Efficient Synthesis of 2-Deoxyglycosyl-1-*O*-Acyl Esters via 2-Deoxyglycosyl Phosphorodithioates as Glycosyl Donors

Joanna Borowiecka, Maria Michalska*

Laboratory of Organic Chemistry, Institute of Chemistry, Medical University, Muszynskiego 1, 90-151 Lodz, Poland

Dedicated to Professor A.R. Katritzky on the occasion of his 65th birthday.

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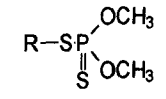
An efficient glycosylation of carboxylic acids **2a–p** has been developed employing 2-deoxyglycosyl phosphorodithioates **1a–h** as glycosyl donors and Ag^+ salts as activators. In the case of aliphatic acids the method is highly β-stereoselective. Stereoselectivity of glycosylation of aromatic acids depends on their structure. The α/β ratio is temperature dependent. Hydroxy groups in α-hydroxycarboxylic acids are not affected by glycosylation under the reaction conditions used.

Glycosyl esters of carboxylic acids represent a class of sugar derivatives of synthetic, biological and pharmacological importance. The 1-*O*-acetates are frequently employed in making further derivatives at the anomeric centre, e.g. in the synthesis of *O*-[1–6], *N*-[7–9] and *C*-glycosides,[10–14] either directly or via glycosyl fluorides.[15–17] They can also serve as intermediates in the synthesis of other glycosyl donors.[18] Biological properties of this class of compounds include, amongst others, inhibitory action on some enzymes[19] and on the growth of leukemia cells.[20] In the case of nonsteroidal, anti-inflammatory agents with a carboxylic acid function, glycosyl esters are potential pro-drug reagents.[21–23] 2-Deoxyglycosyl esters are not easily accessible, there have been, therefore, few studies of their biological function and synthetic applications.

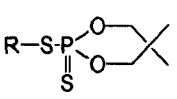
In contrast to the large number of efficient stereoselective procedures developed for the synthesis of 1-*O*-acyl esters of simple mono- and oligosaccharides,[24–31] methods for stereoselective synthesis of sugar 1-*O*-acylates in the 2-deoxy series are scarce. Also they lead mainly to the thermodynamically more stable α-anomers. Most procedures used so far were based on direct acylation of 2-deoxysugar hemiacetals[32] or their silyl ethers[33] and on addition reactions to glycals. In the latter case, glycals were most frequently transformed into glycosyl donors containing a "prodeoxy" function which was removed by a photolytic or hydrogenative procedure upon the formation of the 1-*O*-acyl bonding.[34–37] The "glycal approach" has recently been reinvestigated and successfully modified by performing direct addition of hydroxylic nucleophiles to glycals in the presence of triphenylphosphine hydrobromide.[38] A novel synthetic route was recently reported via glycosyl radicals. These were generated from tetra-*O*-acetyl glycosyl halides or phenyl selenides by reduction with low concentrations of tributylstannanes.[39] The important step in this radical chain reaction is the *cis*-selective migration of an ester group from C-2 to C-1. This forms 2-deoxyglycosyl radicals which, on hydrogen abstraction from Bu_3SnH, are transformed into 2-deoxysugar 1-*O*-acetates.

We now report a general, highly efficient and stereoselective method of synthesis (Scheme 1). It gives fully protected 2-deoxyglycosyl 1-*O*-acyl esters from easily accessible, stable 2-deoxyglycosyl phosphorodithioates as

Table 1. Glycosyl Donors



1a



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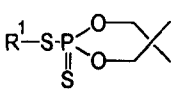
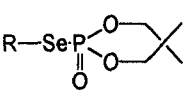
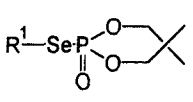


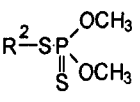
1c



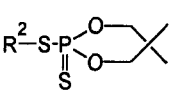
1d



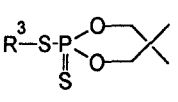
1e



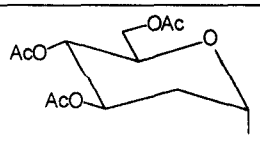
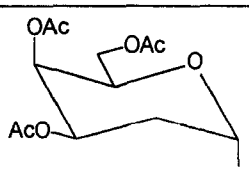
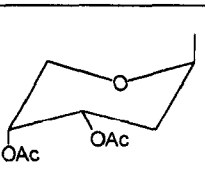
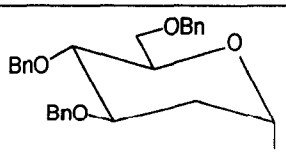
1f

