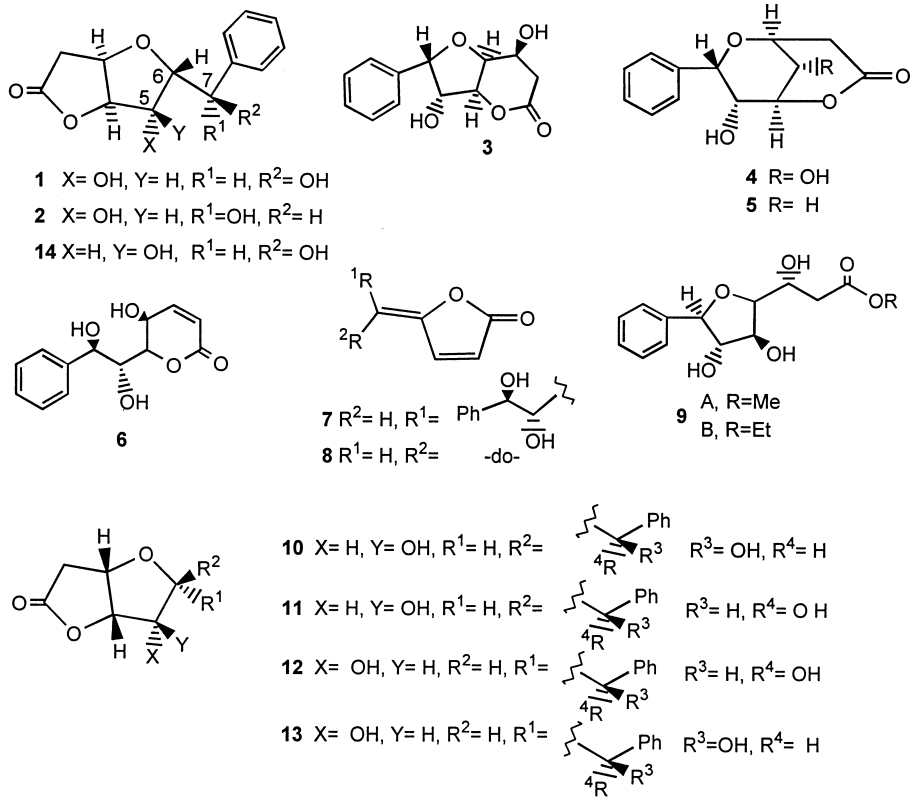
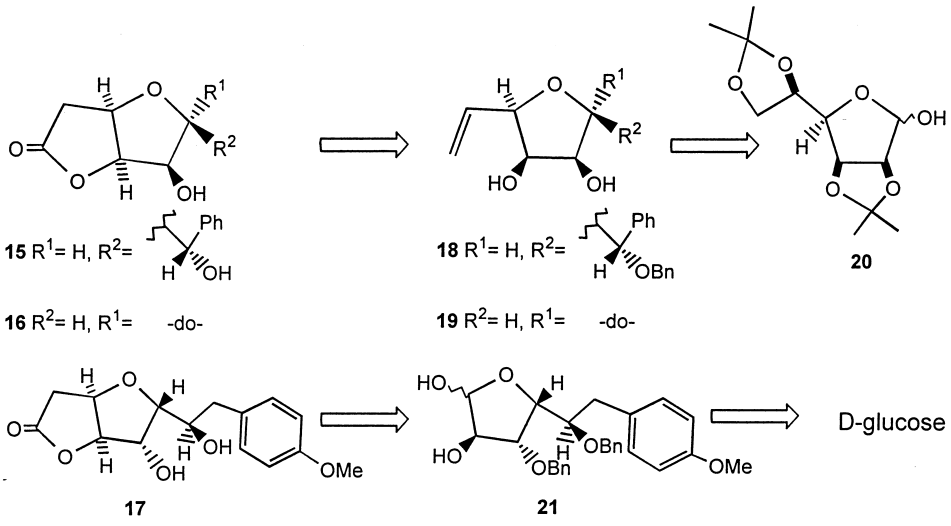
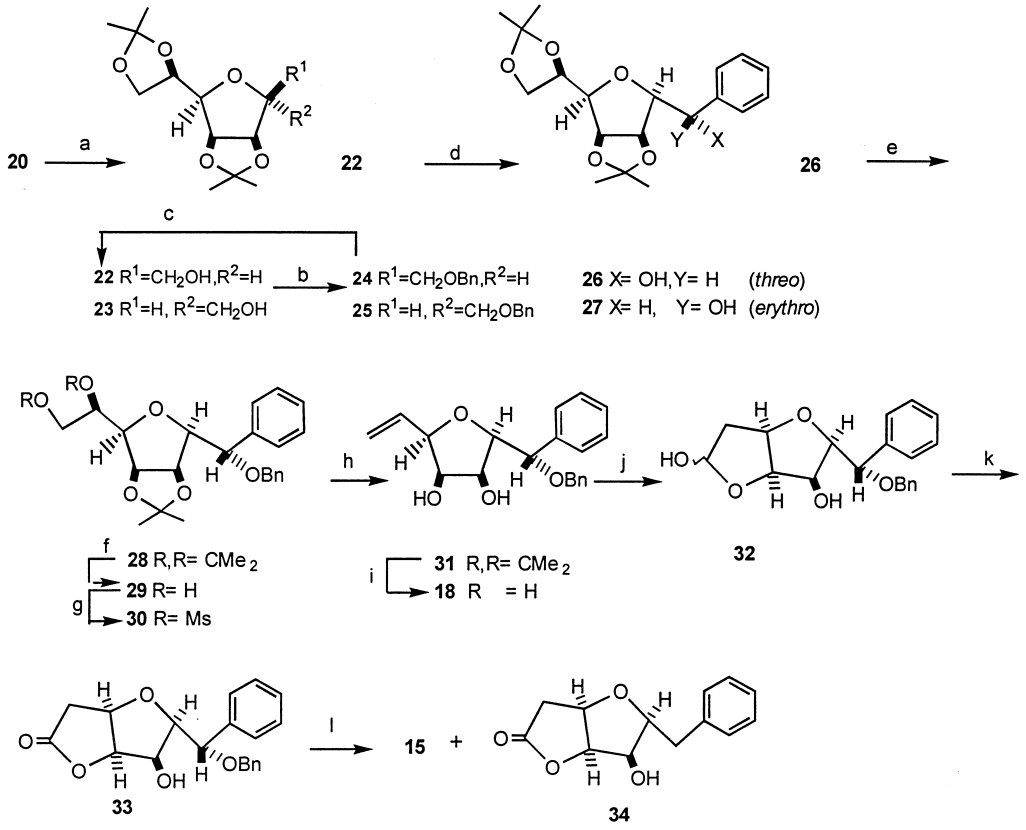


Figure 1.



