Pergamon

Tetrahedron, Vol. 53, No. 44, pp. 15061-15068, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)10005-9

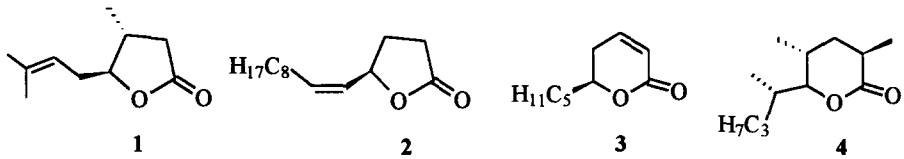
A Facile Synthesis of Optically Active Lactones Using Benzyl-3,6-Anhydro Glucofuranoside as Chiral Auxiliary

Vijay Nair*, Jaya Prabhakaran and Tesmol G. George

Organic Chemistry Division, Regional Research Laboratory, Trivandrum 695 019, INDIA

Abstract: *A highly enantioselective synthesis of γ- and δ-lactones using an anhydrofuranoside derived from D-glucose as chiral auxiliary is described.* © 1997 Elsevier Science Ltd.

A number of biologically active compounds especially pheromones are lactones;[1-4] some examples are given in figure 1. In addition, lactones have assumed importance as building blocks for the synthesis of natural products such as alkaloids, macrocyclic antibiotics and terpenoids.[5]



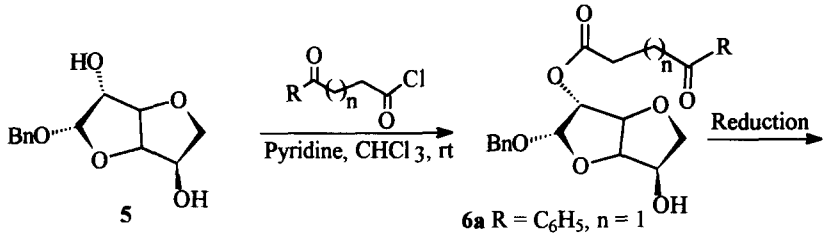
1 Eldanolide — **2** Japanese beetle Pheromone — **3** Massoia lactone — **4** Invictolide

Figure 1

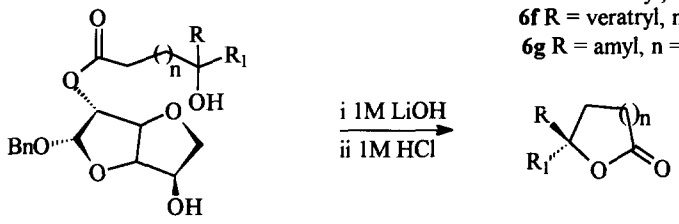
It is worthy of note that the configuration of lactones has a bearing on their biological activity and there has been considerable effort towards the synthesis of lactones in enantiomerically pure form. In general, biologically active lactones are prepared by the microbial reduction of the corresponding ketoester[6] or by the enzymatic resolution[7] of the hydroxyacid precursor. Not surprisingly, these methods often suffer from serious drawbacks. Enzymatic resolutions or microbial reductions are substrate specific while the use of chiral reagents often results in low enantioselectivity. Therefore, it was of interest to investigate the use of chiral auxiliaries in the asymmetric synthesis of these compounds. In particular we have been interested in use of carbohydrates as chiral auxiliaries,[8] especially those derived from D-glucose, the latter being abundant in nature's chiral pool. The anhydrofuranoside **5**, which can be easily synthesized from D-glucose appeared attractive as a chiral auxiliary. Of the two hydroxyl groups present in the molecule, the one attached to C-2 is more reactive compared to the one at C-5 which is projecting towards the wedge shaped ring system. Thus the presence of the two distinguishable hydroxyl groups and a rigid chiral *cis* fused ring system are features that render the molecule ideal for use as a chiral auxiliary. We have investigated the use of **5** as an auxiliary in the asymmetric synthesis of lactones and our results are reported here.

Results and Discussion

The strategy adopted for the synthesis of lactones was to attach prochiral ketoester moieties to the auxiliary and reduction of the keto group followed by removal of the auxiliary (Scheme 1).[9]



6a R = C_6H_5, n = 1
6b R = C_6H_5, n = 2
6c R = CH_3, n =1
6d R = CH_3, n =2
6e R = veratryl, n =1
6f R = veratryl, n =2
6g R = amyl, n =2



7a R = C_6H_5, n = 1, R_1 = H
7b R = C_6H_5, n = 2, R_1 = H
7c R = CH_3, n = 1, R_1 = H
7d R = CH_3, n = 2, R_1 = H
7e R = veratryl, n = 1, R_1 = H
7f R = veratryl, n = 2, R_1 = H
7g R = amyl, n = 2, R_1 = H
7h R = Ph, n = 1, R_1 = CH_3
7i R = Ph, n = 2, R_1 = CH_3

