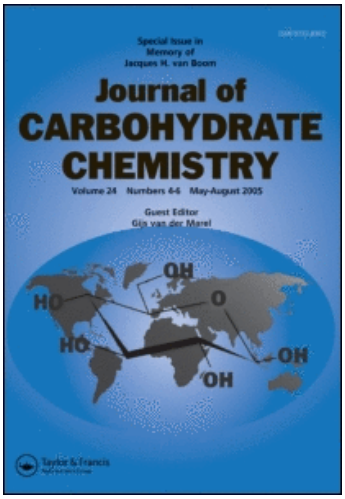

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Widely Applicable Deprotection Method of 2,2,2-Trichloroethoxycarbonyl (Troc) Group Using Tetrabutylammonium Fluoride

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Widely Applicable Deprotection Method of 2,2,2-Trichloroethoxycarbonyl (Troc) Group Using Tetrabutylammonium Fluoride

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The *N*-Troc (2,2,2-trichloroethoxycarbonyl) groups in glucosamine and muramic acid derivatives were removed by treatment with tetrabutylammonium fluoride (TBAF) under mild conditions. The use of Troc protection for the amino group in aminosugars such as glucosamine is increasing the importance for selective and efficient glycosylation, and the cleavage method described here will expand the available opportunities for using the Troc group in the preparation of a variety of glycans. This cleavage is especially advantageous for compounds that are labile or may be decomposed under acidic conditions, strong basic conditions, or reductive conditions.

Keywords 2,2,2-Trichloroethoxycarbonyl group; Tetrabutylammonium fluoride; Glucosamine; Deprotection.

INTRODUCTION

The 2,2,2-trichloroethoxycarbonyl (Troc) group was first introduced in organic synthesis by Woodward in 1966.[1] It is a stable protecting group for hydroxyl and amino groups,[2] and it has been widely used in organic synthesis, including oligosaccharide synthesis. For example, β-selective glycosylation is easily achieved by the effect of neighboring group participation of the 2-*N*-Troc

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group.[3] The Troc group is usually removed by a reductive elimination process. Several deprotection conditions have been published, such as Zn or Zn-Cu in AcOH, Zn-Pb in AcOH, Cd-Pd in AcOH, Li in liquid NH_3, SmI_2 in THF, Cd in AcOH-DMF, electrolysis,[2] Zn-*N*-methylimidazole,[4] mischmetal (50% Ce, 25% La, 16% Nd, 6% Pr) with TMSCl,[5] and $(Bu_3Sn)_2$ in DMF.[6]

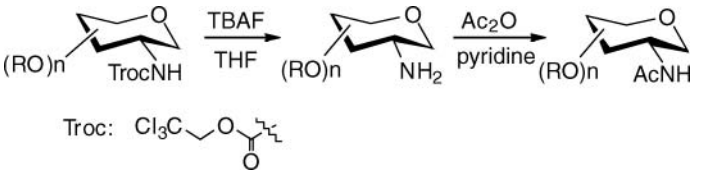
When the reductive conditions, such as Zn or Zn-Cu, are used, reductive substitution of a chlorine atom with a hydrogen one may occur as a side reaction. For the deprotection of Troc groups in an oligosaccharide, this chlorine elimination often causes a problem in obtaining a satisfactory yield. The reductive methods often use acidic conditions, which restrict their application to acid-stable compounds. The Zn-*N*-methylimidazole[4] or mischemetal with TMSCl[5] was developed recently as a milder condition to avoid the acidic conditions. In addition, most of these reactions are carried out under heterogeneous conditions except $(Bu_3Sn)_2$, and in these cases it is difficult to apply these methods to solid-phase synthesis. Therefore, we have developed a new method for the removal of the Troc group under mild conditions in a homogeneous reaction using tetrabutylammonium fluoride (TBAF). Although it is assumed that the Troc group may be removed under basic conditions, such conditions have not been reported to our knowledge, except under particular circumstances[7] or in Coudert's trial for carbamates.[8] Coudert and co-workers reported the deprotection of carbamates with TBAF; however, the conditions were rather harsh. The carbamates of ethyl, allyl (Alloc), benzyl (Z), and t-butyl (Boc) for amino protecting groups were only cleaved by using a large excess of TBAF under reflux conditions with THF for several hours. Only phenyl carbamate was removable at rt, though. Hence, we tried the Troc deprotection with TBAF, and also obtained results with LiOH.

