Phthalimidomethylation of *O*-Nucleophiles with *O*-Phthalimidomethyl Trichloroacetimidate: A Powerful Imidomethylating Agent for *O*-Protection

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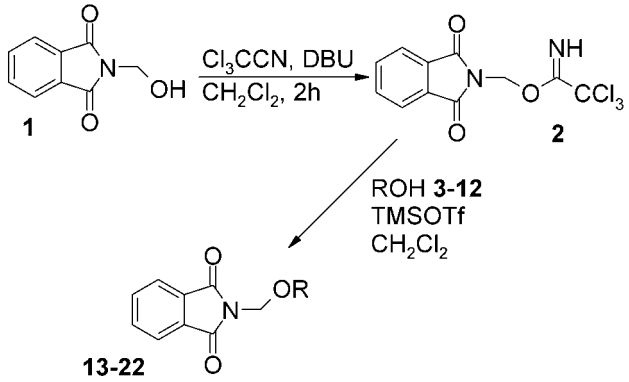
Received 22 January 2003

Abstract: Phthalimidomethylation of oxygen nucleophiles by using *O*-phthalimidomethyl (Pim) trichloroacetimidate in the presence of TMSOTf has been achieved in high yields. Hydrazinolysis of the phthalimido group from the *O*-derivatives leads to the hydroxy precursors. Thus a convenient method for the protection of oxygen nucleophiles is provided, which complements the repertoire of available hydroxy protecting groups.

Key words: imides, alcohols, aminomethylations, phthalimide, nucleophiles, protecting groups

A study on the hypolipidemic activity of phthalimidomethyl (Pim) tetra-*O*-acyl-α-D-mannopyranosides in mice showed significant reduction of plasma cholesterol and triglyceride levels.[1] Moreover, some phthalimidomethyl and phthalimide derivatives possess analgesic,[2] hypolipidemic,[3,4] anticonvulsant,[5] and antitumor[6] activities. They are also useful as synthetic intermediates,[7–16] for instance in polymer chemistry.[17] The phthalimidomethyl derivatives have been used for the identification[18–22] of amines and alcohols via nucleophilic substitution[23] of a leaving group on the Pim moiety. The biological activities as well as our interest in the reactivity of trichloroacetimidates[24–27] attracted our attention to develop a method for introducing the phthalimidomethyl group on nucleophiles to form, for instance, CO bonds under acid catalysis. *O*-Phthalimidomethyl trichloroacetimidate (**2**) (Scheme 1) was expected to serve as an imidomethylating agent; ensuing removal of the phthaloyl residue in the products will readily provide the corresponding aminomethyl derivatives. In the case of *O*-nucleophiles, the *O*-aminomethyl intermediate will liberate the hydroxy group, thus exhibiting that Pim is also a useful protecting group.

The synthesis of **2** was achieved by reaction of *N*-hydroxymethylphthalimide (**1**) with trichloroacetonitrile in dichloromethane as solvent and in the presence of DBU as a base which promotes the addition to the nitrile group (Scheme 1). The product **2** was isolated in 87% yield after column chromatography; its structure was readily assigned from the ^{1}H NMR spectrum (δ = 5.9 for CH_2, 8.59 for NH). Reaction of the trichloroacetimidate **2** with compounds having primary and secondary hydroxy groups,



Scheme 1 Synthesis of the trichloroacetimidate **2** and reaction with *O*-nucleophiles

such as **3**–**5**, in the presence of TMSOTf as catalyst gave the respective phthalimidomethyl derivatives **13**–**15** (Scheme 2; entries 1–3, Table 1) in 77–94% yields. The reaction was then extended to benzyl alcohols **6** and **7**, to cholesterol **8** as well as to carbohydrate derivatives **9**–**12** to give the corresponding imidomethyl derivatives **16**–**22** (entries 4–10, Table 1). None of the *O*-protecting groups of the starting materials was affected under the reaction conditions. The spectral analysis of the products agreed with the assigned structures. They showed in their ^{1}H NMR spectra a singlet at δ = 5.1 confirming the introduction of the NCH_2 group.

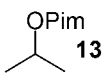
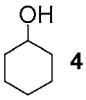
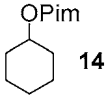
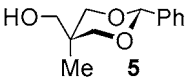
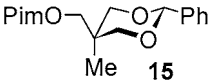
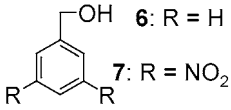
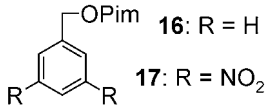
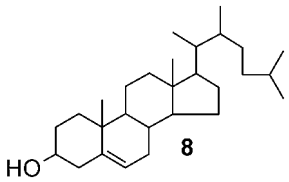
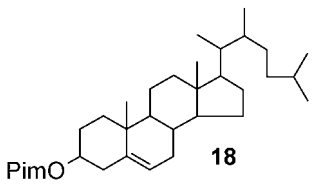
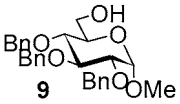
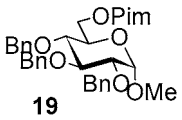
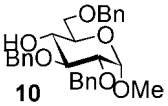
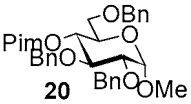
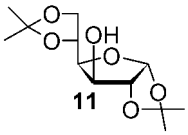
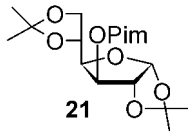
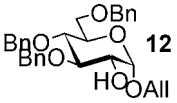
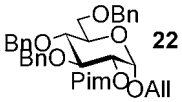
Reaction of **2** can be rationalized by acid catalyzed generation of a carbocation intermediate, which reacts with the nucleophiles to give the products; thus, a method for the imidomethylation of nucleophiles under mild acid conditions is provided. The amido and imidomethylation of nucleophiles under more drastic conditions has been known for many years.[28,29] The trichloroacetamide leaving group offers a particularly convenient method for the synthesis of such compounds.

