# Synthesis of Verbascoside: A Dihydroxyphenylethyl Glycoside with Diverse Bioactivity

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TMSOTf-mediated condensation of ethyl 4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (**2**) with peracetylated α-L-rhamnopyranosyl trichloroacetimidate donor **3a** resulted in the formation of orthoester **4**, which, after acetylation, rearranged into ethyl 3-*O*-(α-L-rhamnopyranosyl)-1-thio-β-D-glucopyranoside derivative **6a**. The latter compound was converted into the corresponding trichloroacetimidate donors **8a–b**. An alternative approach to trichloroacetimidate **8c** commenced with the iodonium ion mediated glycosidation of ethyl 2,3,4-tri-*O*-benzoyl-1-thio-α-L-rhamnopyranside (**15**) with 1,2:5,6-diisopropylidene-D-glucofuranose (**16**) to afford disaccharide **17**, which was transformed into **8c** in five steps. Condensation of **8a–c** with 2-[3,4-di-(*tert*-butyldimethylsilyloxy)phenyl]ethanol (**12**) gave, after deacylation, key intermediate **14**. Protecting-group manipulation of **14** and subsequent esterification of resulting **22** with 3,4-di-*O*-*tert*-butyldimethylsilylcaffeic acid (**27**) gave, after deprotection, verbascoside (**1**).

## Introduction

Phenylethyl glycosides (PhGs) are an interesting group of natural products which are widely distributed in the plant kingdom.[1a,2] They have 2-phenylethyl β-D-glucopyranoside, which is functionalized with an aromatic acid (e.g., cinnamic acid, caffeic acid, ferulic acid), in common. There may also be monosaccharides attached to the glucose moiety.

Verbascoside, also known as[1] acteoside (**1**, see Figure 1), belongs to the largest class of PhGs, those with a rhamnose sugar attached to the 3-position of the central glucose unit. It has been established that verbascoside (**1**) is a potent inhibitor[1] of protein kinase C and aldose reductase. Furthermore, **1** possesses antibacterial,[1] antiviral,[1][3] and antitumor[1] activity, as well as cytotoxic and immunomodulatory properties.[1][4] We present here the first synthesis of verbascoside (**1**).

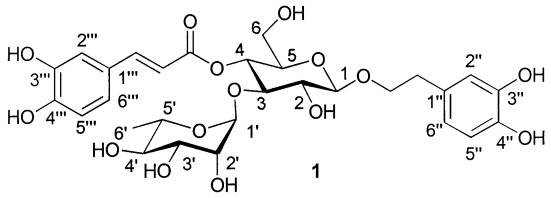


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Figure 1. Verbascoside (Acteoside)

## Results and Discussion

The construction of the target molecule, **1**, entails formation of two 1,2-*trans*-glycosidic bonds, as well as the regioselective introduction of an unsaturated caffeoyl function. The 1,2-*trans*-glycosidic linkages can in principle be formed by neighboring-group participation of a 2-*O*-acyl function in the L-rhamnopyranoside and the D-glucopyranoside building blocks. It is evident, however, that the 2-*O*-acyl functions are not compatible with the caffeoyl group in the target molecule. In line with these considerations, dihydroxyphenylethyl α-L-Rha*p*-(1→3)-β-D-Glc*p* derivative **14** had to be prepared prior to the esterification of HO-4 of the glucopyranosyl moiety with a suitably protected caffeic acid derivative. An approach to key intermediate **14** is depicted in Scheme 1 and commences with the synthesis of the ethyl 3-*O*-(α-L-rhamnopyranosyl)-1-thio-D-glucopyranoside donor **6**, which can be coupled with an appropriately protected 2-[3,4-dihydroxyphenyl]ethanol moiety.

Earlier studies from this laboratory showed[5] that regioselective β-glucosylation of HO-3 in ethyl 4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (**2**) with 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl trichloroacetimidate could be effected in the presence of a catalytic amount of trimethylsilyl triflate (TMSOTf) in dichloromethane at −20 °C. Unfortunately, condensation of **2**, under the same conditions, with the relatively more reactive[6] perbenzoylated α-L-rhamnopyranosyl trichloroacetimidate **3b**[7b] proceeded with a low degree of regioselectivity. Similarly, glycosylation of **2** with the peracetylated α-L-rhamnopyranosyl trichloroacetimidate donor **3a**[7a] gave an intractable mixture of products. On the other hand, TMSOTf-catalyzed condensation of **2** with **3a** in $CH_2Cl_2$/THF[8] at −40 °C led to the exclusive formation of orthoester **4** (see Scheme 1), which could be converted by acetylation to **5**, which subsequently underwent acid-catalyzed (TfOH) rearrangement into the required dimer **6a**, in an overall yield of 54% based on **2**.

At this stage, the glycosidation of **6a** with 2-[3,4-di-(*tert*-butyldimethylsilyloxy)phenyl]ethanol (**12**), prepared (see Scheme 2) from 3,4-dihydroxyphenylacetic acid (**9**) by

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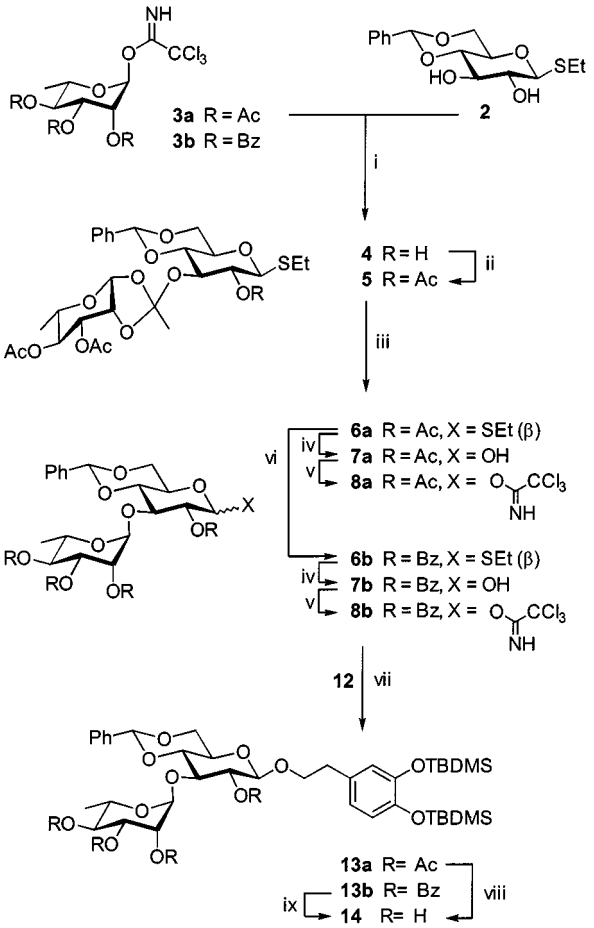
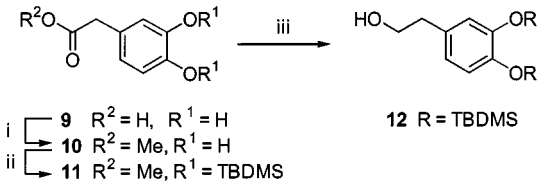



Scheme 1. Reagents and conditions: (i) 0.1 equiv. TMSOTf, $CH_2Cl_2$/THF (3:1, v/v), −40 °C, 81%; (ii) $Ac_2O$, pyridine, 87%; (iii) cat. TfOH, $CH_2Cl_2$, 76%; (iv) NIS/cat. TfOH in $CH_2Cl_2/H_2O$ (100:1, v/v), **7a**: 81%, **7b**: 81%; (v) $CCl_3CN$, $Cs_2CO_3$, $CH_2Cl_2$, **8a**: 86% **8b**: 84%; (vi) (a) NaOMe, MeOH; (b) BzCl, pyridine, 85%; (vii) cat. $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, (**13a**: 58%, **13b**: 74%); (viii) cat. NaOMe, MeOH (99%); (ix) excess of NaOMe, MeOH (42%)

sequential esterification (to form **10**), silylation (to **11**), and reduction, was examined. Condensation of thioethyl donor **6a** with acceptor **12** (see Scheme 1) under the influence of *N*-iodosuccinimide (NIS) and catalytic triflic acid (cat. TfOH)[9] or dimethyl(methylthio)sulfonium triflate (DMTST)[10] was abortive.[11] Alternatively, transformation of **6a** into the corresponding trichloroacetimidate[12] donor **8a** seemed to be a viable option. To this end, the thioethyl group in **6a**[13] was hydrolyzed in good yield[14] with NIS/cat TfOH in wet $CH_2Cl_2$. Treatment of the hemiacetal **7a** with cesium carbonate and excess trichloroacetonitrile furnished[15] trichloroacetimidate donor **8a**. The subsequent $BF_3{\cdot}Et_2O$-assisted glycosylation of **12** with **8a** gave the fully protected derivative **13a** in 58% yield[16]; its deacetylation proceeded in near quantitative yield to afford key intermediate **14** (see Scheme 1). Glycosylation of **12** with the fully benzoylated **8b** (see Scheme 1), readily available from **6a**, proceeded as expected[17] in higher yield (i.e., 74%). However, complete debenzoylation of **13b** was accompanied by the concomitant removal of the phenolic TBDMS groups, resulting in the isolation of **14** in only 42% yield. Rather rigorous basic conditions were used for the removal of the 2-*O*-benzoyl in **13b**, according to observations[18] that the reaction would not proceed otherwise.

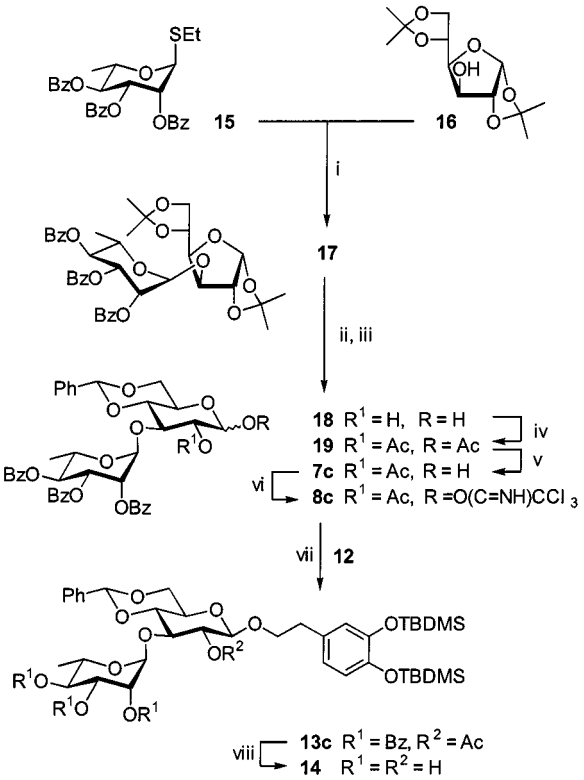



Scheme 2. Reagents and conditions: (i) HCl, MeOH; (ii) TBDMS−Cl, imidazole, DMF, (85%, 2 steps); (iii) $LiAlH_4$, $Et_2O$, 91%

The synthetic route to key intermediate **14** (21% overall yield in 7 steps) is not fully satisfactory due to the formation of orthoester **4** and the necessity to transform ethyl 1-thioglycoside **6a** into trichloroacetimidate donor **8a**. The latter disadvantages could be circumvented, as outlined in Scheme 3, by using 1,2:5,6-diisopropylidene-D-glucofuranose (**16**) as the glycosyl acceptor. Iodonium ion mediated condensation of ethyl 2,3,4-tri-*O*-benzoyl-1-thio-α-L-rhamnopyranoside[19] (**15**) with **16** gave disaccharide **17** in high yield. Deacetonation of **17** with 20% trifluoroacetic acid[20] at elevated temperature followed by acid-catalyzed (*p*-TsOH) acetalization with benzaldehyde dimethyl acetal in acetonitrile gave **18** in 69% yield. Acetylation of diol **18**, followed by selective anomeric deacetylation of **19** with hydrazinium acetate[21] in DMF furnished hemiacetal **7c**, which was transformed into imidate donor **8c** by the action[15] of cesium carbonate and trichloroacetonitrile. $BF_3{\cdot}Et_2O$-mediated condensation of **8c** with phenylethanol derivative **12** gave **13c**, whose deesterification gave **14** in a yield of 24% over the eight steps.