Scheme 1.

mixture of **26** and **27** (3:1 by ^{1}H NMR) that were separated by column chromatography. Characterisation of **26** and **27** was based on literature precedents on the 1,2-addition of Grignard reagents to carbonyl compounds[8,11,34–36] and ^{1}H NMR spectra. 1,2-Addition of alkylmagnesium halide to analogous aldehydes has been reported and to result in the formation of '*threo*' isomer as a major product due to approach of nucleophile from the plane opposite to the furanose ring. Thus **26** was assigned the '*threo*' and **27** '*erythro*' configuration respectively. ^{1}H NMR spectrum of **26** was also in agreement with the assigned structure. Compound **26** was transformed to corresponding benzyl ether **28** and treated with 60% aqueous acetic acid at room temperature to obtain the diol **29**. Reaction of **29** with methanesulfonyl chloride/triethylamine gave dimesylate **30** which on further reaction with NaI/butan-2-one gave the desired olefin **31**[37] in 82% yield. Formation of **31** was evident from the ^{1}H NMR spectrum from the appearance of olefinic protons at δ 5.2 (1H), 5.3 (1H), 5.8–6.0 (1H) and isopropylidene methyl protons at δ 1.4, 1.48 (6H). Reaction of **31** in dioxane containing 5% aqueous H_2SO_4 at reflux temperature for 1.5 h gave the diol **18.** Intramolecular oxidative cyclisation of **18** was achieved by



Scheme 2. Reagents and conditions: (a) TMSOI, NaH, DMSO, 0°C-r.t, 1 h, (b) BnBr, NaH, DMF,0°C, 30 min., (c) Pd/C, MeOH, H_2, r.t, 3 h, (d) Oxalyl chloride, DMSO,TEA, CH_2Cl_2, −78°C, 1 h ; PhMgBr, THF, −20°C, 4 h, (e) BnBr, NaH, DMF,0°C, 30 min, (f) 60% aq.acetic acid, r.t, 12 h, (g) MsCl, TEA, CH_2Cl_2, 0°C-r.t, 1 h, (h) NaI, 2-butanone, reflux,12 h, (i) 5% aq.H_2SO_4, dioxane, reflux, 1.5 h, (j) $PdCl_2$, CuCl, DMF:H_2O (4:1), O_2, r.t, 3 h, (k) PDC, CH_2Cl_2, reflux, 1.5 h, (l) 10% Pd/C, MeOH, H_2, r.t, 2 h.

reaction with $PdCl_2$-CuCl in DMF: water (4:1) while oxygen was bubbled to obtain the lactol **32** in 83% yield. Formation of **32** was evident from the disappearance of olefinic protons between δ 5.2–6.0 (3H) and appearance of acetal proton H-1 at δ 5.2–5.5 (1H) and methylene protons between δ 1.9–2.2 (2H). Oxidation of **32** with PDC in dichloromethane at reflux temperature for 1.5 h gave lactone **33** as a crystalline solid, mp 77–80°C in 78% yield. Compound **33** was characterised from the appearance of carbonyl absorption in the IR at 1782 cm^{-1} for the furanolactone and appearance of H-2 protons at δ 2.6–2.8 (2H). Compound **33** on hydrogenolysis in methanol gave the desired tetrahydrofurofurone **15** in 51% yield along with the deoxygenated product **34** (13%). **15** was characterised by ^1H NMR spectrum from the appearance of H-2,2′ at δ 2.7, H-4 and H-7 protons between δ 4.88–4.93 and characteristic lactone absorption at 1784 cm^{-1} in the IR spectrum. Compound **34** was characterised from the ^1H NMR spectrum from the appearance of benzylic protons at δ 2.8–3.1.

Next, we planned to achieve the synthesis of **16** from **35** by inverting the configuration at C-7 hydroxyl group (Scheme 3) under Mitsunobu reaction conditions. Reaction of **35**[27] with DEAD/triphenylphosphine/*p*-nitrobenzoic acid gave (7*R*)-diastereomer **36** as a white crystalline solid, mp 131–133°C in 83% yield and was characterised by ^1H NMR spectrum from the appearance of H-7 at δ 5.9. Inversion of configuration at C-7 of **36** was evident because H-7 proton of (7*S*)-*p*-nitrobenzoyl derivative **37** appeared relatively downfield at δ 6.1 in the ^1H NMR spectrum. Compound **37** was prepared from **35** by reaction with *p*-nitrobenzoic acid/DCC/r.t. **36** reacted with methanol containing a catalytic amount of sodium methoxide to obtain the alcohol **38** and on further reaction with benzyl bromide/NaH gave the benzyl ether **39**. Acid catalysed deprotection of **39** in 60% aq.HOAc at room temperature for 1 h gave the diol **40** which was further treated with methanesulphonyl chloride to obtain the dimesylate **41**. Compound **41** reacted with sodium iodide in butan-2-one to obtain vinylfuran **42** and on acid catalysed hydrolysis in 5% aq. H_2SO_4 in dioxane gave the vinyl (hydroxy) furan **19** as a crystalline solid, mp 108–110°C in high yield. Pd(II)Cl_2 mediated oxidative cyclisation of **19** was affected as a key step to obtain the lactol **43**. Oxidation of **43** with PDC in CH_2Cl_2 gave the lactone **44** as a crystalline solid, mp 102–104°C. Hydrogenolysis of **44** (10% Pd-$BaSO_4$) in ethyl acetate gave the required (5*R*,7*S*)-diastereomer **16** as a crystalline solid, mp 118–120°C and was characterised from the ^1H NMR and IR spectra.

It was planned to obtain (5*S*,7*S*)-diastereomers **44a** and **45a**, respectively, from the corresponding (5*R*,7*S*)-(**44**), (5*R*, 7*R*)-diastereomers (**45**).[27] This transformation we planned to achieve by use of Mitsunobu reaction conditions. Reaction of **44** and **45** severally with diethyl

azodicarboxylate (DEAD)-triphenylphosphine-*p*-nitrobenzoic acid, however, met with failure; it resulted in the recovery of starting material.

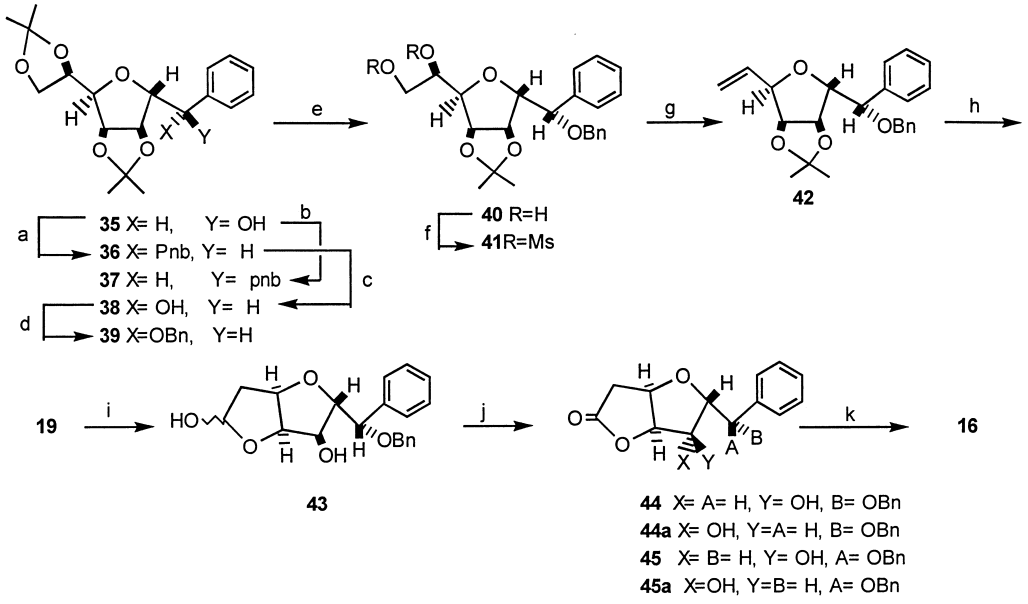
Synthesis of **17** was planned involving Wittig olefination–cyclisation of advanced intermediate **21** (Scheme 1) as a key step to realise the tetrahydrofuranolactone (Scheme 4). Thus, **21** was prepared from diacetone-D-glucose in seven steps by reported procedures.[31] **21** reacted with Ph_3P=CHCOOEt in MeOH at 0°C for 4 h to obtain the lactone **46** and was characterised from the appearance of H-2 and H-4 protons between δ 2.5–3.2 (4H) in the ^1H NMR spectrum and lactone absorption at 1780 cm^{-1} in the IR spectrum. Compound **46** was hydrogenated (Pd/C/MeOH/ 1 atm) to obtain the required lactone **17** and was characterised from ^1H NMR and IR spectra.

