Highly Stereoselective Synthesis of the 1-*O*-Acylglycosyl Ester of Diclofenac via Glycosyl Phosphorothioates, -selenoates and -dithioates as Glycosyl Donors

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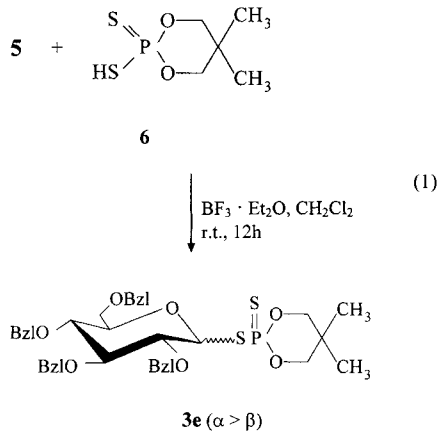
Stereoselective glycosylation of *o*-(2,6-dichloroanilino)phenylacetic acid (Diclofenac, **1**), as a free carboxylic acid with glycosylthio (**2a–c**), -dithio (**3a–e**) and -selenophosphates (**4a–c**) as glycosyl donors is reported. The reactions were carried out in aprotic solvents, in the presence of silver carbonate as a leaving group activator. 1-*O*-Acyl sugars **7a–e**, new derivatives of Diclofenac, were obtained in high yields as stable, crystalline compounds.

Glycosyl esters constitute a class of sugar derivatives that is of interest with regard to biological properties. Such derivatives are components of antibiotics[1], terpene glycosides[2] and plant pigments[3]. Aromatic carboxylic acids as glycosyl esters are metabolized by humans[4]. D-Glycopyranoside esters of fatty acids have been applied as agents inhibiting cellular growth in leukaemia[5] and the development of plants[6]. This class of sugar derivatives also includes compounds of potential pharmaceutical activity[7]. Although 1-*O*-acyl sugars may advantageously be applied in synthesis, few general methods are available for their stereoselective synthesis[8]. A few years ago, a method for the synthesis of prodrugs in the form of glycosyl esters was reported[9]. The sodium salt of acid **1** has been used clinically under the name Diclofenac Sodium as a non-steroidal agent with potent antiinflammatory (NSAID), analgesic and antipyretic activity in rheumatology, laryngology and dental surgery[10]. However, acid **1** and other NSAID preparations with carboxylic groups exert unfavourable pharmacological effects in therapy when administered orally. They cause gastrointestinal disturbances and activate gastric and duodenal ulcers[11]. Recently, considerable attention has been focused on the development of bioreversible derivatives, such as prodrugs, in which the acidic function is temporarily masked. Although there are known Diclofenac prodrugs in the form of salts and esters, e.g. diaryl amine[12], hydroxyethylpyrrolidine[13] and morpholinoalkyl ester[14], further studies aimed at developing a better chemical combination of Diclofenac as a prodrug are needed.

In this paper, a highly stereoselective synthesis of new sugar derivatives of Diclofenac (**1**) via phosphorothio, -dithio and -seleno sugars **2–4** as glucosyl donors is reported.

Results

In previous work in this laboratory it was found that 2-deoxyglycosyl phosphorothioates can be employed as highly efficient glycosyl donors in reactions with alcohols[15], phenols[16], alcohol sugars[17] and amines[18]. Recently, convenient and stereoselective methods have been reported for the synthesis of 2-deoxy[19] and fully protected esters of carboxylic acids in a series of pentoses and hexoses[20]. Donors **2–4** used in the present investigation were obtained by glycosylation of triethylammonium phosphorothioates, -selenoates and -dithioates with glycosyl halides[21] or by the reaction of phosphorodithio acid **6** with fully acetylated sugars[22]. The dithiophosphoro perbenzylated sugar **3e** was prepared according to the approach described in ref.[22], the anomeric mixture of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucose (**5**)[23] being synthesized by acetylation of unprotected benzylated D-glucose[24]. The spectral data (^{31}P, ^{1}H and ^{13}C NMR) of the crude mixture revealed the presence of α and β anomers in a ratio of 64:36 (eq. 1).



Pure α anomer **3e** was isolated by crystallization from diethyl ether. Glycosyl donor **3d** was obtained by the reaction of dithiophosphoro acid **6** with 3,4,6-tri-*O*-acetyl-D-glucal[25].

The phosphoro sugars **2–4** were employed as glycosyl donors in stoichiometric amounts in reactions with acid **1** in aprotic solvents (CH_2Cl_2 or C_6H_6), with silver carbonate added to activate the leaving groups. The progress of each reaction was monitored by TLC and spectroscopic analysis.

