Novel Stereoselective Synthesis of Glycosyl-1-*O*-Acyl Esters via Peracetylglycosyl Phosphorothioates, -selenoates and -dithioates as Glycosyl Donors

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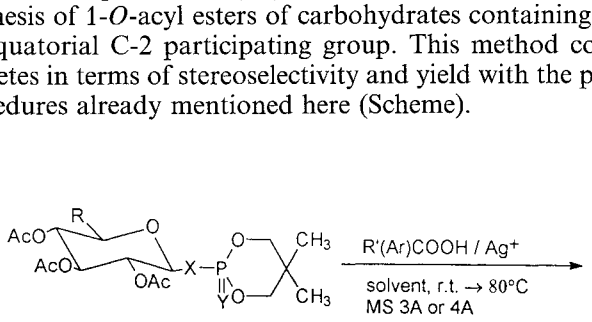
An efficient and highly β-stereoselective synthesis of glycosyl 1-*O*-acyl esters based on reaction of easily accessible glycosylthio-, seleno- and dithiophosphates **1–6** as glycosyl donors with carboxylic acids **7–13** as glycosyl acceptors in the presence of silver salts as activators is described.

Investigations over the last few years have revealed several applications of sugar 1-*O*-acyl esters. Glycosyl carboxylates derived from pharmacologically important compounds are used as prodrugs.[1] Long-chain aliphatic acid glycosyl esters are employed as detergents and food additives because of their emulsifying properties.[2] Furthermore, they also exhibit liquid crystal properties.[3]

Sugar 1-*O*-acyl esters have been obtained in a variety of ways. Methods based on direct acylation of sugar hemiacetals led to a mixture of anomers.[4,5] The same applies to the condensation of carboxylic acids with bromo- and fluorosugars.[6,7] The reaction of glycosyl trimethylsilyl ethers with carboxylic acid anhydrides in the presence of $Et_2O \cdot BF_3$ is also nonstereoselective.[8] Recently, however, β-thioethers of carbohydrates were transformed into β-1-*O*-acyl esters in a stereoselective way,[9–11] and reactions of sugar trichloroacetimidates with carboxylic acids led mainly or exclusively to β-1-*O*-acyl esters.[12]

We have introduced *S*-(2-deoxyglycosyl)phosphorodithioates as efficient and stereoselective glycosyl donors for a variety of *O*- and *N*-nucleophiles,[13–16] and described recently the synthesis of 2-deoxysugar 1-*O*-acyl esters by this methodology.[17]

We now report on a highly efficient β-stereoselective synthesis of 1-*O*-acyl esters of carbohydrates containing an equatorial C-2 participating group. This method competes in terms of stereoselectivity and yield with the procedures already mentioned here (Scheme).



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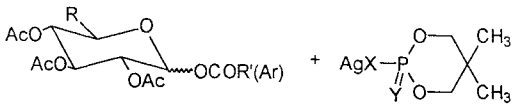


14a-f, 15a-f

X = S,Se; Y = O,S

R = H,CH_2OAc; R'(Ar) **7 -13** (see Table 2)

Scheme

The three types of glycosyl donors (Table 1, donors **1–6**) used in these investigations are easily accessible by reaction of phosphorothio-, dithio- and selenoates with glycosyl halides,[18,19] by reaction of 1-*O*-acetyl sugars with phosphorothioic, selenoic[20] and dithioic acids[21] in the presence of boron trifluoride–diethyl ether complex, and by addition of phosphorodithioic acids to tetra-*O*-acetyl-1,5-anhydro-D-*arabino*-hex-1-enitol, respectively.[22] These glycosylating reagents are crystalline and shelf-stable compounds. Representative carboxylic acids used as glycosyl acceptors, are listed in Table 2.

The glycosylation reaction proceeds in aprotic solvents such as CH_2Cl_2, MeCN, benzene or THF. The choice of solvent is dictated by the solubility of reactants and in some cases the displacement reaction was performed under solvolytic conditions. The reaction requires activation by silver salts such as silver carbonate, silver fluoride or silver perchlorate. Silver salts facilitate the generation of the carboxylic acid anion and activate the leaving group by complexation with sulfur and selenium centres.