Attempted cleavage of the phthalimido group with hydrazine hydrate or methylamine in methanol gave from **19** the respective alcohol **9** whose formation is the result of hydrolysis of intermediate **23** (Scheme 2). Treatment of **21** with aqueous acetic acid (80%) at 80 °C led to selective removal of the 5,6-*O*-isopropylidene group without affecting the Pim *O*-protection. Also hydrogenolysis of **19** in methanol with palladium on carbon as catalyst cleanly

Synthesis 2003, No. 7, Print: 20 05 2003.
Art Id.1437-210X,E;2003,0,07,1065,1070,ftx,en;T00503SS.pdf.

ISSN 0039-7881

Table 1 Phthalimidomethylation of Oxygen Nucleophiles **3**–**12** by **2**

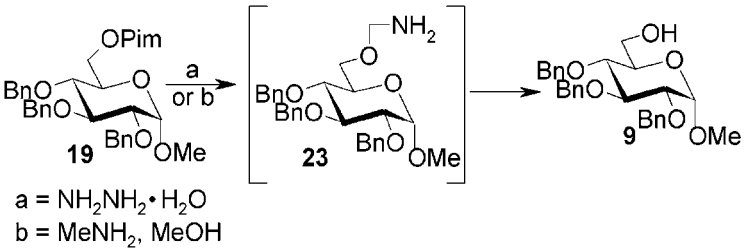
Entry	ROH	Reaction time (min)	RO-Pim	Yield (%)[a]
1	 **3**	180	 **13**	81
2	 **4**	45	 **14**	94
3	 **5**	60	 **15**	77
4	 **6**: R = H	60	 **16**: R = H	87
5	**7**: R = NO_2	90	**17**: R = NO_2	90
6	 **8**	60	 **18**	89
7	 **9**	20	 **19**	75
8	 **10**	30	 **20**	80
9	 **11**	30	 **21**	69
10	 **12**	90	 **22**	80

[a] Isolated yield after column chromatography.

furnished the 2,3,4-*O*-unprotected intermediate; subsequent transformation into the 2,3,4-tri-*O*-acetyl derivative with pyridine–acetic anhydride and de-*O*-acetylation with sodium methoxide in methanol afforded the 2,3,4-*O*-unprotected compound again without affecting the Pim *O*-protection. Hence, the Pim group is compatible with and orthogonal to all important hydroxy protecting groups; it offers selective removal with strong nucleophiles, thus complementing the repertoire of the available hydroxy protecting groups which are generally sensitive to acid, base, or hydrogenolysis, respectively.[30]

Also the effect of a neighboring Pim group on glycoside bond formation has been investigated. To this end, 2-*O*-Pim protected glucopyranoside **22** was de-*O*-allylated with Wilkinson's catalyst to afford glucose derivative **24** (α/β, 2:3) (Scheme 3). Reaction with trichloroacetonitrile in the presence of DBU as a base led to trichloroacetimidate **25**; only the α-anomer was obtained (^{1}H NMR: δ = 6.54; $J_{1,2}$ = 3.3 Hz).

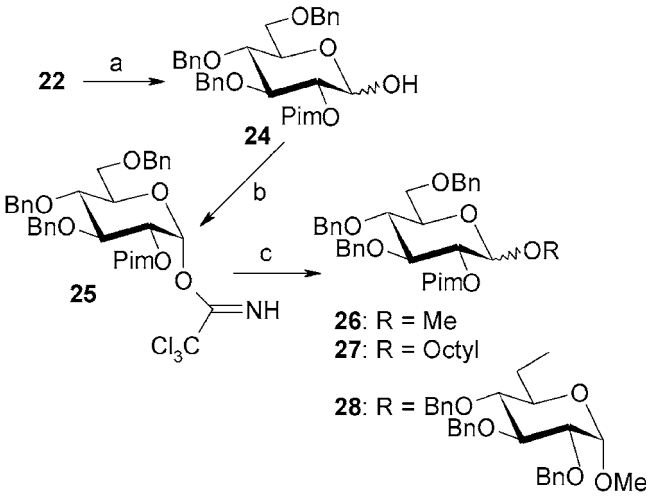
Glycosylation of methanol, octanol and 6-*O*-unprotected glucopyranoside **9** with **25** as glycosyl donor in the presence of TMSOTf as a catalyst afforded glucosides **26**–**28** in high yields; the β-anomers were the main products (α/β, 1:1.5–6.0). The preference for the β-product may be due to a steric effect and/or neighboring group participation via a seven-membered intermediate. Thus, in terms of glycosyl donor properties and anomeric control there is a big difference between a 2-*O*-acyl group and a 2-*O*-Pim group. The Pim group rather resembles the 2-*O*-benzyl group which offers high glycosyl donor properties with little interference in anomeric stereocontrol.[24–26]



Scheme 2 Phthaloyl group removal and deprotection

In conclusion, a general method has been developed for introducing the Pim group on different oxygen nucleophiles. The *O*-Pim trichloroacetimidate, which can be stored without decomposition, can be considered as the reagent of choice for forming CO bonds with *O*-nucleophiles under mild acid conditions. It is characterized by a high reactivity in the electrophilic displacement reactions. The respective Pim products can be easily isolated and identified. The Pim group can be used for the protection of hydroxy groups; with good nucleophiles it can be smoothly removed in a one-pot reaction via two cleavage steps. The Pim group is stable in the presence of weak nucleophiles and under acidic, basic, and hydrogenolytic conditions.