With key intermediate **14** available, we directed our attention to the introduction of the caffeoyl ester function at C-4 of the glucose moiety. Towards this goal, the partially protected derivative **14** was transformed into **22** which has a free HO-4, by the following sequence of manipulations (see Scheme 4). In the first step, the four hydroxy functions in **14** were acylated with phenoxyacetyl chloride to give **20** in high yield. Removal of the benzylidene group under mild acid conditions followed by regioselective tritylation[22] furnished the dimethoxytrityl derivative **22** in an overall yield of 69%. Esterification of **22** with 3,4-di-*O*-acetylcaffeoyl chloride[23] in the presence of pyridine or 4-(dimethylamino)pyridine (DMAP) was not successful. Moreover, dicyclohexylcarbodiimide (DCC)/DMAP-mediated reaction of **22** with 3,4-di-*O*-acetylcaffeic acid[23] led to the isolation of the acetylated product **23**. The unexpected formation of **23** may be explained by reaction of **22** with an acyl−DMAP adduct, which is formed by the reaction of DMAP with the phenolic acetyl groups in the 3,4-di-*O*-acetylcaffeic acid. To overcome this problem, the silyl-protected caffeic acid derivative **27** was considered to be a good alternative.

The preparation of **27** could be realized by the sequence of reactions depicted in Scheme 5. Silylation of known methyl caffeate[23b] (**25**) with *tert*-butyldimethylsilyl chloride and subsequent reduction of **26** with $LiAlH_4$ provided the




Scheme 3. Reagents and conditions: (i) NIS/cat. TfOH, $CH_2Cl_2$, 95%; (ii) 20% TFA in THF/$H_2O$ (4:1), 80 °C; (iii) $PhCH(OCH_3)_2$, cat. TsOH, $CH_3CN$, (69%, 2 steps); (iv) $Ac_2O$, pyridine, 89%; (v) $H_2NNH_2{\cdot}H_2O$, AcOH, DMF, 81%; (vi) $CCl_3CN$, $Cs_2CO_3$, $CH_2Cl_2$, 86%; (vii) cat $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, 59%; (viii) cat NaOMe, MeOH, 98%

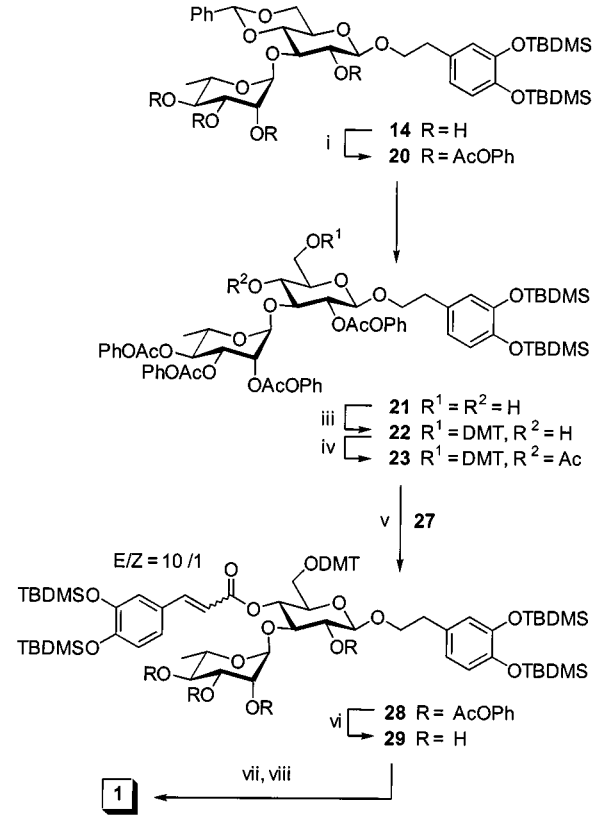
corresponding allylic alcohol, which was transformed into acid **27** by treatment with $MnO_2$ followed by Pinnick oxidation.[24]

Condensation of silyl-protected (*E*)-caffeic acid **27** with **22** in the presence of DCC/DMAP resulted in the isolation of **28**, the fully protected precursor of **1**, as an *E*/*Z* (10/1) mixture in 67% yield. Separation of the resulting isomers was omitted since the *E*- and *Z*-isomers of verbascoside (**1**) could be easily separated[25] by HPLC. Furthermore, it has been reported[25] that storage of a single isomer of **1** in solution resulted in the formation of both isomers.

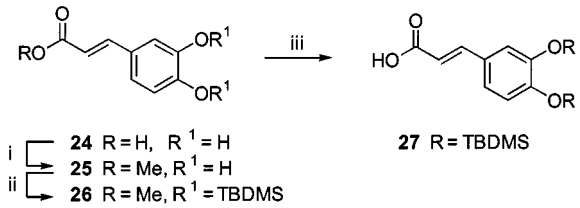
The fully protected verbascoside derivative **28** (see Scheme 4) was completely deblocked as follows. Mild deesterification of the four phenoxyacetyl groups in **28** furnished **29**. In the next step, the four phenolic silyl ethers were removed[26] effectively by the exposure of **29** to a slight excess of $HF{\cdot}Et_3N$. Acid hydrolysis of the dimethoxytrityl group gave, after purification by silica gel column chromatography and subsequent gel filtration, the target molecule **1** in an overall yield of 7.1%. The physical and spectroscopic data of compound **1** were in every aspect identical to those reported[27] for naturally occurring verbascoside.

## Conclusion

The results presented in this paper clearly show that key intermediate **14**, prepared in two different ways, can be




Scheme 4. Reagents and conditions: (i) PhOAc−Cl, pyridine, $CH_2Cl_2$, 90%; (ii) $HOCH_2CH_2OH$, cat. TsOH, $CH_2Cl_2$, 88%; (iii) DMT−Cl, pyridine, $CH_2Cl_2$, 87%; (iv) 3,4-di-*O*-acetylcaffeic acid, DCC, DMAP, $CH_2Cl_2$, 77%; (v) DCC, DMAP, $CH_2Cl_2$, 67%; (vi) 0.001 M $K_2CO_3$ in MeOH/$CH_2Cl_2$ (10:1, v/v), 86%; (vii) $3HF{\cdot}Et_3N$, $Et_3N$, pyridine; (viii) AcOH, EtOH, $CH_2Cl_2$ (4:1:2, v/v/v), (76%, 2 steps)




Scheme 5. Reagents and conditions: (i) HCl, MeOH; (ii) TBDMS−Cl, imidazole, DMF, (81%, 2 steps); (iii) (a) $LiAlH_4$ in $Et_2O$; (b) $MnO_2$, $Et_2O$; (c) $NaClO_2$, $NaH_2PO_4$, *t*BuOH/$H_2O$/2-methyl-2-butene, (5:5:3, v/v/v), (82%, three steps)

transformed into verbascoside (**1**). It may be possible that the same synthetic approach can be adopted to construct other members of the phenylethyl glycoside family.

## Experimental Section

**General Methods and Materials:** $^1$H- and $^{13}$C-NMR spectra were recorded with a Bruker WM-200 (200/50.1 MHz), a Bruker WM-300 (300/75.1 MHz), or a Bruker MDX-600 spectrometer (600/150 MHz). − Electrospray mass spectra were recorded with a Perkin−Elmer SCIEX API 165 Single Quadruple LC/MS instrument. − Optical rotations were measured with a Propol polarimeter. − 1,2-Dichloroethane (Rathburn), *N*,*N*-dimethylformamide (Baker) were stored over molecular sieves (4 Å) and used without further

purification. Dichloromethane was dried by refluxing in the presence of $CaH_2$ (5 g/L) for 5 h, then distilled and stored over molecular sieves (4 Å). Pyridine and toluene were dried by refluxing in the presence of $P_2O_5$ (5 g/L) for 5 h, then distilled and stored over molecular sieves (4 Å). Tetrahydrofuran (Biosolve) and diethyl ether were freshly distilled from $LiAlH_4$ and dried over molecular sieves (4 Å) for 1 h. Methanol (Rathburn, HPLC-grade) was stored over molecular sieves (3 Å). The following chemicals were obtained from Acros Organics Co. and were used as received: triethylamine, trimethylsilyl trifluoromethanesulfonate (TMSOTf), imidazole, trifluoroacetic acid (TFA), trifluoromethanesulfonic acid (TfOH), *N*-iodosuccinimide (NIS), trichloroacetonitrile, benzaldehyde dimethyl acetal, benzoyl chloride, hydrazine monohydrate, phenoxyacetyl chloride, (3,4-dihydroxyphenyl)acetic acid, 2-methyl-2-butene, *p*-toluenesulfonic acid (*p*-TsOH), *tert*-butyldimethylsilyl chloride (TBDMSCl), 4,4′-dimethoxytrityl chloride (DMTCl), manganese(IV) oxide ($MnO_2$), ethylene glycol, *N*,*N*-dicyclohexylcarbodiimide (DCC), 4-(dimethylamino)pyridine (DMAP), and caffeic acid (3,4-dihydroxycinnamic acid). Acetic anhydride (Baker), acetic acid (Baker), acetyl chloride (Merck), boron trifluoride−diethyl ether (Aldrich), and triethylamine trihydrofluoride ($3HF{\cdot}Et_3N$; Aldrich) were used as received. Dowex 50 W X4 was purchased from Fluka. − Reactions were monitored by TLC on Schleicher and Schüll DC Fertigfolien (F 1500 LS 254). Compounds were visualized by UV light and by spraying with 20% sulfuric acid in ethanol, followed by charring at 140 °C. Unsaturated compounds were visualized by spraying with a solution of $KMnO_4$ (2%) and (1%) $K_2CO_3$ in water. Eluents for column chromatography were of technical grade and distilled before use. − All reactions were performed under anhydrous conditions at room temperature unless stated otherwise. − Gel-filtration was performed on Sephadex LH-20 (Pharmacia). − Column chromatography was performed on silica gel 60 (0.063−0.200 mm) (Baker).

**3,4-Di-*O*-acetyl-β-L-rhamnopyranose 1,2-(Ethyl 4,6-*O*-benzylidene-1-thio-β-D-glucopyranose-3-yl) Orthoacetate (4):** To a mixture of ethyl 4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (**2**) (2.03 g, 6.5 mmol) and 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl trichloroacetimidate (**3a**) (3.53 g, 8.1 mmol) in dichloromethane/tetrahydrofuran (160 mL, 3:1, v/v) was added powdered molecular sieves (4 Å) and the solution was placed under nitrogen. After stirring for 30 min, the solution was cooled to −40 °C and a catalytic amount of trimethylsilyl trifluoromethanesulfonate (117 µL, 0.65 mmol) was slowly added. TLC analysis showed complete disappearance of **2** after a reaction time of 30 min. The reaction mixture was neutralized with $Et_3N$ and filtered and subsequently washed with 10% $NaHCO_3$ and water. The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography ($Et_2O$/light petroleum ether, 1:2, v/v) to afford the title compound **4** (3.08 g, 81%) as a colorless foam. − $R_f$ = 0.4 ($Et_2O$/light petroleum ether, 3:1, v/v). − $^1H$ NMR ($CDCl_3$): δ = 0.86 (d, 3 H, $J_{5',6'}$ = 6.7 Hz, 6′-H), 1.31 (t, 3 H, $CH_3$, SEt), 1.79 (s, 3 H, $CH_3$, orthoacetate), 2.02, 2.05 (2 × s, 6 H, $CH_3$, Ac), 2.74 (m, 2 H, $CH_2$, SEt), 2.96 (d, 1 H, 2′-OH), 3.33−3.51 (m, 3 H, 2-H, 5-H, 4-H), 3.69 (t, 1 H, $J_{6a,6b}$ = 9.8 Hz, 6-H[a]), 3.88 (t, 1 H, $J_{3,4}$ = 9.7 Hz, 3-H, $J_{2,3}$ = 9.7 Hz), 4.35 (dd, 1 H, $J_{5,6b}$ = 4.6 Hz, 6-H[b]), 4.42 (d, 1 H, $J_{2,3}$ = 9.7 Hz, 1-H), 4.75 (dd, 1 H, $J_{2',3'}$ = 3.6 Hz, 2′-H), 5.03 (m, 2 H, 3′-H, 4′-H), 5.14 (d, 1 H, $J_{1',2'}$ = 2.4 Hz, 1′-H), 5.49 (s, 1 H, benzylidene), 7.35−7.49 (m, 5 H, CH, Ph). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 14.9 ($CH_3$, SEt), 17.1 (C-6′), 20.4 ($CH_3$, Ac), 24.1 ($CH_2$, SEt), 24.2 ($CH_3$, orthoacetate), 68.2 (C-6), 68.7, 69.5, 69.6, 70.3, 72.0, 75.5, 76.0, 79.0 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 86.3 (C-1), 96.7 (C-1′), 101.1 (PhCH, benzylidene), 123.1 (Cq, orthoacetate), 125.7−128.6 (CH, Ph), 136.9 (Cq, benzylidene), 169.4, 170.0 (C=O, Ac).

