Trimethylsilylnitrate: a useful reagent for direct synthesis of 2-deoxy-*O*-glycosides from glycals[$]

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This paper is respectfully dedicated to Prof. P.T. Narasimhan on the occasion of his 75th birthday

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Abstract: Trimethylsilylnitrate acts as a useful reagent for the addition of alcohols to glycals forming 2-deoxy-*O*-glycosides in good to excellent yields.

Keywords: 2-Deoxy-*O*-glycosides, trimethylsilylnitrate, glycals, $ClSiMe_3$, $AgNO_3$

Introduction

2-Deoxy-*O*-glycosides are integral parts of many prominent biologically active natural products[2] such as aureolic acids,[3] cardiac glycosides[4] and antitumor agents such as calicheamycin.[5] In view of this, many synthetic methods have been developed for the stereoselective synthesis of α or β-2-deoxy-*O*-glycosides. Although, synthesis of 2-deoxy-*O*-glycosides from 2-deoxysugars bearing a leaving group at the anomeric centre is well known, control of the stereochemistry of the *O*-glycosidic bond is somewhat difficult because of the lack of a stereodirecting substituent at C-2. The leaving groups at the anomeric centre include halides,[6a,b] thioglycosides,[6c] n-pentenyl glycosides,[6d] trichloroacetimidates,[6e] sulfoxides,[6f] phosphites,[6g] and phosphoramidites.[6h] These methods, however, need prior preparation of 2-deoxysugars with a desired leaving group at the anomeric centre. Additionally, iodoglycosylation of glycals using iodonium dicollidine perchlorate (IDCP)[7a,b] or ceric ammonium nitrate (CAN)-NaI[7c,d] are other methods reported in literature but they require reductive de-iodination in the next step to obtain 2-deoxy-*O*-glycosides. Apart from this, direct addition of alcohols to glycals catalyzed by a protic acid (MeOH·HCl,[8a] cation-exchange resin AG 50 WX_2,[8b] Ph_3P- HBr[8c]) or a Lewis acid (BBr_3 or BCl_3[9a] and $CeCl_3 \cdot 7H_2O$-NaI[9b]) has also been reported for this purpose. One of the problems, however, in these direct glycosylations is the possibility of the Ferrier reaction and hence not all

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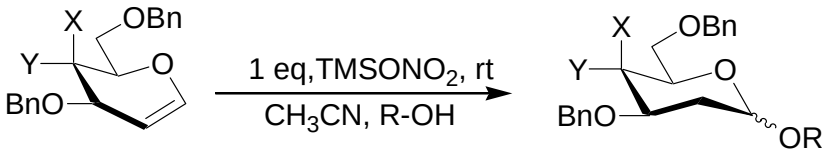
the protic or Lewis acids are suitable for this purpose. Nevertheless this one pot procedure is useful and hence more recently a polymer-bound Lewis acid[10] has also been employed for the synthesis of 2- deoxy-*O*-glycosides.

Results and Discussion

Recently we have reported a CAN catalyzed transformation of glycals to 2-deoxy-*O*-glycosides under mild conditions.[11] As part of our ongoing programme[1,12] to develop newer methods in functionalizing glycals towards obtaining useful carbohydrate intermediates, we have now found that trimethylsilylnitrate ($TMSONO_2$), readily made from $ClSiMe_3$ and $AgNO_3$, works as a useful reagent for the synthesis of 2-deoxy-*O*- glycosides. $TMSONO_2$ has been used[13] in conjunction with $BF_3{\cdot}Et_2O$ as a source of NO_2^+ for nitration of aromatics.