Mps are uncorrected. TLC was performed on plastic plates (Silica Gel 60 F_{254}; E. Merck, layer thickness 0.2 mm). The detection was achieved by treatment with a solution of ammonium molybdate (20 g) and cerium(IV) sulfate (0.4 g) in H_2SO_4 (400 mL of 10%), or with H_2SO_4 (15%), and heating at 150 °C. Flash chromatography was carried out on silica gel (Baker, 30–60 μm). Optical rotations were determined at 20 °C with a Perkin–Elmer 241 MC polarimeter (1 dm cell). NMR spectra were recorded with Bruker AC 250 and 600 DRX instruments, using tetramethylsilane as an internal standard. The assignment of ^{13}C NMR spectra were based on carbon–proton shift-correlation heteronuclear multiple quantum coherence (HMQC). MS spectra were recorded with MALDI-Kompakt (Kratos) and FAB with Finningen Mat 312/AMD instruments. Microanalyses were performed in the unit of Microanalysis at the Department of Chemistry, Universität Konstanz. Petroleum ether refers to the fraction with bp 35–65 ºC.



Scheme 3 Pim as neighbouring group in glycosylation reaction: (a) Wilkinson's catalyst, toluene, EtOAc; (b) CCl_3CN, DBU; (c) HOR, TMSOTf

O-Phthalimidomethyl Trichloroacetimidate (2)

A stirred solution of *N*-hydroxymethylphthalimide (0.58 g, 5 mmol) in anhyd CH_2Cl_2 (30 mL) and trichloroacetonitrile (5 mL, 50 mmol) was treated with DBU (71 μL) at r.t. and then left for 2 h. The solvent was evaporated and the product was purified by column chromatography (5% Et_3N in toluene– EtOAc, 25:1) to give **2**.

Yield: 1.3 g (87%); white powder; mp 145–147 °C.

^1H NMR (250 MHz, $CDCl_3$): δ = 8.59 (s, 1 H, NH), 7.79–7.99 (m, 4 H, HAr), 5.90 (s, 2 H, CH_2).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 64.9 (CH_2), 90.6 (CCl_3), 124.0, 131.8, 134.7 (ArC), 161.2 (CNH), 166.5 (CO).

EI-MS: *m*/*z* = 321.

Reaction of Trichloroacetimidate 2 with Alcohols; General Procedure

A solution of **2** (0.45 g, 1.4 mmol) and alcohol (1.4 mmol) in anhyd CH_2Cl_2 (40 mL) was stirred under nitrogen at r.t. and then TMSOTf (13 μL, 0.06 mmol) was added. After 20 min–3 h, the reaction mixture was neutralized with solid $NaHCO_3$, filtered and concentrated in vacuo. The residue was purified by flash chromatography.

Isopropyl Phthalimidomethyl Ether (13)

Yield: 0.25 g (81%); white powder; R_f 0.54 (petroleum ether–EtOAc, 5:1); mp 92 °C (lit.[30] 92–93 °C).

Cyclohexyl Phthalimidomethyl Ether (14)

Yield: 0.45 g (90%); white powder; R_f 0.81; petroleum ether–EtOAc, 5:1); mp 83 °C (lit.[22] 81–83 °C).

The analytical data **14** are identical with the published values.[22]

5-Methyl-2-phenyl-5-(phthalimidomethyloxy)methyl-1,3-dioxane (15)

Yield: 0.4 g (77%); white powder; R_f 0.65 (petroleum ether–EtOAc, 5:1); mp 76 °C.

^1H NMR (250 MHz, $CDCl_3$): δ = 0.76 (s, 3 H, CH_3), 3.50 (d, J_{gem} = 11.8 Hz, 2 H, CH_2), 3.84 (s, 2 H, CH_2), 4.00 (d, J_{gem} = 11.8 Hz, 2 H, CH_2), 5.20 (s, 2 H, CH_2), 5.32 (s, 1 H, CH), 7.87–7.26 (m, 9 H, ArH).

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 17.2 (CH_3), 34.4, 67.8, 71.6, 73.1 (4 CH_2), 101.8 (CH), 123.5, 123.6, 126.0, 128.1, 128.7, 131.8, 134.2, 138.1 (ArC), 163.7 (C), 168.0 (CO).

EI-MS: *m*/*z* = 367.

Anal. Calcd for $C_{21}H_{21}NO_5$ (367.4): C, 68.65; H, 5.76; N, 3.81. Found: C, 68.82, H, 5.94; N, 4.01

Benzyl Phthalimidomethyl Ether (16)
Yield: 0.32 g (87%); white powder; R_f 0.82 (petroleum ether–EtOAc, 5:1); mp 80 °C (lit.[31] 81 °C).

(3,5-Dinitrobenzyl) Phthalimidomethyl Ether (17)
Yield: 0.45 g (90%); yellow powder; R_f 0.53 (petroleum ether–EtOAc, 4:1); mp 115 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.80 (s, 2 H, CH_2), 5.30 (s, 2 H, CH_2), 8.55–7.70 (m, 7 H, HAr).

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 67.2, 69.4 (2 CH_2), 117.9, 123.9, 134.7 (ArC), 167.7 (CO).

EI-MS: *m*/*z* = 357.

Anal. Calcd for $C_{16}H_{11}N_3O_7$ (357.3): C, 53.78; H, 3.10; N, 11.76. Found: C, 53.51, H, 3.05; N, 11.43

Cholesteryl Phthalimidomethyl Ether (18)
Yield: 0.7 g (89%); white powder; R_f 0.74 (petroleum ether–EtOAc, 25:1); mp 132 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.64–2.28, (m, 43 H, cholesteryl), 3.55 (m, 1 H, CH), 5.36 (m, 1 H, CH), 5.60 (m, 2 H, CH_2), 7.90–7.20 (m, 4 H, ArH).

