Synthesis of Antimetabolites of Sucrose

Luigi Lay, Francesco Nicotra,* Cristina Pangrazio, Luigi Panza and Giovanni Russo
Dipartimento di Chimica Organica e Industriale, Centro per lo Studio delle Sostanze Organiche Naturali del CNR, via Venezian 21, 20133 Milano, Italy

The C-disaccharides D-*glycero*-D-*ido*-D-*lyxo*-7,11-anhydro-6-deoxydodec-5-ulofuranose-(5,2) **7a** and D-*glycero*-D-*ido*-D-*lyxo*-7,11-anhydro-1-*O*-benzyloxysuccinyl-6-deoxydodec-5-ulofuranose-(5,2) **7b**, antimetabolites of sucrose, the second of which is provided with a succinyl group which allows its linkage to biopolymers, have been synthesized. Hydroxymercuriation of the easily available 3-(2',3',4',6'-tetra-*O*-benzyl-α-D-glucopyranosyl)prop-1-ene **1** followed by iododemercuriation, oxidation, and treatment of the so obtained iodo ketone with triphenylphosphine afforded the stabilized ylide 3-(2',3',4',6'-tetra-*O*-benzyl-α-D-glucopyranosyl)-2-oxopropylidenetriphenylphosphorane **2**. Reaction of the ylide **2** with a properly protected D-glyceraldehyde **3** afforded the α,β-unsaturated ketone **4** with a 12-carbon-atom skeleton, the stereoselective osmylation of which, followed by deprotection, gave the C-disaccharide **7a**. To obtain the succinylated C-disaccharide **7b**, (*S*)-2-*O*-benzyl-3-*O*-(benzyloxysuccinyl)glyceraldehyde **3b** was employed, which was obtained by enzymic benzyloxysuccinylation of 2-*O*-benzylglycerol and subsequent oxidation.

Antimetabolites of carbohydrates are molecules of great interest; they can inhibit the biological processes in which the structurally related natural carbohydrates are involved, and can substitute for them in their recognition or regulation roles.

An interesting modification which produces antimetabolites of carbohydrates is the substitution of the glycosidic oxygen with a methylene group, to afford the so-called C-glycosides.

Recently much synthetic effort has been directed towards the synthesis of C-disaccharides[1,2] as potential inhibitors of glycosidases and disaccharidases, and to studies on their conformational preferences compared with those of the structurally related disaccharide.[1f–h]

The synthesis of C-disaccharides of non-reducing sugars, in which the interglycosidic methylene group links the anomeric centres of both sugars, is a difficult task. In fact the most obvious synthetic scheme, which involves the attack of a one-carbon atom unit to the anomeric centre of the first sugar, and then the linkage of the thus obtained intermediate with the second sugar, has serious limitations in terms of β-elimination side-reactions and incorrect stereochemical outcome of the reaction. For these reasons, Kishi[2b,c] and we[2d] projected the synthesis of C-disaccharides related to sucrose following two different synthetic strategies, both of which required the *ex novo* construction of the fructose moiety.

We now describe the improvement of our synthetic scheme, with the introduction of a spacer which protects the hydroxy group at the fructosidic end of the molecule so avoiding the interconversion of the furanosidic form into the corresponding pyranosidic form. Moreover, the spacer allows the conjugation of the antimetabolite to a biopolymer; the thus obtained glycoconjugate may act as immunogen when administered to animals, and stimulate the production of antibodies against the non-metabolizable analogue of sucrose. These antibodies might be able to recognize the sucrose molecule, and, if this is the case, they can be used *inter alia* as biosensors.

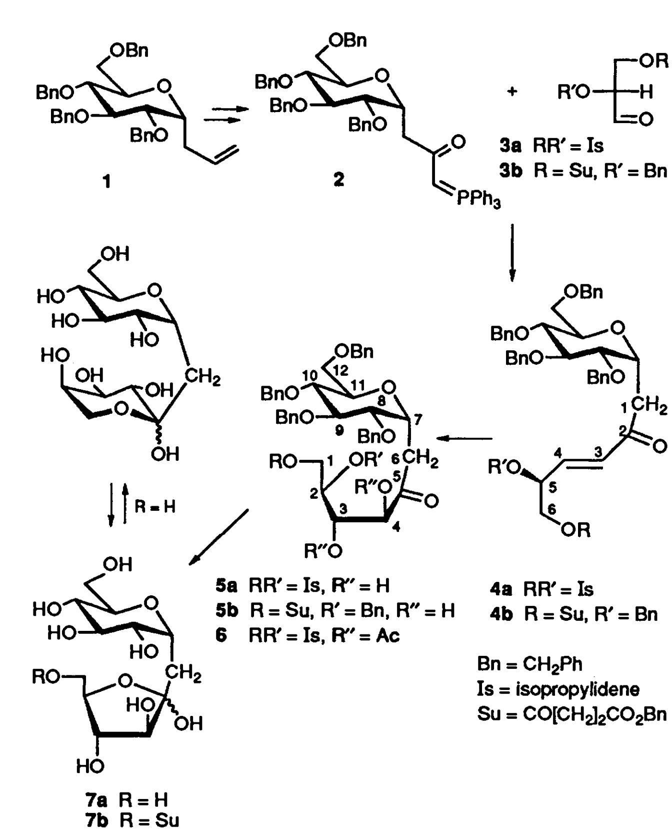
A detailed account of our previous results, which have been reported in a communication,[2d] is also given.

Results and Discussion

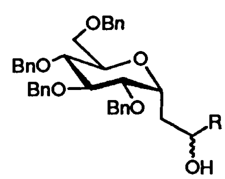
The synthetic strategy (Scheme 1) involves the construction of the C_{12}-skeleton of the C-disaccharide **7** from two fragments: a C_9-fragment **2**, derived from the easily available 3-(2',3',4',6'-tetra-*O*-benzylglucopyranosyl)prop-1-ene **1**[3] and the C_3-fragment of a properly protected D-glyceraldehyde **3**. The assemblage of the two fragments, the stereoselective hydroxylation[4] of the *E*-double bound obtained in this linkage, and the formation of the furanosidic cycle affords the synthetic target **7**. The use of 2,3-*O*-isopropylidene-D-glyceraldehyde **3a** gives rise to the C-disaccharide **7a**, while coupling of compound **2** with 2-*O*-benzyl-3-*O*-(benzyloxysuccinyl)-D-glyceraldehyde **3b** affords the C-disaccharide **7b**, with a spacer for the haptenization of biopolymers.

