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(2-Azidomethyl)phenylacetyl as a new, reductively cleavable protecting group for hydroxyl groups in carbohydrate synthesis

Jinghua Xu, Zhongwu Guo*

Department of Chemistry, Case Western Reserve University, 10900 Euclid Avenue, Cleveland, OH 44106, USA

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Abstract

The (2-azidomethyl)phenylacetyl group (AMPA) is described as a new protecting group for carbohydrates. AMPA was introduced to carbohydrate hydroxyl groups in the presence of DCC, while its removal was conveniently achieved via Lindlar catalyst-catalyzed hydrogenation that had no influence on other protecting groups including benzyl, acyl, acetal and ketal.

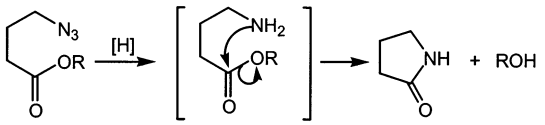
Keywords: Carbohydrates; Protecting group; (2-Azidomethyl)phenylacetyl; Reductive cleavage

1. Introduction

Successful strategies for oligosaccharide synthesis require sophisticated methods for the differentiation of numerous hydroxyl groups on the sugar rings. For this reason, an array of protecting groups, such as acyls, alkyls, acetals and ketals, have been introduced.[1,2] Nevertheless, given the remarkable complexity of oligosaccharide structures, the demands for new, versatile protecting methods for hydroxyl groups still persist in carbohydrate chemistry.

'Assisted cleavage', i.e., cleavage of a bond via intramolecular attack induced by the selective activation of a group in the molecule, has found its applications in the design of special protecting groups in organic chemistry.[2–6] For instance, 4-azidobutanoyl, which has been used as the protecting group of hydroxyls in oligosaccharide synthesis,[6–8] was designed according to this mechanism. It can be selectively removed by reduction of the azido group to a free amino group that attacks the neighboring ester bond to release the alcohol and γ-lactam (Scheme 1). Drawbacks of 4-azidobutanoyl are that its removal needs prolonged heating and that the yield of the deprotection step is generally low.[6–8]

Herein we report a new protecting group, (2-azidomethyl)phenylacetyl (AMPA), which can be easily removed in quantitative yield through the selective reduction of its azido group. Thus, 'assisted cleavage' of AMPA can be achieved under very mild conditions.



Scheme 1. Removal of γ-azidobutanoyl group via assisted cleavage.

2. Results and discussion

As shown in Scheme 2, reduction of the azido group in the ester of AMPA (**1**), followed by intramolecular cyclization, will give a δ-lactam **3** and the free alcohol. Since intramolecular cylclization to form δ-lactams is the most favorable process among lactamizations,[9,10] we anticipated that AMPA might be more easily cleaved than 4-azidobutanoyl upon reduction of the azido group. Indeed, scattered reports suggest that δ-lactamization can occur spontaneously with high selectivity.[11,12] Moreover, the rigid conformation of AMPA, which helps to lock the two involved groups adjacent to

* Corresponding author. Tel.: +1-216-3683736; fax: +1-216-3683006.

E-mail address: zxg5@po.cwru.edu (Z. Guo).

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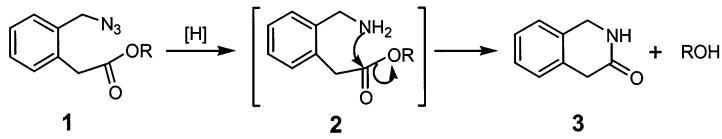
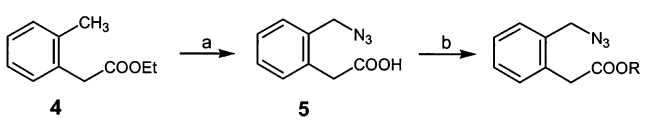


Scheme 2. AMPA as a protecting group and its reductive cleavage.

each other, may further facilitate the intramolecular attack, which is supported by recent reports of others.[3–5] Thus, AMPA was designed in this research as a hydroxyl protecting group that can be easily removed under mild reductive conditions.

