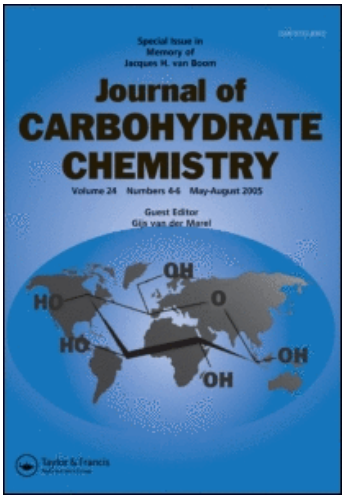

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Lanthanum Trifluoromethane-sulfonate-Catalyzed Facile Synthesis of Per-*O*-acetylated Sugars and Their One-Pot Conversion to *S*-Aryl and *O*-Alkyl/Aryl Glycosides

Somnath Dasgupta[a]; Vishal Kumar Rajput[a]; Bimalendu Roy[a]; Balaram Mukhopadhyay[a]
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Lanthanum Trifluoromethane-sulfonate-Catalyzed Facile Synthesis of Per-*O*-acetylated Sugars and Their One-Pot Conversion to *S*-Aryl and *O*-Alkyl/Aryl Glycosides†

Somnath Dasgupta‡, Vishal Kumar Rajput‡, Bimalendu Roy, and Balaram Mukhopadhyay

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Lanthanum trifluoromethanesulfonate-catalyzed solvent-free per-*O*-acetylation with stoichiometric acetic anhydride proceeds in high yield (95%–99%) to afford exclusively pyranose products as anomeric mixtures. Subsequent anomeric substitution employing borontrifluoride etherate and thiols or alcohols furnished the corresponding 1,2-*trans*-linked thioglycosides and *O*-glycosides, respectively, in good to excellent overall yield (75%–85%). Alternatively, reaction of free sugars in neat alcohol employing the same catalyst at elevated temperature gives the corresponding 1,2-*cis*-linked *O*-glycosides (along with 1,2-*trans*-linked glycosides as minor product) in good yield (73%–80%).

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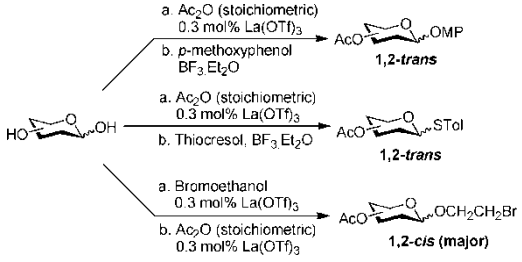
Anomeric mixtures of compounds thus produced were characterized as their per-*O*-acetylated derivatives.



Keywords *O*-Glycoside, *S*-Glycoside, Per-*O*-acetylation, $La(OTf)_3$

Development of glycobiology dealing with the role of carbohydrates in a plethora of biological processes[1] has enforced the search for new and more practical methods for the synthesis of carbohydrate derivatives. Therefore, in recent years major advances have been made through the application of reactivity tuning,[2] based on the concept of armed and disarmed glycosylation reactions,[3] extended to the so-called "programmable" syntheses[4] and ultimately automated glycosylation strategy.[5] However, need for efficient syntheses of suitably protected and/or activated carbohydrate building blocks still remains important. Per-*O*-acetylated sugars[6] and the corresponding *O*-[7] and *S*-glycosides[8] are routinely used building blocks in oligosaccharide synthesis. Hence, a practical one-pot strategy providing access to these building blocks from unprotected reducing sugars would be useful.