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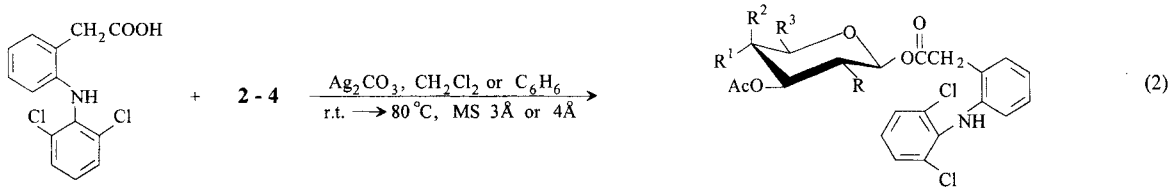


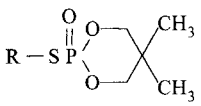
(2)

1 **7a - d**

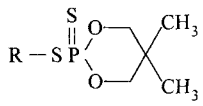
Entry	Product	Donor	Reaction conditions: Solvent	Time	Temp. (°C)
1	**7a**	**2a**	C_6H_6	12h	80
2	**7a**	**3a**	C_6H_6	12h	80
3	**7a**	**4a**	C_6H_6	10h	80
4	**7b**	**2b**	C_6H_6	7h	80
5	**7b**	**3b**	C_6H_6	7h	80
6	**7b**	**4b**	C_6H_6	5h	80
7	**7c**	**2c**	CH_2Cl_2	5d	20
8	**7c**	**3c**	CH_2Cl_2	5d	20
9	**7c**	**4c**	CH_2Cl_2	4d	20
10	**7d**	**3d**	CH_2Cl_2	4d	20
11	**7e**	**5**	CH_2Cl_2[a]	6d	20
12	**7e**	**3e**	C_6H_6	12h	80

Ester	R	R^1	R^2	R^3
7a	OAc	OAc	H	CH_2OAc
7b	OAc	H	OAc	CH_2OAc
7c	OAc	OAc	H	H
7d	H	OAc	H	CH_2OAc

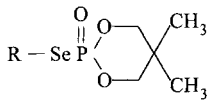
[a] Glycosylation was performed in the presence of $BF_3 \cdot Et_2O$ (45% solution).



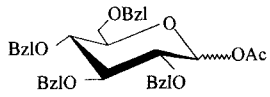
2a - c



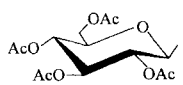
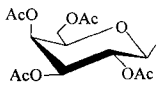
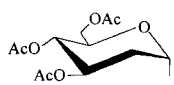
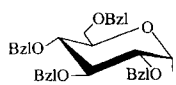
3a - e



4a - c



5

2 - 4	a	b	c	d	e
R					

Upon completion of the reaction, the precipitated silver salt was removed by filtration through Celite and the solvent was evaporated in vacuo. Semicrystalline residues of ester **7a–e** (eq. 2) were obtained in quantitative yields, regardless of the donor employed.

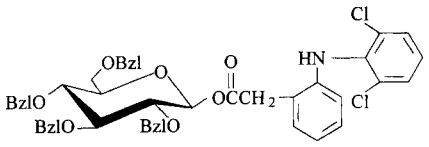
In each case, spectroscopic analysis of the crude mixture of esters indicated stereospecific formation of only the β anomer. The synthesis of esters **7a–b** using glycosyl donor derivatives of D-glucose **2a–4a** or D-galactose **2b–4b** required somewhat more forcing conditions than those described for the synthesis of esters **7c–d** using donors **2c–4c** or **3d**. Esters **7a–c** were observed spectroscopically in an alternative reaction of peracetylated glycosyl halides with the silver salt of acid **1** in a 1:1.2 molar ratio in boiling toluene. By this route, only β-ester **7a** was formed in a highly stereoselective manner from D-glucose; esters **7b** and **7c**, obtained from D-galactose or D-xylose, were formed less stereoselectively (α/β ratio of 20:80).

Perbenzylated D-glucose with various leaving groups, e.g. 1-*O*-acetyl **5** and α-phosphorodithio **3e** at the anomeric center, was employed as starting material for the synthesis of **7e** (eq. 3).