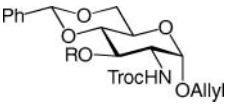
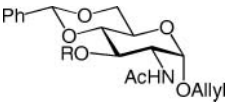
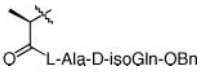
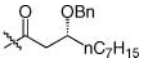
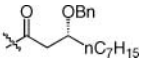
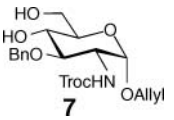
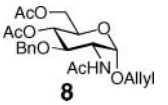
RESULTS AND DISCUSSION

We first examined the cleavage of the *N*-Troc group from the glucosamine derivative **1** with TBAF. When the compound **1** was treated with 1 M TBAF in THF at rt, followed by acetylation, the desired product **2** was obtained in 97% yield. The deprotection reaction was next applied to some different glucosamine derivatives, and they all gave good yields (Table 1). Other functional groups, such as the acetal group (benzylidene group in compounds **1**, **3**, and **5**), ester groups (in compounds **3** and **5**), an amide group (in compound **2**), and the relatively stable ethers (benzyl ether in **1**, **5**, and **7**), were not affected.

Compound **3** is a muramic acid linked to a dipeptide, which contains a carboxylic acid protected with a benzyl ester. Deprotection of the 2-*N*-Troc group of compound **3** with TBAF gave a good yield in 90% after acetylation. The 4-*O*-acylated glucosamine derivative **5** and the 4,6-*O*-dihydroxy glucosamine

Table 1: Cleavage of the Troc group using TBAF



Entry	Substrate	Product	Yield
			
1	**1** R=Bn	**2** R=Bn	97%
2	**3** R= 	**4** R= 	90%*
3	**5** R= 	**6** R= 	77%
4	 **7**	 **8**	78%

*: Reaction with additional 2 equiv. acetic acid.

derivative **7** also gave satisfactory yields in 77% and 78% (in two steps), respectively.

In the case of a muramic acid derivative **9**,[9] which has a relatively reactive ethyl ester, it gave the lactam **10** formed by the intramolecular condensation between the liberated amino group and the ester (Sch. 1). This reaction condition might be useful for other intramolecular lactam formation and peptide bond formation under a mild condition.

We also used lithium hydroxide as the base (Sch. 2). *N*-Troc muramic acid derivative **11**[10] was treated with LiOH in a mixed THF/dioxane/water solution; after stirring at rt for 3 h, the mixture was neutralized by addition of Dowex 50W ion exchange resin. Then the free amino group was protected with the acetyl group to give muramic acid derivative **12** in good yield (87% in two steps). The cleavage reaction in compound **9** also proceeded in good yield (90% in two steps, including acetylation). In both cases, no lactam products were found in the reaction. On the other hand, when the lactam **10** was treated with LiOH under similar reaction conditions, the lactam ring was found to open, followed by acetylation of the intermediate to give the compound **13**.

In conclusion, we have developed a mild and efficient methodology for removing the Troc protecting group. This method tolerates several other types of functional groups. It may further be applied to solid-phase synthesis and other organic syntheses.