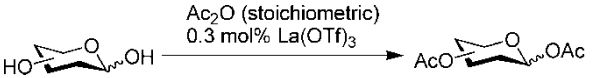
Metal triflates have earned a great deal of attention as catalysts for acylation of phenols, alcohols, and thiols.[9] Several procedures are available in the literature using various metal triflates,[10] but they suffer from one or more of the drawbacks such as moisture sensitivity, requirement of large excess of reagents, need for solvent, high expense, and incompatibility with other protecting groups due to the stringent reaction conditions that make them detrimental for wide application. Recently, $Cu(OTf)_2$ has been used for the per-*O*-acetylation of sugars with stoichiometric Ac_2O, and subsequent anomeric substitution using borontrifluoride etherate and thiols to give the corresponding thioglycosides[6e] as well $BF_3 \cdot Et_2O$ has been used for both acetylation followed by thioglycosylation purpose.[11] However, highly moisture-sensitive $Cu(OTf)_2$ requires absolute anhydrous reaction conditions, which in turn limits the applicability of the catalyst in large-scale preparations. Careful scrutiny of the commercially available metal triflates has revealed $La(OTf)_3$ as a cost-effective, moisture tolerant[12] Lewis acid catalyst that could serve the purpose more efficiently. It is worth noting at this point that reports are available in the literature for successful use of $La(OTf)_3$, $Sc(OTf)_3$, or $LiClO_4$

for per-*O*-acetylation of sugars under stoichiometric and/or solvent-free conditions.[13] We now report a practical one-pot two-step reaction sequence from unprotected reducing sugars, employing stoichiometric reagents, minimal workup, and purification, that provides the access to per-*O*-acetylated sugars, the corresponding per-*O*-acetylated *O*-glycosides, and thioglycosides in excellent yield and exclusive anomeric, stereoselectivity.

Per-*O*-acetylation of D-glucose with 5.0 molar equivalent of acetic anhydride (i.e., 1.0 mol. equiv. per hydroxyl group) and $La(OTf)_3$ (0.3 mol% in respect of the sugar) afforded the complete reaction within 30 min. The exothermic reaction started almost immediately after the addition of the catalyst and gave only D-glucopyranosyl ester (**1**); no trace of the furanosyl product was detected by ^1H NMR spectroscopy of the crude reaction mixture. After complete conversion, the reaction mixture was neutralized with saturated aq. $NaHCO_3$ and the product was extracted with CH_2Cl_2. Results for the per-*O*-acetylation of a range of pentoses, hexoses, and disaccharides are summarized in Table 1. It is worth noting that the use of solvents such as CH_3CN, CH_2Cl_2, or $MeNO_2$ is proved to be detrimental to the catalytic activity of $La(OTf)_3$ toward acetylation.

Successful completion of the solvent-free per-*O*-acetylation of free reducing sugars tempted us to explore the formation of the corresponding thioglycosides. Conventional per-*O*-acetylation using excess Ac_2O inevitably requires neutralization followed by workup and purification of the products. But the use of stoichiometric Ac_2O offers the possibility for a sequential reaction in one-pot fashion, as described recently for $Cu(OTf)_2/BF_3 \cdot Et_2O$[6e] or simply $BF_3 \cdot Et_2O$-mediated per-*O*-acetylation-thioglycoside formation.[12] Thus, after complete conversion of D-glucose to the corresponding per-*O*-acetate (**1**) (as judged by TLC), 1.5 mol. equiv. of each thiocresol and $BF_3 \cdot Et_2O$ were added to the reaction mixture and was allowed to stir at rt. Monitoring the reaction by TLC revealed a slow conversion to the target thioglycoside and 50% conversion was observed after 24 hours. We assumed that the AcOH formed as the byproduct of the initial acetylation reaction must have caused the retardation of the reaction. Hence, after complete acetylation, the reaction mixture was evaporated to dryness in vacuo and the residue was dissolved in the minimum quantity of CH_2Cl_2 (1 mL/mmol of sugar), enough to give a thick syrupy mass, followed by the addition of thiocresol and $BF_3 \cdot Et_2O$ as mentioned above. This way, the reaction was completed within 8 hours giving the corresponding 1,2-*trans*-thiotolyl derivative in 85% isolated yield. It is worth noting that the two previous methods, $Cu(OTf)_2/BF_3 \cdot Et_2O$-mediated[6e] and the $BF_3 \cdot Et_2O$-mediated[12] per-*O*-acetylation-thioglycoside formation, also failed to produce results to our satisfaction when AcOH was not removed after per-*O*-acetylation. Prolonged reactions for the second step (longer by days than reported) also did not lead to the completion of the reaction. To confirm the necessity of AcOH removal, a series of