Anal. Calcd for $C_{36}H_{51}NO_3$ (545.8): C, 79.22; H, 9.41; N, 2.56. Found: C, 79.07; H, 9.49; N, 2.55.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-phthalimidomethyl-α-D-glucopyranoside (19)
Yield: 0.65 g (75%); white powder; R_f 0.38 (petroleum ether–EtOAc, 4:1); $[\alpha]_D^{20}$ + 51.53 (*c* 1.5, CH_2Cl_2); mp 89 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.30 (s, 3 H, OCH_3), 3.45 (dd, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.6 Hz, 1 H, H-2), 3.55 (dd, $J_{4,3}$ = 9.3, $J_{4,5}$ = 9.6 Hz, 1 H, H-4), 3.67 (m, 1 H, H-5), 3.78 (dd, $J_{6',5}$ = 1.3, J_{gem} = 9.6 Hz, 1 H, H-6′), 3.87 (dd, $J_{6,5}$ = 3.6, J_{gem} = 9.6 Hz, 1 H, H-6), 3.92 (dd, $J_{3,4}$ = 9.3, $J_{3,2}$ = 9.6 Hz, 1 H, H-3), 4.35 (d, $J_{1,2}$ = 3.4 Hz, 1 H, H-1), 4.60 (d, J_{gem} = 12.1 Hz, 1 H, CHPh), 4.74 (d, J_{gem} = 12.0 Hz, 1 H, CHPh), 4.78 (d, J_{gem} = 11.0 Hz, 1 H, CHPh), 4.80 (d, J_{gem} = 11.0 Hz, 1 H, CHPh), 4.83 (d, J_{gem} = 12.1 Hz, 1 H, CHPh), 4.94 (d, J_{gem} = 10.9 Hz, 1 H, CHPh), 5.18 (q, J_{gem} = 10.9 Hz, 2 H, CH_2Phth), 7.79–7.11 (m, 19 H, ArH).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 55.1 (OCH_3), 68.6 (C-6), 69.9 (C-5), 77.5 (C-4), 79.8 (C-2), 82.0 (C-3), 89.2 (C-1), 67.8, 73.4, 74.9, 75.6 (4 CH_2), 123.6, 127.5, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 131.8, 134.2, 138.2, 138.3, 138.8 (C-Ar), 167.8 (CO).

EI-MS: *m*/*z* = 623.

Anal. Calcd for $C_{37}H_{37}O_8$ (623.7): C, 71.25; H, 5.97; N, 2.24. Found: C, 70.94; H, 5.82; N, 1.89.

Methyl 2,3,6-Tri-*O*-benzyl-4-*O*-phthalimidomethyl-α-D-glucopyranoside (20)
Yield: 0.7 g (80%); white powder; R_f 0.35 (petroleum ether–EtOAc, 5:1); $[\alpha]_D^{20}$+3.5 (*c* 10, CH_2Cl_2); mp 62 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.25 (s, 3 H, OCH_3), 3.44 (dd, $J_{1,2}$ = 3.3, $J_{2,3}$ = 9.2 Hz, 1 H, H-2), 3.52 (m, 2 H, H-4, H-5), 3.72 (m, 1 H, H-3), 3.84 (m, 2 H, H-6), 4.40 (d, $J_{1,2}$ = 3.3 Hz, 1 H, H-1), 4.5 (m, 2 H, 2 CHPh), 4.54 (d, J_{gem} = 12.1 Hz, 1 H, CHPh), 4.58 (d, J_{gem} = 12.1 Hz, 1 H, CHPh), 4.96 (d, J_{gem} = 11.6 Hz, 1 H, CHPh), 5.04 (d, J_{gem} = 11.2 Hz, 1 H, CHPh), 5.30 (d, J_{gem} = 7.5 Hz, 2 H, CH_2), 7.70–7.30 (m, 19 H, HAr).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 55.0 (OCH_3), 67.8 (C-6), 69.4 (C-4), 69.8 (C-5) 73.3, 79.4, 79.7 (3 CH_2), 79.2 (C-2), 80.9 (C-3), 81.3 (CH_2), 123.3, 123.4, 123.5, 127.2, 127.6, 127.8, 127.9, 128.1, 128.3, 128.4, 131.7, 131.8, 132.0, 133.9, 134., 134.1, 137.9, 138.0, 138.6, 138.7 (CAr), 167.3, 167.8 (CO).

EI-MS: *m*/*z* = 623.

Anal. Calcd for $C_{37}H_{37}NO_8$ (623.7): C, 71.25; H, 5.97; N, 2.24. Found: C, 70.79; H, 6.03; N, 1.80.

1:2,5:6-Di-*O*-isopropylidene-3-*O*-phthalimidomethyl-α-D-glucofuranose (21)
Yield: 0.4 g (69%); colourless oil; R_f 0.65 (petroleum ether–EtOAc, 4:1); $[\alpha]_D^{20}$ –12.5 (*c* 4.0, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.10, 1.20, 1.35, 1.40 (4 CH_3), 3.94 (m, 3 H, H-4, H-6, H-6′), 4.30 (d, *J* = 2.7 Hz, 1 H, H-3), 4.16 (m, 1 H, H-5), 4.58 (d, $J_{2,1}$ = 3.5 Hz, 1 H, H-2), 5.23 (s, 2 H, CH_2), 5.85 (d, $J_{1,2}$ = 3.5 Hz, 1 H, H-1), 7.70–8.00 (m, 4 H, HAr).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 23.8, 24.2, 26.2, 26.8 (4 CH_3), 67.1 (C-6), 67.9 (CH_2), 72.1 (C-5), 80.8 (C-4), 81.0 (C-3), 83.7 (C-2), 105.2 (C-1), 108.8, 112.1, 123.6, 123.7, 131.9, 123.7, 131.9, 132.2, 134.2, 134.3 (CAr), 167.9 (CO).