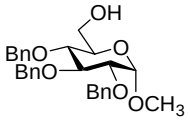
1. X = OBn, Y = H
2. X = H, Y = OBn

3a-o. X = OBn, Y = H
3p,q. X = H, Y = OBn

Scheme 1

We have reported[14] its use along with CrO_3 to convert olefins into α-nitroketones and in converting cyclic ethers into lactones. More recently, we have found[1] that $TMSONO_2$ along with Me_3SiN_3 converts glycals into the corresponding 2-deoxy-1-glycosyl azides which, in turn, can be converted into 2-deoxy-β-1-*N*-glycopeptides. In an effort to explore the potential of $TMSONO_2$, we report in this paper that $TMSONO_2$ permits addition of alcohols to glycals forming 2-deoxy-*O*-glycosides in good to excellent yields at room temperature in 2-5 h. A wide variety of alcohols were added on to glycals in the presence of 1 eq. of $TMSONO_2$. Initial experiments were performed using catalytic amount of $TMSONO_2$, however, the glycals were found to be largely unreacted. Our results are summarized in Table-1. In all the cases, α-isomer was found to be the major product and in some cases, with a galactal derivative **1** (Scheme 1), it was the exclusive product(entries 1, 2, 11). A disaccharide (entry 14) was also made using this method with galactal **1**, although the yield was moderate. When we used compound **2** (a glucal derivative) under the same reaction conditions, we observed formation of a trace amount of the Ferrier product along with 2-deoxy-*O*-glycosides (entries 16, 17).

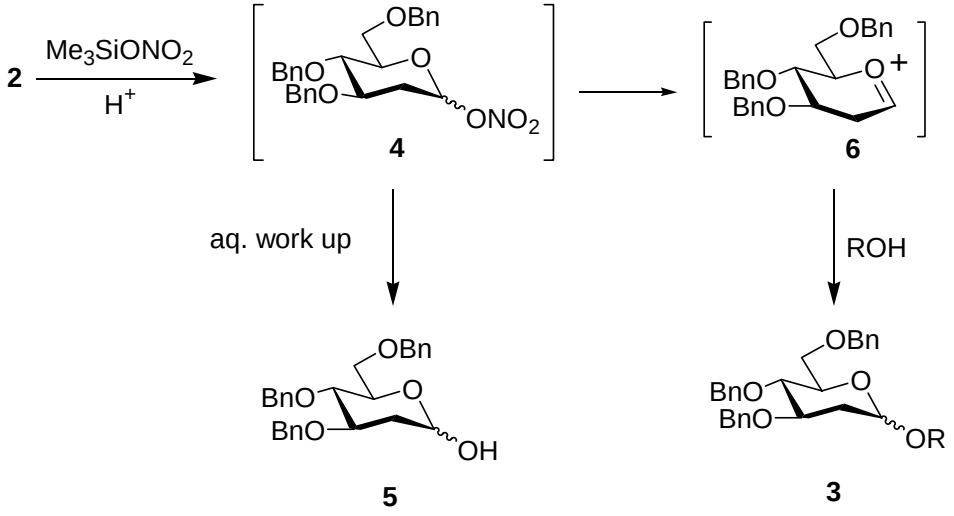
Table 1

Entry	Glycal	Acceptor	Product **3**	Yield %	Time (h)	α:β
1	**1**	Methanol	**a**[11]	85	2	α only
2	**1**	t-Butanol	**b**[11]	52	5	α only
3	**1**	Isopropyl Alcohol	**c**[11]	83	3	90:10
4	**1**	Propargyl Alcohol	**d**	95	3	91:9
5	**1**	Cinnamyl Alcohol	**e**	89	3	90:10
6	**1**	Benzyl alcohol	**f**[11]	85	3	80:20
7	**1**	Homo propargyl Alcohol	**g**	90	3	90:10
8	**1**	3-Bromo-1-pro-panol	**h**	92	3	91:9
9	**1**	Tetrahydro furfuryl alcohol	**i**	84	3	90:10
10	**1**	Cyclohexanol	**j**[11]	80	4	90:10
11	**1**	Allyl alcohol	**k**[11]	81	3	α only
12	**1**	Cholesterol	**l**[11]	68	4.5	81:19
13	**1**	1-Octanol	**m**	88	3.5	96:4
14	**1**		**n**[6h,11]	38	4	92:8
15	**1**	3-Methyl-but-3-en-1-ol	**o**	92	3	80:20
16	**2**	Methanol	**p**[6i,11]	80	2	(70:30)[a],55:45[b],90:10[c]
17	**2**	t-Butanol	**q**[6i,11]	50	4.5	(71:29)[a],74:26[b],65:35[c]

[a] Ratio of 2-deoxy-*O*-glycoside and the Ferrier product. [b] α:β ratio of 2-deoxy–*O*-glycoside. [c] α:β ratio of the Ferrier product.