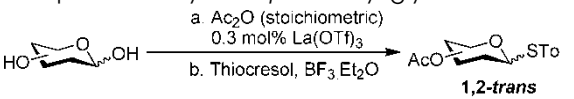
Table 1: La(OTf)$_3$-catalyzed solvent-free per-*O*-acetylation of sugar alcohols with stoichiometric acetic anhydride and catalytic La(OTf)$_3$.[a]

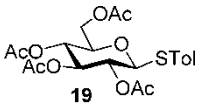
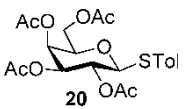
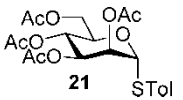
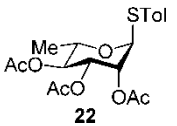
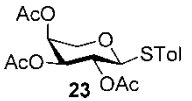


Entry	Sugar	Product	Time (min)	α/β	Yield (%)	Ref.
1	D-Glucose (**1**)	D-Glucopyranose pentaacetate (**10**)	30	11:1	98	(14, 15)
2	D-Galactose (**2**)	D-Galactopyranose pentaacetate (**11**)	30	11:1	97	(14, 15)
3	D-Mannose (**3**)	D-Mannopyranose pentaacetate (**12**)	25	3:1	99	(14, 15)
4	L-Rhamnose monohydrate[b] (**4**)	L-Rhamnopyranose tetraacetate (**13**)	15	4:1	98	(14, 15)
5	L-Fucose (**5**)	L-Fucopyranose tetraacetate (**14**)	15	10:1	97	(14,15)
6	L-Arabinose (**6**)	L-Arabinopyranose tetraacetate (**15**)	25	9:1	96	(14, 15)
7	D-Xylose (**7**)	D-Xylopyranose tetraacetate (**16**)	15	5:1	98	(14, 15)
8	D-Maltose monohydrate[b] (**8**)	D-Maltose octaacetate (**17**)	45	10:1	95	(14, 15)
9	D-Lactose (**9**)	D-Lactose octaacetate (**18**)	45	10:1	97	(14, 15)

[a]With 1.0 mol. equiv. of Ac_2O per hydroxyl group and 0.3 mol% of La(OTf)$_3$.
[b]In the cases of L-Rhamnose and D-Maltose, an additional 1 mol. equiv. of Ac_2O was necessary since these sugars were commercially available only as monohydrates.

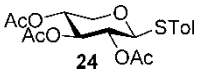
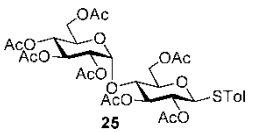
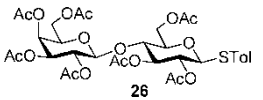
Table 2: One-pot conversion of free sugars to per-*O*-acetylated *p*-thiotolyl glycosides.



Sugar	Product	Method A[a] Time (h)	Method A[a] Yield (%)	Method B[a] Time (h)	Method B[a] Yield (%)	Ref.
D-Glucose (**1**)	 **19**	48	50	8	85 82 (100 mmol scale)	(14)
D-Galactose (**2**)	 **20**	48	52	7	82	(16)
D-Mannose (**3**)	 **21**	48	55	8	83	(17)
L-Rhamnose monohydrate (**4**)	 **22**	48	68	4	85	(14)
L-Arabinose (**6**)	 **23**	48	58	3.5	81	(14)

(*continued*)

Table 2: Continued.