The Wittig reagent **2** was synthesized as follows. The hydroxymercuriation of the alkene **1**, effected with aq. $Hg(OAc)_2$ in acetone, afforded the hydroxymercurial **8** in 97% yield as a mixture of isomers. The iododemercuriation of the hydroxymercurial **8**, effected with I_2 in CH_2Cl_2, gave the hydroxy iodide **9** which was then oxidized with pyridinium chlorochromate (PCC) to the iodo ketone **10** in 87% yield. The reverse sequence, oxidation and then iododemercuriation, is impracticable as the oxidation of the hydroxymercurial **8** affords mainly the methyl ketone **11**. Any attempt to obtain this iodo ketone **10** by different routes, such as treatment of the alkene **1** with Ag_2CO_3–I_2,[5] failed. The conversion of the iodo ketone **10** into the Wittig reagent **2** requires strictly controlled experimental conditions. Simple treatment of the iodo ketone **10** with PPh_3 in benzene afforded quantitatively the methyl ketone **11**. The conversion requires the presence of Et_3N, and must be effected in MeCN at room temperature. The transformation of the thus obtained phosphonium salt into the ylide **2** was effected *in situ* by treatment of the reaction mixture with $NaHCO_3$, and the ylide was purified by silica gel chromatography. Following this protocol, the ylide **2** was obtained in 57% yield together with 40% of the methyl ketone **11**.

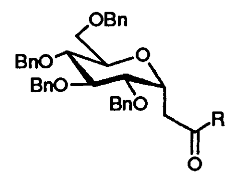
Treatment of the ylide **2** with 2,3-*O*-isopropylidene-D-glyceraldehyde **3a** in MeCN afforded the α,β-unsaturated ketone **4a** in 88% yield. The osmylation of the double bond of compound **4a**, effected in aq. acetone at −30 °C following the catalytic procedure, occurred with 60% diastereoselection to afford the diol **5a**, which was separated from the diastereo-



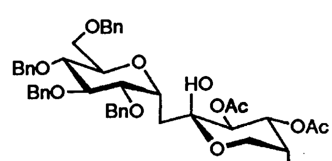
Scheme 1



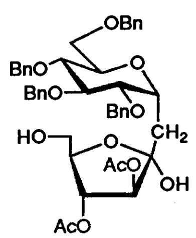
8 R = CH_2HgCl
9 R = CH_2I



10 R = CH_2I
11 R = Me



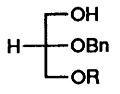
12



13

isomer by acetylation and careful chromatography on silica gel. The deisopropylidenation of **5a** or of its acetate **6** can afford four different hemiacetalic isomers in equilibrium, the desired one being the α-furanoside **13**. Treatment of the diacetate **6** with freshly prepared $FeCl_3$–silica gel, in the absence of solvents,[6] afforded a single product as shown by TLC [hexane–ethyl acetate (1:1); R_f 0.30]. However, isolation of the product by chromatography on Florisil gave rise to two additional isomers (R_f 0.51 and 0.58), which when re-treated with $FeCl_3$–silica gel were reconverted into the former compound (R_f 0.30). The product with R_f 0.30, isolated by silica gel chromatography, was found to be the α-pyranoside **12**, which allowed the easy determination of the stereochemistry of the previous osmylation. Compound **12** shows a 10.5 Hz axial–axial coupling constant between 3-H and 4-H, and a 3 Hz axial–equatorial coupling constant between 3-H and 2-H. Moreover, a 1.5 Hz long-range coupling constant between 4-H and the OH group at C-5 clearly indicates the α-anomeric configuration and the conformational rigidity of the molecule. The presence of a carbonyl group beta to the anomeric carbon, as in compounds **4**, **5**, **6** and **10** in the synthetic scheme, could in principle cause epimerization to the more stable β-isomer.[7] The 5 Hz axial–equatorial coupling constant observed in compound **12** between the anomeric hydrogen (7-H) and the adjacent 8-H clearly indicates that no epimerization occurs in the process.

The filtration of α-pyranoside **12** on Florisil converted it partly into the furanosidic forms, the α-furanose **13** being predominant. The α-anomeric configuration of compound **13** was attributed on the basis of the 1.5 Hz coupling constant between 3-H and 4-H.[8] Deprotection of the mixture of isomers **12** and **13** by treatment with K_2CO_3 in EtOH and subsequent catalytic hydrogenation with Pd/C afforded the analogue of sucrose, compound **7a**, which was crystallized from EtOH. Owing to the hemiketalic nature of the C-disaccharide **7a**, a mixture of furanose and pyranose forms was present in equilibrium, as evidenced by ^{13}C NMR spectroscopy which



14 R = H
15 R = $CO[CH_2]_2CO_2Bn$

shows three signals for the interglycosidic carbon (C-6) (δ_C 33.46, 34.71 and 38.35), the one at highest field being predominant (60%). The highest chemical shift of C-6 in the predominant form suggests that this carbon is *cis*-oriented with the γ-oxygen (γ-effect), as in the α-furanose structure.

Tests of sweetness, effected on a 3% aqueous solution, indicate that compound **7a** is not sweet. In this regard it must be noted that apart from the substitution of the interglycosidic oxygen with a methylene, compound **7a** differs from sucrose in the absence of the C-1 atom of the furanosidic moiety in the natural sugar. Studies on the structural requirements for sweetness[9] indicate that the oxygen linked to C-1 of the fructose moiety, and its distance from the hydroxy group at C-2 of the glucose moiety, are responsible for the sweetness response.