With regards to the mechanism of this reaction, we suggest that 2-deoxy-*O*-glycosides are formed via the corresponding nitrate esters **4** (Scheme 2) by the nucleophilic displacement by alcohols under acidic reaction conditions.[15] Evidence to this effect was gathered from the following observations. Exposure of a solution of 3,4,6-tri-*O*-benzyl-D-glucal **2** in acetonitrile to

Me_3SiONO_2 (1:1 molar equiv) only, followed by analysis of the reaction mixture by thin-layer chromatography showed a polar spot compared to the starting material. Evaporation of solvent under vacuum gave a product which showed in its IR spectrum a strong peak at 1680 cm^{-1}, whereas its ^1H NMR spectrum showed peaks of no specific splitting patterns NMR spectrum. Mass spectral analysis using electrospray technique (+ ion) suggested the presence of 1-hydroxy sugar derivative **5**, however, the –ve ion detection indicated the presence of a peak at *m/z* 479 corresponding to the nitrate ester **4**.



Scheme 2

Further, if the reaction was worked up before the addition of alcohols then the only product that could be isolated was 2-deoxy-3,4,6-tri-*O*-benzyl-D-glucose **5**. It is, therefore, likely that the product of the reaction between a glycal and $TMSONO_2$ is a nitrate ester of type **4** which is relatively unstable and gets hydrolyzed to compound **5**. This is not unexpected, since it is known[16] that anomeric nitrates are susceptible towards hydrolysis on column chromatography. Thus, it is fair to assume that the nitrate esters **4** are formed as intermediates in these reactions and then they are subsequently converted to the corresponding 2-deoxy-*O*-glycosides **3** by treatment with glycosyl acceptors viz. the alcohols. Further, we presume that the nitrate esters **4** are first converted to the corresponding oxocarbocation **6**, under the slightly acidic experimental conditions, before reacting with the glycosyl acceptors. This is in view of the fact that the *O*-glycosides formed are predominantly α in nature, resulting from the dominant anomeric effect.

In conclusion, we have found that $TMSONO_2$ is a new reagent for the synthesis of 2-deoxy-*O*-glycosides in a high stereoselective manner from glycals, and we hope that this methodology will be useful in organic synthesis.

Experimental Section

General Procedures. To a stirred solution of a glycal (0.240 mmol) in CH_3CN (2 mL) at room temperature, were added an alcohol (0.268 mmol) and trimethylsilylnitrate[13] (0.240 mmol). The reaction mixture was stirred for the time indicated in Table-1. After completion of reaction it was extracted with ethyl acetate (2 x 10 mL) and the usual work-up gave a crude product which was purified by column chromatography to give a pure product which was characterized by spectroscopic and analytical means.

Selected data: propargyl 3,4,6-tri-*O*-benzyl-2-deoxy-*α/β*-D-*lyxo*-hexopyranoside (3d). Yield: 95%, liquid. $[\alpha]_D^{25}$ = + 59.5 (*c* 2.15, CH_2Cl_2). IR (CH_2Cl_2) ν_{max}: 3300, 2119, 1162, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.0-2.05 (dd, *J* = 13.0, 4.4 Hz, 1H, H-2), 2.22-2.29 (dt, *J* = 12.6, 3.8 Hz, 1H, H-2′), 2.36 (t, *J* = 2.4 Hz, 1H, -C≡C-*H*), 3.53-3.58 (m, 2H, H-6, H-6′), 3.87-3.93 (m, 3H, H-3, H-4, H-5), 4.16 (t, *J* = 2.4 Hz, 2H, -OC*H*$_2$-C≡C), 4.40-4.49 (q, *J* = 11.7 Hz, 2H, -OC*H*$_2$Ph), 4.59 (br. s, 2H, -OC*H*$_2$Ph), 4.63 (d, *J* = 11.7 Hz, 1H, -OC*H*$_2$Ph), 4.93 (d, *J* = 11.7 Hz, 1H, -OC*H*$_2$Ph), 5.14 (br. d, *J* = 3.1 Hz, 1H, H-1), 7.23-7.35 (m, 15H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.7, 54.0, 69.2, 70.2, 70.3, 72.7, 73.3, 74.2, 74.4, 79.3, 96.5, 127.1-138.7 (m, aromatic). MSES$^+$: 490 $[M + NH_4]^+$. Anal. Calcd for $C_{30}H_{32}O_5$ (472.25): C, 76.25; H, 6.83. Found: C, 76.31; H, 6.88. Characteristic signals for *b*-anomer: ^{13}C NMR: δ 32.4, 54.9, 69.0, 70.9, 71.4, 79.1, 97.6, 137.8, 138.1, 138.6.