EI-MS: *m*/*z* = 419.0.

Anal. Calcd for $C_{21}H_{25}NO_8$ (419.4): C, 60.13; H, 6.00; N, 3.34. Found: C, 60.43; H, 5.90; N, 3.31.

Allyl 3,4,6-Tri-*O*-benzyl-2-*O*-phthalimidomethyl-α-D-glucopyranoside (22)
Yield: 0.7 g (80%); colourless oil; R_f 0.43 (petroleum ether–EtOAc, 5:1); $[\alpha]_D^{20}$ –2.4 (*c* 5.0, CH_2Cl_2).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.45 (dd, $J_{6,5}$ = 3.6, J_{gem} = 10.3 Hz, 1 H, H-6), 3.68 (dd, $J_{6,5}$ = 3.4, J_{gem} = 10.4 Hz, 1 H, H-6′), 3.60 (m, 2 H, H-2, H-4), 3.70 (m, 1 H, H-5), 4.02 (dd, $J_{3,2}$ = 3.8, $J_{3,4}$ = 9.7 Hz, 1 H, H-3), 4.22 (m, 2 H, $CH_2CH{=}CH_2$), 4.42 (d, J_{gem} = 10.5 Hz, 1 H, CHPh), 4.45 (d, J_{gem} = 10.5 Hz, 1 H, CHPh), 4.60 (d, J_{gem} = 10.4 Hz, 1 H, CHPh), 4.64 (d, J_{gem} = 10.4 Hz, 1 H, CHPh), 4.70 (m, 2 H, CH_2=CH), 4.91 (d, J_{gem} = 10.5 Hz, 1 H, CHPh), 5.02 (d, $J_{1,2}$ = 3.1 Hz, 1 H, H-1), 5.17 (d, J_{gem} = 10.5 Hz, 1 H, CHPh), 5.23 (s, 2 H, CH_2), 5.80 (m, 1 H, CH_2=CH), 7.07–7.40 (m, 15 H, HAr), 7.75 (m, 4 H, HAr).

MS (MALDI, positive mode, matrix: DHB): *m*/*z* = 672 $(M + Na)^+$, 688 $(M + K)^+$.

Anal. Calcd for $C_{39}H_{39}NO_8$ (649.74): C, 72.09; H, 6.05; N, 2.15. Found: C, 72.31, H, 6.23; N, 1.92.

3,4,6-Tri-*O*-benzyl-2-*O*-phthalimidomethyl-α,β-D-glucopyranose (24)
To a solution of **22** (1.2 g, 1.85 mmol) in a mixture of toluene–EtOH–H_2O (40:40:2 mL) was added Wilkinson's catalyst (342 mg, 0.36 mmol) and the reaction mixture was refluxed at 110 °C. After stirring for 8 h, the solvent was evaporated in vacuo and the residue was purified by flash chromatography (petroleum ether–EtOAc, 8:1) to give α/β mixture of **24**.

Yield: 0.77 g (68%); colourless oil; R_f 0.35 (petroleum ether–EtOAc, 5:1); $[\alpha]_D^{20}$ + 50.6 (*c* 2.0, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.50 (br, 1 H, OH), 3.47 (m, 1 H, βH-5), 3.54 (m, 3 H, βH-2, βH-3, βH-4), 3.60 (m, 3 H, αH-4, H-6′), 3.80 (dd, $J_{2,1}$ = 3.5, $J_{2,3}$ = 9.4 Hz, 1 H, αH-2), 3.90 (dd, J_{gem} = 9.3 Hz, 1 H, H-3), 4.02 (m, 1 H, H-5), 4.44 (3 d, *J* = 10.4 Hz, 3 H, 3 CHPh), 4.60 (d, $J_{1,2}$ = 9.8 Hz, 1 H, βH-1), 4.70 (m, 3 H, 3 CHPh), 5.25 (d, J_{gem} = 10.9 Hz, 2 H, βCH_2), 5.37 (d, $J_{1,2}$ = 3.4 Hz, 1 H, αH-1), 5.45 (d, J_{gem} = 11.2 Hz, 2 H, αCH_2), 7.00–7.20 (m, 15 H, HAr), 7.25–7.40 (m, 4 H, HAr).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 67.3 (CH_2), 67.9 (CH_2), 68.6 (C-6), 70.3 (C-5), 73.4, 74.8 (2 CH_2), 77.8 (C-4), 79.7 (C-2), 80.9 (C-3), 96.8 (C-1), 123.6, 123.7, 127.4, 127.6, 127.8, 127.9, 128.2, 128.4, 131.7, 134.2, 134.4, 137.8, 138.3, 138.5 (CAr), 167.6, 168.1 (2 CO).

MS (MALDI, positive mode, matrix: DHB): *m*/*z* = 632.5 (M + Na)$^+$.

Anal. Calcd for $C_{36}H_{35}NO_8$ (609.67): C, 70.92; H, 5.78; N, 2.29. Found: C, 70.48; H, 6.20; N, 2.33.

O-3,4,6-Tri-*O*-benzyl-2-*O*-phthalimidomethyl-α-D-glucopyranosyl Trichloroacetimidate (25)

A stirred solution of glucose derivative **24** (0.61 g, 1.0 mmol) in anhyd CH_2Cl_2 (30 mL) and trichloroacetonitrile (1 mL, 10 mmol) was treated with DBU (10 μL) at r.t. and then left for 1.5 h. The solvent was evaporated and the product was purified by column chromatography (5% Et_3N in toluene–EtOAc, 25:1) to give **25**.