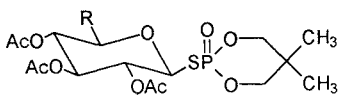
The glycosylation reaction was monitored by TLC and ^{13}C NMR spectroscopy. According to NMR data the yield of 1-*O*-acyl esters is quantitative, regardless of the type of applied glycosyl donor. In general, glycosyl donors **2, 4, 6** derived from D-xylose are more reactive toward carboxylic acids than those derived from D-glucose **1, 3, 5**. Consequently, glycosylations with the aid of reagents **2, 4** and **6** proceed at ambient temperature, while reactions of carboxylic acids with reagents **1, 3** and **5** require warming to 50–80 °C. The method is highly β-stereoselective and in many cases stereospecific. The α/β ratio was estimated by ^1H and ^{13}C NMR spectroscopy on crude reaction mixtures after removal of the precipitated silver salts and molecular sieves.

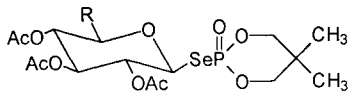
The synthesis of 1-*O*-acyl esters obtained from liquid acids **7** and **8** was performed under various conditions (temperature, activator, glycosyl donor, see Tables 3 and 4). These factors influenced the stereochemical course of glycosylations dramatically. Thus, for example, when acetic acid was used in stoichiometric amounts and the reaction was performed in boiling benzene, in the presence of Ag_2CO_3, the β-1-acetate was formed stereospecifically (Table 3, entry 1). This stereochemical outcome was totally reversed under solvolytic conditions; in the presence of the same activator, on prolonged boiling at 118 °C, the thermodynamically more stable α-1-acetate was formed exclusively (Table 3, entry 2).

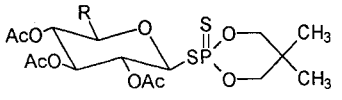
In the case of glycosyl donors derived from D-xylose, the β-1-*O*-acylate was the main product regardless of reaction conditions (Table 4, entries 1, 2 and 3).

Most of the syntheses of fatty acid glycosyl esters described recently are based on enzyme-catalyzed reactions. Here we describe a chemical method for the synthesis of

Table 1. Glycosyl Donors **1–6**







1	$R = CH_2OAc$[18]	**3**	$R = CH_2OAc$[19]	**5**	$R = CH_2OAc$[18]
2	$R = H$[18]	**4**	$R = H$[19]	**6**	$R = H$[a]

[a] Compound **6** was obtained by the same method as described for compounds **1–5**[18,19] (4 h, 80 °C, benzene, mp 163–165 °C; $[\alpha]_D^{20} = +4.5$ ($c = 0.9$, $CHCl_3$); ^{31}P NMR: $\delta = 84.88$; ^{13}C NMR: $\delta = 85.21$ (C–1, $^3J_{P-C} < 1$ Hz).

Table 2. Glycosyl Acceptors **7–13**

7	$MeCO_2H$	**11**	$2\text{-}HOC_6H_4CO_2H$
8	$MeCH_2CO_2H$	**12**	$2\text{-}AcOC_6H_4CO_2H$
9	$Me(CH_2)_{18}CO_2H$	**13**	1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetic acid
10	$2\text{-}AcNHC_6H_4CO_2H$		

arachidic acid esters of both D-glucose and D-xylose. Using our procedure, 1-*O*-arachidic acid esters of both series were obtained mainly as β-anomers (Table 3, entry 3; Table 4, entry 4). Surprisingly, the monothiophosphate of D-xylose underwent exclusive α-substitution when 3 molar equivalents of AgF were used for activation of the leaving group (Table 4, entry 5). In spite of the long-chain aliphatic residue, arachidic acid esters of D-glucose and D-xylose are crystalline (Table 5). The reaction of *N*-acetylanthranilic acid **(10)** with glycosyl donor **1**, performed in boiling THF in the presence of Ag_2CO_3, resulted in stereospecific synthesis of the β-anomer (Table 3, entry 4). Using $AgClO_4$ as activator shifted the α/β ratio in favour of the α-anomer (α/β = 80:20) (Table 3, entry 5). The bifunctional salicylic acid **(11)** reacted fully regio- and stereospecifically with donors **1–4** and **6** in the presence of Ag_2CO_3, yielding the respective β-1-salicylates in quantitative yield (Table 3, entries 6, 7, 8; Table 4, entries 6, 7, 8). No traces of the phenolic glycosides were found. A drastic change of reaction course occurred when the acid **11** was treated with the D-xylose derived donor **2** in the presence of 3 molar equivalents of AgF. In this case the α/β ratio favoured the α-glycosyl ester (77:23) (Table 4, entry 9). The reactions of glycosyl donors **1** and **2** with *O*-acetylsalicylic acid **12** were less stereoselective. The α/β ratio depended on the nature of the activator. Silver fluoride promoted the formation of α-anomers (Table 4, entry 10) and Ag_2CO_3 β-anomers (Table 3, entry 9; Table 4, entry 11). Hydrolysis led to products identical with those obtained from the reaction of glycosyl donors **1** and **3** with unsubstituted salicylic acid (Table 3, entries 6, 7, 8). This result proved the regiospecific course of glycosylation of salicylic acid.