In the presence of $BF_3 \cdot Et_2O$, sugar **5** was converted at ambient temperature to the glycosyl derivative of Diclofenac **7e** as a 17:83 mixture of α and β anomers. It is worth mentioning that under the same conditions a mixture of fully acetylated D-glucose and acid **1** was not transformed into ester **7a**, even after several days. Highly stereoselective glycosylation of acid **1** was observed when the α-phosphorodithio sugar **3e** was applied as glycosyl donor, according to the General Procedure (Method B). The reaction was accomplished with full retention of configuration at the an-

omeric center. Pure β-1-*O*-acyl sugars **7a–e** were isolated as stable products by crystallization from ethanol in 72–84% yield. The chemical shifts of the anomeric protons were found in the range δ = 5.76–5.89 and vicinal coupling constants $J_{1,2}$ = 7.3–9.9 Hz were observed, confirming the β configuration of the synthesized glycosyl derivatives of Diclofenac.

1 + **3e** $\xrightarrow[12\,h,\ MS\ 3Å\ or\ 4Å]{Ag_2CO_3,\ C_6H_6,\ 80\,°C}$



7e (3)

1 + **5** $\xrightarrow[r.t.,\ 6\,d]{BF_3 \cdot Et_2O,\ CH_2Cl_2}$ **7e**(α) + **7e**(β) (α<β)

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Experimental Section

Melting points were determined with a Boetius PHMK 05 apparatus and are uncorrected. – ^{1}H-, ^{13}C- and ^{31}P-NMR spectra were recorded in $CDCl_3$ with a Bruker AC 200 spectrometer operating at 200.11 MHz, 50.33 MHz and 81.01 MHz, respectively. Chemical shifts are reported in parts per million (δ) relative to TMS (1%) as an internal standard. – Specific rotations were measured in chloroform (Polamat A polarimeter). – TLC was carried out on silica-gel plates (Kieselgel 60 F_{254} Merck) with benzene/chloroform/acetone (3:1:1) as the developing solvent. Detection was effected by exposure to iodine vapour. – Silver carbonate was freshly prepared. – Elemental analyses were performed at the Microanalytical Laboratory, Institute of Chemistry, Medical University, Łódź and the Microanalytical Laboratory of the Centre of Molecular and Macromolecular Studies of the Polish Academy of Sciences, Łódź. – The silver salt of acid **1** was prepared by adding an equimolar amount of aqueous silver nitrate to a solution of acid **1** and an equimolar amount of sodium hydroxide in water. The precipitated silver salt was filtered off, washed with ice-cold water and acetone, and dried in vacuo.

5,5-Dimethyl-2-thioxo-2-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosylthio)-1,3,2-dioxaphosphorinane (**3e**): Boron trifluoride etherate (45% solution, 0.84 ml, 3.0 mmol) was added dropwise at 0°C to a solution of sugar **5** (0.59 g, 1.0 mmol) and phosphorodithio acid **6** (0.19 g, 1.0 mmol) in dry dichloromethane (30 ml). The mixture was stirred at room temperature for 12 h, then washed with aqueous sodium hydrogen carbonate solution and water, and dried ($MgSO_4$). Concentration in vacuo afforded a semicrystalline residue containing α and β-anomers (^{31}P NMR: δ = 87.05 and 89.09) in a ratio of 64:36. Crystallization from ethanol gave the pure α anomer **3e** (0.25 g, 35%) as colourless crystals, m.p. 144–145°C. – $[\alpha]_{578}^{25}$ = +11.3 (*c* = 0.6 in $CHCl_3$). – ^{1}H NMR ($CDCl_3$): δ = 0.81 (s) and 0.92 (s, 6H, 2 CH_3), 3.59–4.17 (m, 10H, 2 CH_2O, 2H to H_b), 4.43–4.62 (m, 4H, 2 CH_2Ph), 4.75–5.05 (m, 4H, 2 CH_2Ph), 6.29 (dd, $J_{1,2}$ = 5.1 Hz, $^3J_{H,P}$ = 12.2 Hz, 1H, 1-H), 7.13–7.42 (m, 20H, 4 C_6H_5). – ^{13}C NMR ($CDCl_3$): δ = 20.85 (s, CH_3 eq), 22.21 (s, CH_3 ax), 32.36 [d, $^3J_{P-C}$ = 7.0 Hz, $C(CH_3)_2$], 68.46 (s, C-6), 71.94 (s, $CH_2C_6H_5$), 73.71 (d, $^3J_{P-C}$ = 12.8 Hz, C-2), 75.69, 76.35, 78.06 (3 s, C-3 to C-5), 80.60 (dd, $^3J_{P-C}$ = 7.2 Hz, 2 CH_2O), 88.23 (d, $^3J_{P-C}$ < 1 Hz, C-1), 127.67 (s, arom.), 127.86 (s, arom.), 128.00 (s, arom.), 128.33 (s, arom.). – ^{31}P NMR ($CDCl_3$): δ = 87.03. – $C_{39}H_{45}O_7PS_2$ (720.88): calcd. C 64.98, H 6.29, P 4.30, S 8.89; found C 64.87, H 6.06, P 4.14, S 8.67.