Yield: 0.65 g (86%); oil; R_f 0.43 (2% Et_3N in toluene); $[\alpha]_D^{20}$ + 34.5 (*c* 1.0, CH_2Cl_2).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.88 (m, 2 H, H-6, H-6′), 4.05 (m, 2 H, H-4, H-5), 4.60 (m, 3 H, 2 CHPh, H-3), 4.80 (d, J_{gem} = 9.7 Hz, 1 H, CHPh), 4.83 (d, J_{gem} = 11.1 Hz, 1 H, CHPh), 4.85 (d, J_{gem} = 11.1 Hz, 1 H, CHPh), 5.20 (d, J_{gem} = 9.7 Hz, 1 H, CHPh), 5.30 (d, J_{gem} = 12.7 Hz, 2 H, CH_2), 6.54 (d, $J_{1,2}$ = 3.3 Hz, 1 H, H-1), 7.00–7.28 (m, 15 H, ArH), 7.61–7.77 (m, 4 H, HAr), 8.36 (s, 1 H, NH).

Methyl 3,4,6-Tri-*O*-benzyl-2-*O*-phthalimidomethyl-β-D-glucopyranoside (26)

A solution of the trichloroacetimidate **25** (0.53 g, 0.7 mmol) and anhyd MeOH (0.28 mL, 7.0 mmol) in anhyd CH_2Cl_2 (10 mL) was treated with TMSOTf (13 μL, 0.07 mmol), and then stirred for 1 h. The reaction was quenched by the addition of solid $NaHCO_3$, filtered and concentrated. The crude residue was purified by column chromatography (silica gel; petroleum ether–EtOAc, 15:1) to afford **26**.

Yield: 0.34 g (78%); colourless oil; R_f 0.68 (petroleum ether–EtOAc 5:1); $[\alpha]_D^{20}$ + 10.7 (*c* 0.5, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.28 (s, 3 H, OCH_3), 3.39 (m, 1 H, H-5), 3.54 (dd, $J_{3,2}$ = 7.4, $J_{3,4}$ = 14.4 Hz, 1 H, H-3), 3.55 (dd, $J_{4,3}$ = 7.8, $J_{4,5}$ = 14.6 Hz, 1 H, H-4), 3.59 (dd, $J_{2,1}$ = 7.7, $J_{2,3}$ = 7.4 Hz, 1 H, H-2), 3.64 (dd, $J_{6,5}$ = 4.8, J_{gem} = 10.7 Hz, 1 H, H-6′), 3.72 (m, 1 H, H-6), 4.17 (d, $J_{1,2}$ = 7.7 Hz, 1 H, H-1), 4.48 (d, J_{gem} = 11.0 Hz, 1 H, CHPh), 4.53 (d, J_{gem} = 12.1 Hz, 1 H, CHPh), 4.59 (d, J_{gem} = 12.1 Hz, 1 H, CHPh), 4.70 (d, J_{gem} = 11.0 Hz, 1 H, CHPh), 4.76 (d, J_{gem} = 11.0 Hz, 1 H, CHPh), 4.82 (d, J_{gem} = 11.0 Hz, 1 H, CHPh), 5.33 (q, J_{gem} = 11.1 Hz, 2 H, CH_2), 7.08–7.31 (m, 15 H, HAr), 7.66–7.79 (m, 4 H, H-Ar).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 57.1 (CH_3), 68.2 (CH_2), 68.8 (C-6), 73.5 (CH_2), 74.8 (C-5), 74.9, 75.5 (2 CH_2), 77.8 (C-4), 81.7 (C-2), 84.1 (C-3), 103.7 (C-1), 123.5, 127.2, 127.3, 127.6, 127.7, 127.8, 127.9, 128.2, 128.3,132.0, 134.0, 137.9, 138.1, 138.4 (ArC), 167.9 (CO).

MS (MALDI, positive mode, matrix: DHB): *m*/*z* = 646.2 (M + Na)$^+$, 662.2 (M + K)$^+$.

Anal. Calcd for $C_{37}H_{37}NO_8$ (623.70): C, 71.25; H, 5.97; N, 2.24. Found: C, 71.41, H, 6.05; N, 2.18.

n-Octyl 3,4,6-Tri-*O*-benzyl-2-*O*-phthalimidomethyl-α/β-D-glucopyranoside (27)

A solution of the trichloroacetimidate **25** (0.53 g, 0.7 mmol) and octanol (1.10 mL, 7.0 mmol) in anhyd CH_2Cl_2 (10 mL) was treated with TMSOTf (13 μL 0.07 mmol), and then stirred for 1.5 h. The reaction was processed as above and the product was purified by column chromatography (silica gel; petroleum ether–EtOAc, 20:1) to afford **27**.

Yield: 0.36 g (71%); colourless oil; R_f 0.43 (petroleum ether–EtOAc, 10:1); $[\alpha]_D^{20}$ + 2.6 (*c* 2.0, CH_2Cl_2).