The presence of a succinyl ester in position 1 of the deprotected C-disaccharide, as in compound **7b**, will prevent the formation of the pyranosidic form and will allow linkage to a biopolymer.

The synthesis of the succinylated C-disaccharide **7b** requires the chiral glyceraldehyde **3b**, in which the 2-OH is benzylated and the 3-OH benzyloxysuccinylated so that, at the end of the synthetic procedure, a simple debenzylation by catalytic hydrogenation will afford the desired product.

2-*O*-Benzyl-3-*O*-(benzyloxysuccinyl)-D-glyceraldehyde **3b** was synthesized by taking advantage from the results of Wong,[10] who showed that the lipase from *Pseudomonas* spp. stereoselectively acetylates the *pro-S* hydroxy group of 2-*O*-benzylglycerol **14**. Following this procedure, but employing benzyl trifluoroethyl succinate as the activated ester, we synthesized (*S*)-2-*O*-benzyl-1-*O*-(benzyloxysuccinyl)glycerol **15** in 78% e.e. {determined by HPLC on optically active polyacrylamide and by NMR spectroscopy with europium tris-(heptafluorobutyrylcamphorate) [Eu(hfc)$_3$] as shift reagent}. The oxidation of the free hydroxy group of compound **15** was effected with dimethyl sulfoxide (DMSO)–Ac_2O, and the crude aldehyde **3b** was treated with the ylide **2** in MeCN at room temperature. The desired (*E*)-α,β-unsaturated ketone **4b** was obtained in 59% yield after careful chromatography which allows its separation from *Z*-isomer. In particular, the *E*:*Z* ratio in the crude reaction mixture was 8:1, as shown by ^1H NMR spectroscopy. We also observed that the product with the wrong (*Z*) stereochemistry reacts more slowly than the *E*-isomer in the subsequent reaction. The osmylation of the α,β-unsaturated ketone **4b**, effected at −30 °C, requires 48 h for completion. If the reaction is stopped after 24 h, virtually exclusive formation of compound **5b**, the product of osmylation of the *E*-isomer **4b**, is observed. The stereoselection of the osmylation, investigated by NMR spectroscopy, was higher than 90% (d.e.). Catalytic hydrogenation of the C-disaccharide **5b** afforded the desired succinylated analogue of sucrose, compound **7b**, in an α:β ratio of 4.3:1. The ratio of the two isomers was determined by ^{13}C NMR spectroscopy. In the predominant, α-isomer, the signal of the interglycosidic carbon (C-6) is shifted to higher field (δ_C 39.11 *versus* 41.18) according to the γ-effect due to the *cis*-oriented oxygen on C-4. Moreover, the signal of the anomeric carbon of the predominant α-isomer is shifted to lower field (δ_C 118.18 *versus* 115.19), according with the observation that the anomeric carbon of an α-fructofuranoside resonates at lower fields than that of the β-isomer.[11]

The succinylated analogue of sucrose, compound **7b**, when tested in 3% aqueous solution, was found not to be sweet. Work is in progress to evaluate the effect of these molecules on different α-glucosidases.

Experimental

Mass spectra were recorded on a VG 70-70 EQ spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AC 300, Varian XL 200 and Bruker WP80 spectrometers for solutions in $CDCl_3$, unless otherwise stated; the signals of the aromatic carbons in the ^{13}C NMR spectra are not reported. *J* Values are given in Hz. $[\alpha]_D$ Values were measured at 20 °C on a Perkin-Elmer 241 polarimeter, and are given in units of 10^{-1} deg cm^2 g^{-1}. Column chromatography was performed with the flash procedure using Merck silica gel 60 (230–400 mesh). TLC was performed on Merck silica gel-60 F-254 plates, developed with hexane–ethyl acetate in the ratio reported in parentheses, and visualized by spraying with a solution containing H_2SO_4 (31 cm^3), ammonium molybdate (21 g) and $Ce(SO_4)_2$ (1 g) in water (500 cm^3) and then heating at 110 °C for 5 min. Usual work-up refers to dilution with an organic solvent (CH_2Cl_2), washing with water to neutrality (pH test paper), drying with Na_2SO_4, and evaporation under reduced pressure.

2-Hydroxy-3-(2',3',4',6'-tetra-O-benzyl-α-D-glucopyranosyl)-propylmercury Chloride **8**.—To a solution of compound **1** (17.24 g, 30.6 mmol) in a 1:1 mixture of acetone–water (600 cm^3) was added $Hg(OAc)_2$ (9.75 g, 30.6 mmol) and the mixture was stirred for 4 h (TLC, 6:4). A solution of NaCl (3.55 g, 61.2 mmol) in 1 mol dm^{-3} NaOH (30.6 cm^3) was then added and the mixture was stirred for 45 min. Usual work-up afforded *title compound* **8** (24.2 g, 97%, mixture of two isomers), which was crystallized from hexane. M.p. 93–95 °C; δ_C(75.432 MHz) (for the major isomer): 37.29 (t, C-1), 40.86 (t, C-3), 68.53, 71.68, 72.60, 78.42, 79.87 and 82.51 (6 d), 69.70, 74.03, 74.14, 75.57 and 75.96 (5 t) (Found: C, 53.1; H, 5.1. $C_{37}H_{41}ClO_6Hg$ requires C, 54.3; H, 5.05%).

1-Iodo-3-(2',3',4',6'-tetra-O-benzyl-α-D-glucopyranosyl)propan-2-ol **9**.—To a solution of compound **8** (22 g, 27 mmol) in dry CH_2Cl_2 (70 cm^3) under dry N_2 was added I_2 (6.8 g, 27 mmol). After 4 h (TLC, 6:4) 5% aq. $Na_2S_2O_3$ was added, and the mixture was stirred for 30 min. Usual work-up afforded *title compound* **9** (17.2 g, 90%, mixture of two isomers). Oil; δ_C(75.432 MHz) (for the major isomer): 15.22 (t, C-1), 32.14 (t, C-3), 68.91, 71.53, 72.46, 78.54, 79.97 and 82.69 (6 d), 69.64, 73.86, 74.13, 75.64 and 76.05 (5 t) (Found: C, 62.4; H, 5.6. $C_{37}H_{41}IO_6$ requires C, 62.7; H, 5.8%).