**3,4-Di-*O*-acetyl-β-L-rhamnopyranose 1,2-(Ethyl 2-*O*-acetyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranose-3-yl) Orthoacetate (5):** Compound **4** (2.81 g, 4.8 mmol) was dissolved in a mixture of pyridine and acetic anhydride (25 mL, 2:1, v/v). TLC analysis indicated that complete acetylation required 12 h and then the mixture was concentrated in vacuo. The residual oil was applied to a column of silica gel and elution was effected with ethyl acetate/light petroleum ether (1:1, v/v) to give **5** as a white solid. − Yield: 2.62 g, 87%. − $R_f$ = 0.5 (toluene/ethyl acetate, 4:1, v/v). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 14.4 ($CH_3$, SEt), 17.1 (C-6′), 20.3, 20.6 ($CH_3$, Ac), 24.1 ($CH_2$, SEt), 26.1 ($CH_3$, orthoacetate), 68.1 (C-6), 65.5, 69.1, 69.9, 70.3, 70.5, 73.4, 75.4, 79.6 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 83.8 (C-1), 96.1 (C-1′), 101.4 (PhCH, benzylidene), 121.4 (Cq, orthoacetate), 125.9−128.9 (CH, Ph), 136.8 (Cq, benzylidene), 164.8, 169.4, 169.9 (C=O, Ac).

**Ethyl 2-*O*-Acetyl-4,6-*O*-benzylidene-3-*O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-1-thio-β-D-glucopyranoside (6a):** A catalytic amount of trifluoromethanesulfonic acid (30 µL) was added to a solution of orthoester **5** (2.00 g, 3.19 mmol) in dichloroethane containing powdered molecular sieves (4 Å) under a blanket of nitrogen. After stirring for 6 h, the reaction mixture was neutralized with $Et_3N$, filtered, washed with 10% aq. $NaHCO_3$ and water. The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was crystallized from dichloromethane and light petroleum ether to furnish **6a** (1.52 g, 76%) as a white solid. − $R_f$ = 0.5 (toluene/ethyl acetate, 4:1, v/v). − $[\alpha]_D^{20}$ = −38.2 ($c$ = 1.0, $CHCl_3$). − $^1H$ NMR ($CDCl_3$): δ = 0.64 (d, 3 H, $J_{5',6'}$ = 6.2 Hz, 6′-H), 1.26 (t, 3 H, $CH_3$, SEt), 1.96, 1.99, 2.11, 2.14 (4 × s, 12 H, $CH_3$, Ac), 2.76 (m, 2 H, $CH_2$, SEt), 3.52 (m, 1 H, 5-H), 3.67 (t, 1 H, $J_{4,5}$ = 9.8 Hz, 4-H), 3.78 (t, 1 H, $J_{6a,6b}$ = 9.2 Hz, 6-H[a]), 4.09 (m, 1 H, 5′-H), 4.37 (dd, 1 H, $J_{5,6b}$ = 4.8 Hz, 6-H[b]), 4.45 (d, 1 H, $J_{1,2}$ = 10.2 Hz, 1-H), 4.90 (m, 3 H, 1′-H, 2′-H, 4′-H), 5.28 (dd, 1 H, $J_{3,4}$ = 9.7 Hz, 2-H), 5.38 (dd, 1 H, $J_{1',2'}$ = 3.4 Hz, $J_{2',3'}$ = 10.0 Hz, 2′-H), 5.55 (s, 1 H, benzylidene), 7.26−7.49 (m, 5 H, CH, Ph). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 14.4 ($CH_3$, SEt), 16.1 (C-6′), 20.3 ($CH_3$, Ac), 23.5 ($CH_2$, SEt), 68.0 (C-6), 65.9, 68.0, 71.1, 70.5, 70.8, 71.5, 77.8, 78.0 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 83.7 (C-1), 97.1 (C-1′), 101.4 (PhCH, benzylidene), 126.0−128.8 (CH, Ph), 136.7 (Cq, benzylidene), 169.2, 169.4, 169.5 (C=O, Ac). − MS: $m/z$ = 647.3 $[M + Na]^+$. − $C_{29}H_{38}O_{13}S$ (582.19): calcd. C 55.58, H 6.11; found C 55.7, H 6.1.

**2-*O*-Acetyl-4,6-*O*-benzylidene-3-*O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-α-D-glucopyranose (7a):** Preparation of a 0.1 M stock solution of NIS/cat. TfOH: Trifluoromethanesulfonic acid (60 µL) was added to a solution of *N*-iodosuccinimide (2.25 g, 10 mmol) in a mixture of dichloromethane/tetrahydrofuran (100 mL, 40:1, v/v). To a mixture of thioglycoside **6a** (2.11 g, 3.37 mmol) in dichloromethane/water (25.25 mL, 100:1, v/v) was added in approximately 45 min a 0.1 M stock solution of NIS/cat. TfOH (43 ± 4 mL) and the progress of the reaction was monitored by TLC analysis (40% ethyl acetate in toluene). After complete disappearance of the starting material, the reaction was stopped by adding a 10% aq. $Na_2S_2O_3$ solution. The organic layer was separated and washed with a 10% aq. $NaHCO_3$ solution and water, subsequently dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (toluene/ethyl acetate, 85:15 → 70:30, v/v) to afford the title compound **7a** (1.59 g, 81%) as a foam. − $R_f$ = 0.3 (40% ethyl acetate in toluene). − $^1H$ NMR ($CDCl_3$): δ = 0.81 (d, 3 H, $J_{5',6'}$ = 6.6 Hz, 6′-H), 1.97, 1.99, 2.12, 2.18 (4 × s, 12 H, $CH_3$, Ac), 4.98

(t, 1 H, $J_{3',4'}$ = 9.4 Hz, 4′-H), 5.15 (d, 1 H, $J_{1',2'}$ = 1.4 Hz, 1′-H), 5.30 (m, 3 H, 2-H, 2′-H, 3′-H), 5.55 (s, 1 H, benzylidene), 6.17 (d, 1 H, $J_{1,2}$ = 3.7 Hz, 1-H), 7.26−7.41 (m, 5 H, CH, Ph). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 16.0 (C-6′), 20.1 ($CH_3$, Ac), 68.0 (C-6), 64.5, 65.5, 68.0, 68.9, 68.9, 70.3, 71.2, 74.8, 78.1 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 91.7 (C-1), 97.4 (C-1′), 101.1 (PhCH, benzylidene), 125.9−128.1 (CH, benzylidene), 136.7 (Cq, benzylidene), 169.4, 169.8, 170.0, 170.4 (C=O, Ac).

**2-*O*-Acetyl-4,6-*O*-benzylidene-3-*O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-α/β-D-glucopyranosyl Trichloroacetimidate (8a):** Compound **7a** (1.67 g, 2.87 mmol) was dried by co-evaporation of toluene (3 × 10 mL) and dissolved in $CH_2Cl_2$ (20 mL). Subsequently, cesium carbonate (0.574 mmol, 187 mg) and trichloroacetonitrile (8.61 mmol, 860 μL) were added. After stirring the resulting mixture for 2 h, TLC analysis indicated that the starting material was completely converted into a faster moving product. The reaction mixture was filtered, concentrated in vacuo and the resulting oil was purified by silica gel chromatography (toluene/ethyl acetate/triethylamine, 100:0:0.5 → 80:20:0.5, v/v/v) to yield **8a** (1.79 g, 86%) as a white amorphous solid − $R_f$ = 0.7 (toluene/ethyl acetate/triethylamine, 75:25:1, v/v/v). − $^1H$ NMR ($CDCl_3$): δ = 5.90 (d, 1 H, $J_{1,2}$ = 7.3 Hz, 1-$H^\beta$), 6.53 (d, 1 H, $J_{1,2}$ = 3.6 Hz, 1-$H^\alpha$). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 16.1 (C-6′), 20.2 ($CH_3$, Ac), 67.8 (C-6), 64.9, 65.9, 66.5, 68.0, 69.8, 70.0, 70.6, 71.6, 72.3, 76.0, 77.9, 78.1 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 89.9, 90.3 ($CCl_3$), 93.1, 95.3 (C-1), 96.8, 97.2 (C-1′), 101.3 (PhCH, benzylidene), 124.9−128.7 (CH, Ph), 137.2 (Cq, benzylidene), 160.2 (C=NH), 168.6, 169.3, 169.4, 169.5 (C=O, Ac).

**Methyl [3,4-Bis(*tert*-butyldimethylsilyloxy)phenyl]acetate (11):** At 0°C, acetyl chloride (6 mL) was added dropwise to a solution of (3,4-dihydroxyphenyl)acetic acid (6.51 g, 38.7 mmol) in methanol (240 mL). After 1 h, the mixture was allowed to warm to room temperature. The progress of the reaction was monitored by TLC analysis (light petroleum ether/ethyl acetate) which indicated complete conversion after another 2 h. The solution was concentrated to near dryness under reduced pressure, concentrated with dry toluene and redissolved in dry DMF (60 mL) upon which TBDMSCl (14.0 g, 92.8 mmol) and imidazole (6.81 g, 100 mmol) were added. The mixture was stirred for 2 h and diluted with $Et_2O$. The mixture was transferred to a separation funnel and water was added. The layers were separated and the organic phase was washed with water and dried ($MgSO_4$), filtered and concentrated in vacuo. The residual oil was applied onto a column of silica gel and elution was effected with ethyl acetate (0→10%) in light petroleum ether to give, after concentration of the appropriated fractions, methyl [3,4-bis(*tert*-butyldimethylsilyloxy)phenyl]acetate as an oil. − Yield: 13.51 g, 85%. − $R_f$ = 0.8 (light petroleum ether/ethyl acetate, 3:1, v/v). − $^1H$ NMR ($CDCl_3$): δ = 0.24 (s, 12 H, $CH_3$, TBDMS), 0.95 [s, 18 H, $C(CH_3)_3$, TBDMS], 2.95 (s, 2 H, $CH_2$), 3.10 (s, 3 H, OMe), 5.65 (m, 3 H, CH, Ph). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = −4.3 ($CH_3$, TBDMS), 18.2 (Cq, TBDMS), 25.7 [$C(CH_3)_3$, TBDMS], 40.2 ($CH_2$), 51.5 (OMe), 120.6, 121.9 (CH, Ph), 126.8 (Cq, Ph), 145.7, 146.5 (Cq−O, Ph), 171.7 (C=O).

**2-[3,4-Bis(*tert*-butyldimethylsilyloxy)phenyl]ethanol (12):** Methyl [3,4-bis(*tert*-butyldimethylsilyloxy)phenyl]acetate (**11**, 4.13 g, 10.03 mmol) in diethyl ether (25 mL) was added dropwise to a cooled (0°C) suspension of $LiAlH_4$ (400 mg, 10.5 mmol) in diethyl ether (25 mL) and stirred for 15 min. TLC analysis revealed complete disappearance of the starting material in this time period. The reaction was quenched by dropwise addition of methanol and diluted with diethyl ether and subsequent washed with water. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Silica gel column chromatography (light petroleum ether/ethyl acetate, 1:0 → 1:2, v/v) of the residual oil afforded pure **12** (3.50 g, 91%) as a colorless oil. − $R_f$ = 0.6 (light petroleum ether/ethyl acetate, 3:1, v/v). − $^1H$ NMR ($CDCl_3$): δ = 0.18 (s, 12 H, $CH_3$, TBDMS), 0.98 [s, 18 H, $C(CH_3)_3$, TBDMS], 1.57 (s, 1 H, OH), 2.73 (t, 2 H, $J$ = 6.6 Hz, $CH_2CH_2O$), 3.78 (dd, 2 H, $J$ = 12.4 Hz, $CH_2CH_2O$), 6.67 (m, 3 H, CH, Ph). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = −4.9 ($CH_3$, TBDMS), 17.4 (Cq, TBDMS), 25.1 [$C(CH_3)_3$, TBDMS], 37.7 ($CH_2CH_2O$), 62.6 ($CH_2CH_2O$), 120.0, 121.0 (CH, Ph), 130.9 (Cq, Ph), 144.2, 145.5 (Cq−O, Ph). − MS: $m/z$ = 405.3 $[M + Na]^+$.