8a R = C_6H_5, n = 1, R_1 = H
8b R = C_6H_5, n = 2, R_1 = H
8c R = CH_3, n = 1, R_1 = H
8d R = CH_3, n = 2, R_1 = H
8e R = veratryl, n = 1, R_1 = H
8f R = veratryl, n = 2, R_1 = H
8g R = amyl, n = 2, R_1 = H
8h R = Ph, n = 1, R_1 = CH_3
8i R = Ph, n = 2, R_1 = CH_3

Scheme 1

The ketoesters **6(a-g)** derived from **5** were reduced with a variety of reducing agents like $NaBH_4$, $Zn(BH_4)_2$, $Ce(BH_4)_3$, $LiBH_4$ and $Mg(BH_4)_2$. The lactones formed after the removal of the chiral auxiliary from the hydroxyesters **7(a-i)** were found to be optically active. The best results were obtained with $Zn(BH_4)_2$ as the reducing agent and the *ee* values ranged from 56 to 91%. These are given in Table 1. With $NaBH_4$ the enantiomeric excess was very low (<25%). Similar was the case with $Ce(BH_4)_3$ and $LiBH_4$ while with $Mg(BH_4)_2$ 52% *ee* was obtained for **8a** at -5°C.

Although not conclusive, a rationale invoking the possibility of a chelated intermediate (Fig.2) can explain the stereochemistry of the products. The chelation envisages the involvement of the C-5 hydroxyl group which is β. The borohydride ion preferentially attacks from the α-face due to the presence of the wedge shaped ring system with inaccessible β-face, while the steric compression provided by the benzyl group also makes the ketoester group amenable to better chelation. The decrease in *ee* values on going from γ-butyrolactone to δ-valerolactone may be attributed to the enhanced flexibility of such a chelated intermediate resulting from the presence of the additional methylene group.

Table 1

Entry	Ketoester	*ee**/ Lactone [a]	*de* % [b]	Yield % [c]
1	**6a**	91, **8a**	96:4	82
2	**6b**	56, **8b**	78:22	76
3	**6c**	82, **8c** (S)	90:10	80
4	**6d**	48, **8d** (S)	70:30	75
5	**6e**	89, **8e** (R)	95:5	80
6	**6f**	- ,**8f** (R)	80:20	75
7	**6g**	-, **8g** (R)	85:15	70
8	**6h**	-, **8h** (R)	75:25	70
9	**6i**	-, **8i** (R)	80:20	72

*The absolute rotations of all the compounds are not known. a: The *ee* values of lactones **8a-8e** were calculated by comparison of theiroptical rotations to those in the literature. b: The *de* values were obtained by HPLC analysis (254 nm, ODS column). c: Isolated yields.

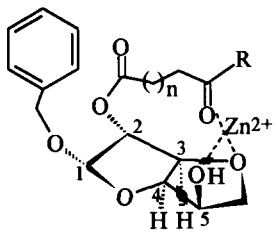
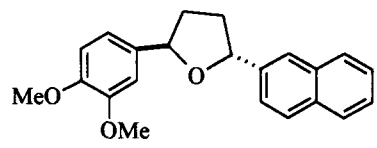


Fig. 2



9

It may be noted that lactone **8e** is a precursor for the dihydrofuran **9**[10] which is a potent antagonist for platelet activating factor (PAF). The strategy described here was applied to the synthesis of dihydromassoia lactone **8g** in optically active form; massoia lactone is a natural product isolated from bark oil of *Cryptocary massoia*, jasmine flowers and the defence secretion of the two species of formicine ants of the genus *Camponotus*.[11]

In conclusion, we have developed a facile synthesis of optically active lactones in high *ee* values using the anhydrofuranoside **5**, readily obtainable from D-glucose, as a chiral auxiliary. It may be noted that the results are comparable with those obtained by enzymatic resolution.[7, 10a, 12] The process described here appears suitable for the practical enantiomeric synthesis of a number of pheromones and biologically active lactones as illustrated by the synthesis of dihydromassoia lactone.

Experimental

Melting points were recorded on a Buchi-530 melting point apparatus and are uncorrected. Optical rotations were measured using a JASCO DIP 370 digital polarimeter. Infrared spectra were recorded on a Perkin-Elmer model 882 spectrophotometer and proton NMR on JEOL. EX-90 MHz, Bruker 200, GE 300 (QE PLUS) or Varian 200 MHz spectrometer. Elemental analysis was done using a Perkin-Elmer 2400 CHN analyser. Mass spectra were obtained using Finnigan MAT Model 8430.All the products were purified by chromatography on silica gel column using mixtures of ethyl acetate and hexane as eluent.