1-Iodo-3-(2',3',4',6'-tetra-O-benzyl-α-D-glucopyranosyl)propan-2-one **10**.—To a stirred solution of the alcohol **9** (9.3 g, 13 mmol) in dry CH_2Cl_2 (60 cm^3), under N_2, was added PCC (4.3 g, 20 mmol). After 6 h (TLC, 7:3) the mixture was filtered on silica gel and eluted with Et_2O. Evaporation afforded crude ketone **10** (8.10 g of labile crude product, 87%), which was crystallized from Et_2O–hexane to afford pure *title compound* **10** (4.3 g). The mother liquor was submitted to chromatography (7:3) to afford the pure salt **8** (1.42 g recovery). Compound **10** had m.p. 81–82 °C (from Et_2O–hexane); $[\alpha]_D$ +13.4 (*c* 1, $CHCl_3$); δ_H(200 MHz) 2.94 (1 H, dd, *J* 14.5, 8, 1-H^a), 3.12 (1 H, dd, *J* 14.5, 6, 1-H^b), 3.66 (1 H, d, *J* 10, 3-H^a), 3.58–3.80 (6 H, m), 3.82 (1 H, d, *J* 10, 3-H^b), 4.48–4.96 (9 H, m) and 7.35 (20 H, Ph); δ_C(20.115 MHz) 7.35 (t, C-1), 36.95 (t, C-3), 71.42, 72.82, 73.47, 77.76 and 79.17 (5 d), 69.12, 73.47, 74.83, 75.13 and 81.78 (5 t) and 199.89 (s, C-2) (Found: C, 62.75; H, 5.5. $C_{37}H_{39}IO_6$ requires C, 62.9; H, 5.6%).

2-Oxo-3-(2',3',4',6'-tetra-O-benzyl-α-D-glucopyranosyl)propylidenetriphenylphosphorane **2**.—A solution containing PPh_3

(1.6 g, 6.1 mmol) and Et_3N (0.11 cm^3, 1.1 mmol) in dry MeCN (60 cm^3) was added, through a double-tipped needle, under N_2, to a solution of ketone **10** (4.3 g, 6.1 mmol) in MeCN (10 cm^3). After 20 h (TLC, 7:3), the mixture was washed with 5% aq. $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was then dried (Na_2SO_4) and evaporated. Chromatographic purification (AcOEt) afforded *title compound* **2** (2.9 g, 57%) and the *methyl ketone* **11** (1.7 g, 40%).

Compound **2**, m.p. 39–41 °C (from AcOEt); $[\alpha]_D$ +43.5 (*c* 1, $CHCl_3$); δ_C(75.432 MHz) 38.06 (dt, $J_{C,P}$ 14.5), 53.68 (dd, $J_{C,P}$ 107.9), 69.75, 72.99, 74.15, 75.66 and 76.04 (5 t), 72.21, 73.50, 78.88, 80.61 and 83.15 (5 d) and 201.22 (s, CO); *m/z* (FAB) 841 (M^+) (Found: C, 78.4; H, 6.1. $C_{55}H_{53}O_6P$ requires C, 78.55; H, 6.35%).

Compound **11**, oil; $[\alpha]_D$ +15.3 (*c* 1, $CHCl_3$); δ_H(300 MHz) 2.18 (1 H, s, Me), 2.77 (1 H, dd, *J* 15.4, 8.3, 1-H^a), 2.89 (1 H, dd, *J* 15.4, 5.5, 1-H^b), 3.60–3.90 (6 H, m), 4.45–5.00 (9 H, OCH_2Ph, 1′-H) and 7.35 (20 H, Ph); δ_C(75.432 Hz) 31.28 (q, Me), 41.68 (d, C-1), 69.45, 74.11, 74.11, 75.69 and 76.11 (5 t), 71.54, 73.05, 78.36, 80.03 and 82.75 (5 d) and 206.76 (s, CO) (Found: C, 76.7; H, 7.2. $C_{37}H_{40}O_6$ requires C, 76.5; H, 6.9%).

(E,S)-5,6-*Isopropylidenedioxy*-1-(2′,3′,4′,6′-*tetra*-O-*benzyl*-α-D-*glucopyranosyl)hex*-3-*en*-2-*one* **4a**.—A solution of the ylide **2** (1.5 g, 1.8 mmol) in MeCN (15 cm^3) was stirred for 2 h under dry N_2 with 2,3-*O*-isopropylidene-D-glyceraldehyde **3a** (2.5 g, 19 mmol). The solvent was then removed under reduced pressure and the residue, submitted to chromatography (7:3), afforded *title compound* **4a** (1.09 g, 88%) as an oil, $[\alpha]_D$ +51.5 (*c* 1, $CHCl_3$); δ_H(200 MHz) 1.39 (3 H, s, Me), 1.41 (3 H, s, Me), 2.84 (1 H, dd, *J* 16, 8, 1-H^a), 3.00 (1 H, dd, *J* 16, 5.5, 1-H^b), 3.50–3.84 (7 H, m), 4.11 (1 H, dd, *J* 8, 6.5), 4.40–4.93 (10 H, m), 6.31 (1 H, dd, *J* 16, 1.3, 3-H), 6.64 (1 H, dd, *J* 16, 5.5, 4-H) and 7.35 (20 H, Ph); δ_C(50.288 MHz) 25.74 (q, Me), 26.52 (q, Me), 37.98 (t, C-1), 68.77, 68.77, 70.78, 72.84, 73.33, 73.50, 74.99, 75.37, 77.70, 79.32, 82.13, 110.22 (s, O–C–O), 130.07 (d, C-3), 142.79 (d, C-4) and 196.87 (s, CO) (Found: C, 74.55; H, 7.0. $C_{43}H_{48}O_8$ requires C, 74.5; H, 7.0%).