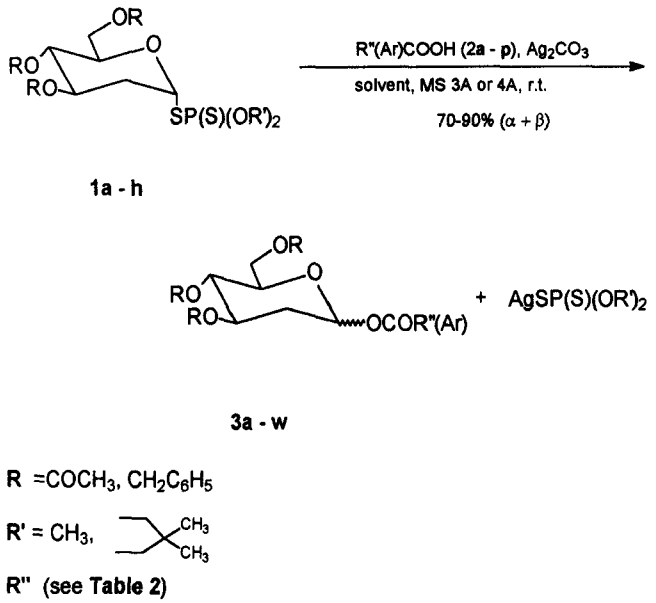


1g



1h

R	R^1	R^2	R^3
			



Scheme 1

glycosylating reagents (Table 1) and carboxylic acids as glycosyl acceptors (Table 2) in the presence of silver salts as activators.

α-2-Deoxyglycosyl phosphorodithioates[40] have already been successfully exploited as glycosyl donors in the synthesis of alkyl 2-deoxyglycosides,[41] 2-deoxydisaccharides,[42,43] aryl 2-deoxyglycosides[44] and *N*-alkyl-(2-deoxyglycosyl)amines.[45] It has been demonstrated that these glycosyl donors, despite the lack of a participating group at C-2, secure a high degree of β-selectivity.[41,44,45]

Extension of this glycosylation procedure to carboxylic acids led to elaboration of an efficient and stereoselective method of synthesis of fully protected 2-deoxyglycosyl 1-*O*-acyl esters. The general character of this approach is illustrated by the synthesis of a wide range of 1-*O*-acyl esters **3a–s** (Table 3) via reaction of 2-deoxyglycosyl phosphorodithioates **1a–h** with a series of aliphatic and aromatic mono- and bifunctional carboxylic acids **2a–p** in the presence of Ag^+ salts as activators.

When equimolar amounts of reagents were allowed to react in the presence of such activators as Ag_2O or Ag_2CO_3 at room temperature and in aprotic solvent (CH_2Cl_2, CH_3CN or THF) (Method A), the displacement of the dithiophosphate group by carboxylate anion was complete within 2–10 days with quantitative overall yield estimated by TLC. The β/α ratio was determined on crude reaction mixtures by ^1H and ^{13}C NMR spectroscopy after removal of insoluble material and evaporation of solvent. The highest β/α ratio was obtained with aliphatic acids including the long-chain arachidic acid. Aromatic acids reacted less β-stereoselectively with the exception of *p*-chlorobenzoic acid which, surprisingly, gave 100% of β-2-deoxyglycosyl-1-*O*-acylate (Table 3). The hydroxy function of α-hydroxycarboxylic acids did not compete with the carboxy group in the glycosylation process under the conditions used (Table 2, glycosyl acceptors **2c** and **2i**).

The time necessary to complete acylation was markedly shorter in the case of liquid acids which also served as solvents (Method B); however, no change in the β/α ratio was observed (Scheme 2). For example, the reaction of equimolar amounts of acetic acid **(2a)**[46] and 2-deoxygalactopyranosyl phosphorodithioate **(1c)** in dichloromethane solution was accomplished within 72 h, whereas under solvolytic conditions it took only 15 minutes (Table 4 for this and other examples of 1-*O*-acetylation under different reaction conditions). The β/α ratio was 83:17 and 87:13, respectively. The most important factor to secure β-selectivity of acylation is temperature. Full inversion of the β/α ratio was observed (14:86) when the donor **1c** was refluxed for 5 h in acetic acid solution (Table 4).

