Mild Synthesis of Protected α-D-Glycosyl Iodides

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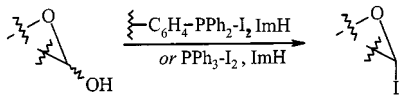
α-D-Glycosyl iodides are stereoselectively obtained by iodine replacement of the free anomeric hydroxyl group of fully protected sugars treated with a polymer bound triarylphosphane-iodine complex and imidazole. High yields and mild conditions, compatible with all the common protecting groups used in carbohydrate chemistry, characterize the conversion.

Glycosyl iodides were first prepared by the reaction of glycosyl bromides with sodium iodide in acetone.[1] Decades later, glycosyl acetates, methyl glycosides, 1,6-anhydrosugars and glycosyl acetals were reported[2] to lead to α-glycosyl iodides by reaction with iodotrimethylsilane. Other procedures include the reaction of anomeric hydroxyls with iodoenamines[3] as well as reaction of anomeric acetates with hydroiodic acid in glacial acetic acid.[4] In situ generation of glycosyl iodides, from activated donors, and their subsequent glycosylation has also been reported.[5] In these reactions, both α- and β-D-glycosyl iodides have been proposed as intermediates, depending upon the stereochemical outcome. α-D-Glycosyl iodides have served as glycosyl donors in only a few cases,[6][7] and the general consensus has been that these compounds are too reactive to be synthetically useful.[8] Until a rather recent report,[9] β-D-glycosyl iodide formation had never been directly observed.

Under these circumstances, it seems to be of interest to report a new and efficient synthesis of α-D-glycosyl iodides which are obtained under smooth conditions and in quite satisfactory yields using a polymer-bound reagent that makes any critical and time consuming workup and purification procedures unnecessary.

The reagent is a complex of polystyryl diphenylphosphane and iodine prepared in situ in anhydrous dichloromethane at room temperature. This species acts as a good electrophile toward oxygen nucleophiles and has been extensively used in our lab for various synthetic transformations.[10] Its efficacy, however, is enhanced by the presence of imidazole which, in principle, should act as a proton trap for the hydrogen ions released during the reaction, although it has also been reported[11] to play an active role in other reactions involving triphenylphosphane-iodine reagent. In our procedure two imidazole equivalents per phosphane were necessary, probably due to the fact that, in the aprotic dipolar dichloromethane solvent, the protonated imidazole is still an appreciably strong acid and, therefore, a hydrogen-bonded dimer of imidazole could be the actual neutralising species.



Scheme 1. Formation of protected α-D-glycosyl iodides

In fact, the addition of a protected sugar to a mixture of polymer bound triarylphosphane-iodine complex and imidazole, at room temperature, results in the quick formation of the corresponding iodide. In all the experiments only α-D-glycosyl iodides were obtained without any traces of their β-anomers (see Table 1). This happens even if assisting groups like OAc or OBz are present at the C-2 position of the starting sugar and, therefore, the process should be thermodynamically controlled, eventually leading to the more stable α-glycosyl iodide anomer.

The α-D-glycosyl iodides thus obtained can often be used as isolated after filtration through Celite® of the precipitated excess imidazole and the solid polymer-bound phosphane oxide which is the only side-product of the reaction. Their stability is greatly dependent on the sugar protecting groups and, as a matter of fact, *O*-benzyl protected α-D-glycosyl iodides are rather unstable at room temperature and have to be used immediately after the preparation. Otherwise, their *O*-acetyl and *O*-benzoyl analogues are quite stable and can be stored for one to two weeks under a nitrogen atmosphere in the refrigerator without appreciable decomposition.

Replacing the polymer-bound triarylphosphane by soluble triphenylphosphane resulted in somewhat lower yields (e.g. in the case of the compounds **1b**, **2b** and **4b**, as shown in Table 1). In addition, the crude reaction products need to be chromatographed on silica gel in order to remove the oxide that accompanies the α-D-glycosyl iodides.