Our synthesis of (2-azidomethyl)phenylacetic acid (**5**) was achieved by a reported procedure (Scheme 3).[11] The radical bromination of ethyl 2-methylphenylacetate (**4**) with *N*-bromosuccinimide (NBS) and benzoyl peroxide, as well as the subsequent nucleophilic azido substitution, was quite straightforward. However, the saponification proved to be problematic, as it was very sensitive to the workup procedures. After testing different acids for neutralization of the reaction mixtures, we found that only carbon dioxide could offer satisfactory results (~ 50% yield). Nevertheless, the pure **5** obtained after column chromatography was rather stable.

The protection of carbohydrate hydroxyl groups with AMPA was realized via the condensation of **5** with alcohols **6**–**10** by means of *N*,*N*-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in dichloromethane at room temperature (Scheme 3 and Table 1). All reactions gave excellent yields regardless of whether the hydroxyl group was primary or secondary. Furthermore, these reaction conditions were compatible with a variety of other protecting linkages, including acetal, benzyl ether, ester and ketal. We have also noticed that the reaction between **5** and a partially blocked derivative of glucosamine **10** could be regioselective under controlled conditions, e.g., use of only 1.1 equiv of **5** at 0 °C. Thus, AMPA was introduced to the primary hydroxyl group in the presence of the secondary one to give a major product **15**. Nonetheless, a substantial amount (12%) of the 3,4,6-tri-*O*-(2-azidomethyl)phenylacetylated product **16** was still formed. The structures of AMPA-protected products **11**–**16**, which were unknown compounds, were confirmed by NMR spectrometry as well as by high-resolution mass spectrometry.

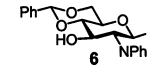
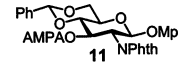
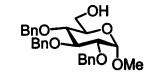
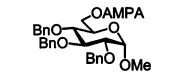
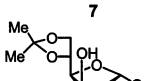
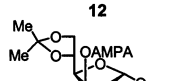
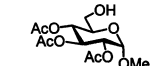
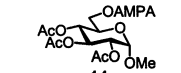
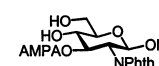
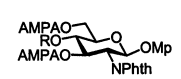


Scheme 3. Synthesis of (2-azidomethyl)phenylacetic acid (**5**) and protection of alcohols as AMPA esters. (a) (i) $(BzO)_2$, NBS, reflux; (ii) NaN_3, DMF, rt; (iii) LiOH, THF, 0 °C to rt, 36% (overall); (b) ROH, DCC, DMAP, CH_2Cl_2, 0 °C to rt, 73–92%.

On the other hand, AMPA was readily cleaved by selective reduction of the azido group. Thus, the exposure of AMPA-protected monosaccharides **11**–**14** to hydrogen and Lindlar catalyst in methanol at room temperature for 3 h resulted in complete removal of their AMPAs. The deprotected products could be very easily separated from the δ-lactam **3** by flash column chromatography, for **3** had much higher polarity than the alcoholic products in our study. Under these mild reductive conditions, other protecting functions in the molecules, such as benzyl, acetyl, ketal and acetal of isopropylidene and benzylidene, were stable. Finally, monosaccharides **6**–**8** were obtained in quantitative yields, and **9** in 81% yield. For the latter, in addition to **9**, methyl 2,3,6-tri-*O*-acetyl-α-D-glucopyranoside (**17**) was also obtained as a side product (19%), which was probably formed by intramolecular acetyl migration.