Table 2. Glycosyl Acceptors **2a–p**

2		2		2	
a	$MeCO_2H$[a]	**f**	$PhCO_2H$	**k**	$4\text{-}ClC_6H_4CO_2H$
b	$MeCH_2CO_2H$	**g**	$2\text{-}AcOC_6H_4CO_2H$	**l**	$4\text{-}HOC_6H_4CO_2H$
c	$MeCH(OH)CO_2H$	**h**	$2\text{-}AcNHC_6H_4CO_2H$	**m**	2-pyridinecarboxylic acid
d	$Me(CH_2)_{18}CO_2H$	**i**	$PhCH(OH)CO_2H$	**n**	3-pyridinecarboxylic acid
e	$AcNHCH_2CO_2H$	**j**	$PhCH{=}CHCO_2H$	**p**	1-(*p*-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetic acid

[a] Derivatives of acetic acid, see Table **4**.

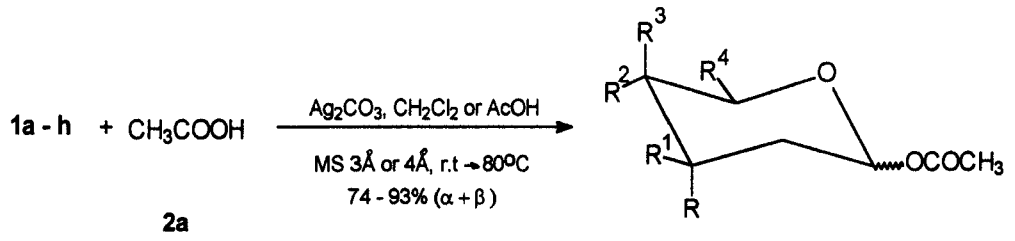
Table 3. 1-*O*-Acyl Esters of 3,4,6-Tri-*O*-acetyl (or 3,4,6-Tri-*O*-benzyl) 2-Deoxy-(α + β)-D-arabinohexopyranose Obtained by Method A[a]

Glycosyl Donor	Glycosyl Acceptor[b]	Product (α + β)	Conditions Solvent	Time	Yield (%) β/α ratio	^1H NMR, δ, J (Hz) H-1(β)	H-1(α)	^{13}C NMR, δ C-1(β)	C-1(α)
1a	**2b**	**3b**	CH_2Cl_2	2.5 h	87 (95 : 5)	5.77 (dd, $J_{1,2a}$ = 10.0, $J_{1,2e}$ = 2.0)	6.20 (dd, $J_{1,2a}$ = 3.5, $J_{1,2e}$ < 1.0)	91.00	90.09
1a	**2c**	**3c**	CH_2Cl_2	4 d	89 (90 : 10)	5.83 (dd, $J_{1,2a}$ = 10.0, $J_{1,2e}$ = 2.0)	6.23 (dd, $J_{1,2a}$ = 4.0, $J_{1,2e}$ = 2.0)	91.75	91.45
1a	**2d**	**3d**	C_6H_6	4 d	90 (82 : 18)	5.81 (dd, $J_{1,2a}$ = 9.9, $J_{1,2e}$ = 2.3)	6.40 (dd, $J_{1,2a}$ = 4.0, $J_{1,2e}$ = 2.0)	91.00	90.63

Table 3. (continued)