Benzyl-2-O-(4-oxo-4-phenylbutanoyl)-3,6-anhydro-α-D-glucofuranoside 6a: A solution of **5** (1.26g, 5 mmol) in $CHCl_3$ (15 mL) containing pyridine (0.81 mL, 10 mmol) was treated with benzoylpropionyl chloride (1.17 g, 6 mmol) in dry $CHCl_3$ (10 mL) at room temp. After 3.5 h the reaction mixture was diluted with $CHCl_3$ (25 mL) and successively washed with satd. aq. $CuSO_4$, aq. $NaHCO_3$, water and brine. The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. Purification of the residue afforded **6a** (1.79 g, 87%) as a colourless solid; mp 105-106° C; IR (CH_2Cl_2) 3515, 2990, 1740, 1735, 1428 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.75 (m, 2H), 7.5 (m, 8H), 4.86 (d, 1H, J = 6.8 Hz), 3.65 (brs, 2H), 3.3-3.2 (m, 6H), 2.9 (m, 4H), 2.1(brs, 1H); ^{13}C NMR (22.4 MHz, $CDCl_3$) δ 192.0, 135.1, 127.0, 88.2, 82.2, 75.9, 76.3, 71.9, 43.5, 42.5; Anal. calcd. for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87. Found: C, 66.95; H, 5.86.

Benzyl-2-O-(5-oxo-5-phenylpentanoyl)-3,6-anhydro-α-D-glucofuranoside 6b: A mixture of **5** (0.504 g, 2 mmol) and pyridine (0.242 mL, 3 mmol) in $CHCl_3$ (15 mL) was treated with benzoylbutyryl chloride (0.502 g, 2.4 mmol) in $CHCl_3$ (10 mL) for 3.5 h as described for compound **6a.** Work-up followed by chromatography afforded **6b** as a colourless solid (0.647 g, 76%); mp 95-96 °C; IR (CH_2Cl_2) 3510, 2995, 1735, 1728, 1430 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.7 (m, 2H), 7.5 (m, 8H), 4.8 (d, 1H, J = 6.75 Hz), 3.8-3.4 (m, 8H), 2.8 (m, 4H), 2.1 (brs, 1H), 1.8 (m, 2H),; HRMS calcd. for $C_{24}H_{26}O_7$: 426.1678, Found: 426.1654; Anal. calcd.: C, 67.59; H, 6.15. Found: C, 67.62; H, 6.17.

Benzyl-2-O-(4-oxo-4-methylbutanoyl)-3,6-anhydro-α-D-glucofuranoside 6c: Anhydrofuranoside **5** (1.01 g, 4 mmol) was treated with acetylpropionyl chloride (0.64 g, 4.8 mmol) in the presence of pyridine (0.38 mL, 4.8 mmol) at room temperature for 2.5 h. The reaction mixture was worked up and the residue was purified as usual to afford **6c** as a colourless semi-solid (1.17 g, 70%); IR (CH_2Cl_2) 3515, 1735, 1720, 1428 cm^{-1}. ^1H NMR ($CDCl_3$, 90 MHz) δ 7.4 (s, 5H), 4.85 (d, 1H), 3.7-3.3 (m, 8H), 2.9 (m, 7H);. GCMS (m/z): 350 (M^+).Anal. calcd. for $C_{18}H_{22}O_7$: C, 61.71; H, 6.33. Found: C, 61.73; H, 6.36,

Benzyl-2-O-(5-oxo-5-phenyl pentanoyl)-3,6-anhydro-α-D-glucofuranoside 6d: A solution of compound **5** (1.01 g, 4 mmol) in $CHCl_3$ (15 mL) containing pyridine (0.38 mL, 4.8 mmol) was stirred with acetylbutyryl chloride (0.71 g, 4.8 mmol) in $CHCl_3$ (10 mL) at room temp. for 2.5 h and worked up as described for compound **6a.** Chromatography afforded **6d** as a colourless semi-solid (1.04 g, 72%); IR (CH_2Cl_2) 3510, 2995, 1728, 1720, 1428 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.4 (s, 5H), 4.8 (d, 1H), 3.6-3.2 (m, 6H), 2.9 (m, 7H), 1.9 (m, 2H); GCMS (m/z): 364 (M^+) Anal. calcd. for $C_{19}H_{24}O_7$: C, 62.63; H, 6.64. Found: C, 62.70; H, 6.62.

Benzyl-2-O-(4-oxo-4-veratryl butanoyl)-3,6-anhydro-α-D-glucofuranoside 6e: A mixture of **5** (0.540g, 2 mmol) and pyridine (0.242 mL, 3 mmol) in $CHCl_3$ (15 mL) was reacted with 4-oxo-4-veratrylbutanoyl chloride (0.57 g, 2.4 mmol) for 4h at room temp. Usual work-up and purification gave **6e** as a colourless solid (0.74g, 79%); mp 97-98°C; IR (KBr) 3540, 2992, 1735, 1725, 1432 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.8 (m, 2H), 7.5 (s, 6H), 4.8 (d, 1H), 3.8 (s, 6H), 3.6 (brs, 2H), 3.4-3.2 (m, 6H), 2.7 (m, 4H), 2.0 (brs, 1H); ^{13}C NMR ($CDCl_3$, 22.4 MHz) δ 196.1, 177.0, 136.1, 127.5, 88.3, 82.5, 75.8, 76.4, 71.5, 64.2, 43.6, 42.4, 25.5; EIMS (*m/z*) 472 (M^+); Anal. calcd. for $C_{25}H_{28}O_9$: C, 63.55; H, 5.97. Found: C, 63.57; H, 5.98.