After the successful introduction and removal of AMPA to and from sugars, we then examined the susceptibility of AMPA linkages to acidic and basic treatment. It turned out that AMPA esters were quite stable in the acidic conditions, e.g., 33% trifluroacetic acid in dichloromethane or 0.25% H_2SO_4 water–MeOH solution, used to deblock acetal or 5,6-ketal in **11** and **13** affording **10** (78%) and 3-*O*-[(2-azidomethyl)-

Table 1
AMPA-protected sugars **11**–**15** produced by esterification

Entry	Alcoholic Substrate	Ester Product	Yield (%)
1	 **6**	 **11**	92
2	 **7**	 **12**	82
3	 **8**	 **13**	88
4	 **9**	 **14**	87
5	 **10**	 **15** R = H, **16** R = AMPA	73 (**15** R = H) + 12 (**16** R = AMPA)

phenylacetyl]-1,2-*O*-isopropylidene-α-D-glucofuranose (**18**, 80%), respectively. In contrast, but not surprisingly, AMPA esters were labile under basic conditions, e.g., to sodium methoxide in methanol, which is used to remove acetyl groups.

In conclusion, AMPA has proved to be a highly versatile protecting group for hydroxyl groups in carbohydrate chemistry. During the process of preparing this report, we noticed that Wada et al.[13] developed a similar protecting group. In view of the mild reaction conditions, high yields and convenient workups during the introduction and deprotection of AMPA esters, as well as its compatibility with other protecting groups commonly used, AMPA can be a generally useful protecting method in oligosaccharide synthesis.

3. Experimental

General methods.—NMR spectra were recorded on a Gemini-300 FT NMR spectrometer. Proton chemical shifts are reported in ppm (δ) downfield from tetramethylsilane (TMS). Coupling constants (J) are reported in hertz (Hz). Carbon chemical shifts are reported in ppm (δ) in reference to solvent $CDCl_3$ (δ 77.00). Fast-atom bombardment mass spectra (FABMS) were obtained with a Kratos MS-25RFA spectrometer. Anhydrous solvents were purchased from Aldrich and were directly used without further distillation. 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**8**) was also purchased from Aldrich. *p*-Methoxyphenyl 4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (**6**),[14] methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**7**),[15] and methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (**9**)[16] were prepared by the reported procedures.

Preparation of (2-azidomethyl)phenylacetic acid (**5**)[10].—To a refluxing solution of ethyl 2-methylphenylacetate (**4**, 3.5 g, 20 mmol) and benzoyl peroxide (0.04 g) in dry benzene (10 mL), was added a mixture of *N*-bromosuccinimide (NBS, 3.4 g, 19 mmol) and benzoyl peroxide (0.04 g) in portions within ca. 15 min. As soon as the foam formed from the last addition of NBS subsided, the flask was cooled down to rt and the succinimide was filtered off and washed with benzene. The filtrates were combined and condensed to yield ethyl (2-bromomethyl)phenylacetate that was used directly in the next step.

NaN_3 (2.6 g, 40 mmol) was added in one portion to a solution of the above product in DMF (20 mL) at rt. After stirring for 6 h, TLC showed complete reaction, and the reaction mixture was partitioned between ether and water. The organic layer was dried over Na_2SO_4 and then concentrated. The residue was purified by column chromatography (eluent: 1:19 EtOAc–hexane) to afford ethyl (2-azidomethyl)phenylacetate (3.2 g, 73% over the two steps) as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 7.33–7.16 (m, 4 H, ArH), 4.47 (s, 2 H, CH_2N_3), 4.15 (q, 2 H, J 7.2 Hz, OCH_2Me), 3.72(s, 2 H, CH_2CO), 1.25 (t, 3 H, CH_3).