Sugar	Product	Method A[a] Time (h)	Method A[a] Yield (%)	Method B[a] Time (h)	Method B[a] Yield (%)	Ref.
D-Xylose (**7**)	 **24**	48	60	4	83	(18)
D-Maltose monohydrate (**8**)	 **25**	48	45	8	75	(18)
D-Lactose (**9**)	 **26**	48	47	8	77	(18, 19)

[a]**Method A**: Acetylation using stoichiometric Ac_2O followed by direct addition of thiocresol (1.5 mol. equiv.) and $BF_3 \cdot Et_2O$ (1.5 mol. equiv.). **Method B**: After acetylation, AcOH was removed in vacuo and thiocresol (1.5 mol. equiv.) and $BF_3B \cdot Et_2O$ (1.5 mol. equiv.) were added.

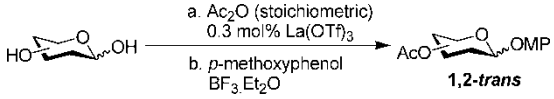
sugars were subjected to the one-pot (without removal of AcOH) and semi-one-pot (after removal of AcOH) reactions in parallel. The results are summarized in Table 2. These observations clearly suggest the necessity of AcOH removal but it is highly rewarding in terms of the shorter reaction time and the improved yield that the method leads to. Interestingly, in the case of the iodine-mediated one-pot acetylation-glycosyl iodide-thioglycoside sequence,[14] no such problem was noted, presumably due to the high reactivity of the intermediate anomeric iodide that is involved.[14]

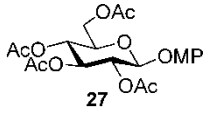
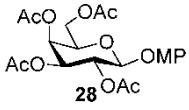
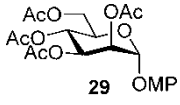
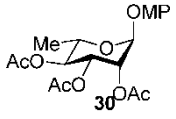
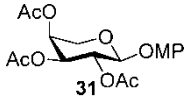
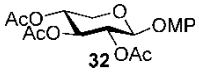
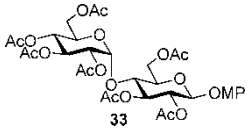
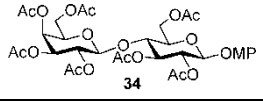
Similarly, the one-pot two-step per-*O*-acetylation-*O*-glycoside formation was investigated. *p*-Methoxyphenyl group has been used extensively as a protecting group for the anomeric center during oligosaccharide glycoconjugate syntheses. Therefore, in a separate experiment, after formation of the D-glucose per-*O*-acetate (**1**), AcOH was removed under reduced pressure and 1.5 mol. equiv. of *p*-methoxyphenol were added followed by 1.5 mol. equiv. of $BF_3 \cdot Et_2O$. After stirring at rt for 8 h, the anticipated 1,2-*trans*-*p*-methoxyphenyl glucoside was obtained in 78% yield. A series of sugars were then successfully converted to their corresponding 1,2-*trans*-*p*-methoxyphenyl glycosides in good yield (74%–81%) and the results are summarized in Table 3.

Finally, we focused our attention on the possible application of $La(OTf)_3$ for Fisher-type glycosylation to afford 1,2-*cis*-*O*-glycosides. Thus, to a slurry of D-glucose in 3 mol. equiv. of 2-bromoethanol was added 0.3 mol% of $La(OTf)_3$, and the mixture was stirred at 70°C for 2 h until the mixture became clear and TLC showed no trace of the starting sugar. Then the mixture was left stirring at rt overnight to achieve maximum thermodynamic 1,2-*cis*-*O*-glycoside product. The resulting solution was directly charged on a flash column of silica and eluted with CH_2Cl_2 to remove the excess alcohol and the compound was eluted with CH_2Cl_2-MeOH (5:1). It was then acetylated using Ac_2O and 0.3 mol% of $La(OTf)_3$ and was characterized by NMR spectroscopy and mass spectrometry. A series of bromoethyl glycosides of other sugars could also be prepared in the same fashion (Table 4). In all the cases the 1,2-*cis*-*O*-glycosides were found as major products. Other glycosides such as benzyl and allyl using benzyl alcohol and allyl alcohol, respectively, also proceeded smoothly leading to 1,2-*cis*-glycosides predominantly. Results are summarized in Table 4.