Due to the mild reaction conditions, a broad range of protecting groups such as ethers (products **1b**, **2b**, **4b**), esters

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Table 1. α-D-Glycosyl iodides from protected sugars and polystyryl diphenylphosphane-iodine complex

Sugar	Protection	**Product**	m.p. °C[a]	$[\alpha]_D$	Yield (%)
D-Glucopyranose	2,3,4,6-tetra-*O*-acetyl	**1a**	106−107	231.1	97
″	″	″	″	″	80[c]
″	2,3,4,6-tetra-*O*-benzyl	**1b**	amorphous	100.4	95
″	″	″	″	″	65[c]
″	2,3,4,6-tetra-*O*-benzoyl	**1c**	132−134	169.2	96[c]
D-Galactopyranose	2,3,4,6-tetra-*O*-acetyl	**2a**	oily	236.9	95
″	″	″	″	″	80[c]
″	2,3,4,6-tetra-*O*-benzyl	**2b**	amorphous	[b]	92
″	″	″	″	″	67[c]
″	2,3,4,6-tetra-*O*-benzoyl	**2c**	″	138.5	97[c]
2-Deoxy-2-azido-D-galactopyranose	3,4,6-tri-*O*-acetyl	**3**	″	173.5	90[c]
D-Mannopyranose	2,3,4,6-tetra-*O*-acetyl	**4a**	oily	190.3	95
″	″	″	″	″	82[c]
″	2,3,4,6-tetra-*O*-benzyl	**4b**	amorphous	[b]	94
″	″	″	″	″	66[c]
″	2,3,4,6-tetra-*O*-benzoyl	**4c**	amorphous	45.3	96[c]
D-Mannofuranose	2,3:5,6-di-*O*-isopropylidene	**5**	45−47	141.7	98

[a] Solvent, hexane/ethyl acetate 1:1. − [b] Not determined due to the product instability. − [c] Reaction carried out with triphenylphosphane.

(products **1a**,**c**, **2a**,**c**, **3**, **4a**,**c**), acetals (product **5**) and the azido group (product **3**) are preserved under the treatment with the triarylphosphane-iodine complex. It is noteworthy that even rather unstable α-D-glycosyl iodides, like **2b**, can be obtained in good yield by this procedure.

Experimental Section

General*:* ^{1}H and ^{13}C NMR spectra: Bruker AM-250 and DRX-400 spectrometers, $CDCl_3$ as solvent, chemical shifts in ppm (δ), TMS as internal standard. − Optical rotations: Perkin-Elmer 141 polarimeter (1.0 dm cell length), $CHCl_3$ as solvent. − Combustion analyses: Perkin-Elmer Series II 2400, CHNS analyzer. − TLC analyses: silica gel Merck 60 F_{254} plates (0.2 mm layer tickness). − Column chromatography: Merck Kieselgel 60 (70−230 mesh). − Dry dichloromethane was distilled from P_2O_5 immediately before use.

Formation of α-D-Glycosyl Iodides by Polystyryl Diphenylphosphane-I_2 Complex: 2,3,4,6-tetra-*O*-Benzyl-α-D-galactopyranosyl Iodide (2b). − General Procedure A: To a magnetically stirred suspension of dry polystyryl diphenylphosphane (0.65 g, ca. 1.9 mmol) in anhydrous dichloromethane (6 mL) at room temp., a solution of I_2 (0.50 g, 1.9 mmol) in the same solvent (6 mL) was added dropwise in the dark and under dry argon (or nitrogen) atmosphere. After 30 min solid imidazole (0.24 g, 3.5 mmol) was also added in one portion and stirring continued for a few more minutes. Then, a solution of 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranose (0.54 g, 1.0 mmol) in the same solvent (6 mL) was slowly added to the suspension. After 2.5 h the starting protected sugar was completely consumed (TLC monitoring). The reaction mixture was then diluted with anhydrous Et_2O (5 mL) to precipitate the excess imidazole and filtered through Celite® (5 g, layer thickness ca. 3 cm). The resulting clear solution was finally evaporated under reduced pressure to give a residue consisting of the nearly pure, rather unstable, iodide 2b (0.60 g, 92%), amorphous. − $C_{34}H_{35}IO_5$ (650.6). − ^{1}H NMR (400 MHz): δ = 3.18 (dd, *J* = 3.9 Hz, 9.6 Hz, 1 H, 2-H), 3.53−3.56 (m, 2 H, 5-H, 6a-H), 3.60 (dd, *J* = 7.6 Hz, 9.4 Hz, 1 H, 6b-H), 3.82 (dd, *J* = 2.6 Hz, 9.7 Hz, 1 H, 3-H), 3.92−3.99 (m, 1 H, 4-H), 4.41 {d, *J* = 11.7 Hz, 1 H, benzyl(i)a-H}, 4.48 {d, *J* = 11.7 Hz, 1 H, benzyl(i)b-H}, 4.55 {d, *J* = 11.1 Hz, 1 H, benzyl(ii)a-H}, 4.68 {d, *J* = 11.7 Hz, 1 H, benzyl(iii)a-H}, 4.72 {d, *J* = 11.7 Hz, 1 H, benzyl(iv)a-H}, 4.74 {d, *J* = 11.7 Hz, 1 H, benzyl(iii)b-H}, 4.84 {d, *J* = 11.7 Hz, 1 H, benzyl(iv)b-H}, 4.93 {d, *J* = 11.1 Hz, 1 H, benzyl(ii)b-H}, 6.93 (d, *J* = 3.8 Hz, 1 H, 1-H), 7.22−7.39 (m, 20 H, aromatic H).