To the solution of ethyl (2-azidomethyl)phenylacetate (3.2 g, 14.6 mmol) in THF (22 mL) was added at 0 °C a solution of LiOH (0.5 g, 21 mmol) in water (22 mL), and the reaction mixture was stirred at 0 °C for 2.5 h. Then, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and brine (100 mL), which was followed by addition of solid CO_2 to neutralize the base. After the organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The organic solutions were combined, and concentrated, and the final product was purified by flash chromatography (eluent: 3:7 EtOAc–hexane) to afford (2-azidomethyl)-phenylacetic acid (**5**, 1.34 g, 48%) as white solid: mp 109–111 °C; ^{1}H NMR ($CDCl_3$) δ 7.24–7.15 (m, 4 H, ArH), 4.52 (s, 2 H, CH_2N_3), 3.60(s, 2 H, CH_2CO).

General procedure for the introduction of AMPA onto carbohydrate hydroxyl groups.—To a stirred solution of **5** (1.1 equiv), the monosaccharide **6**–**10** (1.0 equiv) and DMAP (0.1 equiv) in dry CH_2Cl_2 was added DCC (1.2 equiv) at 0 °C. The mixture was stirred for 5 min at 0 °C and then 4–5 h at rt. The urea precipitates were then filtered off, and the filtrate was concentrated to dryness under vacuum. The residue was dissolved in EtOAc which was sequentially washed with 0.5 M HCl, satd aq $NaHCO_3$ and brine. The solution was dried over Na_2SO_4 and concentrated, and the crude product was purified by column chromatography to afford the AMPA-protected carbohydrates **11**–**15** (Table 1).

p-*Methoxyphenyl 3*-O-*[(2-azidomethyl)phenylacetyl]-4,6*-O-*benzylidene-2-deoxy-2-phthalimido-β*-D-*glucopyranoside* (**11**).—0.62 g, 92% yield; white solid: mp 122–125 °C; $[\alpha]_D^{25}$ +19° (c 1.0, $CHCl_3$); eluent: 15:85 EtOAc–hexane; ^{1}H NMR ($CDCl_3$): δ 7.82–7.71 (m, 4 H, Phth ArH), 7.44–7.37 (m, 4 H, benzylidene ArH), 7.14–7.03 (m, 4 H, AMPA ArH), 6.84–6.71 (m, 4 H, Mp ArH), 5.99 (dd, 1 H, $J_{2,3}$ 10.4, $J_{3,4}$ 9.1 Hz, 3-H), 5.91 (d, 1 H, $J_{1,2}$ 8.5 Hz, 1-H), 5.53 (s, 1 H, PhC*H*), 4.54 (dd, 1 H, 2-H), 4.42 (dd, 1 H, 4-H), 4.15, 4.08 (2 d, 2 H, J 14.0 Hz, CH_2N_3), 4.0–3.79 (m, 3 H, 5-H, 6a-H, 6b-H), 3.72 (s, 3 H, OMe), 3.63, 3.57 (2 d, 2 H, J 12.0 Hz, $PhCH_2CO$); FABMS: 553 [$M^+ - OMp$], 525 [$553 - N_2$], 362 [$553 - AMPA - H$, 100%]; HR-FABMS: Calcd for $C_{37}H_{32}N_4O_9$ [M^+], 676.2169. Found, 676.2163.

Methyl 6-O-*[(2-azidomethyl)phenylacetyl]-2,3,4-tri*-O-*benzyl-α*-D-*glucopyranoside* (**12**).—0.52 g, 82% yield; colorless syrup; $[\alpha]_D^{25}$ +23.6° (c 0.9, $CHCl_3$); eluent: 1:9 EtOAc–hexane; ^{1}H NMR ($CDCl_3$): δ 7.38–7.18 (m, 19 H, ArH), 4.98, 4.80, 4.79, 4.76, 4.67 (5 d, 5 H, $PhCH_2$–), 4.56 (d, 1 H, $J_{1,2}$ 3.5 Hz, 1-H), 4.37 (s, 2 H, CH_2N_3), 4.38–4.32 (m, 2 H, 6a-H, 1 H of $PhCH_2$–), 4.21 (dd, 1 H, $J_{5,6}$ 5.2, $J_{6,6'}$ 11.9 Hz, 6b-H), 3.96 (dd, 1