**2-[3,4-Bis(*tert*-butyldimethylsilyloxy)phenyl]ethyl 2-*O*-Acetyl-4,6-*O*-benzylidene-3-*O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-β-D-glucopyranose (13a):** A mixture of trichloroacetimidate donor **8a** (3.00 g, 4.12 mmol) and alcohol **12** (1.58 g, 4.12 mmol) was dried by evaporation of toluene (3 × 15 mL), dissolved in $CH_2Cl_2$ (40 mL), and crushed molecular sieves (4 Å, 2 g) were added. The resulting mixture was stirred for 20 min under argon and then 250 μL of a 0.2 N solution of $BF_3{\cdot}OEt_2$ in $CH_2Cl_2$ was slowly added (15 min). TLC analysis (toluene/ethyl acetate, 88:12, v/v) showed the disappearance of the imidate **8a** and the formation of two faster moving products. The fastest moving product ($R_f$ = 0.43), presumably an orthoester derivative, was converted into the slower moving product ($R_f$ = 0.31) in the course of the reaction time. When this transformation stopped, an additional amount (± 50 μL) of the 0.2 N $BF_3{\cdot}OEt_2$ stock solution was added. After complete rearrangement, the reaction mixture was neutralized with $Et_3N$, filtered, and the filtrate was washed with water. The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the crude oil was accomplished using a silica gel column, eluted with toluene and a gradient of 0→10% ethyl acetate to afford homogeneous **13a** as a colorless oil. Yield: 2.27 g, 58%. − $[\alpha]_D^{20}$ = −31.5 ($c$ = 1.0, $CHCl_3$). − $^1H$ NMR ($CDCl_3/CD_3OD$): δ = 0.18, 0.19 (2 × s, 12 H, $CH_3$, TBDMS), 0.96, 0.98 (s, 18 H, $C(CH_3)_3$, TBDMS), 0.64 (d, 3 H, $J_{5',6'}$ = 6.2 Hz, 6′-H), 1.97, 1.99, 2.05, 2.11 (4 × s, 12 H, $CH_3$, Ac), 2.74 (t, 2 H, $CH_2CH_2O$), 3.47 (m, 1 H, 5-H), 3.63 (m, 2 H, 4-H, $CH_2-HCH-O$), 3.80 (t, 1 H, $J_{6a,6b}$ = 9.2 Hz, 6-$H^a$), 3.91 (t, 1 H, $J_{3,4}$ = 9.7 Hz, 3-H), 4.05 (m, 2 H, 5′-H, $CH_2-HCH-O$), 4.36 (dd, 1 H, $J_{5,6a}$ = 4.8 Hz, 6-$H^b$), 4.47 (d, 1 H, $J_{1,2}$ = 8.0 Hz, 1-H), 4.87 (d, 1 H, $J_{1',2'}$ = 1.7 Hz, 1′-H), 4.92 (t, 1 H, $J_{3',4'}$ = $J_{4',5'}$ = 10.0 Hz, 4′-H), 4.97 (dd, 1 H, $J_{2',3'}$ = 3.6 Hz, 2′-H), 5.04 (dd, 1 H, $J_{2,3}$ = 9.7 Hz, 2-H), 5.27 (s, 1 H, benzylidene), 6.64 (m, 2 H, 2′-H′, 6′′-H), 6.73 (d, 1 H, $J_{5'',6''}$, 5′-H), 7.26−7.49 (m, 5 H, CH, Ph). − $^{13}C\{^1H\}$ NMR ($CDCl_3/CD_3OD$): δ = −5.4 ($CH_3$, TBDMS), 15.1 (C-6′), 17.1 (Cq, TBDMS), 19.2 ($CH_3$, Ac), 24.6 [$C(CH_3)_3$, TBDMS], 34.0 ($CH_2CH_2O$), 67.2 (C-6), 69.5 ($CH_2CH_2O$), 65.0, 65.3, 67.5, 69.2, 70.0, 72.4, 75.8, 77.7 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 96.3 (C-1), 100.0 (C-1′), 100.7 (PhCH, benzylidene), 119.6, 120.6, 120.7 (C-2′′, C-5′′, C-6′′), 125.2−128.0 (CH, Ph), 130.4 (C-1′′), 135.7 (Cq, benzylidene), 144.0, 145.3 (C-3′′, C-4′′), 168.9, 169.1 (C=O, Ac). − MS: $m/z$ = 969.5 $[M + Na]^+$.

**Ethyl 2-*O*-Benzoyl-4,6-*O*-benzylidene-3-*O*-(2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl)-1-thio-β-D-glucopyranose (6b):** To a solution of compound **6a** (947 mg, 2 mmol), in 10 mL of methanol, was added NaOMe (54 mg, 1 mmol). After stirring for 4 h, the deacetylation was complete, as judged by TLC analysis. The reaction was neutralized with Dowex 50 W X4 ($H^+$ form), filtered, and concentrated in vacuo. The obtained oil was three times concentrated with a small amount of pyridine and subsequently dissolved in pyridine (6 mL). To this solution was added benzoyl chloride and the reaction mixture was stirred until TLC analysis revealed that the benzoylation was complete. The excess of benzoyl chloride was de-

stroyed by addition of water and the mixture was concentrated in vacuo. The oily residue was dissolved in ethyl acetate and washed with water and aq. $NaHCO_3$ (10%). The ethyl acetate layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified on a silica gel column (toluene/ethyl acetate, 1:3 → 0:1, v/v) to furnish the title compound **6b** (1.48 g, 85%) as a colorless foam. − $R_f$ = 0.6 (toluene/ethyl acetate, 4:1, v/v). − $[\alpha]_D^{20}$ = −42.0 ($c$ = 0.5, $CHCl_3$). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 14.5 ($CH_3$, SEt), 16.5 (C-6′), 23.6 ($CH_2$, SEt), 68.2 (C-6), 66.3, 69.3, 70.1, 70.7, 71.3, 72.5, 76.8, 78.6 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 83.8 (C-1), 97.5 (C-1′), 101.5 (PhCH, benzylidene), 124.0−132.9 (CH, Ph, Bz), 127.8 (Cq, Bz), 136.7 (Cq, benzylidene), 164.1, 164.6, 164.9, 165.2 (C=O, Bz). − MS: $m/z$ = 897.1 [M + Na]$^+$.

**2-*O*-Benzoyl-4,6-*O*-benzylidene-3-*O*-(2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl)-α-D-glucopyranose (7b)**: The method for the hydrolysis of the thioethyl group in **6b** (1.31 g, 1.50 mmol) to afford **7b** is identical to that described for the synthesis of hemiacetal **7a** from thioethyl derivative **6a**. Purification by silica gel column chromatography (eluent: toluene/ethyl acetate, 100:0 → 85:15) gave **7b** (1.01 g, 81%) as a foam. − $R_f$ = 0.3 (20% ethyl acetate in toluene). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 16.8 (C-6′), 68.6 (C-6), 65.1, 66.3, 70.2, 70.5, 71.6, 72.2 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 92.9 (C-1), 97.8 (C-1′), 101.6 (PhCH, benzylidene), 125.1−133.5 (CH, Ph), 128.0 (Cq, Bz), 136.9 (Cq, benzylidene), 165.2, 165.5, 165.6, 165.8 (C=O, Bz).

**2-*O*-Benzoyl-4,6-*O*-benzylidene-3-*O*-(2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl)-α/β-D-glucopyranosyl Trichloroacetimidate (8b):** Trichloroacetimidate donor **8b** was prepared from **7b** (1.01 g, 1.21 mmol) in the same way as compound **8a**. Purification by silica gel column chromatography (eluent: toluene/ethyl acetate, 100:0 → 85:15) gave **8b** (997 mg, 84%) as a white amorphous solid. − $R_f$ = 0.8 (toluene/ethyl acetate/triethylamine, 75:25:1, v/v/v). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 16.7 (C-6′), 68.4 (C-6), 65.3, 66.5, 66.7, 69.4, 70.3, 70.1, 70.3, 71.4, 72.7, 73.0, 73.2, 78.5 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 90.1, 90.4 ($CCl_3$), 93.5, 95.7, 97.0, 97.9 (C-1, C-1′), 101.2, 101.8 (PhCH, benzylidene), 124.9−133.0 (CH, Ph, Bz), 128.0 (Cq, Bz), 136.6, 137.5 (Cq, benzylidene), 160.3, 160.7 (C=NH), 164.4, 164.6, 165.1, 165.3 (C=O, Bz).

**2-[3,4-Bis(*tert*-butyldimethylsilyloxy)phenyl]ethyl 2-*O*-Benzoyl-4,6-*O*-benzylidene-3-*O*-(2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl)-β-D-glucopyranoside (13b):** The glycosylation between **8b** (450 mg, 0.46 mmol) and **12** (176 mg, 0.46 mmol) to obtain **13b** was performed as described above for the synthesis of **13a**. Purification by silica gel column chromatography (eluent: toluene/ethyl acetate, 10:0 → 9:1) gave **13b** (407 mg, 74%) as a colorless oil. − $R_f$ = 0.8 (toluene/ethyl acetate, 9:1, v/v). − $[\alpha]_D^{20}$ = −36.3 ($c$ = 1.0, $CHCl_3$). − $^1H$ NMR ($CDCl_3$/$CD_3OD$): δ = 0.18, 0.19 (2 × s, 12 H, $CH_3$, TBDMS), 0.89 (d, 3 H, $J_{5',6'}$ = 6.2 Hz, 6′-H), 0.94, 0.96 [2 × s, 18 H, $C(CH_3)_3$, TBDMS], 2.71 (t, 2 H, $CH_2CH_2O$), 3.66 (m, 2 H, 6-H$^b$, $CH_2$−HCH−O), 3.89 (m, 2 H, 4-H, 5-H), 4.04 (m, 1 H, $CH_2$−HCH−O), 4.25 (t, 1 H, $J_{2,3} \approx J_{3,4}$ = 9.7 Hz, 2-H), 4.47 (m, 2 H, 5′-H, 6-H$^b$), 4.69 (d, 1 H, $J_{1,2}$ = 8.0 Hz, 1-H), 5.12 (s, 1 H, $J_{1',2'}$ = 1.1 Hz, 1′-H), 5.46 (m, 3 H, 2-H, 2′-H, 4′-H), 5.67 (s, 1 H, benzylidene), 5.80 (dd, 1 H, $J_{2',3'}$ = 3.6 Hz, $J_{3',4'}$ = 10.0 Hz, 2′-H), 6.54 (s, 2 H, 2′-H′, 6′′-H), 6.61 (s, 1 H, 5′′-H), 7.26−8.04 (m, 25 H, CH, Ph, Bz). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = −4.3 ($CH_3$, TBDMS), 16.7 (C-6′), 17.1 (Cq, TBDMS), 25.8 [$C(CH_3)_3$, TBDMS], 35.2 ($CH_2CH_2O$), 67.6 ($CH_2CH_2O$), 70.8 (C-6), 66.4, 66.5, 68.6, 69.4, 71.6, 74.2, 78.7 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 97.6 (C-1), 101.3, 101.7 (C-1, PhCH, benzylidene), 120.8, 121.5, 121.7 (C-2′′, C-5′′, C-6′′), 125.0−133.1 (CH, Ph), 129.2 (Cq, Bz), 131.1 (C-1′′), 137.6 (Cq, benzylidene), 145.0, 146.3 (C-3′′, C-4′′), 164.4, 164.7, 165.2, 165.4 (C=O, Bz). − MS: $m/z$ = 1218.8 [M + Na]$^+$.