Cytotoxicities

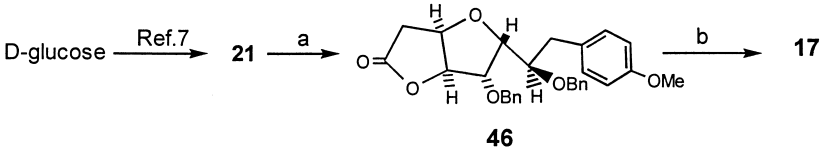
The cytotoxicities of **15**, **16**, **17**, **33** and **46** were tested in vitro by measuring the inhibition of cell growth. As shown in Table 1, goniofufurone analogues generally exhibited weak inhibition in six cell lines.

Conclusion

In conclusion we have described efficient synthesis of goniofufurone analogues **15** and **33** by $Pd(II)Cl_2$ mediated oxidative cyclisation of vinyl (hydroxy) furans as a key step and **17** by Wittig olefination-cyclisation of **21**. We found that change of stereochemistry at C-5, C-6 and C-7 position of goniofufurone (**1**) did not enhance the cytotoxicities significantly.



Scheme 3. Reagents and conditions: (a) DEAD, TPP, Pnb-acid, THF, 0°C, r.t., 6 h, (b) DCC, CH_2Cl_2, Pnb-acid, r.t, 8 h (c) NaOMe, MeOH, r.t, 1 h, (d) BnBr, NaH, DMF, 0°C, 45 min, (e) 60% aq.acetic acid r.t, 9 h, (f) MsCl, TEA, CH_2Cl_2, 0°C, r.t, 30 min, (g) NaI, 2-butanone, reflux, 12 h, (h) 5% aq.H_2SO_4, dioxane, reflux, 1 h, (i) $PdCl_2$, CuCl, DMF:H_2O (4:1), O_2, r.t, 5 h, (j) PDC, CH_2Cl_2, reflux, 1.5 h, (k) 10% Pd/C, EtOAc, H_2, r.t, 1 h.



Scheme 4. Reagents and conditions: (a) Ph_3P=CHCOOEt, MeOH, 0°C, 4 h, (b) 10% Pd/C, MeOH, H_2, r.t, 3 h.

Table 1. Bioactivities of **15**, **16**, **17**, **33** and **46** (GI_{50} values μM)

Tumor type	Cell line	15	16	17	33	46	Adriamycin
Prostate	DU 145	57.95	128.07	144.62	91.93	82.64	0.19
Colon	HT 29	5.68	269.36	147.28	9.21	64.99	0.33
Melanoma	LOX	4.1	217.35	130.9	5.51	29.36	0.03
Breast	MCF	75.74	254.35	72.24	93.14	64.91	0.15
Breast resistant	MCF-7/ADR	>200	134.33	82.53	19.79	27.04	0.12
CNS	U251	60.17	147.83	189.69	66.8	89.34	0.02

Experimental

Chemistry

^{1}H 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 Hz. ^{13}C NMR spectra were taken with a Varian Gemini (50, 100 MHz) with $CDCl_3$ as internal standard (δc 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 g. 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 glassware, which had been flame-dried under a stream of dry nitrogen.

3,6-Anhydro-7-*O*-benzyl-1,2:4,5-di-*O*-isopropylidene-D-*glycero*-D-*galacto*-heptitol (24) and 3,6-anhydro-7-*O*-benzyl-1,2:4,5-di-*O*-isopropylidene-D-*glycero*-D-*manno*-heptitol (25). To a slurry of hexane washed sodium hydride (1.5 g, 62.9 mmol) in dry *N*,*N*-dimethylformamide (DMF) (10 ml) diastereomeric mixture of **22**, **23** (11.5 g, 41.9 mmol) in dry DMF (10 ml) was added at 0°C. To this suspension, benzyl bromide (9.27 g, 54.6 mmol) was added dropwise and stirred for 30 min. After completion of the reaction methanol (1 mL) was added and the reaction mixture was poured into ice cold water and extracted into diethyl ether (2×200 mL). Combined ethereal extracts were dried (Na_2SO_4) and concentrated in vacuo to give a mixture of **24**, **25** that was separated by column chromatography (SiO_2, 60-120 mesh; hexane: EtOAc 4:1) to elute first **24** (4.02 g, 26%) as a syrup. $[\alpha]_D$ −8.8 (c 1.0, $CHCl_3$).^{1}H NMR ($CDCl_3$); δ 1.30, 1.32, 1.42, 1.48 (12H, 4s, 4×C*H*$_3$), 3.52 (2H, d, *J* 4.5, H-7), 4.45–4.82 (9H, m, H-1,1′,2-6 and C*H*$_2$Ph), 7.18–7.42 (5H, m, Ar*H*). Anal. calcd for $C_{20}H_{28}O_6$: C, 65.91; H, 7.74. Found: C, 65.72; H, 67.66 and elute next **25** (9.8 g, 64%) as a syrup. $[\alpha]_D$ 54.3 (c 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$); δ 1.35, 1.38, 1.44, 1.48 (12H, 4s, 4×C*H*$_3$), 3.4–4.1 (6H, m, H-1,1′,2,6,7,7′), 4.4–4.8 (5H, m, H-3-5, and C*H*$_2$Ph), 7.18–7.40 (5H, m, Ar*H*). Anal. calcd for $C_{20}H_{28}O_6$: C, 65.91; H, 7.74. Found: C, 65.83; H, 7.68.