H, $J_{2,3}$ 9.2, $J_{3,4}$ 9.2 Hz, 3-H), 3.79–3.75 (m, 1 H, 5-H), 3.46 (dd, 1 H, $J_{1,2}$ 3.5 Hz, 2-H), 3.31 (dd, 1 H, 4-H), 3.29 (s, 3 H, OMe); FABMS: 606 [$M^+ - OMe$]; 578 [$606 - N_2$, 100%]; HRFABMS: Calcd for $C_{37}H_{40}NO_7$ [$M^+ - N_2 + H$], 610.2804. Found, 610.2787.

3-O-(2-Azidomethyl)phenylacetyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (**13**).—0.38 g, 88% yield; colorless syrup; $[\alpha]_D^{25}$ −62.7° (*c* 1.7, $CHCl_3$); eluent: 1:4 EtOAc–hexane; ^1H NMR ($CDCl_3$) δ: 7.44–7.34 (m, 4 H, AMPA ArH), 5.89 (d, 1 H, $J_{1,2}$ 3.7 Hz, 1-H), 5.21 (bd, 1 H, $J_{3,4}$ 3.0 Hz, 3-H), 4.59 (bd, 1 H, 2-H), 4.53 (s, 2 H, PhCH_2N$_3$), 4.19 (dd, 1 H, $J_{4,5}$ 7.5 Hz, 4-H), 4.14–3.83 (m, 3 H, 5-H, 6a-H, 6b-H), 3.91–3.83 (dd, 2 H, *J* 16.3 Hz, PhCH_2CO), 1.45, 1.33, 1.27, 1.26 (4 s, 12 H, 4 CH_3); ^{13}C NMR (CDCl3): δ 170.65 (C=O), 135.55, 134.26, 132.32, 130.75, 129.62, 128.63 (ArC), 106.21 (1-C), 84.18, 80.75, 77.34, 73.40 (sugar C), 67.66 (6-C), 53.23 (CH_2N$_3$), 38.77 (PhCH$_2$CO), 27.14, 27.09, 26.50, 25.62 (CH_3); FABMS: 243 [$M^+ -$ AMPA], 118 [C_8H_8N, 100%]; HRFABMS: Calcd for $C_{20}H_{24}NO_7$ [$M^+ - CH_3$], 418.1615. Found, 418.1643.

Methyl 2,3,4-tri-O-acetyl-6-O-[(2-azidomethyl)-phenylacetyl]-α-D-glucopyranoside (**14**).—0.43 g, 87% yield; white solid; mp 105–107 °C; $[\alpha]_D^{25}$ +68.8° (*c* 0.7, $CHCl_3$); eluent: 1:2 EtOAc–hexane; ^1H NMR ($CDCl_3$): δ 7.29–7.26 (m, 4 H, AMPA ArH), 5.43 (dd, 1 H, $J_{4,5}$ 10.0, $J_{3,4}$ 9.6 Hz, 4-H), 4.97 (dd, 1 H, $J_{2,3}$ 10.2 Hz, 3-H), 4.88 (d, 1 H, $J_{1,2}$ 3.6 Hz, 1-H), 4.81 (dd, 1 H, 2-H), 4.40 (s, 2 H, CH_2N$_3$), 4.29–4.13 (m, 2 H, 6a-H, 6b-H), 3.97–3.90 (m, 1 H, 5-H), 3.75 (s, 2 H, PhCH_2CO), 3.30 (s, 3 H, OMe), 2.05, 1.98 (2 s, 9 H, 3 CH_3CO); ^{13}C NMR ($CDCl_3$): δ 170.83, 170.23, 170.20, 169.65 (C=O), 134.18, 132.71, 131.42, 129.90, 128.93, 127.97 (ArC), 96.73 (1-C), 70.80, 70.06, 68.51, 67.18 (sugar C), 62.44 (6-C), 55.43 (OCH_3), 52.81 (CH_2N_3), 38.20 (PhCH$_2$CO), 20.78, 20.74, 20.67 (3 CH_3CO); FABMS: 462 [$M^+ -$ OMe], 434 [$462 - N_2$], 118 [C_8H_8N, 100%]; HRFABMS: Calcd for $C_{22}H_{28}NO_{10}$ [$M^+ - N_2 + H$], 466.1712. Found, 466.1710.