**1,2:5,6-Di-*O*-isopropylidene-3-*O*-(2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl)-α-D-glucofuranose (17):** Ethyl 2,3,4-tri-*O*-benzoyl-1-thio-α-L-rhamnopyranoside (**15**, 7.69 g, 14.3 mmol) and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**16**, 4.83 g, 18.6 mmol) were dissolved in 100 mL $CH_2Cl_2$. To the solution was added powdered molecular sieves (4 Å) and the mixture was stirred for 30 min under $N_2$. *N*-Iodosuccinimide (4.18 g, 18.6 mmol) and a catalytic amount of triflic acid were added. After stirring for 1 h, TLC analysis showed complete consumption of the donor. The reaction mixture was filtered, diluted with dichloromethane, washed with aq. $Na_2S_2O_3$ (10%, 50 mL), and aq. $NaHCO_3$ (10%, 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by silica gel column chromatography (eluent: toluene/ethyl acetate, 1:0 to 3:1) afforded disaccharide **17** (9.76 g, 95%) as a colorless oil. − $R_f$ = 0.4 (toluene/ethyl acetate, 4:1, v/v). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 16.9 (C-6′), 25.0, 25.7, 26.4 ($CH_3$, *i*Pr), 67.9 (C-6), 66.7, 69.8, 70.3, 71.2, 71.7, 76.8, 80.7, 94.5 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 94.5 (C-1′), 105.1 (C-1), 108.9, 111.6 (Cq, *i*Pr), 128.3 (Cq, Bz), 127.9−134.8 (CH, Bz), 161.8, 165.1, 165.3 (C=O, Bz). − MS: $m/z$ = 741.3 [M + $Na^+$], 757.3 [M + $K^+$].

**4,6-*O*-Benzylidene-3-*O*-(2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl)-α/β-D-glucopyranose (18):** Both acetonide functions in compound **17** (2.10 g, 2.92 mmol) were removed by heating **17** in a mixture of tetrahydrofuran/water/trifluoroacetic acid (5:1:1, 60 mL) at 100°C. The progress of the reaction was monitored by TLC analysis (toluene/ethyl acetate, 1:3, v/v). After approximately 1 h, the starting material was converted into 1,2-*O*-isopropylidene-3-*O*-(2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl)-α-D-glucofuranose [$R_f$ = 0.85 (ethyl acetate)]. After maintaining the reaction mixture for approximately 12−18 h at elevated temperature, the mixture was cooled, diluted with toluene and concentrated in vacuo. The residue was repeatedly diluted with dry toluene and concentrated under reduced pressure. The thus obtained oil was dissolved in acetonitrile (100 mL) and to the solution were added benzaldehyde dimethyl acetal (1.8 mL) and a catalytic amount of *p*-toluenesulfonic acid. After 6 h, the reaction mixture was neutralized with $Et_3N$ and concentrated in vacuo. Crude **18** was applied onto a column of silica gel. Elution with toluene/ethyl acetate (0:1 → 1:1, v/v) and concentration of the appropriate fractions furnished the title compound **18** (1.46, 69%) as a colorless foam. − 3-*O*-(2,3,4-Tri-*O*-benzoyl-α-L-rhamnopyranosyl)-D-glucose: $R_f$ = 0.2 (ethyl acetate). − **18**: $R_f$ = 0.43 (toluene/ethyl acetate, 1:1, v/v). − $^{13}C\{^1H\}$ NMR ($CD_3CN$): δ = 17.3 (C-6′), 69.7, 69.5 (C-6), 63.5, 66.9, 67.3, 71.2, 71.6, 74.2, 76.3, 77.3, 78.2, 80.0, 80.5 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 94.3 (C-1′), 98.3, 98.6 (C-1), 102.5 (PhCH, benzylidene), 128.3 (Cq, Bz), 127.3−134.6 (CH, Bz), 138.8 (Cq, benzylidene), 166.3 (C=O, Bz).

**1,2-Di-*O*-acetyl-4,6-*O*-benzylidene-3-*O*-(2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl)-α-D-glucopyranose (19):** Diol **18** (2.61 g, 3.6 mmol) was dissolved in a mixture of pyridine/acetic anhydride (2:1, v/v, 50 mL). After stirring for 4 h, the mixture was concentrated in vacuo. Purification of the remaining oil on silica gel using toluene as eluent afforded the title compound **19** (2.60 g, 89%) as an oil. − $R_f$ = 0.56 (toluene/ethyl acetate, 4:1, v/v). − $^1H$ NMR ($CDCl_3$): δ = 0.90 (d, 3 H, $J_{5',6'}$ = 6.0 Hz, 6′-H), 2.16, 2.20 (2 × s, 6 H, $CH_3$, Ac), 3.84 (m, 2 H, 4-H, 6-H$^a$), 4.05 (m, 1 H, 5-H), 4.36 (m, 2 H, 3-H, 6-H$^b$), 4.52 (m, 1 H, 5′-H), 5.15 (dd, 1 H, $J_{2,3}$ = 9.7 Hz, 2-H), 5.31 (s, 1 H, 1′-H), 5.48 (br. s, 1 H, 2′-H), 5.61 (t, 1

H, $J_{3',4'}$ = 9.3 Hz, 4′-H), 5.68 (s, 1 H, benzylidene), 5.47 (dd, 1 H, $J_{2',3'}$ = 3.6 Hz), 6.36 (d, 1 H, $J_{1,2}$ = 3.6 Hz, 1-H), 7.20−8.04 (m, 20 H, CH, Ph, Bz). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 16.9 (C-6′), 20.4, 20.8 ($CH_3$, Ac), 68.5 (C-6), 65.3, 66.4, 69.5, 71.0, 71.5, 72.3, 72.9, 78.9 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 89.8 (C-1′), 97.4 (C-1), 102.0 (CH, Ph), 128.3 (Cq, Bz), 126.1−133.4 (CH, Bz), 136.7 (Cq, benzylidene), 165.4, 165.5 (C=O, Bz), 168.9, 170.1 (C=O, Ac).

**2-*O*-Acetyl-4,6-*O*-benzylidene-3-*O*-(2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl)-α/β-D-glucopyranose (7c):** Hydrazine monohydrate (68 μL, 1.4 mmol) was added to a solution of **19** (1.10 g, 1.36 mmol) in 10 mL of DMF containing acetic acid (85 μL, 1.5 mmol). The mixture was stirred for 1 h and then concentrated in vacuo. The residue was taken up in diethyl ether and washed with water. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by silica gel column chromatography (eluent: toluene/ethyl acetate, 10:0 → 9:1) gave **7c** (847 mg, 81%) as a colorless oil. − $R_f$ = 0.3 (toluene/ethyl acetate, 4:1, v/v). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 16.6 (C-6′), 20.6 ($CH_3$, Ac), 68.8 (C-6), 62.6, 66.3, 68.8, 69.6, 71.0, 71.7, 72.8, 74.4, 79.5 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 90.8 (C-1′), 96.2 (C-1β), 97.4 (C-1α), 101.9 (PhCH, benzylidene), 125.9−128.1 (CH, Ph), 128.9 (Cq, Bz), 136.9 (Cq, benzylidene), 165.4, 165.6 (C=O, Bz), 170.8, 171.7 (C=O α/β, Ac).

**2-*O*-Acetyl-4,6-*O*-benzylidene-3-*O*-(2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl)-α-D-glucopyranosyl Trichloroacetimidate (8c):** Trichloroacetimidate donor **8c** was prepared from **7c** (489 mg, 0.64 mmol) in a way identical to that described for the synthesis of compound **8a**. Purification by silica gel column chromatography (eluent: toluene/ethyl acetate, 100:0 → 85:15) gave **8c** (500 mg, 86%) as a white amorphous solid. − $R_f$ = 0.6 (toluene/ethyl acetate, 4:1, v/v). − $^1H$ NMR ($CDCl_3$): δ = 0.92 (d, 3 H, $J_{5',6'}$ = 6.4 Hz, 6′-H), 2.18 (s, 3 H, $CH_3$, Ac), 3.86, 4.07, 4.44 (3 × m, 5 H, 3-H, 4-H, 5-H, 6-$H^a$, 6-$H^b$), 5.15 (dd, 1 H, $J_{2,3}$ = 9.6 Hz, 2-H), 5.28 (br. s, 1 H, 1′-H), 5.43 (m, 1 H, 2′-H), 5.62 (t, 1 H, $J_{3',4'}$ = 9.3 Hz, 4′-H), 5.70 (s, 1 H, benzylidene), 5.84 (dd, 1 H, $J_{2',3'}$ = 3.3 Hz), 6.60 (d, 1 H, $J_{1,2}$ = 3.5 Hz, 1-H), 7.10−8.14 (m, 20 H, CH, Ph, Bz), 8.67 (s, 1 H, NH). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 16.7 (C-6′), 20.2 ($CH_3$, Ac), 68.4 (C-6), 65.3, 66.0, 69.5, 70.9, 71.5, 72.2, 72.8, 73.1, 78.7 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 90.6 ($CCl_3$), 93.5 (C-1), 97.5 (C-1′), 101.8 (CH, Ph), 125.1−133.3 (CH, Ph), 128.9 (Cq, Bz), 136.6 (Cq, benzylidene), 160.7 (C=NH), 165.4 (C=O, Bz), 170.1 (C=O, Ac).

**2-[3,4-Bis(*tert*-butyldimethylsilyloxy)phenyl]ethyl 2-*O*-Acetyl-4,6-*O*-benzylidene-3-*O*-(2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl)-β-D-glucopyranose (13c):** The glycosylation between **8c** (500 mg, 0.54 mmol) and **12** (210 mg, 0.54 mmol) to obtain **13c** was performed as described above for the synthesis of **13a**. Purification by silica gel column chromatography (eluent: toluene/ethyl acetate, 10:0 → 9:1) gave **13c** (361 mg, 59%) as a colorless oil. − $R_f$ = 0.8 (toluene/ethyl acetate, 7:1, v/v). − $[\alpha]_D^{20}$ = −35.4 (*c* = 1.1, $CHCl_3$). − $^1H$ NMR ($CDCl_3/CD_3OD$): δ = 0.14, 0.17 (2 × s, 12 H, $CH_3$, TBDMS), 0.83 (d, 3 H, $J_{5',6'}$ = 5.8 Hz, 6′-H), 0.94, 0.95 [2 × s, 18 H, $C(CH_3)_3$, TBDMS], 2.05 (s, 3 H, $CH_3$, Ac), 2.71 (t, 2 H, $CH_2CH_2O$), 3.63 (m, 2 H, 6-$H^a$, $CH_2$−HCH−O), 3.78 (m, 3 H, 4-H, 5-H, $CH_2$−HCH−O), 4.19 (t, 1 H, $J_{3,4}$ = 9.7 Hz, 3-H), 4.46 (m, 2 H, 5′-H, 6-$H^a$), 4.52 (d, 1 H, $J_{1,2}$ = 8.0 Hz, 1-H), 5.18 (m, 2 H, 1′-H, 2-H), 5.50 (m, 3 H, 4′-H, 2′-H, benzylidene), 5.79 (dd, 1 H, 3′-H), 6.54 (s, 2 H, 2″-H, 6″-H), 6.61 (s, 1 H, 5″-H), 7.26−8.04 (m, 20 H, CH, Ph, Bz). − $^{13}C\{^1H\}$ NMR ($CDCl_3/CD_3OD$): δ = −4.2 ($CH_3$, TBDMS), 16.5 (C-6′), 18.2 (Cq, TBDMS), 20.6 ($CH_3$, Ac), 25.8 [$C(CH_3)_3$, TBDMS], 35.2 ($CH_2CH_2O$), 68.5 (C-6), 70.6 ($CH_2CH_2O$), 66.4, 66.5, 69.3, 71.3, 71.7, 73.3, 76.3, 79.0 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 97.3 (C-1), 101.4, 101.8 (C-1′, PhCH, benzylidene), 120.7, 120.8, 121.8 (C-2″, C-5″, C-6″), 126.1−133.3 (CH, Ph), 131.2 (C-1″), 136.8 (Cq, benzylidene), 145.1, 146.4 (C-3″, C-4″), 165.2, 165.3, 165.5 (C=O, Bz), 169.4 (C=O, Ac). − MS: *m*/*z* = 1155.8 $[M + Na]^+$.