Benzyl-2-O-(5-oxo-5-veratryl pentanoyl)-3,6-anhydro-α-D-glucofuranoside 6f: Compound **5** (0.50 g, 2 mmol) was treated with 5-oxo-5-veratryl pentanoyl chloride (0.60 g, 2.4 mmol) in presence of pyridine (0.24 mL, 3 mmol) for 4h at room temp. Work-up by the usual procedure followed by chromatographic purification afforded **6f** as a colourless solid; mp 106-107 °C; IR (KBr) 3545, 2990, 1732, 1720, 1430 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.7 (m, 3H), 7.5 (s. 6H), 4.8 (d, 1H), 3.8 (s, 6H), 3.6 (brs, 2H), 3.4-3.2 (m,

6H), 2.6 (m, 4H), 1.9 (m, 2H); ^{13}C NMR ($CDCl_3$, 22.4 MHz) δ 198.5, 176.5, 130.2, 129.0, 126.8, 88.2, 83.0, 76.2, 75.6, 71.0, 63.5, 43.2, 42.0, 25.0; EIMS 486 (M^+);.Anal. calcd. for $C_{26}H_{30}O_9$:C, 64.19; H, 6.22. Found: C, 64.21; H, 6.23.

Benzyl-2-O-(5-oxo-decanoyl)-3,6-anhydro-α-D-glucofuranoside 6g: 5-Oxo-decanoyl chloride (0.489 g, 2.4 mmol) was added to a mixture of **5** (0.50g, 2 mmol) and pyridine (0.24 mL, 3 mmol) in $CHCl_3$ (15 mL) at room temperature and stirred for 5h. The usual work-up and chromatography afforded compound **6g** as a colourless viscous solid (0.67 g, 80%); IR (KBr) 3530, 2992, 1735, 1715, 1420 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.5 (s, 5H), 4.8 (d, 1H), 3.6-3.2 (m, 6H), 2.8-2.6 (m, 6H), 1.7-1.2 (m, 11H); ^{13}C NMR ($CDCl_3$, 22.4 MHz) δ 198.5, 176.5, 129.5, 127.8, 88.5, 82.3, 45.6, 45.0, 22.3; EIMS (*m/z*) 420 (M^+);Anal. calcd. for $C_{23}H_{32}O_7$: C, 65.70; H, 7.67. Found: C, 65.71; H, 7.65.

Benzyl-2-O-(4-hydroxy-4-phenyl butanoyl)-3,6-anhydro-α-D-glucofuranoside 7a: To a stirred solution of **6a** (1.65 g, 4 mmol) in THF (20 mL), $ZnCl_2$ (0.33 g, 2.4 mmol) was added and the mixture was stirred for 10 min. $NaBH_4$ (0.24 g, 4 mmol) was added to it and stirred for 10 min. The excess of $NaBH_4$ was quenched and the reaction mixture was diluted with water (15 mL) and extracted into ethyl acetate (4X15 mL). The combined organic extracts were dried (Na_2SO_4) and was purified by chromatography to afford **7a** as a colourless solid (1.529 g, 92%); mp 102-103 °C; IR (KBr) 3465, 1735, 1425 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.4 (brs, 10H), 4.8 (d, 1H), 3.8-3.6 (m, 9H), 2.8 (m, 2H), 2.0 (brs, 2H), 1.85-1.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 22.4 MHz) δ 179.5, 135.6, 129.2, 127.0, 126.5, 87.5, 86.0, 82.4, 75.6, 44.6, 44.0, 25.7, 25.0; GCMS (m/z) 414 (M^+); $[\alpha]D^{26}$ +81° (c = 1, $CHCl_3$), diastereomeric ratio (96:4); Anal. calcd. for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 66.70;H, 6.39.

Benzyl-2-O-(5-hydroxy-5-phenyl-pentanoyl)-3,6-anhydro-α-D-glucofuranoside 7b: Ketoester **6b** (1.09 g, 3 mmol) in THF (20 mL) was treated with $NaBH_4$ (0.23g, 6 mmol) in presence of $ZnCl_2$ (0.49 g, 3.6 mmol) as described for compound **7a.** The usual work-up and purification afforded **7b** as a colourless semi-solid (1.0 g, 83%); IR (KBr) 3480, 2990, 1635, 1428 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.5 (brs, 10 H), 4.8 (d, 1H), 3.7 -3.6 (m, 9H), 2.7 (m, 2H), 1.9 (brs, 2H), 1.8-1.7 (m, 4H); ^{13}C NMR ($CDCl_3$, 22.4) δ 179.0, 136.5, 130.0, 127.2, 87.2, 86.5, 81.0, 75.5, 44.5, 44.0, 25.7, 25.5; GCMS (*m/z*) 428 (M^+); *de* 78:22.; Anal. calcd. for $C_{24}H_{28}O_7$: C, 67.28; H, 6.59. Found: C, 67.31; H, 6.61.