3,6-Anhydro-1,2:4,5-di-*O*-isopropylidene-D-*glycero*-D-*gal-acto*-heptitol (22). A solution of compound **24** (3.95 g, 10 mmol) in MeOH (30 ml) containing 10% Pd-$BaSO_4$ (0.1 g) was stirred under hydrogen atmosphere for 4 h. After completion of the reaction the catalyst was filtered off and the solvent removed to obtain the title compound **22** (2.85 g. 95%) as a white crystalline solid, mp 58–60°C. $[\alpha]_D$ −9.0 (c 2.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$); δ 1.3, 1.32, 1.41, 1.48 (12H, 4s, 4×C*H*$_3$), 2.2 (1H, br.s, OH), 3.41–4.15 (6H, m, H-1,1′,3,6,7,7′), 4.32 (1H, ddd, *J* 7.01, 7.21, 7.29, H-2), 4.6–4.78 (2H, m, H-4 and 5), Anal. calcd for $C_{13}H_{22}O_6$: C,56.84; H,7.95. Found: C, 56.77; H, 7.89.

7*S*)-3,6-Anhydro-1,2:4,5-di-*O*-isopropylidene-7-*C*-phenyl-D-*glycero*-D-*galacto*-heptitol (26) and (7*R*)-3,6-anhydro-1,2:4,5-di-*O*-isopropylidene-7-*C*-phenyl-D-*glycero*-D-*galacto*- heptitol (27). Dimethyl sulphoxide (2.26 g, 20.9 mmol) was added to a stirred solution of the oxalyl chloride (2.29g, 18.2 mmol) in dichloromethane (10 ml) at −78°C and the resulting solution was stirred for 15 min. A solution of **22** (2.5 g, 9.1 mmol) in dry dichloromethane (15 ml) was added to the above reaction mixture and stirred for 1 h and triethylamine (3.67 g, 36.4 mmol) was added. The reaction mixture was brought gradually to room temperature and diluted with CH_2Cl_2 (100 mL). Organic phase was separated, washed with satd. sodium chloride solution water, dried (Na_2SO_4), filtered and evaporated to obtain the aldehyde, which without further purification was immediately treated with 1 M solution of phenylmagnesium bromide (18 ml, 18.2 mmol) in dry THF (20 mL) under nitrogen atmosphere for 4 h at 0°C. After completion of the reaction it was quenched with satd. aqueous ammonium chloride solution (25 mL) and filtered. The filtrate was concentrated to a syrupy residue and extracted into diethyl ether (2×100 mL). The combined organic extracts were washed with water, dried (Na_2SO_4), filtered and concentrated to obtain a residue which was separated by column chromatography (SiO_2, 60–120 mesh; hexane: EtOAc 4.5:1) to elute first **27** (0.63 g, 20%) as a syrup. $[\alpha]_D$ 1.3 (c 1.5, $CHCl_3$): ^{1}H NMR ($CDCl_3$); δ 1.32, 1.40, 1.45, 1.55 (12H, 4s, 4×C*H*$_3$), 2.75 (1H, br.s, OH), 3.45–3.58 (2H, m, H-1,1′), 3.98–4.8 (5H, m, H-2-6), 5.05 (1H, d, *J* 6.75, H-7), 7.15–7.4 (5H, m, Ar*H*). Anal. calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 65.02; H, 7.39, followed by **26** (1.85 g, 58%) as a white solid; mp 124–126°C. $[\alpha]_D$ 9.0 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$); δ 1.28, 1.52 (12H, 4s, 4×C*H*$_3$), 3.35–4.05 (4H, m, H-1,1′,3,6), 4.32 (1H, ddd, *J* 7.15, 7.02, 7.24, H-2), 4.6–4.75 (2H, m, H-4,5), 4.87 (1H, t, *J* 4.2, H-7), 7.1–7.4 (5H, m, Ar*H)*. Anal. calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 65.01; H, 7.41.

(7*S*)-3,6-Anhydro-7-*O*-benzyl-1,2:4,5-di-*O*-isopropylidene-7-C-phenyl-D-*glycero*-D-g*alacto*-heptitol (28). To a slurry of hexane washed sodium hydride (0.24 g, 10.2 mmol) in DMF (5 ml) was added compound **26** (1.8 g, 5.14 mmol) in DMF (5 mL) at 0°C. To this suspension was added benzyl bromide (1.3 g, 7.65 mmol) and the reaction mixture stirred for 30 min at room temperature. After completion of the reaction it was poured into ice cold water and extracted into diethyl ether (2×75 mL). The combined ethereal layers were washed with water, dried (Na_2SO_4), filtered and concentrated in vacuo to obtain the title compound **28** (2.05 g, 90%) as a syrup. $[\alpha]_D$ 18.0 (c 1.0 $CHCl_3$). ^{1}H NMR ($CDCl_3$); δ 1.29, 1.31, 1.38, 1.49 (12H, 4s, 4×C*H*$_3$), 3.35–3.98 (4H, m, H-1,1′,3, 6), 4.1–4.55 (3H, m, H-2 and C*H*$_2$Ph), 4.6 (1H, d, *J* 6.6, H-7), 4.75 (1H, dd, *J* 5.8,3.4, H-4), 4.9 (1H, dd, *J* 3.6, 5.8, H-5), 7.15–7.45 (10H, m, Ar*H*). Anal. calcd for $C_{26}H_{32}O_6$: C, 70.89; H, 7.32. Found: C, 70.82; H, 7.29.

(7*S*)-3,6-Anhydro-7-*O*-benzyl-4,5-*O*-isopropylidene-7-C-phenyl-D-*glycero*-D-*galacto*-heptitol (29). A solution of compound **28** (2 g, 4.5 mmol) in 60% aq. acetic acid (20 mL) was stirred at room temperature for 8 h and progress of the reaction was monitored by t.l.c. After completion of the reaction solvents were removed in vacuo to obtain a residue which was filtered on a bed of silica gel (hexane:EtOAc 1:1) to obtain the title compound **29** (1.54 g, 85%) as a thick syrup. $[\alpha]_D$ 27.0 (c 2.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$); δ 1.35, 1.5 (6H, 2s, 2×CH_3), 2.5 (1H, br.s, OH), 3.35–4.17 (5H, m, H-1,1′,2,3,6), 4.3–4.5 (2H, 2d, *J* 11.8, CH_2Ph), 4.62 (1H, d, *J* 6.5, H-7), 4.75–4.94 (2H, m, H-4,5), 7.17–7.48 (10H, m, Ar*H*). Anal. calcd for $C_{23}H_{28}O_6$: C, 69.98; H, 7.05. Found: C, 69.89; H, 7.01.

(7*S*)-3,6-Anhydro-7-*O*-benzyl-4,5-*O*-isopropylidene-1,2-bis-*O*-(methylsulfonyl)-7-C-phenyl-D-*glycero*-D-*galacto*-heptitol (30). To a stirred solution of diol **29** (1.2 g, 3 mmol) and triethylamine (1.51 g, 15 mmol) in dichloromethane (25 mL) was added methanesulfonyl chloride (1.02 g, 9 mmol) at 0°C and gradually brought to room temperature. The reaction mixture was diluted with water and organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (2×50 mL) and the combined organic layers were washed with satd. $NaHCO_3$ solution (50 mL), water, dried (Na_2SO_4), filtered and concentrated to obtain a residue. Purification of the crude residue by column chromatography on silica gel (hexane:EtOAc 2:1) gave the title compound **30** (1.42 g, 85%) as a syrup. $[\alpha]_D$ 27.0 (c 2.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$); δ 1.38, 1.49 (6H, 2s, 2×CH_3), 3.05, 3.08 (6H, 2s, 2×SCH_3), 3.6–4.15 (5H, m, H-1,1′,2,3,6), 4.39–4.50 (2H, 2d, *J* 12.0, CH_2Ph), 4.58 (1H, d, *J* 6.3, H-7), 4.75–4.98 (2H, m, H-4,5), 7.18–7.50 (10H, m, Ar*H*). Anal. calcd for $C_{25}H_{32}O_{10}S_2$: C, 53.93; H, 5.79. Found: C, 53.87; H, 5.72.