Glycosyl Donor	Glycosyl Acceptor[b]	Product (α + β)	Conditions Solvent	Time	Yield (%) (β/α ratio)	^{1}H NMR, δ, J (Hz) H-1(β)	H-1(α)	^{13}C NMR, δ C-1(β)	C-1(α)
1a	**2e**	**3e**	CH_2Cl_2	8 d	66 (52 : 48)	5.90 (dd, $J_{1,2a}$ = 10.0, $J_{1,2e}$ = 2.0)	6.40 (dd, $J_{1,2a}$ = 5.0, $J_{1,2e}$ < 1.0)	91.90	91.75
1a	**2f**	**3f**	MeCN	7 d	86 (54 : 46)	6.02 (dd, $J_{1,2a}$ = 7.5, $J_{1,2e}$ < 1.0)	6.50 (dd, $J_{1,2a}$ = 3.34, $J_{1,2e}$ < 1.0)	91.20	91.07
1a	**2g**	**3g**	CH_2Cl_2	10 d	87 (62 : 38)	6.03 (dd, $J_{1,2a}$ = 9.76, $J_{1,2e}$ = 2.34)	6.45 (dd, $J_{1,2a}$ = 4.0, $J_{1,2e}$ < 1.0)	91.82	91.60
1a	**2h**	**3h**	THF	10 d	90 (70 : 30)	6.02 (dd, $J_{1,2a}$ = 9.53, $J_{1,2e}$ = 2.35)	6.50 (dd, $J_{1,2a}$ = 4.0, $J_{1,2e}$ < 1.0)	91.61	91.00
1a	**2i**	**3i**	CH_2Cl_2	48 h	88 (84 : 16)	5.83 (dd, $J_{1,2a}$ = 9.5, $J_{1,2e}$ = 2.4)	6.26 (dd, $J_{1,2a}$ = 4.5, $J_{1,2e}$ = 1.0)	91.82	92.12
1a	**2j**	**3j**	CH_2Cl_2	48 h	98 (100 : 0)	5.96 (dd, $J_{1,2a}$ = 10.0, $J_{1,2e}$ = 2.5)	–	91.30	–
1a	**2j**	**3j**	C_6H_6	50 h, 80 °C	83 (50 : 50)	5.96 (dd, $J_{1,2a}$ = 10.0, $J_{1,2e}$ = 2.5)	6.03 (dd, $J_{1,2a}$ = 5.0, $J_{1,2e}$ = 1.0)	91.30	90.42
1a	**2k**	**3k**	MeCN	10 d	93 (100 : 0)	5.83 (dd, $J_{1,2a}$ = 9.0, $J_{1,2e}$ = 2.0)	–	91.75	–
1a	**2l**	**3l**	MeCN	48 h	68 (46 : 54)	5.86 (dd, $J_{1,2a}$ = 9.5, $J_{1,2e}$ = 1.5)	6.10 (dd, $J_{1,2a}$ = 3.5, $J_{1,2e}$ < 1.0)	91.46	90.15
1a	**2m**	**3m**	MeCN	72 h	78 (70 : 30)	6.03 (dd, $J_{1,2a}$ = 8.5, $J_{1,2e}$ = 2.0)	6.45 (dd, $J_{1,2a}$ = 4.5, $J_{1,2e}$ = 2.0)	92.27	91.52
1a	**2n**	**3n**	MeCN	48 h	76 (56 : 44)	6.20 (dd, $J_{1,2a}$ = 9.5, $J_{1,2e}$ = 3.0)	6.63 (dd, $J_{1,2a}$ = 4.0, $J_{1,2e}$ = 2.0)	92.04	91.82
1a	**2p**	**3p**	CH_2Cl_2	6 d	91 (45 : 55)	5.79 (dd, $J_{1,2a}$ = 9.92, $J_{1,2e}$ = 2.26)	6.24 (dd, $J_{1,2a}$ = 2.0, $J_{1,2e}$ < 1.0)	91.20	90.80
1a	**2p**	**3p**	CH_2Cl_2	3 d[c]	78 (27 : 73)	5.80 (dd, $J_{1,2a}$ = 10.0, $J_{1,2e}$ = 2.0)	6.20 (dd, $J_{1,2a}$ = 2.0, $J_{1,2e}$ < 1.0)	91.33	91.50
1h	**2h**	**3r**	THF	10 d	87 (55 : 45)	5.93 (dd, $J_{1,2a}$ = 10.0, $J_{1,2e}$ = 2.5)	6.33 (dd, $J_{1,2a}$ = 4.0, $J_{1,2e}$ < 1.0)	93.09	92.37
1h	**2j**	**3s**	CH_2Cl_2	48 h	90 (100 : 0)	5.86 (dd, $J_{1,2a}$ = 9.94, $J_{1,2e}$ = 2.0)	–	92.42	–
1h	**2a**	**3w**	CH_2Cl_2	48 h	93 (100 : 0)	5.67 (dd, $J_{1,2a}$ = 9.0, $J_{1,2e}$ = 3.0)	–	92.19	–

[a] Glycosylation was performed with equimolar amounts of reagents, in the presence of Ag_2O or Ag_2CO_3 and in an aprotic solvent.
[b] For reactions with acetic acid (**2a**) see Scheme 2 and Table 4.
[c] Activator: 0.5 equiv Ag_2CO_3/1 equiv $AgClO_4$.