Benzyl-2-O-(4-hydroxy-4-methyl-butanoyl)-3,6-anhydro-α-D-glucofuranoside 7c: Acetyl propionate **6c** (1.05 g, 3 mmol) in THF was stirred with $ZnCl_2$ (0.49 g, 3.6 mmol) and $NaBH_4$ (0.23 g, 6 mmol). The usual work-up and chromatography afforded **7c** as a colourless semi-solid (0.97 g, 92%). IR (KBr) 3470, 2988, 1725, 1630, 1432 cm^{-1}. ^1H NMR ($CDCl_3$, 90 MHz) δ 7.35 (s, 5H), 4.85 (d, 1H), 3.7-3.2 (m, 9H), 2.6 (m, 2H), 2.0 (brs, 2H), 1.8-1.6 (m, 5H); ^{13}C NMR (22.4 MHz, $CDCl_3$) δ 186.0, 135.6, 127.2, 87.5, 86.0, 76.3, 26.5, 26.0, 25.2; GCMS (m/z)352 (M^+), *de*: 90:10; Anal. calcd. for $C_{18}H_{24}O_7$: C, 61.35; H, 6.86. Found: C, 61.38; H, 6.60.

Benzyl-2-O-(5-hydroxy-5-methyl-pentanoyl)-3,6-anhydro-α-D-glucofuranoside 7d: Ketoester **6d** (1.09 g, 3 mmol) was reduced with $NaBH_4$ (0.23 g, 6 mmol) in presence of $ZnCl_2$ (0.49 g, 3.6 mmol) as described earlier. Work-up and purification of the residue by chromatography afforded **7d** as a colourless semi-solid (1.0 g, 83%); IR (KBr) 3450, 2995, 1730, 1428 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.3 (s, 5H), 4.7 (d, 1H), 3.8-3.4 (m, 8H), 2.7 (m 2H), 2.0 (brs, 2H), 1.9 (m, 4H); ^{13}C NMR (22.4 MHz) δ 176.5, 134.0, 127.0, 126.5, 90.2, 87.0, 75.3, 43.0, 25.5, 25.0; GCMS (m/z) 366 (M^+); *de* 70:30; Anal. calcd. for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15. Found: C, 62.30; H, 7.19.

Benzyl-2-O-(4-hydroxy-4-veratryl butanoyl)-3,6-anhydro-α-D-glucofuranoside 7e: Compound **6e** (0.71 g, 1.5 mmol) was treated with $NaBH_4$ (0.11 g, 2 mmol) in presence of $ZnCl_2$ (0.21 g, 1.5 mmol) at -5°C in THF as described for compound **7a**. Usual work-up followed by chromatography afforded compound **7e** (0.60 g, 85%) as a colourless solid; mp 102-103°C; IR (KBr) 3550, 2997, 1718, 1632, 1428 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.5-7.1 (brs, 8H), 4.7 (d, 1H), 3.8 (s, 6H), 3.6 (brs, 2H), 3.4-3.1 (m, 7H), 2.3 (m, 2H), 1.8 (m, 2H); ^{13}C NMR ($CDCl_3$, 22.4 MHz) δ 176.0, 128.0, 127. 5, 126.2, 88.0, 82.0, 76.5, 75.6, 71.0, 63.5, 43.5, 42.0, 25.5; *de* 95:5; Anal. calcd. for $C_{25}H_{30}O_9$: C, 63.28; H, 6.37. Found: C, 63.30; H, 6.41.

Benzyl-2-O-(5-hydroxy-5-veratryl pentanoyl)-3,6-anhydro-α-D-glucofuranoside 7f: Ketoester **6f** (0.73 g, 1.5 mmol) in THF (10mL) was stirred with $ZnCl_2$ (0.21 g, 1.5 mmol) and $NaBH_4$ (0.11g, 2 mmol) for 15 min. Work-up followed by chromatography afforded the product (0.83 g, 85%) as a colourless solid; mp 105-106°C; IR (KBr) 3540, 2992, 1715, 1630, 1420 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.5-7.0 (brs, 8H), 4.8 (d, 1H), 3.8 (s, 6H), 3.6 (brs, 2H); ^{13}C NMR ($CDCl_3$, 22.4 MHz) δ 172.0, 129.5, 127.6, 126.5, 88.5, 82.2, 75.6, 71.0, 63.8, 43.5, 42.4, 25.0; EIMS (*m/z*) 486 (M^+); *de* 80:20; Anal. calcd. for $C_{26}H_{32}O_9$: C, 63.92; H,6.60. Found: C, 64.01; H, 6.62.