D-glycero-D-ido-D-lyxo-7,11-*Anhydro*-8,9,10,12-*tetra*-O-*benzyl*-6-*deoxy*-1,2-O-*isopropylidenedodec*-5-*ulose* **5a**.—To a solution of enone **4a** (1.08 g, 1.56 mmol) and *N*-methylmorpholine *N*-oxide (NMMNO) (424 mg, 3.14 mmol) in acetone–water (8:1, 10 cm^3), cooled at −30 °C, was added a mixture of OsO_4 in Bu^{t}OH (20 mg, 0.07 mmol, in 4 cm^3). The mixture was stirred overnight at −30 °C, and then 5% aq. $Na_2S_2O_3$ was added. After 10 min of stirring, usual work-up afforded *title compound* **5a** and its diastereoisomer at C-3 and C-4 in an 8:2 ratio, determined by ^{13}C NMR spectroscopy (990 mg, 88%). Crude compound **5a** was directly submitted to acetylation which allowed its separation from the isomer; δ_C(20.115 MHz) (for the major isomer in the crude mixture): 25.20 (q, Me), 26.96 (q, Me), 35.44 (t, C-6), 66.89, 69.30, 70.90, 72.39, 72.64, 73.31, 73.61, 74.86, 75.23, 75.49, 77.79, 78.69, 78.89, 81.73, 109.36 (s, O–C–O) and 209.62 (s, CO) (Found: C, 70.8; H, 7.1. $C_{43}H_{50}O_{10}$ requires C, 71.05; H, 6.9%).

The minor isomer: δ_C 25.38 (s, Me), 26.55 (s, Me), 36.78 (t, C-6), 109.78 (s, O–C–O) and 208.59 (s, CO).

D-glycero-D-ido-D-lyxo-3,4-*Di*-O-*acetyl*-7,11-*anhydro*-8,9,-10,12-*tetra*-O-*benzyl*-6-*deoxy*-1,2-O-*isopropylidenedodec*-5-*ulose* **6**.—To a solution of crude compound **5a** (440 mg, 0.60 mmol) in dry pyridine (2 cm^3) was added Ac_2O (0.2 cm^3). After 3 h, usual work-up and careful chromatography (6:4) afforded *title compound* **6** (373 mg, 95% calculated on pure **5a**) as an oil, $[\alpha]_D$ +51.8 (*c* 0.7, $CHCl_3$); δ_H(200 MHz) 1.31 (3 H, s, Me), 1.40 (3 H, s, Me), 1.96 (3 H, s, Ac), 2.17 (3 H, s, Ac), 2.95 (2 H, d, *J* 6.3, 6-H_2), 3.60–3.80 (7 H, m), 3.82 (1 H, dd, *J* 8.6, 5.5, 9-H), 3.95 (1 H, dd, *J* 8.6, 6, 8-H), 4.17 (1 H, q, *J* 6, 7-H), 4.40–4.92 (8 H, OCH_2Ph), 5.77 (1 H, d, *J* 2.2, 4-H), 5.83 (1 H, dd, *J* 6.5, 2.2, 3-H) and 7.35 (20 H, Ph); δ_C(75.432 MHz) 25.74 (q, Me), 27.11 (q, Me), 36.04 (t, C-6), 66.58 and 69.28 (t, C-1 and C-12), 66.57, 69.26, 73.35, 73.68, 75.34 and 75.66 (6 t), 70.06, 70.93, 72.63, 74.19, 77.16, 77.67, 79.20 and 82.14 (8 d), 110.10 (s, O–C–O), 170.01 (s, COO), 170.30 (s, COO) and 201.54 (s, C-5) (Found: C, 69.4; H, 6.4. $C_{47}H_{54}O_{12}$ requires C, 69.6; H, 6.7%).

(5R)-D-glycero-D-ido-D-lyxo-3,4-*Di*-O-*acetyl*-7,11-*anhydro*-8,9,10,12-*tetra*-O-*benzyl*-6-*deoxydodec*-5-*ulopyranoside*-(5,1) **12**.—The diacetate **6** (200 mg, 0.25 mmol) and a sample (200 mg) of a powder obtained by stirring anhydrous $FeCl_3$ and silica gel (8:100, w/w),[7] were mixed by addition of Et_2O (5 cm^3), stirring, and subsequent evaporation of the solvent. After 1 h in the absence of solvent, TLC (1:1) showed the disappearance of the starting material (R_f 0.70) and the formation of a single product (R_f 0.30). The powder was then poured onto a column of silica gel (5 g) and eluted with hexane–ethyl acetate (1:1) to afford *title disaccharide* **12** (148 mg, 78%) as an oil; δ_H(200 MHz) 1.60 (1 H, OH), 1.76 (1 H, dd, *J* 15, 1.5, 6-H^a), 2.07 (3 H, s, Ac), 2.11 (3 H, s, Ac), 2.20 (1 H, dd, *J* 15, 11.5, 6-H^b), 3.43 (1 H, dd, *J* 8.5, 7.7, 10-H), 3.55 (1 H, dd, *J* 7.5, 5, 8-H), 3.56–3.75 (4 H, 1- and 12-H_2), 3.67 (1 H, t, *J* 7.5, 9-H), 3.91 (1 H, ddd, *J* 8.5, 5.5, 4, 11-H), 4.10 (1 H, m, 2-H), 4.40 (9 H, OCH_2Ph and 7-H), 4.95 (1 H, d, *J* 1.5, OH), 5.22 (1 H, dd, *J* 10.5, 1.5, 4-H), 5.32 (1 H, dd, *J* 10.5, 3, 3-H) and 7.3 (20 H, Ph) (Found: C, 68.3; H, 6.6. $C_{44}H_{50}O_{12}$ requires C, 68.6; H, 6.5%).