(7*S*)-3,6-Anhydro-7-*O*-benzyl-1,2-dideoxy-4,5-*O*-isopropylidene-7-C-phenyl-D-*altro*-hept-1-enitol (31). To a solution of **30** (1.4 g, 2.5 mmol) in butan-2-one (50 mL) was added sodium iodide (1.51 g, 12.2 mmol) and refluxed for 12 h. When the reaction was complete, solvent was removed in vacuo; a solution of satd. aqueous sodium thiosulphate was added and extracted into diethyl ether (2×75 ml). Combined organic layers were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure to obtain a syrupy residue which was filtered on a bed of silicagel (hexane:EtOAc 4:1) to obtain the title compound **31** (0.76 g, 82%) as a colourless syrup. $[\alpha]_D$ 1.6 (c 1.4, $CHCl_3$), ^{1}H NMR ($CDCl_3$); δ 1.40, 1.48 (6H, 2s, 2×CH_3), 3.6 (1H, dd, *J* 6.7, 6.3, H-6), 3.88 (1H, m, H-4), 4.3–4.5 (2H, 2d, *J* 11.9, CH_2Ph), 4.65 (2H, m, H-3,7), 4.92 (1H, dd, *J* 3.95, 4.2, H-3), 5.2 (1H, dd, *J* 10.2, 1.9, H-1), 5.25 (1H, dd, *J* 16.3, 1.5, H-1′), 5.78–6.0 (1H, m, H-2), 7.18–7.52 (10H, m, Ar*H*). Anal. calcd for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15%. Found: C, 75.33; H, 7.11.

(7*S*)- 3,6-Anhydro-7-*O*-benzyl-1,2-dideoxy-7-C-phenyl-D-*allo*-hept-1-enitol (18). To a solution of **31** (0.9 g, 2.4 mmol) in 1,4-dioxane (10 ml) was added 5% aq sulphuric acid (0.5 ml) and refluxed for 1 h. After completion of the reaction, solvent was removed in vacuo to obtain a residue which was extracted into ethyl acetate. Combined organic layers were washed with satd. $NaHCO_3$ solution, water, dried (Na_2SO_4), filtered and concentrated to obtain the diol **18** (0.66 g, 82%) as a syrup. $[\alpha]_D$ 7.0 (c, 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$); δ 2.8 (1H, br.s, OH), 3.95 (1H, dd, *J* 6.75, 6.3, H-6), 4.1–4.6 (5H, m, H-3-5 and CH_2Ph), 4.78 (1H, d, *J* 4.2, H-7), 5.21 (1H, dd, *J* 9.9, 1.3, H-1), 5.30 (1H, dd, *J* 16.5, 1.9, H-1'), 5.85–6.03 (1H, m, H-2), 7.17–7.52(10H, m, Ar*H*). Anal. calcd for $C_{20}H_{22}O_4$: C, 73.60, H, 6.79%. Found: C, 73.55, H, 6.73.

(7*S*)-3,6-Anhydro-7-O-benzyl-2-deoxy-7-C-phenyl-D-*allo*-1,4-heptanolactol (32). To a solution of **18** (0.62 g, 1.9 mmol) in DMF-water (4:1, 5 ml) was added palladium (II) chloride (0.067 g, 0.37 mmol), copper (I) chloride (0.19 g, 1.9 mmol) and oxygen was bubbled for 3 h at room temperature. After completion of the reaction 2% aqueous HCl was added to the reaction mixture and extracted into diethyl ether (2×75 ml). Combined ethereal solution was washed with water, dried (Na_2SO_4), filtered and concentrated to obtain the title compound **32** (0.54 g, 83%) as a syrup. ^{1}H NMR ($CDCl_3$); δ 1.9–2.2 (2H, m, H-2,2′), 2.9 (1H, br.s, OH), 3.4–4.88 (7H, m, H-3-7 and CH_2Ph), 5.5–5.75 (1H m, α/β), 7.19–7.52 (10H, m, Ar*H*). Anal. calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48%. Found: C, 70.12; H, 6.39.

(7*S*)-3,6-Anhydro-7-*O*-benzyl-2-deoxy-7-*C*-phenyl-D-*allo*-1,4-heptanolactone (33). To a solution of the lactol **32** (0.5 g, 1.46 mmol) in dry CH_2Cl_2 (10 ml) containing powdered 4A°molecular sieves (20 mg) was added pyridinium dichromate (0.65 g, 1.72 mmol) and refluxed for 1.5 h. When the reaction was complete, diethyl ether was added, reaction mixture was filtered through a bed of silica gel and eluted with diethyl ether. The ethereal solution was concentrated to obtain a brown residue which was purified on a bed of silica gel (hexane: EtOAc 1:1) to yield the title compound **33** (0.39 g, 78%) as a white crystalline solid. Mp 77–80°C. $[\alpha]_D$ 14.0 (c 0.7, $CHCl_3$). IR ν_{max} (KBr). 1782 cm^{-1}. ^{1}H NMR ($CDCl_3$); δ 2.65 (2H, d, *J* 4.6, H-2,2′), 2.9 (1H, br.s, OH), 3.9 (1H, dd, *J* 6.3, 4.5, H-6), 4.05–4.6 (m, 4H, H-3,5 and CH_2Ph), 4.7 (1H, d, *J* 6.3, H-7), 4.95 (1H, t, *J* 4.3, H-4), 7.15–7.52 (10H, m, Ar*H*). ^{13}C NMR ($CDCl_3$, 100MHz) δ 36.8 (C-2), 70.8 (C-5), 73.8 (C-3), 76.6 (C-6), 81.8 (C-4), 82.9 (O*C*H$_2$Ph), 85.0 (C-7), 127.5–137.4 (Aromatic), 175.1 (C=O). Anal. calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92%. Found C, 70.51; H, 5.86.