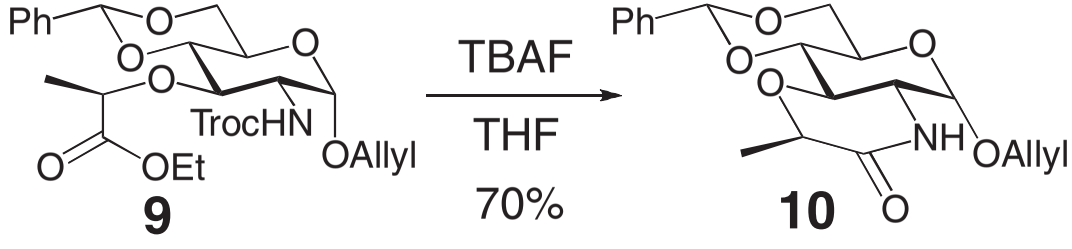
EXPERIMENTAL

General Procedures

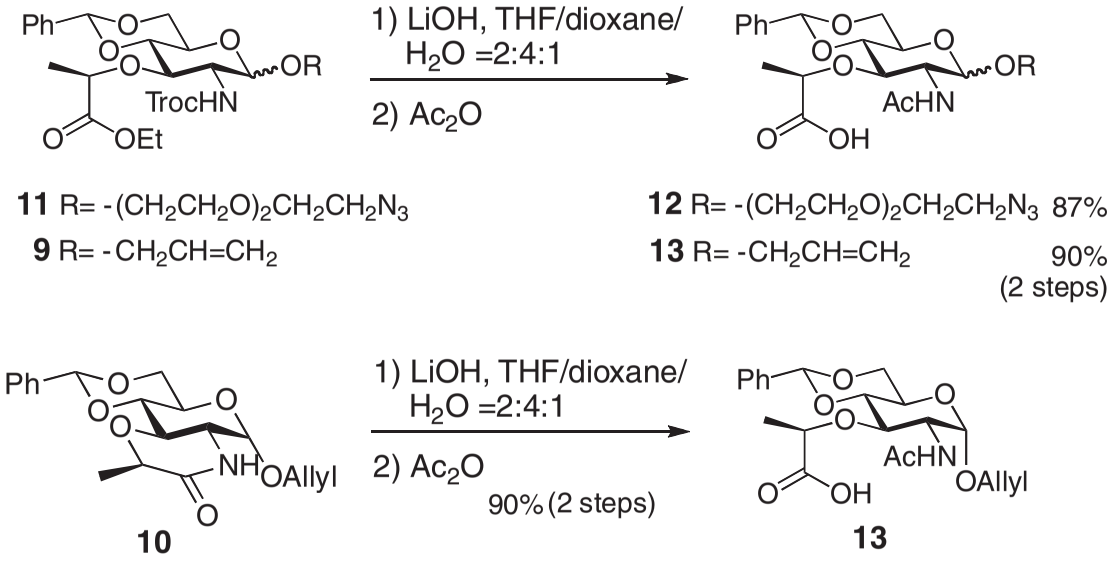
^{1}H NMR spectra were recorded at 500 MHz using a JEOL ECA 500 spectrometer. The chemical shifts in $CDCl_3$ are given in δ values from tetramethylsilane as an internal standard. ESI-TOF mass spectrometry was carried out using an Applied Biosystem Mariner Biospectrometry Workstation. MALDI-TOF mass spectrometry was carried out using an Applied Biosystem Voyager Elite XL (Matrix: α-Cyano-4-hydroxycinnamic acid). ESI-QTOF mass spectrometry was carried out using a Waters-Micromass Q-Tof micro. Elemental analyses were performed with Yanaco CHN corder MT-6. Silica gel column chromatography was carried out using Kieselgel 60 (Merck, 0.040–0.063 mm) at medium pressure (2–4 kg/cm^2). All other reagents and solvents used were purchased from commercial sources.

General Reaction Procedure of the Troc Group Deprotection with TBAF

Compound **1** (26.2 mg, 0.05 mmol) was dissolved in THF (0.4 mL), and then 1 M TBAF in THF (0.2 mL) was added. The mixture was stirred at rt



Scheme 1: Lactam formation of **9** with TBAF.



Scheme 2: Reactions with LiOH for the cleavage of Troc groups on **9** and **11**, and for the lactam opening of **10**.