Cinnamyl 3,4,6-tri-*O*-benzyl-2-deoxy-*α/β*-D-*lyxo*-hexopyranoside (3e). Yield: 89%, liquid. $[\alpha]_D^{25}$ = + 16.0 (*c* 2.5, CH_2Cl_2). IR (CH_2Cl_2) ν_{max}: 1495, 1097, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.02-2.06 (br. dd, *J* = 12.6, 3.4 Hz, 1H, H-2), 2.22-2.29 (dt, *J* = 12.4, 3.68 Hz, 1H, H-2′), 3.54-3.65 (m, 2H, H-6, H-6′), 3.93-3.98 (m, 3H, H-3, H-4, H-5), 4.09-4.14 (dd, *J* = 12.8, 6.7 Hz, 1H, -OC*H*-CH=CH-Ph), 4.26-4.30 (dd, *J* = 12.8, 5.7 Hz, 1H, -OC*H′*-CH=CH-Ph), 4.40-4.52 (q, *J* = 11.7 Hz, 2H, -OC*H*$_2$Ph), 4.60 (br. s, 2H, -OC*H*$_2$Ph), 4.62 (d, *J* = 11.5 Hz, 1H, -OC*H*$_2$Ph), 4.93 (d, *J* = 11.5 Hz, 1H, -OC*H*$_2$Ph), 5.10 (br. d, *J* = 3.1 Hz, 1H, H-1), 6.24-6.31 (m, 1H, -OCH$_2$-C*H*=CHPh), 6.57 (br. d, *J* = 15.8 Hz, 1H, -OCH$_2$-CH=C*H*Ph), 7.21-7.37 (m, 20H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.1, 67.6, 69.6, 69.9, 70.4, 72.9, 73.4, 74.2, 74.7, 97.1, 125.5, 126.4-128.5 (m, aromatic), 132.6, 136.6, 138.0, 138.4, 138.8. MSES$^+$: 568.2 $[M + NH_4]^+$. Anal. Calcd for $C_{36}H_{38}O_5$ (550.68): C, 78.52; H, 6.96. Found: C, 78.58; H, 6.93. Characteristic signals for *b*-anomer: ^1H NMR: δ 4.58-4.60 (dd, *J* = 10.0, 3.8 Hz, 1H, H-1). ^{13}C NMR: δ 32.7, 99.0.

Homo propargyl 3,4,6-tri-*O*-benzyl-2-deoxy-*α/β*-D-*lyxo*-hexopyranoside (3g). Yield: 90%, liquid. $[\alpha]_D^{25}$ = + 40.0 (*c* 1.3, CH_2Cl_2). IR (CH_2Cl_2) ν_{max}: 3293, 2118, 1162, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.94 (t, *J* = 2.6 Hz, 1H, -C≡C-*H*), 1.99-2.03 (m, 1H, H-2), 2.19-2.26 (dt, *J* = 12.6, 3.6 Hz, 1H, H-2′), 2.42-2.47 (dt, *J* = 7.0, 2.6 Hz, 2H, -OCH$_2$-C*H*$_2$-), 3.53-3.63 (m, 3H, H-6, H-6′ and –OC*H*-CH$_2$-), 3.69-3.75 (m, 1H, -OC*H′*-CH$_2$-), 3.89-3.96 (m, 3H, H-3, H-4, and H-5), 4.40-4.51 (q, *J* = 11.9 Hz, 2H, -OC*H*$_2$Ph), 4.59 (br. s, 2H, -OC*H*$_2$Ph), 4.62 (d, *J* = 11.7 Hz, 1H, -OC*H*$_2$Ph), 4.93 (d, *J* = 11.7 Hz, 1H, -OC*H*$_2$Ph), 5.01 (br. d, *J* = 2.9 Hz, 1H, H-1), 7.22-7.34