Under the same conditions, the following α-D-glycosyl iodides were also prepared:

2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl iodide (2a): (95%), oily. − $[\alpha]_D^{25}$ = +236.9 (*c* = 1.2) {ref.[12] $[\alpha]_D^{25}$ = +235 (*c* = 1.7), $CHCl_3$}. − $C_{14}H_{19}IO_9$ (458.2): calcd. C 54.29, H 4.50; found C 54.71, H 4.38. − ^{1}H NMR (400 MHz): δ = 1.98, 2.03, 2.08, 2.12 (4 s, 4 × 3 H, 4 × CH_3), 4.08 (dd, *J* = 6.3 Hz, 10.6 Hz, 1 H, 6b-H), 4.15−4.21 (m, 2 H, 5-H, 6a-H), 4.32 (dd, *J* = 4.1 Hz, 10.5 Hz, 1 H, 2-H), 5.25 (dd, *J* = 3.3 Hz, 10.5 Hz, 1 H, 3-H), 5.45 (d, *J* = 2.4 Hz, 1 H, 4-H), 7.05 (d, *J* = 4.1 Hz, 1 H, 1-H). − ^{13}C NMR: δ = 20.75, 20.45, 20.40 (*C*H_3), 60.51 (*C*-6), 66.51, 67.42, 69.61 73.60 (*C*-2, *C*-3, *C*-4, *C*-5), 75.24 (*C*-1), 169.50, 169.69, 169.71, 170.18 (*C*=O).

2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl iodide (1b): (95%), amorphous. − $C_{34}H_{35}IO_5$ (650.6): calcd. C 62.77, H 5.42; found C 63.15, H 5.33. − $[\alpha]_D^{25}$ = +100.4 (*c* = 1.2). − ^{1}H NMR (400 MHz): δ = 2.80 (dd, *J* = 3.9 Hz, 9.0 Hz, 1 H, 2-H), 3.61 (d, *J* = 9.7 Hz, 1 H, 6a-H), 3.76−3.80 (m, 3 H, 4-H, 5-H, 6b-H), 3.88 (t, *J* = 8.9 Hz, 1 H, 3-H), 4.43 {d, *J* = 11.9 Hz, 1 H, benzyl(i)a-H}, 4.47 {d, *J* = 10.7 Hz, 1 H, benzyl(ii)a-H}, 4.54 {d, *J* = 11.9 Hz, 1 H, benzyl(i)b-H}, 4.61 {d, *J* = 11.7 Hz, 1 H, benzyl(iii)a-H}, 4.68 {d, *J* = 11.7 Hz, 1 H, benzyl(iii)b-H}, 4.78 {d, *J* = 10.9 Hz, 1 H, benzyl(iv)a-H}, 4.82 {d, *J* = 10.9 Hz, 1 H, benzyl(iv)b-H}, 4.94 {d, *J* = 10.7 Hz, 1 H, benzyl(ii)b-H}, 6.82 (d, *J* = 3.9 Hz, 1 H, 1-H), 7.22−7.40 (m, 20 H, aromatic H). − ^{13}C NMR: δ = 67.51 (*C*-6), 72.45, 73.42, 75.15, 75.63 (benzyl *C*H_2), 75.55 (*C*-1), 77.85, 79.04, 80.73, 83.69 (*C*-2, *C*-3, *C*-4, *C*-5).