for 3 h. The mixture was diluted with ethyl acetate, washed with water and brine, and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was treated with a pyridine:acetic anhydride 1:1 solution (1 mL). The mixture was stirred at rt for 1 h. The solvent was removed under vacuum, followed by coevaporation with toluene (×4). The residue was purified by flash silica gel column chromatography to give the product **2** 19.5 mg (yiled 97%). ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 7.46$–7.45 (m, 2H, ($C_6\underline{H}_5$)-CH_2-), 7.36–7.33 (m, 8H, ($C_6\underline{H}_5$)-CH_2-), 7.22–7.21 (d, $J = 7.9$ Hz, 1H, D-isoGln-NH), 7.09–7.08 (d, $J = 6.3$ Hz, 1H, L-Ala-NH), 6.28–6.26 (d, $J = 9.0$ Hz, 1H, H-1), 5.94–5.85 (m, 1H, -CH_2-$C\underline{H}$=CH_2), 5.56 (s, 1H, Ph-$C\underline{H}$=), 5.31–5.24 (m, 3H, -CH_2-CH=$C\underline{H}_2$, Ph-$C\underline{H}_2$-), 4.48–4.46 (m, 1H, D-isoGln-αH), 4.30–4.25 (m, 2H, H2, H5), 4.20–4.13 (m, 2H, -$C\underline{H}_2$-CH=CH_2, L-Ala-αH), 4.08–4.07 (q, $J = 6.7$ Hz, 1H, Lac-αH), 4.02–3.99 (m, 1H, -$C\underline{H}_2$-CH=CH_2), 3.86–3.81 (m, 1H, H-4), 3.78–3.74 (m, 1H, H-6), 3.70–3.63 (m, 2H, H-3, H-6), 2.60–2.47 (m, 2H, D-isoGln-γH), 2.29–2.20 (m, 1H, D-isoGln-βH), 2.09–2.01 (m, 4H, D-isoGln-βH, N-Ac), 1.41–1.36 (m, 6H, L-Ala-βH, Lac-Me). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 169.7$, 138.6, 137.4, 133.4, 128.9, 128.3, 128.2, 127.9, 127.6, 126.0, 117.9, 101.3, 97.4, 82.8, 76.0, 74.0, 68.9, 68.4, 62.9, 52.4, 23.3. HRMS (ESI-QTOF) for $C_{25}H_{30}NO_6^+$ $[M+H]^+$ calcd 440.2073; found 440.2061. $[\alpha]_D = +121.3^\circ$ (c 0.23, $CHCl_3$). Anal. Calcd for $C_{25}H_{29}NO_6$: C, 68.32%; H, 6.65%; N, 3.19%. Found: C, 68.02%; H, 6.48%; N, 3.19%.

Compounds **4**, **6**, **8**, and **10** were also synthesized with a similar procedure, and the spectroscopic data were as follows:

4: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46–7.45 (m, 2H, ($C_6\underline{H}_5$)-CH_2-), 7.36–7.33 (m, 8H, (($C_6\underline{H}_5$)-CH_2-), 7.22–7.21 (d, J = 7.9 Hz, 1H, D-isoGln-NH), 7.09–7.08 (d, J = 6.3 Hz, 1H, L-Ala-NH), 6.28–6.26 (d, J = 9.0 Hz, 1H, H1), 5.94–5.85 (m, 1H, -CH_2-$C\underline{H}$=CH_2), 5.56 (s, 1H, Ph-$C\underline{H}$=), 5.31–5.24 (m, 3H, -CH_2-CH=$C\underline{H}_2$, Ph-$C\underline{H}_2$-), 4.48–4.46 (m, 1H, D-isoGln-αH), 4.30–4.25 (m, 2H, H-2, H-5), 4.20–4.13 (m, 2H, -$C\underline{H}_2$-CH=CH_2, L-Ala-αH), 4.08–4.07 (q, J = 6.7 Hz, 1H, Lac-αH), 4.02–3.99 (m, 1H, -$C\underline{H}_2$-CH=CH_2), 3.86–3.81 (m, 1H, H-4), 3.78–3.74 (m, 1H, H-6), 3.70–3.63 (m, 2H, H-3, H-6), 2.60–2.47 (m, 2H, D-isoGln-γH), 2.29–2.20 (m, 1H, D-isoGln-βH), 2.09–2.01 (m, 4H, D-isoGln-βH, N-Ac), 1.41–1.36 (m, 6H, L-Ala-βH, Lac-Me); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.1, 173.8, 173.3, 172.1, 170.7, 137.1, 135.6, 133.1, 129.1, 128.6, 128.4, 128.3, 128.2, 126.0, 118.7, 101.5, 97.2, 81.3, 78.1, 76.8, 68.8, 68.7, 66.7, 63.0, 53.1, 52.7, 50.0, 30.8, 26.4, 23.6, 19.4, 16.8. ESI-TOF MS (positive) for $C_{36}H_{47}N4O_{11}^+$ $[M+H]^+$ calcd 711.3241; found 711.43. $[\alpha]_D = +66.0^\circ$ (c 0.18, $CHCl_3$). Anal. Calcd for $C_{36}H_{46}N_4O_{11}$: C, 60.83%; H, 6.52%; N, 7.88%. Found: C, 60.46%; H, 6.51%; N, 7.92%.