Benzyl-2-O-(5-hydroxy-decanoyl)-3,6-anhydro-α-D-glucofuranoside 7g: Ketoester **6g** (0.84 g, 2 mmol) in THF (10 mL) was treated with $NaBH_4$ (0.13 g, 2.4 mmol) in presence of $ZnCl_2$ (2.4 mmol, 0.33 g) for 20 min. The reaction mixture was processed as usual and chromatography afforded the product **7g** (0. 69 g, 82%) as a colourless solid; mp 120-121°C; IR (KBr) 3540, 2993, 1718, 1426 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.3 (s, 5H), 4.8 (d, 1H), 3.5-3.2 (m, 7H), 2.7-2.5 (m, 2H), 1.7-1.1 (m, 15H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 177.0, 128.5, 127.7, 88.6, 82.5, 45.5, 45.0, 25.4, 22.3, 21.5; *de* 85:15; Anal. calcd. for $C_{23}H_{34}O_7$: C, 65.38; H, 8.11; Found: C, 65.41; H, 8.13.

Benzyl-2-O-(4-hydroxy-4-phenylpentanoyl)-3,6-anhydro-α-D-glucofuranoside 7h: Magnesium (0.07 g, 2.8 mmol) was taken in dry ether and MeI (0.15 g, 2.3 mmol) was added slowly under argon atmosphere. After 30 min. the ketoester **6a** (0.62 g, 1.5 mmol) in dry ether (10 mL) was added. The reaction mixture was quenched after 15 min. with sat. NH_4Cl and extracted into ethyl acetate. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified by chromatography to afford **7h** as a colourless solid (0.51 g, 80%); mp 108-109°C; IR (KBr) 3550, 1715, 1635, 1430 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.3 (s, 10H), 4.8 (d, 1H), 3.6-3.1 (m, 6H), 2.5 (m, 2H), 2.0 (brs, 2H), 1.8 (s, 3H), 1.7 (m, 2H); ^{13}C NMR ($CDCl_3$, 22.4 MHz) δ 176.5, 129.0, 128.0, 127.5, 88.5, 82.5, 45.6, 45.0, 25.6, 25.5, 25.0, 22.3; EIMS (*m/z*) 428 (M^+); *de* 75:25; Anal. calcd. for $C_{24}H_{28}O_7$: C, 67.28; H, 6.59. Found: C, 67.30; H, 6.61.

Benzyl-2-O-(5-hydroxy-5-phenylhexanoyl)-3,6-anhydro-α-D-glucofuranoside 7i: The ketoester **6b** (0.64 g, 1.5 mmol) was treated with methyl magnesium iodide in ether as described for compound **7h**. After 15 min. the reaction mixture was worked up as usual and the residue was purified by chromatography to obtain **7i** as a colourless solid; mp 110-111°C; IR (KBr) 3550, 1720, 1632, 1430 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.5 (s, 10H), 4.8 (d, 1H), 3.7-3.4 (m, 6H), 2.5 (m, 2H), 1.9 (brs, 2H), 1.8 (s, 3H), 1.7-1.2 (m, 4H); ^{13}C NMR ($CDCl_3$, 22.4 MHz) δ 177.0, 129.5, 128.2, 127.5, 88.2, 82.6, 45.6, 45.0, 25.5, 25.2, 22.5; EIMS (*m/z*) 442 (M^+); *de* 80:20; Anal. calcd. for $C_{25}H_{30}O_7$: C, 67.86; H, 6.83. Found:C, 67.89; H, 6.89.

γ-Phenyl-γ-butyrolactone 8a: Typical experimental procedure: Hydroxyester **7a** (1.014 g, 3 mmol) in THF (30 mL) was stirred with 1M LiOH (10 mL) at room temperature for 4 h. The reaction mixture was acidified using 1M HCl (5 mL), diluted with water (30 mL), extracted into ethyl acetate and washed with

water, saturated $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous Na_2SO_4; removal of the solvent under reduced pressure followed by chromatographic purification afforded **8a** as a viscous liquid (0.403 g, 83%); $[\alpha]_D^{26}$ +23° (c = 1.0, $CHCl_3$); lit. +32.5° (c = 4.3, $CHCl_3$);[12b] IR (film) 1778 cm^{-1}; ^1H NMR δ 7.26-7.47 (m, 5H), 5.51(dd, J= 8.0 and 6.2Hz, 1H), 2.57-2.75 (m, 3H), 2.06-2.032 (m, 1H); ^{13}C NMR δ 176.89, 139.36, 128.75, 128.43, 125.27, 81.21, 30.97, 28.95; Anal. calcd. for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.10; H, 6.24.