2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranosyl iodide (5): (98%), m.p. 45−47°C (dec.) (from hexane/AcOEt). − $[\alpha]_D^{25}$ = +141.7 (*c* = 1.4). − $C_{10}H_{19}IO_5$ (346.2): calcd. C 34.70, H 5.53; found C 34.53, H 5.62. − ^{1}H NMR (400 MHz): δ = 1.29, 1.36, 1.43, 1.46 (4 s, 4 × 3 H, 4 × CH_3), 3.91−3.96 (m, 2 H, 4-H, 6a-H), 4.06 (dd, *J* = 6.2 Hz, 8.9 Hz, 1 H, 6b-H), 4.47−4.52 (m, 1 H, 5-H), 4.83 (dd,

J = 3.7 Hz, 5.8 Hz, 1 H, 3-H), 5.33 (d, J = 5.8 Hz, 1 H, 2-H), 6.65 (d, J = 0.7 Hz, 1 H, 1-H). − ^{13}C NMR: δ = 24.25, 24.95, 25.64, 26.57 (CH_3), 66.29 (C-6), 73.14 (C-2), 79.45, 79.79 (C-3, C-5), 85.34 (C-4), 100.91 (C-1), 108.96, 112.41 (Me_2C).

2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl iodide (1a): (97%), m.p. 106−107°C (dec.) (from hexane/AcOEt) [ref.[12] m.p. 108°C]. − $[\alpha]_D^{25}$ = +231.1 (c = 1.1) {ref.[2] $[\alpha]_D^{25}$ = +233 (c = 1), $CHCl_3$}. − $C_{14}H_{19}IO_9$ (458.2): calcd. C 54.29, H 4.50; found C 54.81, H 4.43. − ^{1}H NMR (400 MHz): δ = 2.02, 2.04 (2s, 2 × 3 H, 2 × CH_3), 2.09 (s, 6 H, 2 × CH_3), 3.98−4.29 (m, 3 H, 2-H, 5-H, 6a-H), 4.33 (dd, J = 12.8 Hz, 3.5 Hz, 1 H, 6b-H), 5.17 (t, J = 9.9 Hz, 1 H, 4-H), 5.46 (t, J = 9.8 Hz, 1 H, 3-H), 6.98 (d, J = 3.8 Hz, 1 H, 1-H). − ^{13}C NMR: δ = 20.51, 20.72 (CH_3), 60.70 (C-2), 66.73 (C-6), 70.12, 71.56, 72.88 (C-3, C-4, C-5), 74.75 (C-1), 169.33, 169.44, 169.69, 170.33 (C=O).

2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl iodide (4a): (95%), oily. − $[\alpha]_D^{25}$ = +190.3 (c = 1.2) {ref.[12] $[\alpha]_D^{25}$ = +190 (c = 1), $CHCl_3$}. − $C_{14}H_{19}IO_9$ (458.2): calcd. C 54.26, H 4.50; found C 53.83, H 4.47. − ^{1}H NMR (400 MHz): δ = 2.01, 2.08, 2.10, 2.17 (4s, 4 × 3 H, 4 × CH_3), 3.96 (ddd, J = 9.9 Hz, 4.7 Hz, 2.0 Hz, 1 H, 5-H), 4.14 (dd, J = 2.0 Hz, 12.7 Hz, 1 H, 6a-H), 4.35 (dd, J = 4.9 Hz, 12.6 Hz, 1 H, 6b-H), 5.38 (t, J = 9.9 Hz, 1 H, 4-H), 5.48 (dd, J = 3.5 Hz, 1.4 Hz, 1 H, 2-H), 5.80 (dd, J = 3.5 Hz, 10.0 Hz, 1 H, 3-H), 6.71 (d, J = 1.4 Hz, 1 H, 1-H). − ^{13}C NMR: δ = 21.34, 21.44, 21.53 (CH_3), 62.03 (C-6), 66.10, 66.90, 69.30 (C-2, C-3, C-4), 74.03 (C-5), 76.04 (C-1), 170.23, 170.41, 171.20 (C=O).