3,6-Anhydro-2,7-dideoxy-7-C-phenyl-D-*allo*-1,4-heptanolactone 34 and (7*S*)- 3,6-Anhydro-2-deoxy-7-*C*-phenyl-D-*allo*-1,4-heptanolactone (15). Compound **33** (0.3 g, 0.88 mmol) was dissolved in methanol (5 ml), 10% Pd/C (10 mg) was added and the reaction mixture was stirred under hydrogen atmosphere (1 atm) for 3 h. The catalyst was filtered off and the solvent removed in vacuo to obtain a mixture of **34** and **15** that were separated by column chromatography (SiO_2, 60–120 mesh, hexane: EtOAc 1:1). Eluted first was **34** (0.026 g, 13%) as a crystalline solid, mp 109–111°C. $[\alpha]_D$. 11.0 (c 1.0, $CHCl_3$). IR ν_{max} (KBr).1782 cm^{-1}. ^{1}H NMR ($CDCl_3$); δ 2.2 (1H, br.s, OH), 2.6–3.2 (4H, m, H-2,2′,7,7), 3.88–4.6 (3H, m, H-3,5,6), 4.92 (1H, d, *J* 6.7, H-4), 7.1–7.4 (5H, m, Ar*H*). Anal. calcd for $C_{13}H_{14}O_4$: C,66.66 ; H,6.02%. Found.: C,66.62; H, 5.98. Eluted next was compound **15** (0.112 g, 51.0%) as a white crystalline solid, mp 52–54°C. $[\alpha]_D$ 82.0 (c 0.95, $CHCl_3$). IR ν_{max} (KBr) 1784 cm^{-1}. ^{1}H NMR ($CDCl_3$); δ 2.7 (2H, m, H-2,2), 3.9–4.2 (3H, m, H-3,5,6), 4.88–4.93 (2H, m, H-4,7), 7.14–7.50 (5H, m, Ar*H*). ^{13}C NMR ($CDCl_3$, 50MHz) δ 36.8 (C-2),

71.1 (C-5), 73.8 (C-3), 82.1 (C-6), 83.08 (C-4), 85.3 (C-7), 127.7–137.7 (Aromatic), 175.1 (C=O). Anal. calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64%. Found: C, 62.31; H, 5.59.

(7*S*)-3,6-Anhydro-1,2:4,5-di-*O*-isopropylidene-7-*C*-phenyl-7-*O*-(4-nitro-benzoyl)-D-*glycero*-D-manno-heptitol (36). To a solution of alcohol **35** (3.8 g, 10.8 mmol) in dry THF (75 ml) was added 4-nitrobenzoic acid (5.4 g, 32.3 mmol), triphenylphosphine (10.4 g, 39.6 mmol), diethylazadicarboxylate (7.5 g, 43.1 mmol) at 0°C and the reaction mixture was stirred for 8 h. After completion of the reaction solvent was removed in vacuo to obtain a residue which was purified by column chromatography (SiO_2,60–120 mesh, hexane:EtOAc 4:1) to obtain the title compound **36** (4.5 g, 83%) as a crystalline solid, mp 131–133°C. $[\alpha]_D$ 36.0 (c 0.9, $CHCl_3$). ^1H NMR ($CDCl_3$); δ 1.35, 1.48,1.55 (12H 4s, 4×C*H*$_3$), 3.7–4.05 (3H, m, H-1,1′,2), 4.2–4.35 (1H, m, H-2), 4.40 (1H, d, *J* 6.95, H-6), 4.75–4.90 (2H, m, H-4,5), 5.98 (1H, d, *J* 6.95, H-7), 7.3–7.5 (5H, m, Ar*H*), 8.18–8.4 (4H, m, Ar*H*). Anal. calcd for $C_{26}H_{29}NO_9$. : C, 62.51, H, 5.85, N, 2.86%. Found: C, 62.46, H, 5.75, N, 2.78.

(7*R*)-3,6-Anhydro-1,2:4,5-di-*O*-isopropylidene-7-*C*-phenyl-7-*O*-(4-nitrobenzoyl)-D-*glycero*-D-manno-heptitol (37). To a solution of alcohol **35** (0.5 g, 1.42 mmol) in CH_2Cl_2 (25 ml) was added DCC (0.58 g, 2.8 mmol) and 4-nitrobenzoic acid (0.35 g, 2.1 mmol) and stirred for 7 h. After completion of the reaction dicyclohexylurea was removed by repeated crystallisation with hexane: EtOAc and the crude was filtered on a bed of silica gel (hexane: EtOAc 4:1) to obtain the title compound **37** (0.56 g, 78%) as a crystalline solid. Mp 141–142°C. $[\alpha]_D$ 28.0 (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$); δ 1.3, 1.38, 1.45, 1.48 (12H, 4s, 4×C*H*$_3$), 3.78–4.05 (5H, m, H-1,1′,2,3,4,6), 4.6 (1H, d, *J* 3.9, H-5), 4.8 (1H, dd, *J* 3.9, 4.2, H-4), 6.1 (1H, d, *J* 6.75, H-7), 7.31–7.5 (5H, m, Ar*H*), 8.1–8.4 (4H, m, Ar*H*). Anal. calcd for $C_{26}H_{29}NO_9$: C, 62.51; H, 5.85, N, 2.86%. Found: C, 62.45; H, 5.81, N, 2.82.

(7*S*)-3,6-Anhydro-1,2:4,5-di-*O*-isopropylidene-7-*C*-phenyl-D-*glycero*-D-manno-eptitol (38). To a solution of **36** (4.1 g, 8.2 mmol) in methanol (20 mL) was added sodium methoxide (prepared from 0.37 g sodium in 20 mL methanol) and stirred for 1.5 h. After completion of the reaction it was neutralised with carbon dioxide and solvent removed in vacuo to obtain a residue which was filtered on a bed of silica gel (hexane:EtOAc 2:1) to yield the title compound **38** (2.6 g, 93%) as a syrup. $[\alpha]_D$ 36.0 (c 0.9, $CHCl_3$). ^1H NMR ($CDCl_3$) 1.28,1.37,1.5 (12H, 4s, 4×C*H*$_3$), 2.1 (1H, d, *J* 2.1, OH), 3.9–4.4(5H, m, H-1,1′,2,3,6), 4.77–4.90(3H, m, H-4,5,7), 7.2–7.45 (5H, m, Ar*H*). Anal. calcd for $C_{19}H_{22}O_6$: C, 65.12 ; H, 7.48%. Found: C, 65.04; H, 7.39.

(7*S*)-3,6-Anhydro-7-*O*-benzyl-1,2:4,5-di-*O*-isopropylidene-7-*C*-phenyl-D-*glycero*-D-*manno*-heptitol (39). To a slurry of hexane washed sodium hydride (0.27 g, 11.4 mmol) in DMF (5 ml) was added a solution of compound **38** (2.5 g, 7.14 mmol) in DMF (5 mL) at 0°C followed by the addition of benzyl bromide (1.69 g, 9.9 mmol). The reaction mixture was stirred for 30 min at room temperature, poured into ice cold water and extracted into diethyl ether (2×60 mL). The combined ethereal extracts were washed with water, dried over Na_2SO_4, filtered and concentrated in vacuo to yield the title compound **39** (3 g, 96%) as a syrup. $[\alpha]_D$ −23.0 (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$); δ 1.3, 1.39, 1.45 (12H, 4s, 4×C*H*$_3$), 3.85–4.48 (7H, m, H-1, 1′, 2, 3, 6 and C*H*$_2$Ph), 4.57 (1H, dd, *J* 4.1, 3.92, H-5), 4.78 (1H, dt, *J* 3.9, H-4), 4.98 (1H, d, *J* 6.9, H-7), 7.1–7.45 (10H, m, Ar*H*). Anal. calcd for $C_{26}H_{32}O_6$: C, 70.89; H, 7.32%. Found: C, 70.83; H, 7.28.