**2-[3,4-Bis(*tert*-butyldimethylsilyloxy)phenyl]ethyl 4,6-*O*-Benzylidene-3-*O*-(α-L-rhamnopyranosyl)-β-D-glucopyranose (14):** To a solution of compound **13a** (947 mg, 1 mmol) or **13c** (1.13 g, 1 mmol) in 10 mL of methanol was added NaOMe (26 mg, 0.5 mmol). After stirring for 3.5 h, the deacylation was complete, as judged by TLC analysis. The reaction mixture was neutralized with Dowex 50 W X4 ($H^+$ form), filtered, and concentrated in vacuo. The crude product was purified on a silica gel column (toluene/ethyl acetate, 1:3 → 0:1, v/v) to furnish the title compound **14** (764 mg, 98%) as a white amorphous solid. − $[\alpha]_D^{20}$ = −21.3 (*c* = 0.4, $CHCl_3$). − $R_f$ = 0.3 (8% MeOH in $CH_2Cl_2$). − $^1H$ NMR ($CD_3OD$): δ = 0.18, 0.19 (2 × s, 12 H, $CH_3$, TBDMS), 0.87 (d, 3 H, $J_{5',6'}$ = 6.2 Hz, 6′-H), 0.99, 1.00 [s, 18 H, $C(CH_3)_3$, TBDMS], 2.81 (t, 2 H, $CH_2CH_2O$, *J* = 6.6 Hz), 3.25−4.01 (m, 11 H, 2-H, 3-H, 4-H, 5-H, 6-$H^a$, 6-$H^b$, 2′-H, 4′-H, 5′-H, $CH_2CH_2O$), 4.27 (dd, 1 H, $J_{2',3'}$ = 3.6 Hz, 3′-H, $J_{3',4'}$ = 10.2 Hz), 4.42 (d, 1 H, $J_{1,2}$ = 7.4 Hz, 1-H), 5.14 (d, 1 H, $J_{1',2'}$ = 1.5 Hz, 1′-H), 5.52 (s, 1 H, benzylidene), 6.75 (m, 3 H, 2″-H, 5″-H, 6″-H), 7.30−7.51 (m, 5 H, CH, Ph). − $^{13}C\{^1H\}$ NMR ($CD_3OD$): δ = −3.8, −3.7 ($CH_3$, TBDMS), 17.6 (C-6′), 19.2 (Cq, TBDMS), 26.5 [$C(CH_3)_3$, TBDMS], 36.4 ($CH_2CH_2O$), 69.9 (C-6), 72.2 ($CH_2CH_2O$), 67.7, 69.5, 72.1, 73.8, 76.6, 79.5, 80.6, 84.3 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 102.4, 102.7 (C-1, C-1′), 105.0 (PhCH, benzylidene), 122.0, 122.9, 123.0 (C-2″, C-5″, C-6″), 127.5−129.9 (CH, Ph), 133.3 (C-1″), 138.9 (Cq, benzylidene), 146.3, 147.6 (C-3″, C-4″). − MS: *m*/*z* = 801.3 $[M + Na^+]$. − $C_{39}H_{62}O_{12}Si_2$ (778.37): calcd. C 60.13, H 8.02; found C 60.1, H 8.0.

**2-[3,4-Bis(*tert*-butyldimethylsilyloxy)phenyl]ethyl 4,6-*O*-Benzylidene-2-*O*-phenoxyacetyl-3-*O*-(2,3,4-tri-*O*-phenoxyacetyl-α-L-rhamnopyranosyl)-β-D-glucopyranose (20):** Phenoxyacetyl chloride (350 μL, 2.52 mmol) was added dropwise over a period of 15 min to a mixture of 2-[3,4-bis(*tert*-butyldimethylsilyloxy)phenyl]ethyl 4,6-*O*-benzylidene-3-*O*-(α-L-rhamnopyranosyl)-β-D-glucopyranose (411 mg, 0.526 mmol) in $CH_2Cl_2$ (7.8 mL) and pyridine (340 μL, 4.5 mmol). After stirring for 2 h, TLC analysis (toluene/ethyl acetate, 7:1, v/v) showed the formation of one major spot. The reaction was quenched by addition of methanol, diluted with dichloromethane, and washed with water. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The resulting syrup was applied onto a column of silica gel. Elution was performed with toluene/ethyl acetate (100:0 → 97:3, v/v), to furnish, after concentration of the appropriate fractions, pure **20** as a light yellow oil. Yield: 622 mg, 90%. − $R_f$ = 0.7 (toluene/ethyl acetate, 7:1, v/v). − $^1H$ NMR ($CDCl_3$): δ = 0.19, 0.23 (2 × s, 12 H, $CH_3$, TBDMS), 0.69 (d, 3 H, $J_{5',6'}$ = 6.2 Hz, 6′-H), 1.00, 1.02 [s, 18 H, $C(CH_3)_3$, TBDMS], 2.76 (t, 2 H, *J* = 7.1 Hz, $CH_2CH_2O$), 3.48 (m, 1 H, 5-H), 3.60 (m, 1 H, $CH_2$−HCH−O), 3.71 (t, 1 H, 4-H), 3.82 (t, 1 H, $J_{6a,6b}$ = 9.6 Hz, 6-$H^a$), 3.98 (m, 2 H, 3-H, $CH_2$−HCH−O), 4.14 (m, 1 H, 5′-H), 4.35 (m, 3 H, 6-$H^b$, $CH_2$, PhOAc), 4.39 (AB, 2 H, $CH_2$, PhOAc), 4.47 (d, 1 H, $J_{1,2}$ = 7.8 Hz, 1-H), 4.49 (AB, 2 H, $CH_2$, PhOAc), 4.68 (AB, 2 H, $CH_2$, PhOAc), 5.03 (t, 1 H, $J_{3',4'} \approx J_{4',5'}$ = 9.8 Hz, 4′-H), 5.05 (d, 1 H, $J_{1',2'}$ = 1.8 Hz, 1′-H), 5.17 (m, 2 H, 2-H, 2′-H), 5.47 (dd, 1 H, $J_{2',3'}$ = 3.6 Hz), 5.27 (s, 1 H, benzylidene), 6.75−7.36 (m, 28 H, 2″-H, 6″-H, 5″-H, CH, arom.). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = −4.2 ($CH_3$, TBDMS), 16.3 (C-6′), 18.3 (Cq, TBDMS), 25.8 [$C(CH_3)_3$, TBDMS], 35.2 ($CH_2CH_2O$), 64.6, 65.1 ($CH_2$, PhOAc), 68.5 (C-6), 70.8 ($CH_2CH_2O$), 65.9, 66.5, 69.0, 70.7, 71.7, 74.1, 76.7, 78.7 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-

4′, C-5′), 97.2 (C-1), 100.9 (C-1′), 101.9 (PhCH, benzylidene), 114.4, 114.5 (CH, PhOAc), 120.8, 121.7 (C-2″, C-5″, C-6″), 126.3−129.5 (CH, arom.), 131.0 (C-1″), 136.8 (Cq, benzylidene), 145.2, 146.5 (C-3″, C-4″), 157.4 (Cq, PhOAc), 167.6, 167.8, 168.0, 168.2 (C=O, PhOAc). − MS: *m/z* = 1337.6 $[M + Na]^+$.

**2-[3,4-Bis(*tert*-butyldimethylsilyloxy)phenyl]ethyl 2-*O*-Phenoxyacetyl-3-*O*-(2,3,4-tri-*O*-phenoxyacetyl-α-L-rhamnopyranosyl)-β-D-glucopyranose (21):** To a solution of **20** (2.303 g, 1.75 mmol) in dichloromethane was added ethylene glycol and a catalytic amount (17 mg) of *p*-toluenesulfonic acid. After 48 h, the reaction mixture was neutralized with triethylamine and concentrated in vacuo. The resulting oil was purified on silica gel using light petroleum ether/$CH_2Cl_2$/MeOH (10:90:0 → 0:100:0 → 0:96:4, v/v/v) as eluent to afford the title compound **21** as a colorless foam and the starting material (**20**). − Yield: 1.31 g, 61% (88% based on consumed **20**). − $R_f$ = 0.3 (4% MeOH in $CH_2Cl_2$). − $^1$H NMR ($CDCl_3$): δ = 0.15, 0.18 (2 × s, 12 H, $CH_3$, TBDMS), 0.96, 0.98 [2 × s, 18 H, $C(CH_3)_3$, TBDMS], 1.18 (d, 3 H, $J_{5',6'}$ = 5.8 Hz, 6′-H), 2.70 (t, 2 H, $CH_2CH_2O$, *J* = 7.3 Hz), 3.32 (m, 1 H, 5-H), 3.50, 3.65, 3.88 (3 × m, 6 H, $CH_2CH_2O$, 3-H, 4-H, 6-H$^a$, 5′-H), 4.19 (m, 1 H, 6-H$^b$), 4.31 (s, 2 H, $CH_2$, PhOAc), 4.40 (d, 1 H, $J_{1,2}$ = 8.0 Hz, 1-H), 4.48 (s, 2 H, $CH_2$, PhOAc), 4.57 (s, 2 H, $CH_2$, PhOAc), 4.65 (AB, 2 H, $CH_2$, PhOAc), 5.02 (m, 2 H, 2′-H, 4′-H), 5.13 (t, 1 H, $J_{2,3}$ = 9.4 Hz, 2-H), 5.26 (d, 1 H, $J_{1',2'}$ = 1.4 Hz, 1′-H), 5.38 (dd, 1 H, $J_{2',3'}$ = 3.6 Hz, 3′-H), 6.58−7.16 (m, 23 H, 2″-H, 6″-H, 5″-H, CH, arom.). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = −4.2 ($CH_3$, TBDMS), 17.2 (C-6′), 18.4 (Cq, TBDMS), 25.9 [$C(CH_3)_3$, TBDMS], 35.3 ($CH_2CH_2O$), 62.0 (C-6), 64.6, 65.2 ($CH_2$, PhOAc), 70.4 ($CH_2CH_2O$), 67.2, 69.2, 69.7, 70.4, 71.2, 72.6, 75.1, 83.1 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 97.2 (C-1), 100.3 (C-1′), 114.4, 114.6 (CH, PhOAc), 121.5, 121.7, 121.8 (C-2″, C-5″, C-6″), 129.4, 129.6 (CH, PhOAc), 131.1 (C-1″), 145.4, 146.5 (C-3″, C-4″), 157.4, 157.7 (Cq, PhOAc), 167.8, 168.0, 168.3 (C=O, PhOAc).

**2-[3,4-Bis(*tert*-butyldimethylsilyloxy)phenyl]ethyl (4,4′-Dimethoxytrityl)-2-*O*-phenoxyacetyl-3-*O*-(2,3,4-tri-*O*-phenoxyacetyl-α-L-rhamnopyranosyl)-6-*O*-β-D-glucopyranoside (22):** Diol **21** (1.17 g, 0.89 mmol) was dissolved in a mixture of $CH_2Cl_2$ (9 mL) and pyridine (144 uL, 1.78 mmol) and 4,4′-dimethoxytrityl chloride (392 mg, 1.15 mmol) was added. After stirring for 1 h, complete conversion of the starting material had occurred, as was shown by TLC analysis. Addition of a small amount of methanol destroyed the excess of 4,4′-dimethoxytrityl chloride. The reaction mixture was diluted with dichloromethane and transferred into a separation funnel. The dichloromethane layer was washed with aq. $NaHCO_3$ (10%) and water and dried ($MgSO_4$). The mixture was filtered and concentrated under reduced pressure. The residue was subjected to silica gel purification (eluent: toluene/ethyl acetate/triethylamine, 100:0:1 → 85:15:1, v/v/v) to afford **22** (1.18 g, 87%) as a light yellow oil. − $R_f$ = 0.5 (toluene/ethyl acetate/triethylamine, 85:15:0.1, v/v/v). − $^1$H NMR ($CDCl_3$): δ = 0.20, 0.21 (2 × s, 12 H, $CH_3$, TBDMS), 1.01 [s, 18 H, $C(CH_3)_3$, TBDMS], 1.18 (d, 3 H, $J_{5',6'}$ = 5.9 Hz, 6′-H), 2.80 (t, 2 H, $CH_2CH_2O$, *J* = 7.3 Hz), 3.14 (d, 1 H, 4-OH), 3.45, 3.75, 4.30 (3 × m, 5 H, 3-H, 4-H, 6-H$^a$, 6-H$^b$, 5′-H), 3.66 (m, 1 H, $CH_2$−HCH−O), 3.80 (s, 6 H, OMe, DMT), 4.01 (m, 1 H, $CH_2$−HCH−O), 4.36 (AB, 2 H, $CH_2$, PhOAc), 4.36 (d, 1 H, $J_{1,2}$ = 8.0 Hz, 1-H), 4.53 (AB, 2 H, $CH_2$, PhOAc), 4.57 (AB, 2 H, $CH_2$, PhOAc), 4.67 (AB, 2 H, $CH_2$, PhOAc), 5.08 (d, 1 H, $J_{1',2'}$ = 1.5 Hz, 1′-H), 5.14 (t, 1 H, $J_{3',4'} \approx J_{4',5'}$ = 9.8 Hz, 4′-H), 5.18 (t, 1 H, $J_{2,3}$ = 9.4 Hz, 2-H), 5.49 (dd, 1 H, $J_{2',3'}$ = 3.5 Hz, 3′-H), 6.75−7.40 (m, 36 H, 2″-H, 6″-H, 5″-H, CH, arom.). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = −4.2 ($CH_3$, TBDMS), 16.9 (C-6′), 18.3 (Cq, TBDMS), 25.8 [$C(CH_3)_3$, TBDMS], 35.3 ($CH_2CH_2O$), 55.0 (OMe, DMT), 63.6 (C-6), 64.5, 65.1 ($CH_2$, PhOAc), 70.5 ($CH_2CH_2O$), 66.6, 69.3, 70.5, 71.5, 73.0, 73.9, 81.9 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 86.5 (Cq, DMT), 97.7 (C-1), 100.3 (C-1′), 113.1−114.6 (CH, PhOAc, DMT), 120.7, 121.3, 121.7 (C-2″, C-5″, C-6″), 126.8−129.8 (CH, PhOAc, DMT), 131.2 (C-1″), 135.4 (Cq, DMT), 144.3 (Cq, DMT), 145.2, 146.4 (C-3″, C-4″), 157.3, 157.6, 158.4 (Cq, PhOAc), 167.8, 167.9, 168.2 (C=O, PhOAc).