δ-Phenyl-δvalerolactone 8b: A solution of **7b** (1.06 g, 3 mmol) in THF (25 mL) was reacted with LiOH at room temperature. After 4.5 h the reaction mixture was processed as described for compound **8a**. Purification of the residue by chromatography afforded **8b** (0.42 g, 79 %) as a viscous liquid; $[\alpha]_D^{26}$ +16° (c = 1.0, $CHCl_3$); lit. +52° (c = 1.0, $CHCl_3$);[12c] IR (film) 2978, 1730, 1460 cm^{-1}; ^1H NMR ($CDCl_3$, 90MHz) δ 7.2 (s, 5H),4.5 (t, 1H), 2.3 (m, 2H), 2.2-1.9 (m, 4H); Anal. calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.01; H, 6.89.

γ-Methyl-γ-butyrolactone 8c: Hydroxyester **7c** (0.70 g, 2 mmol) in THF (25 mL) was saponified using 1M LiOH (10 mL) and the reaction mixture was worked up as described for compound **8a**. The residue on purification by chromatography afforded **8c** (0.16 g, 80%) as a colourless viscous liquid; $[\alpha]_D^{26}$ -30° (c = 1.0, $CHCl_3$); lit $[\alpha]_D^{26}$ -36.8° (c = 1.44, CH_2Cl_2);[12d] IR 2980,1768,1461cm^{-1}; ^1H NMR. ($CDCl_3$, 90 MHz) δ 4.3 (m, 1H), 2.2 (m, 2H), 1.7 (m, 2H), 1.3 (d, J=7, 3H); Anal. calcd. for$C_5H_8O_2$: C, 59.98; H, 8.05. Found: C, 60.01; H, 8.09.

δ-Methyl-δ-valerolactone 8d: Hydroxyester **7d** (1.10 g, 3 mmol) in THF (25 mL) was treated with 1M LiOH (10 mL) for 4 h The reaction mixture was worked up as detailed for compound **8a** and the residue was purified by chromatography to afford **8d** as a viscous liquid, (0.26 g, 75%); $[\alpha]_D^{26}$ -23° (c = 1.0, $CHCl_3$); lit. $[\alpha]_D^{26}$ -48° (c = 1.0, CH_2Cl_2);[12d,e] IR (film) 2975, 1732, 1456 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 4.4 (m, 1H), 1.9 (m, 2H), 1.7-1.2 (m, 7H); Anal. calcd. for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.18; H, 8.88

γ-veratryl-γ-butyrolactone 8e: Hydroxy ester **7e** (0.71 g, 1.5 mmol) was dissolved in THF (20 mL) and treated with 1M LiOH (10 mL) for 4h. The reaction mixture was worked up as detailed for compound **8a** and the residue was purified by chromatography to afford **8e** as a colourless solid (0.27 g, 80%), mp.117-118°C, lit[10a]118-119°C; [a]$_D^{26}$ +16° (c = 1.0, $CHCl_3$); lit. $[\alpha]_D^{23}$ +18° (c = 2.0, $CHCl_3$);[10] ^1H NMR ($CDCl_3$, 250 MHz) δ 7.5 (s, 1H), 7.3(brs, 2H), 4.7 (t, 1H), 3.6 (s, 6H), 2.3 (m, 2H); Anal. calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.90; H, 6.40.

δ-veratryl-δ-valerolactone 8f: Hydroxyester **7f** in THF (0.74 g, 1.5 mmol) was saponified with 1M LiOH (10 mL) for 4h. The reaction mixture was processed as described for compound **8a** and purified by chromatography to afford **8f** as a colourless solid (0.27 g, 75%); mp 123-124°C; $[\alpha]_D^{26}$ +14° (c = 1.0, $CHCl_3$); IR (KBr) 1739, 752, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.4-7.2 (m, 3H), 5.5 (m, 1H), 3.6 (s, 6H), 2.5 (m, 2H), 2.0-1.7 (m, 4H); GCMS (*m/z*) 236 (M^+); Anal. calcd. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.12; H, 6.88.

δ-pentyl-δ-valerolactone 8g: Saponification of hydroxy ester **7g** (0.63 g, 1.5 mmol) was done at room temperature using 1M LiOH (10 mL). Usual work-up followed by chromatography afforded **8g** as a semi-solid; $[\alpha]_D^{26}$ +42° (c = 1.0, $CHCl_3$); IR (KBr) 1738, 765, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 5.2 (m, 1H), 2.5 (m, 2H), 1.8-1.2 (m, 15H); EIMS (*m/z*) 170 (M^+); Anal. calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found, C, 70.59; H, 10.69.

γ-methyl-γ-phenyl-γ-butyrolactone 8h: Hydroxyester **7h** (0.64 g, 1.5 mmol) was treated with 1M LiOH (10 mL) at room temperature. Work-up by the usual procedure followed by chromatographic purification afforded **8h** as a colourless solid (0.18 g, 70%); mp 92-93°C; $[\alpha]_D^{26}$ +21° (c = 1.0, $CHCl_3$); IR (KBr) 1775, 750, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.5 (m, 5H), 2.6 (m, 2H), 1.8-1.6 (m, 2H), 1.5 (s, 3H); EIMS (*m/z*) 176 (M^+);Anal. calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.11; H, 6.90.