2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl iodide (4b): (94%), amorphous. − $C_{34}H_{35}IO_5$ (650.6). − ^{1}H NMR (250 MHz): δ = 3.55−3.70 (m, 2 H, 5-H, 6a-H), 3.85 (dd, J = 4.1 Hz, 11.2 Hz, 1 H, 6b-H), 3.99 (dd, J = 1.4 Hz, 3.0 Hz, 1 H, 2-H), 4.10 (t, J = 9.7 Hz, 1 H, 4-H), 4.40 (dd, J = 3.1 Hz, 9.6 Hz, 1 H, 3-H), 4.44 {d, J = 11.0 Hz, 1 H, benzyl(i)a-H}, 4.52−4.70 (m, 6 H, benzyl CH_2), 4.90 {d, J = 11.0 Hz, 1 H, benzyl(i)b-H}, 6.91 (d, J = 1.4 Hz, 1 H, 1-H), 7.21−7.43 (m, 20 H, aromatic H). − ^{13}C NMR: δ = 67.73 (C-6), 72.21, 72.53, 73.12, 73.73 (benzyl CH_2), 74.74 (C-4), 75.11 (C-1), 78.32, 78.61, 79.85 (C-2, C-3, C-5).

Formation of α-D-Glycosyl Iodides by Triphenylphosphane-I_2 Complex: 2,3,4,6-tetra-*O*-Benzoyl-α-D-glucopyranosyl Iodide (1c). − General Procedure B: A magnetically stirred solution of I_2 (0.50 g, 1.9 mmol) in dry dichloromethane (6 mL) at room temp. was titrated with a solution of triphenylphosphane (0.50 g, 1.9 mmol) in the same solvent (6 mL) in the dark and under dry argon (or nitrogen) atmosphere. After 30 min solid imidazole (0.24 g, 3.5 mmol) was added, in one portion, to the pale yellow solution of triphenylphosphane−I_2 complex. After a few more minutes 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranose (0.60 g, 1.0 mmol), dissolved in the same solvent (6 mL), was also added. Within 3.5 h the starting protected sugar was completely consumed (TLC monitoring) and the reaction mixture was evaporated under reduced pressure. A quick chromatography of the residue on silica gel (light petroleum ether/AcOEt, 7:3) yielded the pure iodide **1c** (0.68 g, 96%), m.p. 132−134°C (dec.) (from hexane/AcOEt). − $[\alpha]_D^{25}$ = +169.2 (c = 1.1). − $C_{34}H_{27}IO_9$ (706.5): calcd. C 60.19, H 4.61; found C 60.75, H 4.58. − ^{1}H NMR (400 MHz): δ = 4.49−4.55 (m, 2 H, 5-H, 6a-H), 4.66 (d, J = 10.1 Hz, 1 H, 6b-H), 4.74 (dd, J = 4.3 Hz, 9.8 Hz, 1 H, 2-H), 5.87 (t, J = 9.8 Hz, 1 H, 4-H), 6.19 (t, J = 9.8 Hz, 1 H, 3-H), 7.24 (d, J = 4.3 Hz, 1 H, 1-H), 7.26−7.58 (m, 12 H, aromatic H), 7.86, 7.95, 8.00, 8.06 (4 d, J = 8.5 Hz, 4 × 1 H, *ortho*-H). − ^{13}C NMR: δ = 61.85 (C-6), 67.75, 71.01, 72.31, 73.02, (C-2, C-3, C-4, C-5), 75.45 (C-1), 164.85, 165.07, 165.49, 165.93 (C=O).