(m, 15H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7, 31.0, 65.4, 69.2, 69.4, 69.9, 70.4, 72.8, 73.4, 74.2, 74.7, 81.3, 97.9, 127.2-128.3 (m, aromatic), 138.1, 138.4, 138.8. MSES$^+$: 504 [M + NH_4]$^+$. Anal. Calcd for $C_{31}H_{34}O_5$ (486.59): C, 76.52; H, 7.04. Found: C, 76.55; H, 7.10. Characteristic signals for *b*-anomer: ^{1}H NMR: δ 2.06-2.10 (m, 2H, H-2, H-2′), 4.56-4.59 (dd, *J* = 10.0, 2.2 Hz, 1H, H-1), 4.91 (d, *J* = 11.7 Hz, 1H, -OC*H*$_2$Ph). ^{13}C NMR: δ 20.0, 32.6, 66.9, 70.1, 71.5, 73.4, 74.0, 100.3, 138.0, 138.3, 138.7.

3-Bromo-*n*-propyl 3,4,6-tri-*O*-benzyl-2-deoxy-*α/β*-D-*lyxo*-hexopyranoside (3h). Yield: 92%, liquid. $[\alpha]_D^{25}$ = + 24.4 (*c* 2.05, CH_2Cl_2). IR (CH_2Cl_2) ν_{max}: 1162, 1096 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95-1.99 (dd, *J* = 12.9, 4.1 Hz, 1H, H-2), 2.03-2.14 (m, 2H, H$_a$-2), 2.25-2.26 (dt, *J* = 12.7, 3.9 Hz, 1H, H-2′), 3.43-3.62 (m, 6H, H-5, H-6, H-6′, H$_a$-3 and H$_a$-1), 3.73-3.78 (m, 1H, H$_a$-1′), 3.87-3.92 (m, 2H, H-3, H-4), 4.41-4.94 (m, 6H, 3 x -OC*H*$_2$Ph), 4.96 (br. d, *J* = 3.1 Hz, 1H, H-1), 7.23-7.36 (m, 15H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.4, 31.1, 32.5, 64.7, 69.4, 69.9, 70.3, 72.8, 73.4, 74.2, 74.6, 97.9, 126.9-128.4 (m, aromatic), 138.0, 138.4, 138.8. MSES$^+$: 574 [M + NH_4]$^+$. Anal. Calcd for $C_{30}H_{35}BrO_5$ (555.40): C, 64.86; H, 6.35. Found: C, 64.90; H, 6.41. Characteristic signals for *b*-anomer: ^{13}C NMR: δ 30.6, 32.6, 32.7, 66.6, 69.2, 69.6, 70.3, 71.0, 71.5, 73.5, 74.1.

Tetrahydrofurfuryl 3,4,6-tri-*O*-benzyl-2-deoxy-*α/β*-D-*lyxo*-hexopyranoside (3i). Yield: 84%, liquid. $[\alpha]_D^{25}$ = + 31.3 (*c* 1.15, CH_2Cl_2). IR (CH_2Cl_2) ν_{max}: 1202, 1104 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50-1.57 (m, 4H, H$_a$-3, H$_a$-4), 1.96-2.0 (br. dd, *J* = 12.4, 4.6 Hz, 1H, H-2), 2.18-2.25 (dt, *J* = 13.0, 3.8 Hz, 1H, H-2′), 3.32-3.66 (m, 6H, H$_a$-1, H$_a$-5, H-6 and H-6′), 3.81-3.95 (m, 4H, H-3, H-4, H-5 and H$_a$-2), 4.42 and 4.50 (2d, *J* = 11.9 Hz, 2H, -OC*H*$_2$Ph), 4.59 (br. s, 2H, -OC*H*$_2$Ph), 4.61 (d, *J* = 11.5 Hz, 1H, -OC*H*$_2$Ph), 4.93 (d, *J* = 11.5 Hz, 1H, -OC*H*$_2$Ph), 4.95 (br. d, *J* = 3.0 Hz, 1H, H-1), 7.23-7.34 (m, 15H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.3, 29.4, 31.8, 67.4, 69.3, 69.5, 69.7, 70.4, 72.9, 73.4, 74.0, 74.2, 74.9, 97.6, 127.2-138.8 (m, aromatic). MSES$^+$: 536 [M + NH_4]$^+$. Anal. Calcd for $C_{32}H_{38}O_6$ (518.64): C, 74.11; H, 7.39. Found: C, 74.17; H, 7.45. Characteristic signals for *b*-anomer: ^{1}H NMR: δ 2.03-2.10 (m, 2H, H-2, H-2′), 4.57-4.59 (dd, *J* = 9.7, 2.0 Hz, 1H, H-1), 4.91 (d, *J* = 11.5 Hz, 1H, -OC*H*$_2$Ph). ^{13}C NMR: δ 26.0, 29.5, 31.2, 100.4, 138.2, 138.8.