(7*S*)-3,6-Anhydro-7-*O*-benzyl-1,2-*O*-isopropylidene-7-*C*-phenyl-D-*glycero*-D-*manno*-heptitol (40). A solution of compound **39** (2.95 g, 6.7 mmol) in 60% aq. acetic acid (25 ml) was stirred at room temperature for 8 h. Progress of the reaction was monitored by TLC and when complete solvents were removed under high vacuum to obtain a residue which was filtered on a bed of silica gel (hexane:EtOAc 1:1) to yield the title compound **40** (2.3 g, 86%) as a thick syrup. $[\alpha]_D$ −29.0 (c 1.6, $CHCl_3$). ^1H NMR ($CDCl_3$); δ 1.25,1.4 (6H, 2s, 2xC*H*$_3$), 1.95 (1H, br.s, OH), 3.5–4.12 (5H, m, H-1,1′,2,3,6), 4.23 (1H, d, *J* 11.3, C*H*$_2$Ph), 4.4–4.55 (2H, m, H-5 and C*H*$_2$Ph), 4.74 (1H, dd, *J* 3.8, 4.4, H-4), 4.9 (1H, d, *J* 6.7, H-7), 7.15–7.4 (10H, m, Ar*H*). Anal. calcd for $C_{23}H_{28}O_6$: C, 69.98; H, 7.05%. Found: C, 69.88; H, 6.99.

(7*S*)-3,6-Anhydro-7-*O*-benzyl-4,5-*O*-isopropylidene-1,2-bis-*O*-(methylsulfonyl)-7-*C*-phenyl-D-*glycero*-D-*manno*-heptitol (41). To a stirred solution of diol 40 (2.2 g, 5.5 mmol) and triethylamine (2.22 g, 22 mmol) in dichloromethane (50 mL) was added methanesulfonyl chloride (1.8 g, 16.5 mmol) at 0°C and brought to room temperature. After completion of the reaction it was diluted with water and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (2×50 mL) and the combined organic layers were washed with satd. $NaHCO_3$ solution (50 mL), water, dried (Na_2SO_4), filtered and concentrated to obtain a syrupy residue which was filtered on a bed of silica gel (hexane:EtOAc 2:1) to yield the title compound **41** (2.6 g, 84%) as a syrup. $[\alpha]_D$ −26.0 (c 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$); δ 1.2, 1.48 (6H, 2s, 2xC*H*$_3$), 2.95, 3.03 (6H, 2s, 2×SC*H*$_3$), 4.05 (1H, d, J 4.6, H-6), 4.23–4.90 (8H, m, H-1, 1′, 2, 3, 4, 5 and C*H*$_2$Ph), 4.95 (1H, H-7), 7.13–7.44 (10H, m, Ar*H*). Anal. calcd for $C_{25}H_{32}O_{10}S_2$: C,53.93; H, 5.79%. Found: C, 53.89; H, 5.68.

(7*S*)-3,6-Anhydro-7-*O*-benzyl-1,2-dideoxy-4,5-*O*-isopropylidene-7-*C*-phenyl-D-*altro*-hept-1-enitol (42). A solution of **41** (2.5 g, 4.4 mmol) in butan-2-one (50 mL) containing sodium iodide (2.69 g, 17.9 mmol) was refluxed for 12 h. After completion of the reaction solvent was removed in vacuo to obtain a residue which was extracted into diethyl ether (2×100 mL). Combined organic phases were separated washed with aqueous sodium thiosulphate solution (75 mL), water, dried (Na_2SO_4) and concentrated under reduced pressure to obtain a residue which was filtered on a bed of silica gel (hexane:EtOAc 4:1) to yield the title compound **42** (1.37 g, 85%) as a syrup. $[\alpha]_D$ 59.0 (c 1.4, $CHCl_3$).^1H NMR $CDCl_3$); δ 1.2, 1.31 (6H, 2s, 2×C*H*$_3$), 4.1 (1H, d, *J* 4.4, H-6), 4.3 (1H, d, *J* 12.8, C*H*$_2$Ph), 4.35–4.80(4H, m, H-4, 5,7), 4.95 (1H,

dd, *J* 3.8, 3.4, H-3), 5.18 (1H, dd, *J* 9.88, 1.2, H-1), 5.29 (1H, dd, *J* 16.5, 1.9, H-1′), 5.75–5.95(1H, m, H-2) 7.15–7.45 (10H, m, Ar*H*). Anal. calcd for $C_{23}H_{26}O_4$: C,75.38; H, 7.15%. Found: C, 75.29; H, 7.12.

(7*S*)- 3,6-Anhydro-7-*O*-benzyl-1,2 dideoxy-7-*C*-phenyl-D-*altro*-hept-1-enitol (19). To a solution of **42** (1.3 g, 3.55 mmol) in 1,4-dioxane (10 ml) was added 5% aq. sulphuric acid (1 ml) and refluxed for 1 h. After completion of the reaction, solvent was removed in vacuo and to obtain a residue which was extracted into ethyl acetate. Organic phase was washed with satd. $NaHCO_3$ solution, water, dried (Na_2SO_4), filtered and concentrated to obtain the title compound **19** (0.99 g, 86%) as a white crystalline solid. Mp 108–110°C. $[\alpha]_D$ −52.0 (c, 0.95, $CHCl_3$). ^1H NMR ($CDCl_3$); δ 2.4 (1H, br.s, OH), 2.5 (1H, br.s, OH), 4.05–4.7 (7H, m, H-3-7 and C*H*$_2$Ph), 5.25 (1H, dd, *J* 9.9, 1.0, H-1), 5.34 (1H, dd, *J* 16.6, 1.5, H-1′), 5.85–6.05 (1H, m, H-2), 7.2–7.55 (10H, m, Ar*H*). ^{13}C NMR ($CDCl_3$, 100MHz) δ 70.9 (C-4), 73.3 (C-5), 74.17 (C-6), 82.0 (C-3),82.4(O*C*H$_2$Ph), 85.1 (C-7), 118.3 (C-1), 127.3–138.0 (C-2 and Aromatic). Anal. calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79%. Found: C, 73.57; H, 6.75.

(7*S*)- 3,6-Anhydro-7-*O*-benzyl-2-deoxy-7-*C*-phenyl-D-altro-1,4-heptanolactol (43). To a solution of **19** (0.95 g, 2.9 mmol) in aqueous DMF (20%) was added palladium (II) chloride (0.10 g, 0.58 mmol), copper (I) chloride (0.29 g, 2.9 mmol) and oxygen was bubbled for 3 h at room temperature. After completion of the reaction it was diluted with 2% aqueous HCl and extracted into diethyl ether (2×80 mL). Combined ethereal solution was washed with water, dried, filtered and concentrated to obtain the title compound **43** (0.84 g,85%) as a syrup. ^1H NMR ($CDCl_3$); δ 175 (1H, br.s, OH), 2.02–2.3 (2H, m, H-2, 2′), 3.3 (1H, br.s, OH), 3.9–4.93 (7H, m, H-3-7 and C*H*$_2$Ph), 5.48–5.7 (1H, m, α/β) 7.15–7.45 (10H, m, Ar*H*). Anal. calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48%. Found: C, 70.11; H, 6.43.