**2-[3,4-Bis(*tert*-butyldimethylsilyloxy)phenyl]ethyl 4-*O*-Acetyl-6-*O*-(4,4′-dimethoxytrityl)-2-*O*-phenoxyacetyl-3-*O*-(2,3,4-tri-*O*-phenoxyacetyl-α-L-rhamnopyranosyl)-β-D-glucopyranoside (23):** *N*,*N*-Dicyclohexylcarbodiimide (74 mg, 0.35 mmol) and 4-(dimethylamino)pyridine (8 mg) were added to a mixture of compound **22** (0.272 mg, 0.177 mmol) and 3,4-di-*O*-acetylcaffeic acid (96 mg, 0.35 mmol) in dichloromethane (1.6 mL). After stirring for 12 h, the reaction mixture was diluted with diethyl ether (50 mL) and the dicyclohexylurea salt was removed by filtration. The filtrate was washed with water (10 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification was performed by column chromatography (toluene/ethyl acetate/triethylamine, 100:0:0.1 → 95:5:0.1, v/v/v) to afford **23** (214 mg, 77%) as an oil. − $R_f$ = 0.8 (toluene/ethyl acetate/triethylamine, 75:25:0.1, v/v/v). − $^1$H NMR ($CDCl_3$): δ = 0.14, 0.15 (2 × s, 12 H, $CH_3$, TBDMS), 0.96, 0.97 (2 × s, 18 H, $C(CH_3)_3$, TBDMS), 1.06 (d, 3 H, $J_{5',6'}$ = 5.9 Hz, 6′-H), 1.74 (s, 3 H, Ac), 2.82 (t, 2 H, *J* = 7.1 Hz, $CH_2CH_2O$), 3.12 (m, 2 H, 6-H$^a$, 6-H$^b$), 3.40 (m, 1 H, 5-H), 3.64 (m, 1 H, $CH_2$−HCH−O), 3.76 (s, 6 H, OMe, DMT), 3.80 (t, 1 H, 3-H), 3.87 (m, 1 H, 5′-H), 3.99 (1 H, $CH_2$−HCH−O), 3.87 (m, 1 H, 5′-H), 4.24 (AB, 2 H, $CH_2$, PhOAc), 4.38 (m, 3 H, 1-H, $CH_2$, PhOAc), 4.56 (s, 2 H, $CH_2$, PhOAc), 4.68 (s, 2 H, $CH_2$, PhOAc), 4.88 (d, 1 H, $J_{1',2'}$ = 1.6 Hz, 1′-H), 5.03−5.29 (m, 5 H, 2′-H, 3′-H, 4′-H, 2-H, 4-H), 6.70−7.33 (m, 36 H, 2″-H, 6″-H, 5″-H, CH, arom.). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = −4.5 ($CH_3$, TBDMS), 17.0 (C-6′), 18.4 (Cq, TBDMS), 20.6 ($CH_3$, Ac), 25.9 [$C(CH_3)_3$, TBDMS], 35.5 ($CH_2CH_2O$), 55.1 (OMe, DMT), 61.9 (C-6), 64.6, 65.3 ($CH_2$, PhOAc), 70.8 ($CH_2CH_2O$), 67.1, 69.6, 70.2, 71.0, 72.8, 73.5, 81.4, 86.9 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 86.0 (Cq, DMT), 98.9 (C-1), 100.5 (C-1′), 112.9−114.6 (CH, PhOAc, DMT), 120.8, 121.3, 121.8 (C-2″, C-5″, C-6″), 126.7−129.5 (CH, PhOAc, DMT), 131.2 (C-1″), 135.7 (Cq, DMT), 144.3 (Cq, DMT), 145.3, 146.6 (C-3″, C-4″), 157.4, 157.8, 158.3 (Cq, PhOAc), 167.7, 168.0, 168.8 (C=O, PhOAc, Ac). − MS: *m/z* = 1593.8 $[M + Na]^+$. − $C_{87}H_{102}O_{23}Si_2$ (1570.63): calcd. C 66.48, H 6.54; found C 66.6, H 6.6.

**Methyl 3,4-Bis(*O*-*tert*-butyldimethylsilyl)caffeate (26):** Caffeic acid (3,4-dihydroxycinnamic acid) (1.68 g, 10 mmol) was converted into methyl 3,4-bis(*O*-*tert*-butyldimethylsilyl)caffeate (**26**) as described for the synthesis of methyl [3,4-bis(*tert*-butyldimethylsilyloxy)phenyl]acetate (**11**) from (3,4-dihydroxyphenyl)acetic acid (**9**). The crude methyl 3,4-bis(*O*-*tert*-butyldimethylsilyl)caffeate was purified on a silica gel column, which was eluted with toluene/ethyl acetate (3:1, v/v) to afford **26** (3.42 g, 81%) as a colorless oil. − $R_f$ = 0.8 ($CH_2Cl_2$/MeOH, 9:1, v/v). − $^1$H NMR ($CDCl_3$): δ = 0.20 (s, 12 H, $CH_3$, TBDMS), 0.98 (s, 18 H, $C(CH_3)_3$, TBDMS), 3.78 (s, 3 H, OMe), 6.24 (d, 1 H, $J_{H,H}$ = 15.8 Hz, HC=CH−C=O), 6.81 (d, 1 H, Ph), 7.00 (m, 2 H, CH, Ph), 7.57 (d, 1 H, HC=CH−C=O). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = −4.2 ($CH_3$, TBDMS), 18.3 (Cq, TBDMS), 25.7 [$C(CH_3)_3$, TBDMS], 51.3 (OMe), 115.3 (CH=CHC=O), 120.2, 121.0, 122.1 (CH, Ph), 127.9 (Cq, Ph), 144.5 (CH=CHC=O), 147.0, 149.2 (Cq, Ph), 167.4 (C=O).

**3,4-Bis(*O*-*tert*-butyldimethylsilyl)caffeic Acid (27):** Methyl 3,4-bis(*O*-*tert*-butyldimethylsilyl)caffeate (**26**, 2.37 g, 6 mmol) in diethyl ether (25 mL) was added dropwise to a cooled (0 °C) suspension of $LiAlH_4$ (228 mg, 9 mmol) in diethyl ether (25 mL) and stirred for

15 min. After this time, TLC analysis revealed complete disappearance of the starting material. The reaction was quenched by dropwise addition of methanol and washed with water. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude allylic alcohol was dissolved in freshly distilled diethyl ether and treated with 6 g of $MnO_2$. After stirring for 2 h, the mixture was filtered, and the filtrate was concentrated in vacuo. The resulting crude aldehyde was taken up in a mixture of *tert*-butyl alcohol/water/2-methyl-2-butene (200 mL, 15:15:9, v/v/v) and to this mixture was added 5 g of $NaH_2PO_4 \cdot H_2O$, followed by the addition of sodium chlorite (5 g). After stirring for 17 h, the reaction mixture was diluted with diethyl ether. The organic solution was washed with water, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford a solid. Purification by silica gel column chromatography (light petroleum ether/diethyl ether, 2:1, v/v) gave **27** (2.01 g, 82%) as a colorless solid. − 3,4-Bis(*tert*-butyldimethylsilyloxy)cinnamyl alcohol: $R_f$ = 0.6 (light petroleum ether/diethyl ether, 3:1, v/v). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = −4.2 ($CH_3$, TBDMS), 18.4 (Cq, TBDMS), 25.9 [$C(CH_3)_3$, TBDMS], 63.5 ($CH_2$), 118.9, 119.9, 121.0 (CH, Ph), 126.4 (PhCH=CH), 130.4 (Cq, Ph), 130.8 (PhCH=CH), 146.7 (Cq, Ph). − 3,4-Bis(*tert*-butyldimethylsilyloxy)cinnamaldehyde: $R_f$ = 0.2 (light petroleum ether/diethyl ether, 3:1, v/v). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = −4.2 ($CH_3$, TBDMS), 18.3 (Cq, TBDMS), 25.7 [$C(CH_3)_3$, TBDMS], 120.3, 121.1, 123.0 (CH, Ph), 126.5 (CH=CHC=O), 127.5 (Cq, Ph), 150.2, 148.7 (Cq, Ph), 152.7 (CH=CHC=O), 193.3 (C=O). − **27**: $R_f$ = 0.6 (light petroleum ether/diethyl ether, 3:1, v/v). − $^1H$ NMR ($CDCl_3$): δ = 0.22 (s, 12 H, $CH_3$, TBDMS), 0.98 [s, 18 H, $C(CH_3)_3$, TBDMS], 6.26 (d, 1 H, $J_{H,H}$ = 16.1 Hz, HC=CH−C=O), 6.83 (d, 1 H, Ph), 7.03 (m, 2 H, CH, Ph), 7.68 (d, 1 H, HC=CH−C=O), 10.0 (br. s, 1 H, OH). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = −4.2 ($CH_3$, TBDMS), 18.4 (Cq, TBDMS), 25.8 [$C(CH_3)_3$, TBDMS], 114.9 (CH=CHC=O), 120.5, 121.1, 122.6 (CH, Ph), 127.6 (Cq, Ph), 146.8 (CH=CHC=O), 147.1, 149.7 (Cq, Ph), 172.5 (C=O). − MS: *m*/*z* = 431.9 $[M + Na]^+$.