A stereospecific course of glycosylation was observed in the case of indomethacine derivatives, which yielded exclusively β-esters (Table 3, entries 10, 11; Table 4, entries 12,13). In this case, in both the D-xylose and D-glucose series, even addition of 3 molar equivalents of AgF failed to influence the stereochemical course of glycosylation (Table 3, entry 11; Table 4, entry 13). This contrasted with the case of arachidic acid which under the same conditions gave the α-ester stereospecifically (Table 4, entry 5). Table 5 contains selected physical and NMR data for anomerically pure β-1-*O*-acyl esters **(14b, d, 15c, d, f)** and for (α + β) compound **14f**.

In conclusion, a new and efficient synthesis of glycosyl 1-*O*-acyl esters has been worked out based on easily accessible glycosyl donors. Activation by silver carbonate leads preferentially to β-1-*O*-acyl esters, while activation by silver perchlorate and a large excess of silver fluoride favours the formation of α-anomers. This novel synthesis represents a valuable alternative to existing methods.

Melting points were determined with a Boetius PHMK 05 apparatus and are uncorrected. ^1H NMR (Bruker AC, 200.113 MHz) and ^{13}C (Bruker AC 200, 50.33 MHz) spectra were recorded in $CDCl_3$ using TMS as internal standard. ^{31}P NMR were recorded in $CDCl_3$ (Bruker AC 200, 81.04 MHz, using H_3PO_4 as external standard). Specific rotations were determined with a Polamat polarimeter. TLC was carried out on silica gel plates (Kieselgel 60 F_{254} Merck) with benzene/$CHCl_3$/acetone (3:1:1) as the developing solvent. Detection was effected by exposure to I_2 vapours. Ag_2CO_3 was freshly prepared.

1-*O*-Acyl Esters of Peracetylated Monosaccharides 14a–15f; General Procedure:

Method A: To a solution of glycosyl donor **1–6** (1 mmol) in anhyd solvent (Tables 3 and 4) was added carboxylic acid **7–13** (1 mmol) in anhyd solvent (minimum amount) followed by Ag_2CO_3 (0.5 mmol) in the presence of molecular sieves 3Å or 4Å (Tables 3 and 4 for specific conditions). The mixture was stirred in the dark and the reaction was monitored by TLC. The precipitated silver salts and molecular sieves were removed by filtration through Celite 535 and the filtrate concentrated under reduced pressure. The residue was diluted with benzene. The benzene solution was washed with 5% aq Na_2CO_3, water, dried ($MgSO_4$) and concentrated in vacuo. The semicrystalline residue containing (α + β) isomers was purified by crystallization to give the pure 1-*O*-acyl esters.

Method B (for **14a**, **15a**, **15b**): Donors **2** or **5** (2 mmol) were dissolved in a minimum amount of the acid **7** or **8** and a stoichiometric amount of Ag_2CO_3 was added, followed by molecular sieves (3Å or 4Å). The solution was heated under reflux to the boiling point of the acid in the dark (time, Tables 3 and 4) until TLC analysis showed the absence of the glycosyl donor. The reaction mixture was diluted with $CHCl_3$, washed with 5% aq Na_2CO_3 and water, then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The α/β ratios are presented in Tables 3 and 4.