In summary, $La(OTf)_3$ is a moisture-tolerant, cost-effective catalyst for the solvent-free per-*O*-acetylation of free sugars using stoichiometric Ac_2O. Without workup, using thiols or alcohols in conjunction with $BF_3 \cdot Et_2O$, these acetylated carbohydrates afforded the respective 1,2-*trans*- thioglycosides or *O*-glycosides in good to excellent yield with absolute stereospecificity. Furthermore, Fisher-type glycosylation catalyzed by $La(OTf)_3$ using neat alcohol afforded 1,2-*cis*-glycosides predominantly in good yield. All the reactions referred to in Tables 1 to 4 have been carried out on a 10-mmol scale, but a 100-mmol scale thioglycosylation reaction using D-glucose revealed

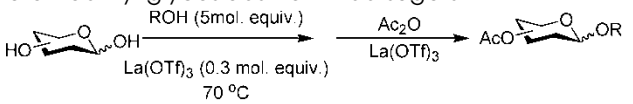
Table 3: One-pot conversion of free sugars to per-*O*-acetylated *p*-methoxyphenyl glycosides.[a]

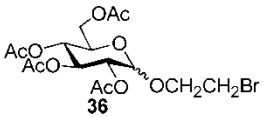
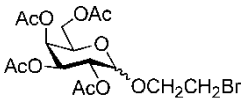
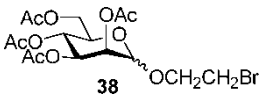
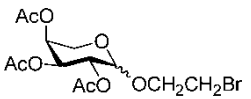
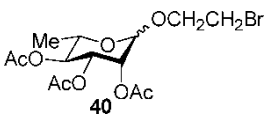


Sugar	Product	Time (h)	Yield (%)	Ref.
D-Glucose (**1**)	 **27**	8	78	(20)
D-Galactose (**2**)	 **28**	7	75	(21)
D-Mannose (**3**)	 **29**	8	80	(22)
L-Rhamnose monohydrate (**4**)	 **30**	5	81	(23)
L-Arabinose (**6**)	 **31**	4	76	
D-Xylose (**7**)	 **32**	5	75	(24)
D-Maltose monohydrate (**8**)	 **33**	8	74	(25)
D-Lactose (**9**)	 **34**	8	76	(26)

[a]Per-*O*-acetylation with stoichiometric Ac_2O followed by the addition of *p*-methoxyphenol (1.5 mol. equiv.) and $BF_3 \cdot Et_2O$(1.5 mol. equiv.).

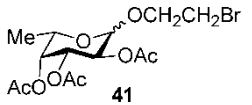
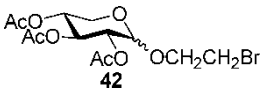
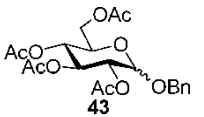
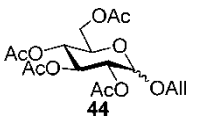
Table 4: Synthesis of per-*O*-acetylated bromoethyl glycosides from free sugars.



Sugar	Product	Time (h)[a]	α/β	Yield (%)	Ref.
D-Glucose (**1**)	 **36**	13	2.6:1	73	(27)
D-Galactose (**2**)	 **37**	13	2.6:1	76	(28)
D-Mannose (**3**)	 **38**	13	10:1	75	(29)
N-acetyl-D-glucosamine (**35**)	 **39**	13	8:1	80	(30)
L-Rhamnose monohydrate (**4**)	 **40**	13	4:1	79	

(*continued*)

Table 4: Continued.