(5S)-D-glycero-D-ido-D-lyxo-3,4-*Di*-O-*acetyl*-7,11-*anhydro*-8,9,10,12-*tetra*-O-*benzyl*-6-*deoxydodec*-5-*ulofuranose*-(5,2) **13**.—Compound **6** (200 mg, 0.25 mmol) was treated with $FeCl_3$–silica gel as described before. After 1 h, Et_2O (20 cm^3) was added, and the mixture was filtered on Florisil and evaporated. Chromatography (6:4) afforded *inter alia* isomers **12** (28 mg) and **13** (20 mg) (R_f 0.58 in 1:1). *Compound* **13**: oil, δ_H(200 MHz) 2.07 (3 H, s, Ac), 2.11 (3 H, s, Ac), 2.35 (2 H, m, 6-H_2), 3.58–3.82 (10 H), 4.44 (1 H, d, *J* 12, OC*H*Ph), 4.47 (1 H, d, *J* 11, OC*H*Ph), 4.59 (1 H, d, *J* 11, OC*H*Ph), 4.63 (1 H, m, 7-H), 4.64 (1 H, d, *J* 12, OC*H*Ph), 4.65 (1 H, d, *J* 11, OC*H*Ph), 4.70 (1 H, d, *J* 1.5, 4-H), 4.76 (1 H, d, *J* 11, OC*H*Ph), 4.81 (1 H, d, *J* 11, OC*H*Ph), 4.92 (1 H, d, *J* 11, OC*H*Ph), 4.98 (1 H, t, *J* 1.5, 3-H) and 7.3 (20 H, Ph); δ_C(50.288 MHz) 20.79 (Me), 20.88 (Me), 24.93 (C-6), 66.19, 68.70, 69.67, 71.58, 72.50, 73.47, 74.96, 75.37, 77.77, 78.95, 79.33, 80.33, 81.19, 82.13, 107.16 (C-5), 170.26 (CO) and 170.57 (CO) (Found: C, 68.3; H, 6.8%).

D-glycero-D-ido-D-lyxo-7,11-*Anhydro*-6-*deoxydodec*-5-*ulose* **7a**.—The crude mixture from the deisopropylidenation of compound **6** (**12**, **13** and its β-isomer, see preparation of compound **13**) (200 mg, 25 mmol) in 90% EtOH (5 cm^3) was treated with K_2CO_3 (350 mg). After 2.5 h, dilution with water, extraction with ethyl acetate, drying with Na_2SO_4, and evaporation of the solvent afforded the crude deacetylated product, which was dissolved in MeOH (10 cm^3) and submitted to catalytic hydrogenation with Pd/C (10%, 40 mg). After 3 h, filtration and evaporation of the solvent afforded *title compound* **7a** (65 mg, 80%) as a mixture of pyranosidic and furanosidic forms (A), (B) and (C), m.p. 75 °C (decomp.) (from EtOH); δ_C(50.288 MHz; CD_3OD) (A) 33.46 (C-6) and 101.68 (C-5); (B) 34.71 (C-6) and 104.83 (C-5); (C) 38.35 (C-6) and 117.70 (C-5) (Found: C, 44.35; H, 6.7. $C_{12}H_{22}O_{10}$ requires C, 44.2; H, 6.8%). Crystallization from EtOH enriched the sample in the form A: δ_C 33.46 (t, C-6), 63.80 (t), 66.09 (t), 71.91 (d), 72.20 (d), 72.99 (d), 73.38 (d), 74.29 (d), 74.50 (d), 75.80 (d), 75.96 (d) and 101.68 (s, C-5).

Benzyl 2,2,2-*Trifluoroethyl Succinate*.—A mixture of succinic anhydride (5 g, 50 mmol), toluene (250 cm^3), Et_3N (7 cm^3, 10 mmol) and benzyl alcohol (5 cm^3, 50 mmol) was stirred for 24 h. Usual work-up and chromatography [hexane–ethyl acetate–MeOH (65:20:5)] afforded the monobenzyl succinate triethylammonium salt (6.5 g, 64%). A mixture of the monobenzyl succinate (6.5 g, 31 mmol) in dry CH_2Cl_2 (120 cm^3) was then treated overnight with 2,2,2-trifluoroethanol (6 cm^3) and dicyclohexylcarbodiimide (13 g). Water was then added and the mixture was stirred for 1 h, filtered, and submitted to usual work-up. Chromatography (7:3) of the crude product afforded benzyl 2,2,2-trifluoroethyl succinate (9.0 g, quant.) as an oil, δ_H(80 MHz) 2.71 (4 H, s, CH_2CO), 4.45 (2 H, q, *J* 8, OCH_2CF_3), 5.14 (2 H, s, OCH_2Ph) and 7.35 (5 H, s, Ph) (Found: C, 53.6; H, 4.6. $C_{13}H_{13}F_3O_4$ requires C, 53.8; H, 4.5%).

(S)-2-O-*Benzyl*-1-O-(*benzyloxysuccinyl*)*glycerol* **15**.—A solution of 2-*O*-benzylglycerol **14** (728 mg, 4 mmol) and benzyl trifluoroethyl succinate (4.6 g) in $CHCl_3$ (12 cm^3) was stirred for 40 h at room temperature with lipase from *Pseudomonas* sp. (EC 3.1.1.3, Fluka) (50 mg; 42 U mg^{-1}). The enantiomeric excess of the reaction, determined by HPLC (6:3) on an optically active polyacrylamide column (Chiraspher 5 μm, Merck), was 78%. Filtration of the reaction mixture on Celite, evaporation, and chromatography (7:3) afforded *title compound* **15** (1.5 g, quant.) as an oil, $[\alpha]_D$ −11 {*c* 1.2, $CHCl_3$; $[\alpha]_D$ −14 calculated for the pure (*S*)-isomer}, δ_H(300 MHz) 2.20 (1 H, OH), 2.53 (4 H, s, CH_2CO), 3.77 (3 H, m, 2-H and 3-H_2), 4.24 (2 H, d, *J* 5, 1-H_2), 4.58 (1 H, d, *J* 12, OC*H*Ph), 4.69 (1 H, d, *J* 12, OC*H*Ph), 5.13 (2 H, s, CO_2CH_2Ph) and 7.35 (10 H, Ph). Addition of Eu(hfc)$_3$ split the singlet at δ 5.13 into two signals in the ratio 89:11, respectively, at δ 5.66 and 5.57; δ_C(75.432 MHz) 29.70 (t, 2 × CH_2CO), 62.46 (t, C-3), 63.81 (t, OCH_2Ph), 67.26 (t, C-1), 72.80 (t, $PhCH_2OCO$), 77.66 (d, C-2), 172.28 (s, CO) and 172.87 (s, CO) (Found: C, 67.5; H, 6.7. $C_{21}H_{24}O_6$ requires C, 67.7; H, 6.5%).