General Procedure. – β-1-O-Acyl Ester Monosaccharides (**7a–e**): To a solution of carboxylic acid **1** (1 mmol) in an anhydrous solvent (benzene or dichloromethane) containing molecular sieves (MS, 3 or 4 Å), an equivalent amount of glycosyl donor (**2–4**) was added. Subsequently, silver carbonate (0.5 mmol) was added and the mixture was stirred in the dark (see Table 2 for specific conditions). The reaction was monitored by TLC, ^{1}H- and ^{13}C-NMR spectroscopy. The precipitated silver phosphoro acid salt and the molecular sieves were removed by filtration through Celite 535 and the filtrate was washed with aqueous sodium carbonate solution and water, and dried ($MgSO_4$). Concentration in vacuo afforded semicrystalline residues of **7a–e** in quantitative yield. The residues were confirmed by ^{1}H- and ^{13}C-NMR spectroscopy to consist exclusively of the β anomers. Crystallization from ethanol gave pure β-1-*O*-acyl sugars **7a–e**.

1-O-[o-(2,6-Dichloroanilino)phenylacetyl]-2,3,4,6-tetra-O-acetyl-β-D-glucopyranose (**7a**): Donor **3a** (0.26 g, 0.5 mmol), acid **1** (0.15 g, 0.5 mmol) and Ag_2CO_3 (0.07 g, 0.25 mmol) in benzene, 80°C; 12 h. Yield 0.25 g (81%), colourless crystals, m.p. 151–152°C (ethanol). – $[\alpha]_{578}^{25}$ = +1.0 (*c* = 1.4 in $CHCl_3$). – ^{1}H NMR ($CDCl_3$): δ = 1.56 (s, 1H, NH), 1.76 (s, 3H, CH_3CO), 1.99 (s, 3H, CH_3CO), 2.02 (s, 3H, CH_3CO), 2.08 (s, 3H, CH_3CO), 3.75–3.94 (m, 3H, CH_2, AB, 5-H), 4.10 (dd, J_{gem} = 12.5 Hz, $J_{5,6b}$ = 2.2 Hz, 1H, H-6_b), 4.29 (dd, $J_{5,6a}$ = 4.4 Hz, 1H, 6_a-H), 5.08–5.28 (m, 3H, 2-H to 4-H), 5.76 (d, $J_{1,2}$ = 8.0 Hz, 1H, 1-H), 6.56–6.60 (m, 2H, arom.), 6.91–7.41 (m, 5H, arom.). – ^{13}C NMR ($CDCl_3$): δ = 20.07 (s, CH_3CO), 20.41 (s, 2 CH_3CO), 20.55 (s, CH_3CO), 38.01 (s, CH_2), 61.27 (s, C-6), 67.20, 69.96, 72.46, 72.72 (4 s, C-2 to C-5), 91.99 (s, C-1), 118.43, 122.18, 123.29, 124.11, 128.19, 128.76, 129.39, 130.74, 137.54, 142.52 (10 s, arom.), 168.96 (s, CH_2OCO), 169.21 (s, CH_3CO), 169.89 (s, CH_3CO), 170.22 (s, CH_3CO), 170.42 (s, CH_3CO). – $C_{28}H_{29}Cl_2NO_{11}$ (626.49): calcd. C 53.69, H 4.67, N 2.24; found C 53.71, H 4.83, N 2.21.