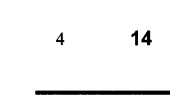
p-*Methoxyphenyl 3,6-di-O-[(2-azidomethyl)phenylacetyl]-2-deoxy-2-phthalimido-β-D-glucopyranoside* (**15**).—0.56 g, 73% yield; colorless syrup; $[\alpha]_D^{25}$ +3.6° (*c* 1.4, $CHCl_3$); eluent: 1:4 EtOAc–hexane; ^1H NMR ($CDCl_3$): δ 7.81–7.69 (m, 4 H, Phth protons), 7.35–7.32 (m, 4 H, 6-AMPA ArH), 7.12–7.05 (m, 4 H, 3-AMPA ArH), 6.85–6.70 (m, 4 H, Mp ArH), 5.76 (d, 1 H, $J_{1,2}$ 8.6 Hz, 1-H), 5.68 (dd, 1 H, $J_{2,3}$ 10.8, $J_{3,4}$ 9.0 Hz, 3-H), 4.76 (d, 2 H, $J_{5,6}$ 3.3 Hz, 6a-H, 6b-H), 4.41 (s, 2 H, 6-PhCH_2N$_3$), 4.37 (dd, 1 H, 2-H), 4.20, 4.15 (d, 2 H, *J* 13.8 Hz, 3-PhCH_2N$_3$), 3.80 (d, 2 H, *J* 11.9 Hz, PhCH_2CO), 3.78–3.67 (m, 1 H, 5-H), 3.72 (s, 3 H, OMe), 3.61 (d, 2 H, *J* 12.9 Hz, PhCH_2COO), 3.58–3.55 (m, 1 H, 4-H), 3.14 (d, 1 H, *J* 4.4 Hz, 4-OH); ^{13}C NMR ($CDCl_3$): δ 171.47, 155.75, 150.58 (C=O), 134,26, 134.09, 133.73, 132.99, 132.31, 131.30, 131.03, 129.91, 129.08, 128.90, 128.09, 127.90, 123.75, 118.93, 114.53 (ArC), 97.52 (1-C), 73.83, 69.52, 55.65, 54.22 (sugar C), 63.22 (6-C), 52.93, 53.71 (2 CH_2N_3), 38.44, 38.25 (2 PhCH$_2$CO); FABMS: 638 [$M^+ -$ OMp], 610 [$638 - N_2$], 447 [$638 -$ AMPA $- H$], 419 [$447 - N_2$, 100%]; HRFABMS: Calcd for $C_{37}H_{36}N_5O_{10}$ [$M^+ - N_2 + H$], 734.2461. Found, 734.2459.