Product (α + β)	R	R[1]	R[2]	R[3]	R[4]	Product (α + β)	R	R[1]	R[2]	R[3]	R[4]
3a	H	OAc	OAc	H	CH_2OAc	**3u**	OAc	H	OAc	H	H
3t	H	OAc	H	OAc	CH_2OAc	**3w**	H	OBn	OBn	H	CH_2OBn

Scheme 2

Table 4. Reaction of Glycosyl Donors **1a–h** with Acetic Acid (**2a**)

Glycosyl Donor	Product ($\alpha + \beta$)	Method	Reaction Activator	Conditions Time, Temp. (°C)	Yield (%)	β/α[a]
1a	**3a**[b]	B	Ag_2CO_3	10 min, r.t.	90	91 : 9
1a	**3a**	A	Ag_2CO_3	72 h, r.t.	87	62 : 38
1b	**3a**	B	Ag_2O	75 h, r.t.	90	100 : 0
1c	**3t**[b]	B	Ag_2O	15 min, r.t.	90	87 : 13
1c	**3t**	A	Ag_2O	72 h, r.t.	84	83 : 17
1c	**3t**[b]	B	Ag_2O	5 h, 80	83	14 : 86
1d	**3a**	B	Ag_2O	10 min, r.t.	82	90 : 10
1d	**3a**	A	Ag_2O	7 h, r.t.	82	71 : 29
1d	**3a**	B	Ag_2O	5 h, 50	70	27 : 73
1e[c]	**3t**	B	Ag_2O	10 min, r.t.	78	58 : 42
1f	**3u**	B	Ag_2CO_3	30 min, r.t.	74	35 : 65
1f	**3u**[b]	B	Ag_2O	10 h, 45	74	84 : 16
1g	**3u**	B	Ag_2CO_3	10 min, r.t.	81	78 : 22
1h	**3w**	A	Ag_2CO_3	48 h, r.t.	93	100 : 0

[a] β/α Ratio determined by ^1H and ^{13}C NMR on crude products.
[b] The physical and spectroscopic data of pure **3a** (β), **3t** (α), **3t** (β), and **3u** (β) correspond to data published in Ref. 47, 48 and 49, respectively.
[c] Glycosyl donor **1e** was obtained as described for **1d** in Ref. 40; oil, ^{31}P NMR: $\delta = 9.97$.

Although selenophosphates can be efficiently used for the synthesis of 1-*O*-acyl esters, they have no advantage over the sulfur analogs because they are less readily available and give products contaminated with elemental selenium. The β/α ratio and optimal reaction conditions are similar for both glycosyl donors.

Table 5 contains selected physical and NMR data for pure anomers of **3d, 3f-3h, 3j** and **3p**.

It can be concluded that the use of 2-deoxyglycosyl phosphorodithioates as glycosylating reagents provides the most effective procedure known hitherto for the synthesis of 1-*O*-acyl esters of 2-deoxysugars. The 2-deoxyglycosyl donors are readily available and stable. The method is highly β-stereoselective, in particular, with respect to aliphatic carboxylic acids.

Melting points were determined with a Boetius PHMK 05 apparatus and are uncorrected. ^1H NMR spectra were determined in $CDCl_3$ (Bruker AC 200 MHz, Bruker MSL 300 MHz and Varian 60 MHz) using TMS as internal standard. ^{13}C NMR were determined in $CDCl_3$ (Bruker 300 MHz operating at 36.43 MHz, Tesla 100 MHz operating at 25.2 MHz). Specific rotations were determined with a Polamat A 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 affected by exposure to iodine vapours. Silver oxide and silver carbonate were freshly prepared.

2-Deoxyglycosyl-1-*O*-acyl Esters (3b-w); General Procedure:

Method A: To the solution of **1a** or **1h** (1 mmol) in dry solvent (Table 3) was added carboxylic acid **2a–p** (1 mmol) in dry solvent (10–50 mL) followed by silver carbonate (0.5 mmol) in the presence of molecular sieves (MS) (3 or 4Å). The mixture was stirred (Table 3 for specific conditions) in the dark at r.t. Reaction was monitored by TLC. The precipitated silver phosphorodithioate and molecular sieves were filtered off through Celite 535. The filtrate was concentrated under reduced pressure and the residue was diluted with benzene. The organic phase was washed with aq Na_2CO_3, water, dried ($MgSO_4$) and evporated in vacuo. The syrupy or semi-crystalline mixture containing ($\alpha + \beta$) isomers was separated by crystallization to give pure β-1-*O*-acyl esters.