Compound 27α

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.84–1.50 [m, 13 H, $CH_3(CH_2)_5$], 1.57–1.60 (m, 2 H, CH_2), 3.43 (m, 2 H, CH_2), 3.61 (m, 2 H, H-4, H-6), 3.71 (m, 1 H, H-6), 3.78 (m, 1 H, H-5), 3.79 (m, 1 H, H-2), 3.90 (dd, $J_{3,2}$ = 9.2, $J_{3,4}$ = 9.3 Hz, 1 H, H-3), 4.52 (d, J_{gem} = 12.2 Hz, 1 H, CHPh), 4.64 (d, J_{gem} = 11.2 Hz, 1 H, CHPh), 4.72 (m, 2 H, 2 CHPh), 4.75 (d, J_{gem} = 11.2 Hz, 1 H, CHPh), 4.81 (d, J_{gem} = 11.1 Hz, 1 H, CHPh), 4.98 (d, $J_{1,2}$ = 3.4 Hz, 1 H, H-1), 5.32 (s, 2 H, CH_2), 7.09–7.32 (m, 15 H, ArH), 7.44–7.60 (m, 4 H, ArH).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 14.1, 22.6, 25.8, 26.0, 29.1, 31.8, 32.7 [$CH_3(CH_2)_5$], 67.3, 68.4 (2 CH_2), 68.7 (C-6), 70.2 (C-5), 73.5, 75.3, 75.4 (3 CH_2), 78.0 (C-4), 79.7 (C-2), 81.3 (C-3), 96.7 (C-1), 123.5, 127.1, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.1, 128.3,133.9, 134.3 (ArC), 167.6, 167.8 (2 CO).

MS (MALDI, positive mode, matrix: DHB): *m*/*z* = 744.4 (M + Na)$^+$, 760 (M + K)$^+$.

Anal. Calcd for $C_{44}H_{51}NO_8$ (721.9): C, 73.21; H, 7.12; N, 1.94. Found: C, 73.04; H, 7.32; N, 1.83.

Compound 27β

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.84–1.50 [m, 13 H, $CH_3(CH_2)_5$], 1.57–1.60 (m, 2 H, CH_2), 3.39 (m, 3 H, CH_2, H-5), 3.53 (m, 2 H, H-3, H-4), 3.64 (m, 2 H, H-2, H-6), 3.71 (m, 1 H, H-6′), 4.27 (d, $J_{1,2}$ = 7.8 Hz, 1 H, H-1), 4.52 (d, J_{gem} = 12.2 Hz, 1 H, CHPh), 4.64 (d, J_{gem} = 11.2 Hz, 1 H, CHPh), 4.72 (m, 2 H, 2 CHPh), 4.75 (d, J_{gem} = 11.2 Hz, 1 H, CHPh), 4.81 (d, J_{gem} = 11.1 Hz, 1 H, CHPh), 5.26 (q, J_{gem} = 10.8 Hz, 2 H, CH_2), 7.09–7.32 (m, 15 H, ArH), 7.44–7.60 (m, 4 H, ArH).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 14.1, 22.6, 25.8, 26.0, 29.1, 31.8, 32.7 [$CH_3(CH_2)_5$], 67.3, 68.4 (2 CH_2), 68.7 (C-6), 73.5 (CH_2), 74.9 (C-5), 75.3, 75.4 (2 CH_2), 78.0 (C-3), 81.7 (C-2), 84.3 (C-4), 102.6 (C-1), 123.5, 127.1, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.1, 128.3,133.9, 134.3 (ArC), 167.6, 167.8 (2 CO).

MS (MALDI, positive mode, matrix: DHB): *m*/*z* = 744.4 (M + Na)$^+$, 760 (M + K)$^+$.

Anal. Calcd for $C_{44}H_{51}NO_8$ (721.9): C, 73.21; H, 7.12; N, 1.94. Found: C, 73.04; H, 7.32; N, 1.83.

Methyl *O*-(3,4,6-Tri-*O*-benzyl-2-*O*-phthalimidomethyl-α/β-D-glucopyranosyl)-(1-6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (28)

A solution of the trichloroacetimidate **25** (0.53 g, 0.7 mmol) and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (0.325 g, 0.7 mmol) in anhyd CH_2Cl_2 (30 mL) was treated with TMSOTf (13 μL, 0.07 mmol), and then stirred for 1.5 h. The reaction proceeded as above. The crude residue was purified by column chromatography (silica gel; petroleum ether–EtOAc, 20:1) affording **28**.

Yield: 0.42 g (56%); colourless oil; R_f 0.68 (petroleum ether–EtOAc, 5:1); $[\alpha]_D^{20}$ + 13.7 (*c* 1.0, CH_2Cl_2).

Compound 28β

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.41 (s, 3 H, OCH_3), 3.43 (m, 2 H, H-4$_a$, H-5$_b$), 3.51 (m, 2 H, H-2$_a$, H-3$_b$), 3.57 (dd, $J_{4,3}$ = 9.2, $J_{4,5}$ = 9.4 Hz, 1 H, H-4$_b$), 3.66 (m, 2 H, H-6$_b$, H-6′$_b$), 3.70 (m, 1 H, H-6$_a$), 3.74 (dd, $J_{2,1}$ = 7.8, $J_{2,3}$ = 8.6 Hz, 1 H, H-2$_b$), 3.84 (m, 1 H, H-5$_a$), 3.99 (dd, $J_{3,2}$ = 9.2, $J_{3,4}$ = 9.3 Hz, 1 H, H-3$_a$), 4.11 (m, 1 H, H-6′$_a$), 4.36 (d, $J_{1,2}$ = 7.8 Hz, H-1$_b$), 4.48 (d, J_{gem} = 10.7 Hz, 1 H, CHPh), 4.54 (d, J_{gem} = 12.1 Hz, 1 H, CHPh), 4.61(d, $J_{1,2}$ = 3.3 Hz, 1 H, H-1$_a$), 4.62 (m, 2 H, 2 CHPh), 4.66 (d, J_{gem} = 12.1 Hz, 1 H, CHPh), 4.72 (d, J_{gem} = 10.7 Hz, 1 H, CHPh), 4.75 (d, J_{gem} = 12.1 Hz, 1 H, CHPh), 4.78 (d, J_{gem} = 12.1 Hz, 1 H, CHPh), 4.80 (d, J_{gem} = 10.7 Hz, 1 H, CHPh), 4.83 (d, J_{gem} = 10.7 Hz, 1 H, CHPh), 4.88 (d, J_{gem} = 10.7 Hz, 1 H, CHPh), 4.97 (d, J_{gem} = 10.7 Hz, 1 H, CHPh), 5.37 (q, J_{gem} = 11.1 Hz, 2 H, CH_2Phth), 7.06–7.55 (m, 34 H, HAr).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 55.2 (OCH_3), 68.1 (CH_2), 68.5 (C-6_b), 68.8 (C-6_a), 70.0 (C-5_a), 73.3, 73.4, 73.8 (3 CH_2), 74.9 (C-5_b), 75.0, 75.1, 75.7 (3 CH_2), 77.8 (C-4_b), 78.1 (C-4_a), 79.8 (C-2_a), 81.2 (C-2_b), 81.9 (C-3_a), 83.8 (C-3_b), 97.8 (C-1_a), 103.1 (C-1_b), 123.5, 126.7, 126.9, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3, 128.4, 131.7, 134.0, 137.8, 138.1, 138.2, 138.3 (CAr), 167.6, 167.8 (2 CO).