In addition to the major product **15**, the reaction between **5** and **10** also gave a minor product, *p*-methoxyphenyl 3,4,6-tri-*O*-[(2-azidomethyl)phenylacetyl]-2-deoxy-2-phthalimido-β-D-glucopyranoside (**16**).—0.11 g, 12% yield; colorless syrup; ^1H NMR ($CDCl_3$) δ 7.80–7.70 (m, 4 H, Phth ArH), 7.35–7.26 (m, 8 H, AMPA ArH), 7.20–6.93 (m, 4 H, AMPA ArH), 6.82–6.69 (m, 4 H, Mp ArH), 5.83 (dd, 1 H, $J_{2,3}$ 10.9, $J_{3,4}$ 9.2 Hz, 3-H), 5.73 (d, 1 H, $J_{1,2}$ 8.5 Hz, 1-H), 5.12 (dd, 1 H, $J_{4,5}$ 9.3 Hz, 4-H), 4.42 (dd, 1 H, 2-H), 4.37, 4.30 (2 s, 2 H each, 2 CH_2N$_3$), 4.19–4.02 (m, 2 H, 6a-H, 6b-H), 4.11 (d, 2 H, *J* 14.8 Hz, PhCH_2N$_3$), 3.88–3.83 (m, 1 H, 5-H), 3.77, 3.58, 3.36 (3 s, 2 H each, 3 PhCH_2CO), 3.72 (s, 3 H, OCH_3); FABMS: 811 [$M^+ -$ OMp], 783 [$811 - N_2$], 620 [$811 -$ AMPA $-$ Hz], 592 [$620 - N_2$], 429 [$811 - 2 \times$ AMPA $- H$), 592 [$429 - N_2$], 238 [$811 - 3 \times$ AMPA $- H$], 118 [C_8H_8N, 100%]; HRFABMS: Calcd for $C_{48}H_{43}N_8O_{11}$ [$M^+ - N_2 + H$], 907.3051. Found, 907.3045.

General procedure for selective removal of AMPA from carbohydrates.—A solution of AMPA-protected sugar **11**–**14** in MeOH was stirred with Lindlar catalyst (60% weight) under a hydrogen atmosphere for 3 h. The solids were then filtered off through filter paper, and the solutions were concentrated to dryness. The remains were dissolved in a small amount of CH_2Cl_2 and applied to silica-gel flash chromatography to give the deprotected sugars **6**–**9**, respectively, in quantitative yields (Table 2).

p-*Methoxyphenyl 3-O-[(2-azidomethyl)phenylacetyl]-2-deoxy-2-phthalimido-β-D-glucopyranoside* (**10**).—To a mixture of 1:2 trifluoroacetic acid and CH_2Cl_2 (5 mL) was added **11** (0.40 g, 0.6 mmol) at 0 °C. After 1 h of

Table 2
Removal of AMPA in compounds **11**–**14** by catalytic hydrogenation

Entry	Ester Substrate	Alcoholic Product	Yield (%)
1	**11**	**6**	Quant.
2	**12**	**7**	Quant.
3	**13**	**8**	Quant.
4	**14**	**9** +  **17**	81% +19%

stirring at rt, the mixture was diluted with CH_2Cl_2 (10 mL) and then poured into satd aq $NaHCO_3$ (100 mL). The organic layer was washed with satd aq $NaHCO_3$ (2×100 mL) and water. The solution was dried over Na_2SO_4 and concentrated under vacuum, and the crude product was purified by flash chromatography (eluent: 1:1 EtOAc–hexane) to afford **10** (0.28 g, 78%) as white solid: mp 50 °C (dec); $[\alpha]_D^{25}$ +21.3° (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.82–7.70 (m, 4 H, Phth ArH), 7.12–7.07 (m, 4 H, AMPA ArH), 6.82–6.69 (m, 4 H, Mp ArH), 5.84 (d, 1 H, $J_{1,2}$ 8.5 Hz, 1-H), 5.71 (dd, 1 H, $J_{2,3}$ 10.6, $J_{3,4}$ 8.8 Hz, 3-H), 4.44 (dd, 1 H, 2-H), 4.20 (s, 2 H, PhCH_2N$_3$), 3.94–3.71 (m, 4 H, 4-H, 5-H, 6a-H, 6b-H), 3.70 (s, 3 H, OMe), 3.62 (d, 2 H, PhCH_2CO), 2.94 (bs, 1 H, OH), 2.03 (bs, 1 H, OH); HRFABMS: Calcd for $C_{23}H_{21}N_4O_7$ [$M^+ - OMp$], 465.1411. Found, 465.1402.