**2-[3,4-Bis(*tert*-butyldimethylsilyloxy)phenyl]ethyl [(*E*,*Z*)-3,4-Bis-(*O*-*tert*-butyldimethylsilyl)caffeoyl]-6-*O*-(4,4′-dimethoxytrityl)-2-*O*-phenoxyacetyl-3-*O*-(2,3,4-tri-*O*-phenoxyacetyl-α-L-rhamnopyranosyl)-4-*O*-β-D-glucopyranose (28):** To a solution of 3,4-bis(*O*-*tert*-butyldimethylsilyl)caffeic acid (**27**) (1.147 g, 2.25 mmol) and compound **23** (918 mg, 0.75 mmol) in $CH_2Cl_2$ (4 mL) was added *N*,*N*-dicyclohexylcarbodiimide (463 mg, 2.25 mmol) and a catalytic amount of 4-(dimethylamino)pyridine (27 mg, 0.225 mmol). To the stirring mixture were added additional amounts of 4-(dimethylamino)pyridine (15 mg) after 15 h, 24 h, and 40 h reaction time. The progress of the esterification was monitored by TLC analysis (toluene/ethyl acetate/triethylamine, 92:8:0.1, v/v/v) and showed that the reaction was complete after 48 h. The reaction mixture was diluted with diethyl ether (50 mL) and the dicyclohexylurea salt was removed by filtration. The filtrate was washed with water (10 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the residual oil was accomplished by silica gel column chromatography (eluent: toluene/ethyl acetate/triethylamine, 100:0:1 → 97:3:1, v/v/v). Concentration of the appropriate fractions furnished **28** as an oil. − Yield: 949 mg, 67%. − $R_f$ = 0.6 (toluene/ethyl acetate/triethylamine, 92:12:0.1, v/v/v). − $^1H$ NMR ($CDCl_3$): δ = 0.17 (m, 12 H, $CH_3$, TBDMS), 0.96 [m, 21 H, 6′-H, $C(CH_3)_3$, TBDMS], 2.85 (t, 2 H, *J* = 7.1 Hz, $CH_2CH_2O$), 3.18 (m, 2 H, 6-H$^a$, 6-H$^b$), 3.51 (m, 1 H, 5-H), 3.61, 3.63 (2 × s, 6 H, OMe, DMT), 3.64 (m, 1 H, $CH_2$−HCH−O), 3.84 (m, 1 H, 5′-H), 4.00 (m, 2 H, 3-H, $CH_2$−HCH−O), 4.26 (m, 2 H, $CH_2$, PhOAc), 4.32 (m, 2 H, $CH_2$, PhOAc), 4.40 (m, 1 H, 1-H), 4.51 (m, 2 H, $CH_2$, PhOAc), 4.64 (m, 2 H, $CH_2$, PhOAc), 5.01 (m, 2 H, 1′-H, 4′-H), 5.26 (m, 4 H, 2′-H, 3′-H, 2-H, 4-H), 5.52 [d, 0.09 H, $J_{H,H}$ = 12.4 Hz, HC=CH−C=O (*Z*)], 5.96 [d, 0.91 H, $J_{H,H}$ = 15.6 Hz, HC=CH−C=O (*E*)], 6.71−7.30 (m, 40 H, 2″-H, 6″-H, 5″-H, 2‴-H, 5‴-H, 6‴-H, HC=CH−C=O, CH, arom.). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = −4.9 ($CH_3$, TBDMS), 17.4 (C-6′), 18.4 (Cq, TBDMS), 26.4 [$C(CH_3)_3$, TBDMS], 35.6 ($CH_2CH_2O$), 54.9 (OMe, DMT), 61.9 (C-6), 64.4, 64.6, 65.3 ($CH_2$, PhOAc), 70.8 ($CH_2CH_2O$), 66.7, 69.1, 69.3, 70.5, 71.3, 73.7, 73.9, 80.3 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 86.0 (Cq, DMT), 98.5 (C-1), 100.6 (C-1′), 113.0−129.8 (C-2″, C-5″, C-6″, C-2‴, C-5‴, C-8‴, C-9‴, CH, DMT, PhOAc), 127.5 (C-4‴), 131.3 (C-1″), 135.6, 135.9 (Cq, DMT), 144.1 (Cq, DMT), 145.3, 146.5, 147.2, 149.9 (C-3″, C-4″, C-6‴, C-7‴), 145.3 (C-3‴), 157.4, 157.8, 158.2 (Cq, PhOAc), 165.0 (C-1‴), 167.6, 167.9, 168.0, 168.3 (C=O, PhOAc). − MS: *m*/*z* = 1941.7 $[M + Na]^+$.

**2-[3,4-Bis(*tert*-butyldimethylsilyloxy)phenyl]ethyl 4-*O*-[(*E*,*Z*)-3,4-Bis(*O*-*tert*-butyldimethylsilyl)caffeoyl]-6-*O*-(4,4′-dimethoxytrityl)-3-*O*-(α-L-rhamnopyranosyl)-β-D-glucopyranose (29):** To a stirred solution of compound **29** (384 mg, 0.20 mmol) in $CH_2Cl_2$ (18 mL) was added dropwise 2 mL of a 0.01 M $K_2CO_3$ solution in MeOH. The reaction mixture was stirred for 2 h, after which TLC analysis revealed complete conversion of the starting material into a slower moving product. Silica gel (1 g), first rinsed with $CH_2Cl_2/Et_3N$ (99:1, v/v) and dried, was added and the mixture was concentrated under reduced pressure. The resulting silica gel mixture was applied to a column of silica gel (10 g) and eluted with $CH_2Cl_2$/MeOH/$Et_3N$ (100:0:1 → 98:2:1, v/v/v), furnishing pure **29** as a white foam. − Yield: 238 mg, 86%. − $R_f$ = 0.36 ($CH_2Cl_2$/MeOH/$Et_3N$, 94:6:0.1, v/v/v). − $^1H$ NMR ($CDCl_3$): δ = 0.17 (m, 12 H, $CH_3$, TBDMS), 0.96 [m, 8 H, $C(CH_3)_3$, TBDMS], 0.97 [d, 3 H, $J_{5',6'}$ = 5.9 Hz, 6′-H (*E*)], 1.01 [d, 3 H, $J_{5',6'}$ = 5.9 Hz, 6′-H (*Z*)], 2.93 (t, 2 H, $CH_2CH_2O$, *J* = 7.1 Hz), 3.70 (s, 6 H, OMe, DMT), 4.32 [d, 1 H, $J_{1,2}$ = 8.0 Hz, 1-H (*Z*)], 4.35 [d, 1 H, $J_{1,2}$ = 8.0 Hz, 1-H (*E*)], 4.96 [t, 1 H, $J_{3',4'} \approx J_{4',5'}$ = 9.8 Hz, 4′-H (*Z*)], 5.09 [t, 1 H, $J_{3',4'} \approx J_{4',5'}$ = 9.8 Hz, 4′-H (*E*)], 5.16 [d, 1 H, $J_{1',2'}$ = 1.5 Hz, 1′-H (*E*)], 5.18 [d, 1 H, $J_{1',2'}$ = 1.5 Hz, 1′-H (*Z*)], 5.53 [d, 0.09 H HC=CH−C=O (*Z*), $J_{H,H}$ = 12.4 Hz], 6.00 [d, 0.91 H, $J_{H,H}$ = 15.3 Hz, HC=CH−C=O (*E*)], 6.71−7.30 (m, 20 H, 2″-H, 6″-H, 5″-H, 2‴-H, 5‴-H, 6‴-H, HC=CH−C=O, CH, arom.). − $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = −4.4 ($CH_3$, TBDMS), 17.4 (C-6′), 18.1 (Cq, TBDMS), 25.6 [$C(CH_3)_3$, TBDMS], 35.5 ($CH_2CH_2O$), 54.7 (OMe, DMT), 62.3 (C-6), 71.0 ($CH_2CH_2O$), 68.6, 69.0, 70.5, 70.7, 72.3, 73.6, 74.6, 80.2 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 85.7 (Cq, DMT), 101.3 (C-1), 102.9 (C-1′), 112.7 (CH, DMT), 114.5 (C-2‴), 120.0−129.8 (C-2″, C-5″, C-6″, C-5‴, C-8‴, C-9‴, CH, DMT), 127.4 (C-4‴), 131.1 (C-1″), 135.5, 137.7 (Cq, DMT), 144.4 (Cq, DMT), 145.1, 146.4, 146.9, 149.5 (C-3″, C-4″, C-6‴, C-7‴), 145.1 (C-3‴), 166.0 (C=O). − MS: *m*/*z* = 959.0 $[M + Na]^+$.

**2-(3,4-Dihydroxyphenyl)ethyl 4-*O*-(*E*,*Z*)-Caffeoyl-3-*O*-(α-L-rhamnopyranosyl)-β-D-glucopyranose (1, Verbascoside):** Preparation of a stock solution of 1.56 M HF·$Et_3N$ in pyridine: 3HF·$Et_3N$ (1.22 mmol, 200 μL) was added to a mixture of pyridine (1.80 mL) and triethylamine (2.44 mmol, 339 μL). To a solution of compound **29** (246 mg, 188 μmol) in 4 mL of pyridine was added 800 μL of 1.56 M HF·$Et_3N$ in pyridine. After stirring for 3 h, TLC analysis showed complete formation of a slower moving compound. The mixture was diluted with methanol and applied to a column of Dowex 50 W X4 in $Na^+$ form, which was eluted with methanol. The filtrate was concentrated in vacuo and the residue was redissolved in a mixture of $CH_2Cl_2$/EtOH/AcOH (12 mL, 3:1:8, v/v/v). The reaction mixture was stirred for 8 h, after which TLC analysis revealed complete removal of the dimethoxytrityl function. The mixture was concentrated in vacuo and purification was performed

on a silica gel column. Elution was effected with dichloromethane/methanol (9:1 → 8:2, v/v). Subsequent concentration of the appropriate fractions furnished verbascoside (89 mg, 76%) as a white amorphous solid. – $R_f$ = 0.2 ($CH_2Cl_2$/MeOH/$H_2O$, 80:20:1, v/v/v). – $[\alpha]_D^{20}$= –86.1 ($c$ = 1, MeOH). – $^1$H NMR ($CD_3OD$): δ = 1.15 [d, 0.91 H, $J_{5',6'}$ = 7.2 Hz, 6′-H (*E*)], 1.22 [d, 0.09 H, $J_{5',6'}$ = 7.2 Hz, 6′-H (*Z*)], 2.82 (br. t, 2H $CH_2CH_2O$), 3.32 (dd, 1 H, $J_{4',3'}$ = 9.2 Hz, 4′-H), 3.45 (t, 1 H, $J_{2,3}$ = 8.5 Hz, 2-H), 3.59 (m, 2 H, 5-H, 6-H$^a$), 3.62 (m, 1 H, 5′-H), 3.64 (dd, 1 H, $J_{3',4'}$ = 9.2 Hz, 3′-H), 3.66 (m, 1 H, 6-H$^b$), 3.76 (m, 1 H, $CH_2$–HCH–O, $J$ = 7.1 Hz), 3.83 (t, 1 H, $J_{2,3}$ = 8.9 Hz, 3-H), 3.93 (dd, 1 H, $J_{2',3'}$ = 3.0 Hz, 2′-H), 4.09 (m, 1 H, $CH_2$–HCH–O, $J$ = 7.1 Hz), 4.32 [d, 0.09 H, $J_{1,2}$ = 8.7 Hz, 1-H (*Z*)], 4.34 [d, 0.91 H, $J_{1,2}$ = 8.7 Hz, 1-H (*E*)], 4.92 [t, 0.09 H, $J_{3,4}$ = 8.5 Hz, 4-H (*Z*)], 4.94 [t, 0.91 H, $J_{3,4}$ = 8.5 Hz, 4-H (*E*)], 5.18 [d, 0.09 H, $J_{1',2'}$ = 1.6 Hz, 1′-H (*Z*)], 5.20 [d, 0.91 H, $J_{1',2'}$ = 1.6 Hz, 1′-H (*E*)], 5.76 [d, 0.09 H, $J_{H,H}$ = 12.2 Hz, HC=CH–C=O (*Z*)], 6.25 [d, 0.91 H, $J_{H,H}$ = 18.1 Hz, HC=CH–C=O (*E*)], 6.58 (dd, 1 H, $J_{6'',2''}$ = 1.9 Hz, $J_{6'',5''}$ = 8.0 Hz, 6′-H), 6.74 (m, 2 H, 2′′-H, 5′′-H), 6.79 [d, 0.09 H, $J_{6''',5'''}$ = 7.8 Hz, 5′′′-H (*Z*)], 6.81 [d, 0.91 H, $J_{6''',5'''}$ = 7.8 Hz, 5′′′-H (*E*)], 6.91 [d, 0.09 H, $J_{H,H}$ = 12.2 Hz, HC=CH–C=O (*Z*)], 6.94 [dd, 0.91 H, 6′′′-H (*E*)], 7.04 [dd, 0.09 H, 6′′′-H (*Z*)], 7.06 [d, 0.91 H, $J_{6'',2''}$ = 2.1 Hz, 2′′′-H (*E*)], 7.50 [d, 0.09 H, $J_{6'',2''}$ = 2.1 Hz, 2′′′-H (*Z*)], 7.60 [d, 0.91 H, $J_{H,H}$ = 18.1 Hz, HC=CH–C=O (*E*)]. – $^{13}$C{$^1$H} NMR ($CD_3OD$): δ = 19.3 (C-6′), 37.4 ($CH_2CH_2O$), 63.4 (C-6), 71.4 (C-5′), 71.7 (C-4), 73.1 ($CH_2CH_2O$), 73.2 (C-2′), 73.0 (C-3′), 74.6 (C-4′), 77.2 (C-2), 77.1 (C-5), 82.6 (C-3), 103.8 (C-1′), 105.1 (C-1), 115.8 (HC=CH–C=O), 116.2 (C-2′′′), 117.4 (C-2′′), 117.6 (C-5′′′), 118.2 (C-5′′), 122.3 (C-6′′), 124.1 (C-6′′′), 128.9 (C-1′′′), 132.4 (C-1′′), 145.5 (C-3′′), 147.0 (C-4′′), 147.7 (C-3′′′), 148.8 (HC=CH–C=O), 150.7 (C-4′′′), 169.3 (C=O). MS: $m/z$ = 647.3 [M + Na]$^+$. – $C_{29}H_{36}O_{15}$ (624.21): calcd. C 55.77, H 5.81; found C 55.8, H 5.8.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