(7*S*)- 3,6-Anhydro-7-*O*-benzyl-2-deoxy-7-*C*-phenyl-D-*altro*-1,4-heptanolactone (44). To a solution of the lactol **43** (0.8 g, 2.3 mmol) in dry CH_2Cl_2 (15 mL) was added powdered 4A°molecular seives (20 mg), pyridinium dichromate (1 g, 2.8 mmol) and refluxed for 1.5 h. After completion of the reaction solvent was removed to obtain a residue. The residue was extracted into diethyl ether (50 mL) filtered on a bed of silica gel first by eluting with diethyl ether followed by hexane:EtOAc (1:1) to obtain the title compound **44** (0.61 g, 77%) as a white crystalline solid. Mp 102–104°C. $[\alpha]_D$. −2.25 (c 1.3, $CHCl_3$). IR ν_{max}(KBr).1782 cm^{-1}. ^1H NMR ($CDCl_3$); δ 2.35, (1H, br.d, OH), 2.65–2.75 (2H, m, H-2), 4.05 (1H, dd, *J* 4.5, 4.65, H-6), 4.18–4.4 (4H, m, H-5 and C*H*$_2$Ph), 4.52 (1H, d, *J* 5.6, H-7), 4.59 (1H, d, *J* 11.2, C*H*$_2$Ph), 4.72–4.85(1H, m, H-3), 4.9 (1H, dt, *J* 4.2, 4.1, H-4), 7.18–7.5 (10H, m, Ar*H*). Anal. calcd for $C_{20}H_{20}O_5$: C,70.57; H, 5.92%. Found: C, 70.51; H, 5.88.

(7*S*)-3,6-Anhydro-2-deoxy-7-*C*-phenyl-D-*altro*-1,4-heptanolactone (16). Compound **44** (0.5 g, 1.4 mmol) was dissolved in ethyl acetate (10 mL), 10% Pd/C (30 mg) was added and stirred under hydrogen atmosphere (1 atm) for 3 h. After completion of the reaction the catalyst was filtered off and solvent was removed in vacuo to obtain the title compound **16** (0.31 g, 84%) as white crystalline solid. Mp 118–120°C. $[\alpha]_D$ 58.0 (c 0.8, MeOH). IR ν_{max}(KBr).1782 cm^-. ^1H NMR ($CDCl_3$); δ 2.16 (1H, br.s, OH), 2.52 (1H, br.s, OH), 2.72 (1H, d, *J* 17.2, H-2), 2.76 (1H, dd, *J* 17.2, 6.1, H-2′), 4.02 (1H, dd, *J* 4.2,4.6, H-6), 4.35, (1H, m, H-5), 4.84 (1H, ddd, *J* 5.7, 4.3, 1.5, H-3), 4.96 (2H, m, H-4, 7), 7.15–7.4 (5H, m, Ar*H*). ^{13}C NMR ($CDCl_3$, 100MHz) δ 36.3 (C-2), 71.9 (C-5), 73.4 (C-3), 75.6 (C-6), 82.8 (C-4), 85.0 (C-7), 126.9–140.2 (Aromatic), 175.1 (C=O). Anal. calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64%. Found C, 62.31; H, 5.58.

3,6-Anhydro-2-deoxy-5,7-di-*O*-benzyl-7-*C*-[4-methoxyphenylmethyl]-D-*ido*-1,4-heptanolactone (46). To a stirred solution of lactol **21** (0.7 g, 1.61 mmol) in methanol (10 mL) at 0°C was added carboethoxymethylene triphenylphosporane (1.12 g, 3.2 mmol) and stirred for 4 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 (hexane:EtOAc 1:1) to yield the title compound **46** (0.63 g, 82%) as a thick syrup. $[\alpha]_D$. −12.0 (c 1.2, $CHCl_3$). IR ν_{max} (KBr). 1780 cm^{-1}. ^1H NMR ($CDCl_3$); δ 2.5–3.2 (4H, m, H-2, 2′, 8.8′), 3.8 (3H, s, OMe), 3.6–5.05 (9H, m, H-3-7 and 2xC*H*$_2$Ph), 6.8–7.4 (14H, m, Ar*H*). Anal. calcd for $C_{29}H_{30}O_6$: C, 73.40; H, 6.37%. Found: C, 73.37; H, 6.33.

3,6-Anhydro-2-deoxy-7-*C*-[4-methoxyphenylmethyl]-D-*ido*-1,4-heptanolactone (17). Compound **36** (0.6 g, 1.2 mmol) was dissolved in methanol (10 mL), 10% Pd/C (30 mg) was added and stirred under hydrogen atmosphere (1 atm) for 4 h. The catalyst was filtered off and solvent removed in vacuo to obtain the title compound **8** (0.3 g, 86%) as white crystalline solid. Mp 49–51°C. IR ν_{max} (KBr).1782 cm^{-1}. ^1H NMR ($CDCl_3$); δ 2.4 (1H, br.s, OH), 2.6–3.0 (4H, m, H-2,2′, 8.8′), 3.78 (3H, s, OC*H*$_3$), 3.9 (1H, dd, *J* 2.6, 4.7, H-6), 4.10 (1H, d, *J* 2.6, H-5), 4.25 (1H, m, H-7), 4.6 (1H, br.s, OH), 4.9 (1H, d, *J* 4.2, H-4), 5.05 (1H, m, H-3), 6.8 (2H, d, *J* 8.0, Ar*H*), 7.15 (2H, d, *J* 8.0, Ar*H*). ^{13}C NMR ($CDCl_3$, 50MHz) δ 29.6 (C-8), 36.1 (C-2), 38.8 (OCH$_3$), 72.2 (C-5), 74.8 (C-3), 76.9 (C-6), 81.6 (C-7), 87.8 (C-4), 114.2–130.2 (Aromatic), 175.1 (C=O). Anal. calcd for $C_{15}H_{18}O_6$: C, 61.21; H, 6.17%. Found: C, 61.17; H, 6.14.

Antitumour assay

In screening, each compound was tested over a broad concentration range (tenfold dilutions starting from ⩾100 to 10 μM) against 6 human cancer cell lines comprised of different tumor types maintained in growing condition in RPMI 1640 medium containing 10% foetal calf serum and incubated at 37°C under 5% CO_2 atmosphere. All cell lines were inoculated onto a series of standard 96-well microtitre plate on day zero, followed by twenty-four hour incubation in the absence of test compound. The inoculation density used in the screen was as per Monk et al.[38] All the new compounds were dissolved in DMSO and diluted further in culture medium. An aliquot of each dilution was added to the growing cells in 96 well plates and incubated for 48 h. After

incubation, the assay was terminated by adding 50 μL of trichloroacetic acid (TCA) and incubating at 4°C for 30 min. The precipitated cells were washed and stained with sulforhodamine B dye for 30 min and the excess dye washed off with acetic acid. Adsorbed dye was solubilised in Tris base (alkaline pH) and quantitated by measuring the OD at 490 nm in an ELISA reader. GI50 concentration which inhibits the cell growth by 50% was calculated according to Boyd and Paull.[39]

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