MS (MALDI, positive mode, matrix: DHB): *m*/*z* = 1080 $(M + Na)^+$, 1096 $(M + K)^+$.

Anal. Calcd for $C_{64}H_{65}NO_{13}$ (1056.2): C, 72.77; H, 6.20; N, 1.32. Found: C, 72.3, H, 6.32; N, 1.32.

Compound 28α

Colourless oil; R_f 0.72 (petroleum ether–EtOAc, 5:1); $[\alpha]_D^{20}$ + 9.1 (*c* 0.5, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.33 (s, 3 H, OCH_3), 3.51 (dd, $J_{2,1}$ = 3.3, $J_{2,3}$ = 9.6 Hz, 1 H, H-2_a), 3.58 (m, 3 H, H-4_a, H-4_b, H-6_b), 3.63 (dd, $J_{6',5}$ = 3.8, J_{gem} = 10.8 Hz, 1 H, H-6′$_b$), 3.71 (m, 2 H, H-5_a, H-6_a), 3.73 (m, 2 H, H-2_b, H-5_b), 3.79 (m, 1 H, H-6′$_a$), 3.85 (dd, $J_{3,2}$ = 9.1, $J_{3,4}$ = 9.2 Hz, 1 H, H-3_b), 3.96 (dd, $J_{3,2}$ = 9.2, $J_{3,4}$ = 9.3 Hz, 1 H, H-3_a), 4.41 (d, J_{gem} = 10.7 Hz, 1 H, CHPh), 4.44 (d, J_{gem} = 10.7 Hz, 1 H, CHPh), 4.52 (d, $J_{1,2}$ = 3.3 Hz, 1 H, H-1_a), 4.58 (d, J_{gem} = 12.1 Hz, 1 H, CHPh), 4.61 (d, J_{gem} = 10.7 Hz, 1 H, CHPh), 4.69 (d, J_{gem} = 12.1 Hz, 1 H, CHPh), 4.71 (d, J_{gem} = 12.1 Hz, 1 H, CHPh), 4.74 (d, J_{gem} = 10.7 Hz, 1 H, CHPh), 4.77 (d, J_{gem} = 12.1 Hz, 1 H, CHPh), 4.79 (m, 1 H, CHPh), 4.85 (d, J_{gem} = 10.7 Hz, 1 H, CHPh), 4.89 (d, J_{gem} = 10.7 Hz, 1 H, CHPh), 4.94 (d, J_{gem} = 10.7 Hz, 1 H, CHPh), 5.13 (d, $J_{1,2}$ = 3.3 Hz, 1 H, H-1_b), 5.16 (q, J_{gem} = 11.0 Hz, 2 H, CH_2Phth), 7.36–7.08 (m, 34 H, HAr).

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 55.1 (OCH_3), 65.9 (C-6_a), 66.6 (CH_2), 68.6 (C-6_b), 70.1 (C-5_b), 70.2 (C-5_a), 73.3, 73.4, 74.8, 74.9, 75.3, 75.7 (6 CH_2), 77.8 (C-4_a), 77.9 (C-4_b), 79.1 (C-2_b), 79.8 (C-2_a), 81.1 (C-3_b), 82.0 (C-3_a), 97.0 (C-1_b), 97.9 (C-1_a), 123.6, 127.2, 127.5, 127.6, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.6, 131.8, 134.2, 138.0, 138.2, 138.4, 138.6, 138.7 (CAr), 167.6 (CO).

MS (MALDI, positive mode, matrix: DHB): *m*/*z* = 1080 $(M + Na)^+$, 1096 $(M + K)^+$.

Anal. Calcd for $C_{64}H_{65}NO_{13}$ (1056.2): C, 72.77; H, 6.20; N, 1.32. Found: C, 72.3, H, 6.32; N, 1.32.

Removal of the Phthaloyl Group

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-phthalimidomethyl-α-D-glucopyranoside **19** (0.2 g, 0.32 mmol) was dissolved in MeOH (10 mL) and hydrazine (1 mL) and the reaction mixture refluxed for 1 h, the solvent was evaporated in vacuo and the residue was purified by flash chromatography (petroleum ether–EtOAc, 2:1) to give **9**. Methylamine can be used instead of hydrazine.

Yield: (76%); white powder.

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. I. A. I. Ali is grateful for a stipend within the fellowship program from the Egyptian government. A. A.-H. A. R. is grateful for an Alexander von Humboldt-Fellowship. The continued support from the Alexander von Humboldt Stiftung for El S. H. El Ashry is highly appreciated.

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