Sugar	Product	Time (h)[a]	α/β	Yield (%)	Ref.
L-Fucose (**5**)	 **41**	13	2:1	76	(31)
D-Xylose (**7**)	 **42**	13	2.5:1	73	
D-Glucose (**1**)	 **43**	13	2.8:1	79	(32)
D-Glucose (**1**)	 **44**	13	2.7:1	75	(32)

[a]After addition of 2-bromoethanol (5 mol. equiv.) and $La(OTf)_3$ (0.3 mol%), the mixture was heated at 70°C for 3 h and then stirred at rt. for 10 h.

that the procedure is well suited for larger-scale preparations as well. The present method minimizes the reagent use and workup while providing different classes of commonly used sugar building blocks in a practical way.

EXPERIMENTAL

General Methods

Solvents were purified and dried prior to use.[33] Flash chromatography[34] was carried out with silica gel 60 (230–400 mesh). TLC was performed on precoated aluminium plates of silica gel 60 F254. Detection was executed under UV and by spraying 10% H_2SO_4 in EtOH followed by heating on a hot plate. ^1H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, on a Bruker Avance instrument. Chemical shifts are in ppm from Me_4Si or generated from $CHCl_3$ at δ 7.24 ppm. Mass spectra were obtained in EI mode.

General Procedure for Per-*O*-acetylation of Unprotected Reducing Sugars

To a mixture of sugar (10 mmol) and stoichiometric amount of Ac_2O (1 mol. equiv. per hydroxyl group), $La(OTf)_3$ (0.3 mol%) was added and the mixture was allowed to stir at rt until the solution became clear and TLC (2:1, *n*-hexane-EtOAc) showed complete conversion (15–45 min). The solution was carefully neutralized with saturated aq. NaHCO3 and the compound was extracted with CH_2Cl_2 (2×10 mL). Combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo and purified by flash chromatography using *n*-hexane-EtOAc (3:1) as eluent to afford the per-*O*-acetylated pyranoses in excellent yield (Table 1).

General Procedure for Semi-One-Pot Per-*O*-acetylation-Thioglycoside Formation of Unprotected Reducing Sugars

Per-*O*-acetylation reaction was carried out by the same procedure as described above. When TLC showed complete conversion, the 'solvent' was evaporated in vacuo and the residue was dissolved in CH_2Cl_2 (2 mL). *p*-Thiocresol (15 mmol, 1.5 mol. equiv.) was added followed by $BF_3 \cdot Et_2O$ (15 mmol)

and the solution was stirred at rt until TLC (*n*-hexane-EtOAc; 3:1) showed complete consumption of the per-*O*-acetate. The solution was then diluted with CH_2Cl_2 (15 mL) and washed successively with H_2O (15 mL), satd. aq. $NaHCO_3$ (2×15 mL) and brine (15 mL). Organic layer was collected, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by flash chromatography

using *n*-hexane-EtOAc (4:1) to afford pure per-*O*-acetylated *p*-tolyl thioglycosides in good to excellent yield (Table 2).

General Procedure for One-Pot Per-*O*-acetylation-Thioglycoside Formation of Unprotected Reducing Sugars

The procedure followed was the same as described above except *p*-methoxyphenol (15 mmol, 1.5 mol. equiv.) was used instead of *p*-thiocresol (Table 3).

General Procedure for 1,2-*cis*-*O*-glycosylation of Unprotected Sugars in Neat Alcohol

To a mixture of sugar (10 mmol) and 2-bromoethanol (50 mmol), $La(OTf)_3$ (3 mmol) was added and the mixture was stirred at 70°C for 3 h until the solution become clear. Then the solution was left stirring at rt for an additional 10 h. The whole reaction mixture was charged on a flash column after neutralizing with Et_3N and eluted with CH_2Cl_2 until complete removal of the excess alcohol. The product was eluted with CH_2Cl_2-MeOH (7:1) to afford the target product as anomeric mixture. The otherwise free bromoethyl glycosides thus obtained were acetylated with stoichiometric Ac_2O and $La(OTf)_3$ (0.3 mol%). The residue were subjected to flash chromatography using *n*-hexane-EtOAc (4:1) to afford pure per-*O*-acetylated bromoethyl glycosides.