(E,S)-5-*Benzyloxy*-6-(*benzyloxysuccinyloxy*)-1-(2′,3′,4′,6′-*tetra*-O-*benzyl*-α-D-*glucopyranosyl*)*hex*-3-*en*-2-*one* **4b**.—Compound **15** (1.5 g, 4 mmol) was treated under N_2 with DMSO (39 cm^3, 40 mmol) and Ac_2O (20 cm^3, 28 mmol). After 4 h (TLC, 6:4), dilution with CH_2Cl_2, washing many times with water, drying with Na_2SO_4, and evaporation under reduced pressure (20 mmHg and then 0.1 mmHg) afforded the crude aldehyde **3b** (1.1 g).

Compound **3b** was dissolved in dry MeCN (35 cm^3) and added, under N_2, to compound **2** (1.4 g, 1.7 mmol). After 4 days (TLC, 7:3), evaporation and chromatography (8:2) afforded pure *title enone* **4b** (917 mg, 59%) and its *Z*-isomer (51 mg, 3.3%). Oil, $[\alpha]_D$ +42 (*c* 1, $CHCl_3$); δ_H(300 MHz) 2.62 (4 H, s, CH_2CO), 2.84 (1 H, dd, *J* 15.5, 8, 1-H^a), 3.01 (1 H, dd, *J* 15.5, 5, 1-H^b), 3.55–3.83 (6 H, m, 2′-, 3′-, 4′- and 5′-H and 6′-H_2), 4.11 (3 H, m, 5-H and 6-H_2), 4.35–4.95 (10 H, m, 5 × OCH_2Ph), 4.79 (1 H, m, 1′-H), 5.10 (2 H, s, CO_2CH_2Ph), 6.34 (1 H, d, *J* 16, 3-H), 6.62 (1 H, dd, *J* 16, 5, 4-H) and 7.06–7.50 (30 H, Ph); δ_C(75.432 MHz) 29.61 (t, 2 × CH_2CO), 38.60 (t, C-1), 66.05, 67.21, 69.35, 72.17, 73.98, 74.13, 75.64 and 76.03 (8 t), 71.38, 73.10, 76.46, 78.24, 79.98 and 82.69 (6 d), 132.25 (d, C-3), 142.32 (d, C-4), 172.57 (s, 2 × CO_2) and 197.36 (s, CO) (Found: C, 74.4; H, 6.3. $C_{57}H_{60}O_{11}$ requires C, 74.3; H, 6.6%).

D-glycero-D-ido-D-lyxo-7,11-*Anhydro*-2,8,9,10,12-*penta*-O-*benzyl*-1-O-(*benzyloxysuccinyl*)-6-*deoxydodec*-5-*ulose* **5b**.—A solution of enone **4b** (880 mg, 0.94 mmol) in acetone–water (15 cm^3; 8:1) was treated at −30 °C with NMMNO (255 mg, 1.9 mmol) and a solution (0.25 cm^3) of OsO_4 in Bu^tOH (5 mg cm^{-3}). After 48 h, aq. $Na_2S_2O_3$ was added and the mixture was stirred for 1 h. Usual work-up and chromatography (7:3) afforded *title compound* **5b** (793 mg, 87%) as an oil, $[\alpha]_D$ +32 (*c* 1.6, $CHCl_3$); δ_H(300 MHz) 2.63 (4 H, s, CH_2CO), 2.74 (1 H, d, *J* 8, OH), 2.96 (2 H, d, *J* 7, 6-H_2), 3.45–3.80 (8 H, m), 4.00 (1 H, br t, *J* 8, 3-H), 4.22 (1 H, dd, *J* 12, 4, 1-H^a), 4.36 (1 H, br d, *J* 6, 4-H), 4.42–4.90 (12 H, OCH_2Ph, 1-H^b and 7-H), 5.08 (2 H, s, CO_2CH_2Ph) and 7.10–7.40 (30 H, Ph); δ_C(75.432 MHz) 29.43 (t, 2 × CH_2CO), 35.59 (t, C-6), 63.42, 66.96, 69.25, 73.14, 73.70, 73.82, 75.27 and 75.73 (8 t), 70.41, 71.34, 72.78, 77.20, 77.20, 78.06, 79.29 and 82.18 (8 d), 172.48 (s, CO_2), 172.79 (s, CO_2) and 210.04 (s, CO) (Found: C, 71.9; H, 6.7. $C_{58}H_{62}O_{13}$ requires C, 72.0; H, 6.5%).

D-glycero-D-ido-D-lyxo-7,11-*Anhydro*-1-O-(*benzyloxysuccinyl*)-6-*deoxydodec*-5-*ulofuranose*-(5,2) **7b**. A solution of ketone **5b** (319 mg, 0.33 mmol) in MeOH (12 cm^3) was submitted to hydrogenation with Pd/C (32 mg). After 20 h, filtration on Celite and evaporation afforded *title compound* **7b** (137 mg, 96%) as a deliquescent solid, δ_H(300 MHz; D_2O; 50 °C) (for the major isomer): 2.56 (1 H, dd, *J* 15, 7, 6-H^a), 2.81 (1 H, dd, *J* 15, 6, 6-H^b), 3.06 (4 H, m, CH_2CO), 3.70 (1 H, s, 4-H), 3.80 (1 H, t, *J* 7.5, 10-H), 3.88–4.20 (4 H, m, 9- and 11-H, and 12-H_2), 4.28–4.65 (4 H, m, 1-H^a, 2-, 3- and 8-H), 4.72 (1 H, br d, *J* 13, 1-H^b) and 5.07 (1 H, m, 7-H); δ_C(75.432 MHz; D_2O) (for the major isomer): 31.99 and 32.10 (t, CH_2CO), 39.11 (t, C-6), 63.73 (t, C-12), 67.18 (t, C-1), 71.19 (d, C-4), 75.60 (d, C-7), 76.94 (d, C-9), 79.46 (d, C-10), 80.15 (d, C-11), 82.86 (d, C-8), 83.81 (d, C-2), 84.68 (d, C-3), 118.18 (s, C-5) and 177.79 and 180.23 (s, CO_2). The minor isomer (4.3:1 ratio) showed δ_C 41.18 (t, C-6) and 115.19 (s, C-5).