6: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.46$–7.22 (m, 10H, $C_6\underline{H}_5CH_2$-, $C_6\underline{H}_5CH$ =), 5.93–5.85 (m, 1H, -$CH_2C\underline{H}$=CH_2), 5.79 (d, $J = 9.3$ Hz, 1H, -N$\underline{H}$Ac), 5.49 (s, 1H, PhC$\underline{H}$=), 5.37 (t, $J = 10.1$ Hz, 1H, H-3), 5.32–5.23 (m, 2H, -CH_2CH=C$\underline{H}_2$), 4.89 (d, $J = 3.7$ Hz, 1H, H-1), 4.51, 4.41 (d, $J = 11.7$ Hz, each 1H, PhC$\underline{H}_2$-), 4.35 (dt, $J = 10.1$, 3.7 Hz, 1H, H-2), 4.28 (dd, $J = 10.2$, 4.7 Hz, 1H, H-6), 4.20, 4.00 (m, each 1H, -C$\underline{H}_2$CH=CH_2), 3.93 (dt, $J = 9.9$, 4.7 Hz, 1H, H-5),

3.81–3.69 (m, 3H, H-4, H-6, -CH(OBn)-), 2.69, 2.45 (dd, J = 15.2, 6.1 Hz, each 1H, α-H), 1.91 (s, 3H, -COCH$_3$), 1.58–1.11 (m, 12H, -(CH$_2$)$_6$-), 0.86 (t, J = 7.1 Hz, 3H, -CH$_2$CH$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 172.2, 169.9, 138.6, 137.0, 133.2, 129.1, 128.3, 128.2, 127.7, 127.5, 126.1, 118.3, 101.6, 97.2, 79.1, 75.5, 71.1, 70.2, 68.9, 68.7, 63.0, 52.6, 39.6, 34.5, 31.8, 29.5, 29.3, 25.1, 23.2, 22.6, 14.1. MALDI-TOF MS (positive) for $C_{35}H_{47}NNaO_8^+$ $[M+Na]^+$ calcd 632.3199; found 632.4486. HRMS (ESI-QTOF) (positive) for $C_{35}H_{48}NO_8^+$ $[M+H]^+$ calcd 610.3380; found 610.3371. $[\alpha]_D$ = +38.9° (c 0.28, $CHCl_3$). Anal. Calcd for $C_{35}H_{47}NO_8 \cdot H_2O$: C, 66.96%; H, 7.87%; N, 2.23%. Found: C, 66.80%; H, 7.87%; N, 2.16%.

8: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 5H, C$_6$H$_5$CH$_2$-), 5.92–5.82 (m, 1H, -CH$_2$CH=CH$_2$), 5.33 (d, J = 9.3 Hz, 1H, -NHAc), 5.30–5.22 (m, 2H, -CH$_2$CH=CH$_2$), 5.17 (dd, J = 10.1, 9.3 Hz, 1H, H-4), 4.89 (d, J = 3.6 Hz, 1H, H-1), 4.63, 4.54 (d, J = 11.5 Hz, each 1H, PhCH$_2$-), 4.37 (ddd, J = 10.7, 9.3, 3.6 Hz, 1H, H-2), 4.20 (dd, J = 12.3, 5.0 Hz, 1H, H-6), 4.16, 3.99 (m, each 1H, -CH$_2$CH=CH$_2$), 4.09 (dd, J = 12.3, 2.5 Hz, 1H, H-6), 3.90 (ddd, J = 10.1, 5.0, 2.5 Hz, 1H, H-5), 3.77 (dd, J = 10.7, 9.3 Hz, 1H, H-3), 2.09 (s, 3H, -COCH$_3$), 2.03 (s, 3H, -COCH$_3$), 1.88 (s, 3H, -COCH$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.8, 169.6, 169.4, 138.0, 133.3, 128.5, 128.0, 127.9, 118.1, 96.8, 77.6, 72.8, 69.9, 68.6, 68.4, 62.4, 51.7, 23.4, 20.8, 20.77. HRMS (ESI-QTOF) for $C_{22}H_{29}NNaO_8^+$ $[M+Na]^+$ calcd 458.1791; found 458.1722. $[\alpha]_D$ = +98.8° (c 0.25, $CHCl_3$). Anal. Calcd for $C_{22}H_{29}NO_8 \cdot 0.6H_2O$: C, 59.21%; H, 6.82%; N, 3.14%. Found: C, 59.18%; H, 6.92%; N, 2.95%.