δ-methyl-δ-phenyl-δ-valerolactone 8i: Hydroxyester **7i** (0.73 g, 1.5 mmol) in THF (20 mL) was saponified using 1M LiOH (10 mL). The reaction mixture was worked up as described for compound **8a** and the residue was purified by chromatography to afford **8i** as a colourless solid (0.20g, 70%); mp 96-97°C; $[\alpha]_D^{26}$ +16° (c = 1.0, $CHCl_3$); IR (KBr) 1740, 755, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.4 (m, 5H), 2.5 (m, 2H), 1.9-1.7 (m, 4H), 1.6 (s, 3H); EIMS (*m/z*)190 (M^+); Anal. calcd. for $C_{12}H_{14}O_2$: C, 75.76; H,7.42. Found: C, 75.87, H, 7.55.

Acknowledgements

The authors thank Professor G. Mehta, Central University Hyderabad for 200 MHz NMR, Professor S. Chandrasekaran, IISc, Bangalore for CHN analysis and Dr. J. M. Rao, RRL, Trivandrum for optical rotation measurements. JP and TGG thank CSIR, New Delhi for financial support.

References

1. Mori, K. In *Techniques in Pheromone Research*; Hummel, H.; Miller, T., Eds. Springer Verlag, New York, 1984, chapter 12.
2. Iino, Y.; Tanaka, A.; Yamashita, K. *Agric. Biol. Chem.* **1972**, *36*, 2505.
3. (a) Ohloff, G. In *Progress in Organic Chemistry*, Springer Verlag, Wien, 1978, vol.35 (b) May, W. A.; Peterson, R. J.; Chang, S. S.; *J. Food Sci.*, **1978**, *43*, 1248. (c) Kingston, B. H.; *Pafai, J.* **1983**, *5*, 11.
4. Tumlinson, J. M.; Klien, M. G.; Dolittle, R. E.; Ladd, T. L.; Proveaux, A. T. *Science*, **1977**, *197*, 789.
5. Koch, S.S.C.; Chamberline, A.R.. *J. Org. Chem.* **1993**, *58*, 2725 and references cited therein.
6. (a) Robin, S.; Huet, F.; *Tetrahedron Lett.* **1993**, *34*, 2945 (b) Aquino, M.; Cardani, S.; Fronza, G.; Fuganti, C.; Fernandez, R. P.; Tagliani, A. *Tetrahedron*, **1991**, *47*, 7887. (c) Gopalan, A.; Lucero, R.; Jacobs, H.; Berryman, K. *Synth. Commun.* **1991**, *21*, 1321.
7. (a) Jacobs, H. K.; Muller, B. H.; Gopalan, A. *Tetrahedron* **1992**, *48*, 8891. (b) Sibi, M. P.; Gaboury, J. A. *Tetrahedron Lett.* **1992**, *33*, 5681. (c) Sugai, T.; Ohsawa, S.; Yamada, H.; Ohta, H. *Synthesis*, **1990**, 1112. (d) Taylor, S. K.; Chmiel, N. K.; Simons, L. J.; Vyvyan, J. R. *J. Org. Chem.* **1996**, *61*, 9084.
8. Kunz, H.; Ruck, K. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 336.
9. For a preliminary report see: Nair, V.; Prabhakaran, J.; *J. Chem. Soc., Perkin Trans. 1*, **1996**, 593.
10. (a) Corey, E.J.; Raman, K.B.; Saizo, S.; Chung-P.C.; Vinod, K. S. *J. Am. Chem. Soc.* **1987**, *109*, 7925-7926.(b) Braquet, P.; Goodfroid, J. *J. Trends Pharmacol. Sci.* **1986**, *7*, 397-403. (c) Hwang, S.-B.; Lam, M. H.; Biftu, T.; Beattie, T. R.; Shen, T. -Y. Eur. Pat. Appl. EP 199324; *Chem. Abstr.* **1987**, *106*, 50026r.
11. Bonini, C.; Pucci, P.; Racioppi, R.; Viggiani, L. *Tetrahedron Asym.* **1992**, *3*, 29.
12. (a) Gutman, A. L.; Zuobi, K.; Boltasky, A. *J. Org. Chem.* **1990**, *55*, 3546. (b) Brown, H. C.; Kulkarni, S. V.; Racherla, U. S. *J. Org. Chem.* **1994**, *59*, 365. (c) Armstrong, D. W.; Stalcup, A. M.; Hilton, M. L.; Duncan, J. D.; Faulkner, Jr. J. R.; Cang, S-C. *Anal. Chem.* **1990**, *62*, 1610. (d) Enders, D.; Grobner, R.; Runsink, J. *Synthesis* **1995**, 949 and references cited therein. (e) Gutman, A.L.; Oren, D.; Boltanski, A. *Tetrahedron Lett.* **1987**, *28*, 3861.

(*Received in UK* 11 *March* 1997; *revised* 2 *September* 1997; *accepted* 4 *September* 1997)