1-O-[o-(2,6-Dichloroanilino)phenylacetyl]-2,3,4,6-tetra-O-acetyl-β-D-galactopyranose (**7b**): Donor **2b** (0.51 g, 1.0 mmol), acid **1** (0.29 g, 1.0 mmol) and Ag_2CO_3 (0.14 g, 0.5 mmol) in benzene, 80°C, 7 h. Yield 0.48 g (77%), colourless crystals, m.p. 129–131°C (ethanol). – $[\alpha]_{578}^{25}$ = +1.1 (*c* = 2.0 in $CHCl_3$). – ^{1}H NMR ($CDCl_3$): δ = 1.57 (s, 1H, NH), 1.76 (s, 3H, CH_3CO), 1.97 (s, 3H, CH_3CO), 2.03 (s, 3H, CH_3CO), 2.18 (s, 3H, CH_3CO), 3.73–3.98 (m, 2H, CH_2, AB), 4.02–4.23 (m, 3H, 5-H, 6-H_a, 6-H_b), 5.05 (dd, $J_{2,3}$ = $J_{3,4}$ = 3.4 Hz, 1H, 3-H), 5.33–5.43 (m, 2H, 2-H, 4-H), 5.79 (d, $J_{1,2}$ = 7.3 Hz, 1H, 1-H), 6.53–6.56 (m, 2H, arom.), 6.91–7.42 (m, 5H, arom.). – ^{13}C NMR ($CDCl_3$): δ = 20.20 (s, CH_3CO), 20.44 (s, CH_3CO), 20.56 (s, 2 CH_3CO), 38.09 (s, CH_2), 60.95 (s, C-6), 66.71, 67.57, 70.59, 71.77 (4 s, C-2 to C-5), 92.33 (s, C-1), 118.54, 122.19, 123.33, 124.09, 128.22, 128.81, 129.36, 130.74, 137.60, 142.56 (10 s, arom.), 169.11 (s, CH_2OCO), 169.83 (s, CH_3CO), 170.01 (s, CH_3CO), 170.25 (s, 2 CH_3CO). – $C_{28}H_{29}Cl_2NO_{11}$ (626.49): calcd. C 53.69, H 4.67, N 2.24; found C 53.72, H 4.58, N 2.15.

1-O-[o-(2,6-Dichloroanilino)phenylacetyl]-2,3,4-tri-O-acetyl-β-D-xylopyranose (**7c**): Donor **2c** (0.44 g, 1.0 mmol), acid **1** (0.29, 1.0 mmol) and Ag_2CO_3 (0.14 g, 0.5 mmol) in CH_2Cl_2, room temp., 5

d. Yield 0.40 g (72%), colourless crystals, m.p. 150–152°C (ethanol). – $[\alpha]_{578}^{25} = -1.3$ (c = 1.3 in $CHCl_3$). – ^1H NMR ($CDCl_3$): δ = 1.55 (s, 1H, NH), 1.85 (s, 3H, CH_3CO), 2.03 (s, 3H, CH_3CO), 2.05 (s, 3H, CH_3CO), 3.50 (dd, J_{gem} = 12.0 Hz, $J_{4,5a}$ = 8.5 Hz, 1H, 5-H_a), 4.92–5.24 (m, 3H, 2-H to 4-H), 5.76 (d, $J_{1,2}$ = 6.8 Hz, 1H, 1-H), 6.52–6.59 (m, 2H, arom.), 6.91–7.35 (m, 5H, arom.). – ^{13}C NMR ($CDCl_3$): δ = 20.20 (s, CH_3CO), 20.53 (s, 2 CH_3CO), 38.08 (s, CH_2), 62.82 (s, C-5), 68.19 (s, C-4), 69.34 (s, C-2), 70.86 (s, C-3), 92.46 (s, C-1), 118.47, 122.18, 123.46, 124.12, 128.18, 128.76, 129.45, 130.71, 137.60, 142.56 (10 s, arom.), 169.82 (s, CH_2OCO), 170.34 (s, 2 CH_3CO), 171.03 (s, CH_3CO). – $C_{25}H_{25}Cl_2NO_9$ (554.38): calcd. C 54.16, H 4.55, N 2.53; found C 54.24, H 4.54, N 2.44.