10: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55–7.34 (m, 5H, C$_6$H$_5$CH=), 6.06 (br s, 1H, -NH), 5.95–5.86 (m, 1H, -CH$_2$CH=CH$_2$), 5.58 (s, 1H, PhCH=), 5.35–5.25 (m, 2H, -CH$_2$CH=CH$_2$), 4.88 (d, J = 3.6 Hz, 1H, H-1), 4.33 (q, J = 6.9 Hz, 1H, Lac-αH), 4.28 (dd, J = 10.3, 4.8 Hz, 1H, H-6), 4.24, 4.02 (m, each 1H, -CH$_2$CH=CH$_2$), 4.10 (t, J = 9.4 Hz, 1H, H-4), 3.96 (dt, J = 9.4, 4.8 Hz, 1H, H-5), 3.80 (t, J = 10.3 Hz, 1H, H-6), 3.77 (t, J = 9.3 Hz, 1H, H-3), 3.66 (dd, J = 9.3, 3.6 Hz, 1H, H-2), 1.50 (d, J = 6.9 Hz, 3H, CH$_3$- of Lac). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 171.8, 136.9, 133.2, 129.2, 128.3, 126.3, 118.2, 102.0, 96.2, 79.1, 74.4, 72.3, 69.2, 68.8, 63.9, 56.1, 17.8. HRMS (ESI-QTOF) for $C_{19}H_{24}NO_6^+$ $[M+H]^+$ calcd 362.1604; found 362.1603. $[\alpha]_D$ = +91.3° (c 0.27, $CHCl_3$). Anal. Calcd for $C_{19}H_{23}NO_6 \cdot 0.7H_2O$: C, 61.02%; H, 6.58%; N, 3.75%. Found: C, 60.98%; H, 6.50%; N, 3.62%.

General Reaction Procedure of the Troc Group Deprotection with LiOH

Compound **11** (200.7 mg, 0.287 mmol) was dissolved in a mixture of THF:dioxane:water = 4:2:1 (9 mL), and then LiOH (65.9 mg, 1.57 mmol) was added. The mixture was stirred at rt for 3 h. The solution was neutralized by adding Dowex 50W (H^+) resin (260 mg) and filtered, and the filtrate was evaporated under vacuum. The crude residue (142.9 mg) was treated with a

pyridine:acetic anhydride 1:1 solution (10.8 mL). The mixture was stirred at rt for 1 h. The solvent was removed under vacuum, followed by coevaporation with toluene (×4). The residue was purified by flash silica gel column chromatography to give the product **12** 131.8 mg (yield 87%). ^{1}H NMR (500 MHz, $CDCl_3$:CD_3OD, 9:1) δ = 7.46–7.36 (m, 5H, ArH), 5.56 (s, 1H, Ph-CH=), 4.69 (d, J = 7.9 Hz, 1H, H-1), 4.31 (dd, J = 4.85 Hz, J = 10.45 Hz, 1H, H-6), 4.24 (q, J = 6.75 Hz, 1H, Lac-αH), 3.95–3.91 (m, 1H, PEG-H-1), 3.82–3.77 (m, 3H, H-6, H-3, H-2), 3.74–3.71 (m, 1H, PEG-H-1), 3.70–3.63 (m, 8H, PEG-H-2, PEG-H-3, PEG-H-4, PEG-H-5), 3.44–3.38 (m, 4H, H-5, H-4, PEG-H-6), 2.00 (s, 3H, CH_3-CO-), 1.38 (d, J = 6.9 Hz, 3H, Lac-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$:CD_3OD, 9:1) δ = 176.5, 172.7, 137.0, 128.9, 128.1, 125.8, 101.7, 101.1, 81.8, 78.1, 70.40, 70.36, 70.34, 69.8, 68.7, 68.5, 66.0, 55.9, 55.83, 50.5, 22.8, 18.8; ESI-TOF-MS (m/z): $[M+H]^+$ calcd. for $C_{24}H_{35}N_4O_{10}$, 539.23; found 539.23. $[M+Na]^+$ calcd. for $C_{24}H_{34}N_4O_{10}Na$, 561.23; found 561.21. $[M-H]^-$ calcd. for $C_{24}H_{33}N_4O_{10}$, 537.23; found 537.23. $[\alpha]_D$ = –28.3° (*c* 1.03, $CHCl_3$:MeOH = 9:1). Anal. Calcd for $C_{24}H_{34}N_4O_{10}$: C, 53.52%; H, 6.36%; N, 10.40%. Found: C, 53.01%; H, 6.21%; N, 9.83%.