3-Methyl-3-butenyl 3,4,6-tri-*O*-benzyl-2-deoxy-*α/β*-D-*lyxo*-hexopyranoside (3o). Yield: 92%, liquid. $[\alpha]_D^{25}$ = + 36.5 (*c* 1.4, CH_2Cl_2). IR (CH_2Cl_2) ν_{max}: 1603, 1163, 1095 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.71 (s, 3H, -C(C*H*$_3$)=CH$_2$), 1.95-2.0 (dd, *J* = 12.8, 4.4 Hz, 1H, H-2), 2.18-2.32 (m, H-2′ and -OCH$_2$-C*H*$_2$-), 3.45-3.64 (m, 4H, H-5, H-6, H-6′ and –OC*H*-CH$_2$-), 3.69-3.75 (m, 1H, -OC*H*′-CH$_2$-), 3.88-3.94 (m, 2H, H-3, H-4), 4.40-4.52 (q, *J* = 11.7 Hz, 2H, -OC*H*$_2$Ph), 4.60 (br. s, 2H, -OC*H*$_2$Ph), 4.62 (d, *J* = 11.7 Hz, 1H, -OC*H*$_2$Ph), 4.93 (d, *J* = 11.7 Hz, 1H, -OC*H*$_2$Ph), 4.72 (d, *J* = 11.0 Hz, 2H, -C=C*H*$_2$), 4.97 (br. d, *J* = 2.9 Hz, 1H, H-1), 7.23-7.34 (m, 15H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.8, 31.2, 37.6, 65.8, 69.5, 69.8, 70.3, 72.9, 73.4, 74.2, 74.7, 97.6, 111.48, 127.2-138.8 (m, aromatic), 142.8. Characteristic signals for *b*-anomer: δ 22.7, 32.7, 37.5, 67.5, 69.2, 70.1, 71.6, 73.5, 74.0, 74.1, 100.3, 111.42, 142.6. MSES$^+$: 520 [M + NH_4]$^+$. Anal. Calcd for $C_{32}H_{38}O_5$ (502.64): C, 76.46; H, 7.62. Found: C, 76.49; H, 7.66.

Octyl 3,4,6-tri-*O*-benzyl-2-deoxy-*α/β*-D-*lyxo*-hexopyranoside (3m). Yield: 88%, liquid. $[\alpha]_D^{25}$ = + 27.5 (*c* 1.7, CH_2Cl_2). IR (CH_2Cl_2) ν_{max}: 1163, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.83-1.2 (m, 13H, *octyl*), 1.5-1.54 (m, 2H, -OCH_2CH_2-), 1.96-2.00 (dd, *J* = 12.4, 3.6 Hz, 1H, H-2), 2.18-2.25 (dt, *J* = 13.0, 3.6 Hz, 1H, H-2′), 3.32-3.38 (m, 1H, -OC*H*-CH_2-), 3.54-3.66 (m, 3H, H-6, H-6′ and –OC*H*-CH_2-), 3.89-395 (m, 3H, H-3, H-4, H-5), 4.40-4.52 (q, *J* = 11.9 Hz, 2H, -OCH_2Ph), 4.60 (br. s, 2H, -OCH_2Ph), 4.62 (d, *J* = 11.5 Hz, 1H, -OCH_2Ph), 4.93 (d, *J* = 11.5 Hz, 1H, -OCH_2Ph), 4.96 (br. d, *J* = 3.1 Hz, 1H, H-1), 7.23-7.34 (m, 15H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 26.2, 29.2, 29.3, 29.5, 29.6, 31.2, 31.8, 60.4, 69.5, 69.7, 70.4, 73.0, 73.4, 74.2, 74.9, 97.6, 127-128 (m, aromatic), 138.3, 138.5, 138.9. $MSES^+$: 546 $[M + NH_4]^+$. Anal. Calcd. for $C_{36}H_{50}O_5$ (562.78): C, 76.83; H, 8.96. Found: C, 76.88; H, 8.99.

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