1-O-[o-(2,6-Dichloroanilino)phenylacetyl]-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranose (**7d**): Donor **2d** (0.47 g, 1.0 mmol), acid **1** (0.29, 1.0 mmol) and Ag_2CO_3 (0.14 g, 0.5 mmol) in CH_2Cl_2, room temp., 4 d. Yield 0.48 g (84%), colourless crystals, m.p. 141–142°C (ethanol). – $[\alpha]_{578}^{25} = -0.3$ (c = 1.0 in $CHCl_3$). – ^1H NMR ($CDCl_3$): δ = 1.56 (s, 1H, NH), 1.81–1.98 (m, 1H, 2-H ax), 2.02 (s, 3H, CH_3CO), 2.04 (s, 3H, CH_3CO), 2.08 (s, 3H, CH_3CO), 2.32–2.40 (m, 1H, 2-H eq), 3.70–3.78 (m, 1H, 5-H), 3.87 (d, 2H, CH_2), 4.08 (dd, $J_{5,6b}$ = 2.3 Hz, J_{gem} = 12.4 Hz, 1H, 6-H_b), 4.32 (dd, $J_{5,6a}$ = 4.6 Hz, J_{gem} = 12.4 Hz, 1H, 6-H_a), 5.01–5.08 (m, 2H, 3-H, 4-H), 5.84 (dd, $J_{1,2a}$ = 9.9 Hz, $J_{1,2e}$ = 2.3 Hz, 1H, 1H, 1-H), 6.54–7.35 (m, 7H, arom.). – ^{13}C NMR ($CDCl_3$): δ = 20.60 (s, CH_3CO), 20.71 (s, 2 CH_3CO), 34.55 (s, C-2), 38.20 (s, CH_2), 61.83 (s, C-6), 68.10, 69.89, 72.80 (3 s, C-3 to C-5), 91.65 (s, C-1), 118.61, 122.22, 123.71, 123.99, 128.15, 128.75, 129.28, 130.84, 137.70, 142.62 (10 s, arom.), 169.24 (s, CH_2OCO), 169.62 (s, CH_3CO), 169.93 (s, CH_3CO), 170.12 (s, CH_3CO). – $C_{26}H_{27}Cl_2NO_9$ (568.44): calcd. C 54.94, H 4.79, N 2.46; found C 55.11, H 4.85, N 2.49.

1-O-[o-(2,6-Dichloroanilino)phenylacetyl]-2,3,4,6-tetra-O-benzyl-β-D-glucopyranose (**7e**). – *Method A:* To a solution of sugar **5** (0.58 g, 1.0 mmol) in CH_2Cl_2 (7 ml), a solution of acid **1** (0.29 g, 1 mmol) in the same solvent (15 ml) was added and the mixture was stirred at 0°C. Then, boron trifluoride diethyl ether was added (45% solution, 0.84 ml, 3.0 mmol) and the reaction mixture was stirred for 6 d at room temp., with monitoring by TLC, ^1H-, ^{13}C-NMR spectroscopy. After completion of the reaction, the organic phase was washed with aqueous sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and concentrated in vacuo. The oily residue of **7e** was found to consist of a mixture of α and β anomers in a ratio of 17:83. – ^1H NMR: δ = 5.42 (d, $J_{1,2}$ = 7.3 Hz, 1H, 1-H, β) and δ = 6.40 (d, $J_{1,2}$ = 3.5 Hz, 1H, 1-H, α). – ^{13}C NMR: δ = 81.96 (s, C-1, β) and δ = 81.38 (s, C-1, α). – Crystallization from ethanol gave the β-1-*O*-acyl sugar **7e** (0.34 g, 41%), the spectral data (^1H and ^{13}C NMR) of which corresponded to those of the **7e** obtained by Method B.

Method B (Following the General Procedure): Donor **3e** (0.24 g, 0.3 mmol), acid **1** (0.09 g, 0.3 mmol) and Ag_2CO_3 (0.04 g, 0.15 mmol) in benzene (25 ml), 80°C, 12 h. Yield 0.13 g (53%). **7e** (β): Colourless crystals, m.p. 149–151°C from ethanol (after several days at −15°C). – $[\alpha]_{578}^{25} = +2.2$ (c = 1.0 in $CHCl_3$). – ^1H NMR ($CDCl_3$): δ = 1.61 (s, 1H, NH), 3.36–4.19 (m, 6H, 2-H to 6-H_b), 4.43–5.36 (m, 10H, 5 CH_2), 5.42 (d, $J_{1,2}$ = 7.3 Hz, 1H, 1-H), 6.95–7.54 (m, 27H, arom.). – ^{13}C NMR ($CDCl_3$): δ = 29.52 (s, C-2), 35.48 ($OCOCH_2$), 65.24 (s, C-6), 71.57 (s, 4 CH_2Ph), 76.15, 76.37, 76.79 (3 s, C-3 to C-5), 81.96 (s, C-1), 100.43, 108.89, 122.84, 124.63, 125.88, 127.57, 127.66, 127.72, 128.18, 128.61, 128.80, 129.29, 129.47, 129.67, 130.60, 131.08, 135.27, 137.77 (18 s, arom.), 142.59 (s, $OCOCH_2$). – $C_{48}H_{45}Cl_2NO_7$ (819.26): calcd. C 70.48, H 5.55, N 1.71; found C 70.28, H 5.39, N 1.59.

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