3-O-[(2-Azidomethyl)phenylacetyl]-1,2-O-isopropylidene-α-D-glucofuranose (**18**).—A solution of 3-*O*-[(2-azidomethyl)phenyl acetyl]-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**13**, 0.13 g, 0.3 mmol) in MeOH (4 mL) was treated with 0.8% aq H_2SO_4 (2 mL) at rt for 20 h. At this point, another portion (1 mL) of 0.8% aq H_2SO_4 was added, and the mixture was stirred for another 18 h. After neutralization with sodium bicarbonate, MeOH was removed under vacuum, and the remaining aqueous solution was extracted with CH_2Cl_2. The organic layer was washed with water and dried over Na_2SO_4. After condensation under vacuum, the crude product was purified by flash chromatography (eluent: 1:1 EtOAc–hexane) to afford **18** (94 mg, 80%) as colorless syrup: $[\alpha]_D^{25}$ +10.7° (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.39–7.30 (m, 4 H, AMPA ArH), 5.88 (d, 1 H, $J_{1,2}$ 3.6 Hz, 1-H), 5.28 (bd, 1 H, $J_{3,4}$ 2.6, 3-H), 4.53 (bd, 1 H, 2-H), 4.43, 4.38 (2 d, 1 H each, *J* 13.8 Hz, PhCH_2N$_3$), 4.18 (dd, 1 H, $J_{4,5}$ 9.0 Hz, 4-H), 3.80 (s, 2 H, PhCH_2CO), 3.80 (dd, 1 H, $J_{5,6a}$ 3.5, $J_{6a,6b}$ 11.3 Hz, 6a-H), 3.66 (dd, 1 H, 6b-H), 3.57–3.51 (m, 1 H, 5-H), 1.51, 1.31 (2 s, 9 H, 3 CH_3); HRFABMS: Calcd for $C_{17}H_{20}NO_7$ [$M^+ - CH_3$], 378.1302. Found, 378.1295.

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References

1. Grindley, T. B. In *Modern Methods in Carbohydrate Synthesis*; Khan, S. H.; O'Neill, R. A., Eds.; Harwood Academic: New York, 1996; pp. 225–250.
2. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; pp. 17–254.
3. Ziegler, T.; Pantkowski, G. *Tetrahedron Lett*. **1995**, *36*, 5727–5730.
4. Ziegler, T.; Pantkowski, G. *Liebigs Ann. Chem*. **1994**, 659–664.
5. Watanabe, Y.; Ishimaru, M.; Ozaki, S. *Chem. Lett*. **1994**, 2163–2166.
6. Kusumoto, S.; Sakai, K.; Shiba, T. *Bull. Chem. Soc. Jpn*. **1986**, *59*, 1296–1298.
7. Velarde, S.; Urbina, J.; Pena, M. R. *J. Org. Chem*. **1996**, *61*, 9541–9545.
8. Thompson, C.; Ge, M.; Kahne, D. *J. Am. Chem. Soc*. **1999**, *121*, 1237–1244.
9. Entwistle, I. D. *Tetrahedron Lett*. **1979**, 555–558.
10. Davies, J. A.; Hassall, C. H.; Rogers, I. H. *J. Chem. Soc. (C)* **1969**, 1358–1363.
11. Tang, Z.; Pelletier, J. C. *Tetrahedron Lett*. **1998**, *39*, 4773–4776.
12. Ellervik, U.; Grundberg, H.; Magnusson, G. *J. Org. Chem*. **1998**, *63*, 9323–9338.
13. Wada, T.; Ohkubo, A.; Mochizuki, A.; Sekine, M. *Tetrahedron Lett*. **2001**, *42*, 1069–1072.
14. Nakano, T.; Ito, Y.; Ogawa, T. *Tetrahedron Lett*. **1990**, *31*, 1597–1600.
15. Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990–2016.
16. Grzeszczyk, B.; Zamojski, A. *Collect. Czech. Chem. Commun*. **2000**, *65*, 610–620.