Table 3. 1-*O*-Acyl Esters of 2,3,4,6-Tetra-*O*-acetyl-(α,β)-D-glucopyranose **14a–f** (Method A)

Entry	Glycosyl Donor	Glycosyl Acceptor	Product (α + β)	Solvent	Time[a] (h)	Activator	Ratio of α/β (%)[b]	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)		^{13}C NMR ($CDCl_3$/TMS) δ	
								H-1 (α)	H-1 (β)	C-1 (α)	C-1 (β)
1	**1**	**7**	**14a**	benzene	10	Ag_2CO_3	0 : 100	6.33 (d, $J_{1,2}$ = 3.6)	5.72 (d, $J_{1,2}$ = 7.3)	89.13	91.65
2	**5**	**7**	**14a**[c]	$MeCO_2H$[b]	2	Ag_2CO_3	100 : 0				
3	**1**	**9**	**14b**[c]	benzene	20	Ag_2CO_3	30 : 70	6.25 (d, $J_{1,2}$ = 4.0)	5.74 (d, $J_{1,2}$ = 8.0)	91.17	91.36
4	**1**	**10**	**14c**	THF	30	Ag_2CO_3	0 : 100	6.25 (d, $J_{1,2}$ = 3.8)	5.52 (d, $J_{1,2}$ = 8.9)	90.32	91.46
5	**1**	**10**	**14c**	THF	20	$AgClO_4$	80 : 20				
6	**1**	**11**	**14d**	C_6H_6	9	Ag_2CO_3	0 : 100		5.68 (d, $J_{1,2}$ = 7.8)		92.20
7	**1**	**11**	**14d**	MeCN	6	Ag_2CO_3	0 : 100				
8	**3**	**11**	**14d**	benzene	5	Ag_2CO_3	0 : 100				
9	**1**	**12**	**14e**	benzene	9	Ag_2CO_3	50 : 50	6.29 (d, $J_{1,2}$ = 2.4)	5.80 (d, $J_{1,2}$ = 7.9)	91.97	92.19
10	**1**	**13**	**14f**	benzene	6	$5Ag_2CO_3$	0 : 100		5.68 (d, $J_{1,2}$ = 8.0)		91.86
11	**1**	**13**	**14f**	benzene	10	3AgF	0 : 100				

[a] Time measured for the reaction performed at bp of the respective solvent.
[b] α/β Ratio determined by ^{13}C NMR on crude products.
[c] Obtained by method B.

Table 4. 1-*O*-Acyl Esters of 2,3,4-Tri-*O*-acetyl-(α,β)-D-xylopyranose **15a–f** (Method A)

Entry	Glycosyl Donor	Glycosyl Acceptor	Product (α + β)	Solvent	Time[a]	Activator	Ratio of α/β (%)[b]	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)		^{13}C NMR ($CDCl_3$/TMS) δ	
								H-1 (α)	H-1 (β)	C-1 (α)	C-1 (β)
1	**2**	**7**	**15a**	CH_2Cl_2	7 d	Ag_2CO_3	10 : 90	6.24 (d, $J_{1,2}$ = 3.7)	5.70 (d, $J_{1,2}$ = 6.8)	91.16	91.70
2	**2**	**7**	**15a**[c]	$MeCO_2H$	20 min	Ag_2CO_3	0 : 100				
3	**2**	**8**	**15b**[c]	$EtCO_2H$	20 min	Ag_2CO_3	6 : 94	6.20 (d, $J_{1,2}$ = 3.6)	5.68 (d, $J_{1,2}$ = 6.7)	90.86	91.34
4	**2**	**9**	**15c**	CH_2Cl_2	8 d	Ag_2CO_3	30 : 70	6.12 (d, $J_{1,2}$ = 3.7)	5.69 (d, $J_{1,2}$ = 6.8)	91.27	91.60
5	**2**	**9**	**15c**	CH_2Cl_2	7 d	3AgF	100 : 0				
6	**2**	**11**	**15d**	CH_2Cl_2	4 d	Ag_2CO_3	0 : 100	6.50 (d, $J_{1,2}$ = 3.7)	5.98 (d, $J_{1,2}$ = 5.7)	90.18	91.65
7	**6**	**11**	**15d**	CH_2Cl_2	4 d	Ag_2CO_3	15 : 85				
8	**4**	**11**	**15d**	CH_2Cl_2	2 d	Ag_2CO_3	0 : 100				
9	**2**	**11**	**15d**	CH_2Cl_2	4 d	3AgF	77 : 23				
10	**2**	**12**	**15e**	CH_2Cl_2	3 d	3AgF	60 : 40	6.11 (d, $J_{1,2}$ = 3.7)	5.87 (d, $J_{1,2}$ = 6.4)	89.85	91.45
11	**2**	**12**	**15e**	CH_2Cl_2	12 d	Ag_2CO_3	20 : 80				
12	**4**	**13**	**15f**	CH_2Cl_2	6 d	Ag_2CO_3	0 : 100		5.68 (d, $J_{1,2}$ = 7.16)		92.57
13	**2**	**13**	**15f**	CH_2Cl_2	6 d	3AgF	0 : 100				

[a] Time measured for the reaction performed at 20 °C.
[b] α/β Ratio determined by ^{13}C NMR on crude products.
[c] Obtained by method B.