Method B (for **3a, 3t, 3u**):

Donors **1a–g** (2 mmol) were dissolved in glacial acetic acid **2a** (10–25 mL) and a stoichiometric amount of Ag_2CO_3 was added, followed by MS (3 or 4Å). The mixture was stirred in the dark (time, Table 4) until TLC showed no presence of the glycosyl donor. The reaction mixture was diluted with $CHCl_3$. The precipitated

Table 5. Selected Physical and NMR Data for Pure Anomers of **3d, f–h, j** and **p**[a]

Product	Yield (%)	mp[b] (°C) (solvent)	$[\alpha]_{578}^{20}$ (*c*, $CHCl_3$)	^1H NMR[c] δ, *J* (Hz)	^{13}C NMR[c] δ
3d(β)	57	81–83 (Et_2O)	+0.08 (2.5)	0.88 (t, 3H, CH_3), 1.26 (t, 26H, CH_2), 1.84–1.95 (m, 2H, H-2a, H-2e), 2.04, 2.05, 2.09 (3s, 9H, OAc), 4.09 (dd, 2H, $OCOCH_2$)	13.98 (CH_3), 20.57 ($COCH_3$), 20.68 (CH_3CH_2), 31.80 (C-2), 33.92 ($OCOCH_2CH_2$), 34.64 ($OCOCH_2$), 61.86 (C-6)
3f(α)	29	121–123 (Et_2O)	+10.56 (2.6)	2.01–2.15 (m, 1H, H-2a), 2.39 (ddd, 1H, H-2e), 7.50, 7.59, 8.06 (H_{arom})	33.53 (C-2), 61.36 (C-6), 128.13, 128.85, 129.32, 133.13 (C_{arom}), 163.66 (OCOPh)
3g(β)	37	97–99 (EtOH)	−28.90 (1.7)	1.27–1.99 (m, 1H, H-2a), 2.35 (s, 3H, $PhOCOCH_3$), 2.41–2.61 (m, 1H, H-2e), 7.11, 7.32, 7.59 (H_{arom})	15.22 ($PhOCOCH_3$), 34.78 (C-2), 61.96 (C-6), 162.14 (OCOPh)
3h(β)	46	115–117 (EtOH)	−28.30 (1.5)	2.23 (s, 3H, NHAc), 2.03–2.11 (m, 1H, H-2a), 2.45–2.53 (m, 1H, H-2e), 7.08, 7.57, 8.05, 8.69 (H_{arom}), 10.78 (s, 1H, NHAc)	20.69, 20.84 (2s, $OCOCH_3$), 25.47 ($NHCOCH_3$), 61.90 (C-6), 166.15 (OCOPh), 169.99 ($NHCOCH_3$)
3j(β)	76	115–116 (Et_2O)	+1.37 (1.4)	1.88–2.02 (m, 1H, H-2a), 2.05, 2.05, 2.08 (3s, 9H, OAc), 2.37–2.48 (m, 1H, H-2e), 6.43 (d, 1H, CH=CHPh, $J_{H,H} = 16.01$), 7.76 (d, $OCOCH$=CH, $J_{H,H} = 15.69$)	20.75, 20.90 (2s, $COCH_3$), 34.93 (C-2), 62.18 (C-6), 116.90 (CHPh), 164.61 (OCOCH), 170.73 (OCOCH)
3p(β)	37	128–129 (Et_2O)	−0.78 (2.3)	1.80–1.98 (m, 1H, H-2a), 2.28–2.32 (m, 1H, H-2e), 2.37 (s, 3H, Me), 3.72 (s, 2H, CH_2), 3.93 (s, 3H, OMe)	13.31 (CH_3), 30.07 (CH_2), 34.64 (C-2), 61.84 (C-6), 155.97 ($OCOCH_2$), 168.62 (OCPh), 169.64, 169.98, 170.58 ($OCOCH_3$)

[a] Satisfactory elemental analyses obtained: C ± 0.30, H ± 0.25, N ± 0.30.
[b] Mp uncorrected.
[c] Data for H-1 and C-1, see Table 3.

silver phosphorodithioate and molecular sieves were filtered off. The filtrate was evaporated in vacuo. The residue was dissolved in $CHCl_3$ (25 mL) the $CHCl_3$ solution washed with aq Na_2CO_3 and dried ($MgSO_4$). After evaporation, the residual mixture of anomers was purified by crystallization.

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