Under the same conditions, the following α-D-glycosyl iodides were also obtained and found to be identical with the samples prepared according to procedure A:

2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl iodide (1a): (80%)

2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl iodide (1b): (65%)

2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl iodide (2a): (80%)

2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl iodide (2b): (67%)

2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl iodide (4a): (82%)

2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl iodide (4b): (66%)

Also under the same conditions:

2-Deoxy-2-azido-3,4,6-tri-*O*-acetyl-α-D-galactopyranosyl iodide (3): (90%), amorphous. − $[\alpha]_D^{25}$ = +173.5 (c = 1.2). − $C_{12}H_{16}IN_3O_7$ (441.2): calcd. C 32.67, H 3.66; found C 32.80, H 3.71. − ^{1}H NMR (400 MHz): δ = 2.04, 2.06, 2.11 (3 s, 3 × 3 H, 3 × CH_3), 3.38 (dd, J = 10.6 Hz, 4.1 Hz, 1 H, 2-H), 4.08 (dd, J = 6.4 Hz, 10.8 Hz, 1 H, 6a-H), 4.13−4.29 (m, 2 H, 5-H, 6b-H), 5.16 (dd, J = 10.6 Hz, 3.3 Hz, 1 H, 3-H), 5.43−5.46 (m, 1 H, 4-H), 6.79 (d, J = 4.1 Hz, 1 H, 1-H). − ^{13}C NMR: δ = 20.52, 20.43 (CH_3), 58.48 (C-2), 60.50 (C-6), 66.10, 71.90, 73.90 (C-3, C-4, C-5), 74.70 (C-1), 169.38, 169.64, 170.21 (C=O).

2,3,4,6-Tetra-*O*-benzoyl-α-D-mannopyranosyl iodide (4c): (96%), amorphous. − $[\alpha]_D^{25}$ = +45.3 (c = 1.2) {ref.[4] $[\alpha]_D^{25}$ = +45 (c = 1, $CHCl_3$)}. − $C_{34}H_{27}IO_9$ (706.5): calcd. C 60.19, H 4.61; found C 60.54, H 4.69. − ^{1}H NMR (400 MHz): δ = 4.40 (dt, J = 9.9 Hz, 2.8 Hz, 1 H, 5-H), 4.55 (dd, J = 3.9 Hz, 12.5 Hz, 1 H, 6a-H), 4.76 (dd, J = 2.4 Hz, 12.5 Hz, 1 H, 6b-H), 5.92 (dd, J = 1.5 Hz, 3.1 Hz, 1 H, 2-H), 6.28 (t, J = 9.9 Hz, 1 H, 4-H), 6.40 (dd, J = 3.2 Hz, 10.2 Hz, 1 H, 3-H), 6.96 (d, J = 1.5 Hz, 1 H, 1-H), 7.18−8.15 (m, 20 H, aromatic H). − ^{13}C NMR: δ = 61.45 (C-6), 65.86, 66.30, 69.65 (C-2, C-3, C-4), 73.98 (C-5), 75.39 (C-1), 164.65, 165.07, 165.12, 165.62 (C=O).

2,3,4,6-Tetra-*O*-benzoyl-α-D-galactopyranosyl iodide (2c): (97%), amorphous. − $[\alpha]_D^{25}$ = +138.5 (c = 1.2). − $C_{34}H_{27}IO_9$ (706.5): calcd. C 60.19, H 4.61; found C 60.32, H 4.59. − ^{1}H NMR (400 MHz): δ = 4.32−4.36 (m, 1 H, 5-H), 4.49 (dd, J = 5.5 Hz, 11.4 Hz, 1 H, 6a-H), 4.69 (dd, J = 5.3 Hz, 11.4 Hz, 1 H, 6b-H), 5.02 (dd, J = 4.3 Hz, 10.5 Hz, 1 H, 2-H), 5.95 (dd, J = 3.2 Hz, 10.6 Hz, 1 H, 3-H), 6.10 (d, J = 3.2 Hz, 1 H, 4-H), 7.19−7.68 (m, 21 H, 1-H, aromatic H). − ^{13}C NMR: δ = 61.51 (C-6), 67.70 (C-5), 68.31 (C-4), 70.78 (C-3), 74.17 (C-2), 74.95 (C-1), 163.58, 164.80, 165.65, 166.11 (C=O).

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