Table 5. Selected Physical and NMR Data for Pure 1-*O*-Acyl Esters of **14b,d,f**[a] and **15c,d,f**[a]

Product	Yield (%)	mp (°C)[b] (solvent)	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	^1H NMR ($CDCl_3$/TMS)[c] δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS)[c] δ
14b(β)	45	71–72 (EtOH)	−1.72 (0.9)	0.87 (t, CH_3, 3H), 1.24 (s, 16×CH_2, 32H), 1.56–1.63 (m, CH_2CH_3, 2H), 2.00, 2.01, 2.02, 2.08 (4s, 4×OAc, 12H), 2.31–2.43 (m, $OCOCH_2$, 2H), 3.80–3.87 (m, H-5, 1H), 4.09 (dd, H-6′, $J_{6,6'}$ = 12.5, $J_{5,6'}$ = 2.0, 1H), 4.29 (dd, H-6, 1H, $J_{6,6'}$ = 12.5, $J_{5,6}$ = 4.4), 5.07–5.30 (m, H-2, H-3, H-4, 3H)	14.10 (CH_3CH_2), 20.54 ($OCOCH_3$), 20.65 (CH_3CH_2), 22.67 ($CH_3CH_2CH_2$), 24.52 ($CH_3CH_2CH_2CH_2$), 29.67 (CH_2, 10C, s), 31.91 ($OCOCH_2CH_2$), 34.02 ($OCOCH_2$), 61.45 (C-6), 67.78, 70.20, 72.68, 72.77 (C-2 to C-5, 4s), 169.21, 169.41, 169.48, 169.65, 169.87 (4×$OCOCH_3$, $OCOCH_2$, 5s)
15c(β)	46	104–105 (EtOH)	−0.09 (1.0)	0.87 (t, CH_3, 3H), 1.23 (s, 16×CH_2, 32H), 1.55–1.64 (m, CH_2CH_3, 2H), 2.04, 2.05, 2.06 (3s, 3×OAc, 9H), 2.30–2.37 (m, $OCOCH_2$, 2H), 3.50 (dd, H-5a, 1H, $J_{4,5a}$ = 8.4, $J_{5a,5e}$ = 12.0), 4.14 (dd, H-5e, 1H, $J_{4,5e}$ = 5.0, $J_{5a,5e}$ = 12.0), 4.91–5.07 (m, H-3, H-4, 2H); 5.16–5.25 (m, H-2, 1H)	14.05 (CH_3CH_2), 20.61 ($COCH_3$), 22.63 (CH_3CH_2), 24.56 ($CH_3CH_2CH_2$), 29.62 (CH_2, 13C, s), 31.87 ($OCOCH_2CH_2$), 34.04 ($OCOCH_2$), 62.73 (C-5), 68.30, 69.30, 71.00 (C-2 to C-4, 4s), 169.74 ($OCOCH_2$)
14d(β)	61	195–197 (EtOH)	−4.81 (0.9)	2.00, 2.04, 2.05, 2.07 (3s, 4×OAc, 12H), 3.91–3.97 (m, H-5, 1H), 4.13 (dd, H-6, 1H, $J_{6,6'}$ = 12.5, $J_{5,6}$ = 2.3), 4.32 (dd, H-6′, 1H, $J_{6,6'}$ = 12.5, $J_{5,6'}$ = 4.5) 5.17–5.24 (m, H-3, 1H), 5.32–5.37 (m, H-2, H-4, 2H)	20.51 ($OCOCH_3$), 61.36 (C-6), 67.77 (C-4), 69.91 (C-2), 72.44 (C-5), 72.81 (C-3), 110.96 (COH), 117.65, 119.69, 130.32, 136.81 (C-arom, 4s), 162.07 ($OCOC_6H_4$), 168.10, 169.20, 169.31, 169.96 (4×$COCH_3$, 4s)