p-Methoxyphenyl 2,3,4-tri-*O*-acetyl-α-L-arabinopyranoside (31)

Colorless foam. $[\alpha]_D^{25}$ +31 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.98, 6.79 (2d, 4H, ArH); 5.66 (d, 1H, *J* 3.6 Hz, H-1); 5.55 (dd, 1H, *J* 3.6 Hz, 9.8 Hz, H-2); 5.41 (bs, 1H, H-4); 5.28 (dd, 1H, *J* 0.9 Hz, 9.8 Hz, H-3), 4.09 (d, 1H, *J* 13.2 Hz, H-5a), 3.73 (s, 3H, $C_6H_4OCH_3$); 3.72 (bd, 1H, *J* 13.2 Hz, H- 5b); 2.14, 2.06, 2.03 (3s, 9H, 3 $COCH_3$).[13] C NMR ($CDCl_3$, 75 MHz) δ: 169.9, 169.8, 169.6 (3 $COCH_3$),155.0, 150.1, 118.2, 114.3 (ArC), 95.6 (C-1), 68.6, 67.8, 66.8, 60.7, 55.2 ($C_6H_4OCH_3$), 20.4, 20.3, 20.2 (3 $COCH_3$). HRMS: m/z calcd. for $[C_{18}H_{22}O_9]NH_4$+: 400.1608. Found: 400.1606.

2-Bromoethyl 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranoside (40)

Colorless glass. $[\alpha]_D^{25}$ +39 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.48 (bs, 1H, H-2); 5.46 (dd, 1H, *J* 0.9 Hz, 9.9 Hz, H-3); 5.06 (t, 1H, *J* 9.9 Hz, H-4); 4.77 (s, 1H, H-1); 3.99 (m, 2H, H-5, OCH_2CH_2Br); 3.93 (m, 1H, OCH_2CH_2Br); 3.48 (t, 2H, *J* 6.0 Hz, OCH_2CH_2Br), 2.13, 2.04, 1.97 (3s, 9H, 3 $COCH_3$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 170.3, 170.0, 169.9 (3 $COCH_3$), 97.5 (C-1), 70.9,

69.6 (OCH_2CH_2Br), 68.9, 68.0, 66.7, 29.6 (OCH_2CH_2Br), 20.8, 20.7, 20.6 (3 $COCH_3$). HRMS: m/z calcd. for $[C_{14}H_{21}O_8Br]NH_4+$: 414.0764. Found: 414.0761.

2-Bromoethyl 2,3,4-tri-*O*-acetyl-β-D-xylopyranoside (42)

Colorless oil. $[\alpha]_D^{25}$ +68 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ: 5.46 (t, 1H, *J* 9.3 Hz, H-3); 5.06 (d, 1H, *J* 3.3 Hz, H-1); 4.91 (m, 1H, H-4); 4.74 (dd, 1H, *J* 3.3 Hz, 9.3 Hz, H-2); 3.96 (m, 1H,OCH_2CH_2Br); 3.75 (m, 2H, H-5a, H-5b); 3.68 (m, 1H, OCH_2CH_2Br); 3.46 (t, 2H, *J* 6.0 Hz,OCH_2CH_2Br); 2.08, 1.99 (2s, 9H, 3 $COCH_3$). ^1C NMR ($CDCl_3$, 75 MHz) δ: 170.1, 169.8, 169.6 (3 $COCH_3$), 95.8 (C-1), 70.9, 69.2 (OCH_2CH_2Br), 69.0, 68.8, 68.2, 58.5, 29.9 (OCH_2CH_2Br), 20.6 (3 $COCH_3$). HRMS: m/z calcd. for $[C_{13}H_{19}O_8Br]NH_4+$: 414.0607. Found: 414.0610.

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