Acknowledgements

We thank 'Progetto Finalizzato Chimica fine II' and MURST for financial support.

References

1 (*a*) D. Rouzaud and P. Sinaÿ, *J. Chem. Soc., Chem. Commun.*, 1983, 1353; (*b*) B. Aebischer, J. H. Bieri, R. Prewo and A. Vasella, *Helv. Chim. Acta*, 1982, **65**, 2251; (*c*) F. Baumberger and A. Vasella, *Helv. Chim. Acta*, 1983, **66**, 2211; (*d*) B. Giese and T. Witzel, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 450; (*e*) S. A. Babirad, Y. Wang and Y. Kishi, *J. Org. Chem.*, 1987, **52**, 1372; (*f*) P. G. Geokjián, T.-C. Wu, H.-Y. Kang and Y. Kishi, *J. Org. Chem.*, 1987, **52**, 4823; (*g*) S. A. Babirad, Y. Wang, P. G. Goekjian and Y. Kishi, *J. Org. Chem.*, 1987, **52**, 4825; (*h*) W. H. Miller, D. M. Ryckman, P. G. Goekjian, Y. Wang and Y. Kishi, *J. Org. Chem.*, 1988, **53**, 5582; (*i*) B. Giese, M. Hoch, C. Lamberth and R. R. Schmidt, *Tetrahedron Lett.*, 1988, **29**, 1375; (*j*) S. M. Daly and R. W. Armstrong, *Tetrahedron Lett.*, 1989, **30**, 5713; (*k*) R. R. Schmidt and R. Preuss, *Tetrahedron Lett.*, 1989, **30**, 3409; (*l*) W. B. Motherwell, B. C. Ross and M. J. Tozer, *Synlett*, 1989, 68; (*m*) S. Jarosz and B. Fraser-Reid, *Tetrahedron Lett.*, 1989, **30**, 2359; (*n*) R. Preuss and R. R. Schmidt, *J. Carbohydr. Chem.*, 1991, **10**, 887; (*o*) P. G. Goekijan, T.-C. Wu, H.-Y. Kang and Y. Kishi, *J. Org. Chem.*, 1991, **56**, 6422; (*p*) Y. Wang, S. A. Babirad and Y. Kishi, *J. Org. Chem.*, 1992, **57**, 468; (*q*) Y. Wang, P. G. Goekjian, D. M. Ryckman, W. H. Miller, S. A. Babirad and Y. Kishi, *J. Org. Chem.*, 1992, **57**, 482; (*r*) R. W. Armstrong and B. R. Teegarden, *J. Org. Chem.*, 1992, **57**, 915; (*s*) R. M. Bimwala and P. Vogel, *J. Org. Chem.*, 1992, **57**, 2076; (*t*) O. R. Martin, F. Xie, R. Kakarla and R. Benhamza, *Synlett*, 1993, 165; (*u*) Y. Chao Xin, J.-M. Mallet and P. Sinaÿ, *J. Chem. Soc., Chem. Commun.*, 1993, 864.

2 (*a*) J.-M. Beau and P. Sinaÿ, *Tetrahedron Lett.*, 1985, **26**, 6189; (*b*) U. C. Dyer and Y. Kishi, *J. Org. Chem.*, 1988, **53**, 3383; (*c*) D. J. O'Leary and Y. Kishi, *J. Org. Chem.*, 1993, **58**, 308; (*d*) M. Carcano, F. Nicotra, L. Panza and G. Russo, *J. Chem. Soc., Chem. Commun.*, 1989, 642; (*e*) A. Boschetti, F. Nicotra, L. Panza, G. Russo and L. Zucchelli, *J. Chem. Soc., Chem. Commun.*, 1989, 1085; (*f*) O. R. Martin and W. Lai, *J. Org. Chem.*, 1990, **55**, 5188; (*g*) E. Dubois and J.-M. Beau, *J. Chem. Soc., Chem. Commun.*, 1990, 1191; (*h*) O. R. Martin and W. Lai, *J. Org. Chem.*, 1993, **58**, 176.

3 A. Hosomi, Y. Sakata and H. Sakurai, *Tetrahedron Lett.*, 1984, **25**, 2383.
4 J. K. Cha and Y. Kishi, *Tetrahedron*, 1984, **40**, 2247.
5 G. Cardillo and M. Shimizu, *J. Org. Chem.*, 1977, **42**, 4268.
6 A. Fadel, R. Yefsah and J. Salaun, *Synthesis*, 1987, 37.
7 W. R. Kobertz, C. R. Bertozzi and M. D. Bednarski, *Tetrahedron Lett.*, 1992, **33**, 737.
8 D. E. Iley and B. Fraser-Reid, *Can. J. Chem.*, 1979, **57**, 653.
9 L. Hough, *Chem. Soc. Rev.*, 1985, **14**, 357.
10 Y.-F. Wang and C.-H. Wong, *J. Org. Chem.*, 1988, **53**, 3127.
11 A. Boschetti, L. Panza, F. Ronchetti and L. Toma, *J. Chem. Soc., Perkin Trans. 1*, 1988, 3352 and references cited therein.

Paper 3/03816E
Received 2nd *July* 1993
Accepted 23rd *September* 1993