15d(β)	45	141–143 (EtOH)	−9.76 (1.2)	2.05, 2.08, 2.09 (3s, 3×OAc, 9H), 3.61–3.71 (dd, H-5a, 1H, $J_{4,5a}$ = 7.1, $J_{5a,5e}$ = 12.3), 4.19–4.27 (dd, H-5e, 1H, $J_{4,5a}$ = 4.4, $J_{5a,5e}$ = 12.3), 4.94–5.03, 5.13–5.29 (2×m, H-3, H-4, 2H), 6.84–6.99, 7.44–7.52, 7.78–7.83 (dd, 2×m, H-arom, 3H), 10.27 (s, OH, 1H)	20.37 ($OCOCH_3$), 62.03 (C-5), 67.50 (C-4), 68.26 (C-2), 69.34 (C-3), 111.06 (COH), 117.56, 119.27, 129.84, 136.42 (C-arom, 4s), 161.79 ($OCOC_6H_4$), 169.01, 169.20, 169.48 ($OCOCH_3$, 3s)
14f (α + β)[d]	48	160–162 (EtOH)	+0.4 (0.7)	1.97, 1.99, 2.01, 2.02, 2.03, 2.08 (6s, 4×OAc, 12H), 1.55 (s, CH_3, 3H), 3.84 (d, OCH_3, 3H, $J_{H,H}$ = < 1), 3.70–4.14 (m, H-5, H-6, 2H), 4.30 (dd, H-6′, 1H, $J_{5,6'}$ = 4.5, $J_{6,6'}$ = 12.5), 4.99–5.38 (m, H-2, H-3, H-4, 3H), 5.68 [d, $J_{1,2}$ = 8.0, 0.68H(β)], 6.30 [d, $J_{1,2}$ = 3.5, 0.32H(α)], 6.67, 6.89, 6.96, 7.48, 7.63–7.71 (dd, t, d, m, 2×H-arom, 7H)	13.28 (CH_3), 20.51 ($OCOCH_3$-α), 20.64 ($OCOCH_3$-β), 55.67 (OCH_3), 61.19 (C-6α), 61.43 (C-6β), 67.73, 72.61, 72.85 (C-4, C-3, C-5, 3s), 69.71 (C-2α), 69.87 (C-2β), 91.14 (C-1α), 91.86 (C-1β), 111.17, 111.93, 115.04, 115.15, 129.15, 130.12, 130.78, 131.16, 133.86, 136.28 (C-arom, 10s), 156.19 ($OCOCH_2$), 168.48 (C=O), 168.76, 168.90, 169.32, 169.97, 170.52 (8×$OCOCH_3$, 5s).
15f(β)	50	128–130 (EtOH)	−6.4 (1.0)	1.68 (s, CH_3, 3H), 2.00, 2.04 (2s, 3×OAc, 9H), 2.35 (s, CH_2, 2H), 3.47 (dd, H-5a, $J_{4,5a}$ = 8.9, $J_{5a,5e}$ = 11.9), 3.83 (s, OCH_3, 3H), 4.10 (dd, H-5e, 1H, $J_{4,5e}$ = 5.1, $J_{5a,5e}$ = 12.9), 4.90–5.00, 5.03–5.17 (3×m, H-3, H-4, H-2, 3H), 6.67, 6.88–6.92, 7.45–7.49, 7.66–7.70 (dd, H-arom, 3×m, 7H).	13.17 (CH_3), 20.55 ($OCOCH_3$), 55.55 (OCH_3), 62.89 (C-5), 68.23, 69.41, 71.07 (C-2 to C-4, 3s), 100.84, 111.20, 111.72, 114.90, 129.01, 130.64, 131.05, 136.08, 139.16 (C-arom, 9s), 156.04 ($OCOCH_2$), 168.17 (C=O), 168.79, 168.89, 169.66 ($OCOCH_3$, 3s).

[a] Satisfactory elemental analyses obtained: C ± 0.30, H ± 0.25, N ± 0.30.
[b] Uncorrected.
[c] Data for H-1 and C-1, see Tables 3 and 4.
[d] The pure β-anomer gave on repeated crystallization an inseparable mixture of α + β-anomers in 32 : 68 ratio.

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