Compound **13** was also synthesized with a similar procedure, and the spectroscopic data were as follows:

13: ^{1}H NMR (500 MHz, $CDCl_3$:CD_3OD = 9:1): δ = 7.50–7.23 (m, 5H, C_6H_5CH=), 5.91–5.81 (m, 1H, -CH_2CH=CH_2), 5.58 (s, 1H, PhCH=), 5.30–5.00 (m, 3H, H-1, -CH_2CH = CH_2), 4.33 (q, J = 6.6 Hz, 1H, Lac−αH), 4.24 (dd, J = 9.5, 3.9 Hz, 1H, H-6), 4.15, 3.99 (m, each 1H, -CH_2CH=CH_2), 3.93 (dd, J = 10.3, 2.7 Hz, 1H, H-2), 3.88–3.60 (m, 4H, H-3, H-4, H-5, H-6), 2.01 (s, 3H, -$COCH_3$), 1.41 (d, J = 6.6 Hz, 3H, Lac−CH_3). ^{13}C NMR (125 MHz, $CDCl_3$:CD_3OD = 9:1) δ = 179.0, 172.2, 137.1, 133.5, 128.8, 128.0, 125.7, 117.3, 101.2, 96.6, 82.3, 75.2, 68.7, 68.6, 62.9, 54.2, 29.5, 22.3, 18.7. ESI-TOF MS (positive) for $C_{21}H_{27}NO_8Na^+$ $[M+Na]^+$ calcd 444.1634; found 444.1740. HRMS (ESI-QTOF) (positive) for $C_{21}H_{28}NO_8^+$ $[M+H]^+$ calcd 422.1815; found 422.1812. $[\alpha]_D$ = +83.0° (*c* 0.23, $CHCl_3$). Anal. Calcd for $C_{21}H_{27}NO_8 \cdot 0.5H_2O$: C, 58.60%; H, 6.36%; N, 3.25%. Found: C, 58.66%; H, 6.70%; N, 2.95%.

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10. Compound **11** was obtained with the glycosylataion of 4,6-*O*-benzylidene 2-*N*-Troc muramic acid (4,6-benzylidene-MurNTroc) with the same procedure with the synthesis of **9**.[9] Namely, 4,6-benzylidene-MurNTroc (44.9 mg, 0.083 mmol) and $CsCO_3$ (17.3 mg, 0.053 mmol) were dispersed in dry CH_2Cl_2 (0.9 mL). To this mixture was added CCl_3CN (0.083 mL, 0.83 mmol), and the mixture was stirred for 3.5 h. The reaction mixture was then filtrated with celite, and the solvent was removed in vacuo. The obtained trichloroacetimidate compound was used after lyophilization with benzene, without further purification. The imidate (60.8 mg), $HO(CH_2)_2O(CH_2)_2O(CH_2)N_3$ (44.2 mg, 0.252 mmol), and MS 4A were added in CH_2Cl_2 (2.7 mL) and cooled to –15°C. To the reaction mixture, a solution of TMSOTf (1.6 μL, 8.7 μmol) in CH_2Cl_2 (0.08 mL) was added. The mixture was stirred for 1.5 h, quenched with sat. $NaHCO_3$aq, and then filtrated. The combined organic layer was washed with sat. $NaHCO_3$aq. and then brine. The solvent was removed in vacuo, and the crude material was purified by silica gel flash chromatography (toluene:AcOEt = 4:1) to give **11** (51.3 mg, 88%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46–7.36 (m, 5H, $C_6\underline{H}_5CH$=), 5.56 (s, 1H, PhC$\underline{H}$=), 4.79–4.73 (m, 2H, -CO-O-C$\underline{H}_2$-CCl_3), 4.67 (d, J = 8.0 Hz, 1H, H-1), 4.50 (q, J = 7.0 Hz, 1H, Lac-αH), 4.34 (dd, J = 4.9, 5.7 Hz, 1H, H-6), 4.23–4.09 (m, 2H, -CO-O-C$\underline{H}_2$-CH_3), 3.96–3.92 (m, 1H, PEG-H-1), 3.86–3.76 (m, 4H, H-6, H-3, H-2), 3.75–3.63 (m, 7H, H-2, PEG-H-3, PEG-H-4, PEG-H-5), 3.60–3.55 (m, 1H, H-4), 3.44–3.39 (m, 3H, H-5, PEG-H-6), 1.39 (d, J = 6.85 Hz, 3H, Lac-CH_3). ESI-TOF MS for $C_{27}H_{38}Cl_3N_4O_{11}$, $[M+H]^+$ calcd 699.15, found 699.13.