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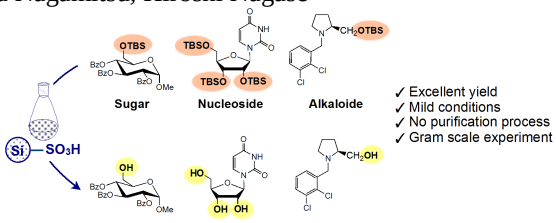

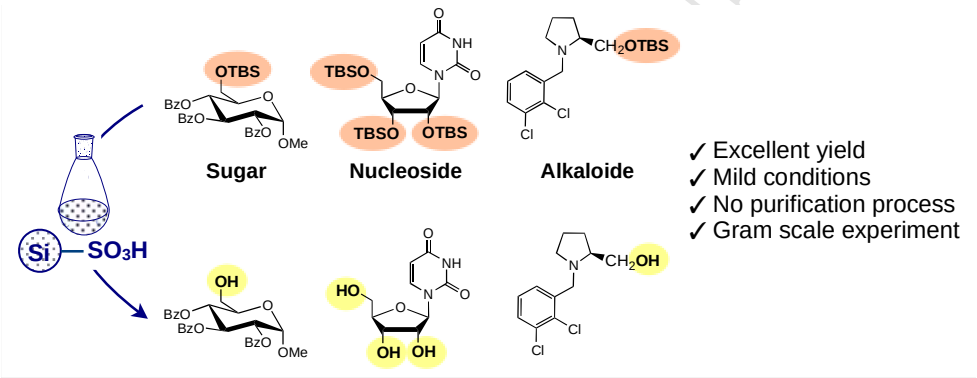

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Deprotection of silyl ethers by using SO_3H silica gel: Application to sugar, nucleoside, and alkaloid derivatives

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ABSTRACT

We applied a desilylation procedure using SO_3H silica gel, with the surface modified by alkylsulfonic acid groups, to silylated sugar, nucleoside, and alkaloid derivatives. The treatment with SO_3H silica gel provided desilylated products in good to excellent yield. In the reactions of sugar and nucleoside derivatives, no silyl residue was detected in the crude products, but the crude products of the reaction of alkaloids contained small amounts of silyl residues. Even though the sugar and nucleoside derivatives had a labile glycosyl and C-N bond, respectively, these bonds tolerated the reaction conditions. These outcomes suggested that the desilylation procedure using SO_3H silica gel would be applicable to the deprotection of a variety of types of compounds protected by silyl groups. In a gram scale experiment, the desilylation procedure successfully proceeded without the observation of any silyl residue in the crude product.

1. Introduction

The synthetic processes to obtain chemical products, pharmaceutical products, agrichemicals, *etc*. have recently been required to use environmentally benign processes. From such a viewpoint, solid-supported reagents have been widely used in organic synthesis.[1] We have also already developed and reported the desilylation process using a silica gel (SO_3H silica gel)[2] whose surface was modified by alkylsulfonic acid groups.[3] The SO_3H silica gel could be repeatedly used for the desilylation without complicated pretreatment before its reuse. Furthermore, the desilylation procedure did not require a purification process because the silyl residues formed during the deprotection were captured by the silanol groups on the surface of the silica gel (Scheme 1).[2] This feature was observed in the 10th repeated use of the SO_3H silica gel.[4] We attempted to apply the desilylation process to various types of compounds. Herein, we report the application of a SO_3H silica gel to the deprotection of silyl ethers in sugar, nucleoside, and alkaloid derivatives.

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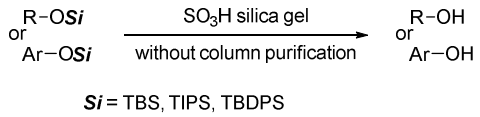
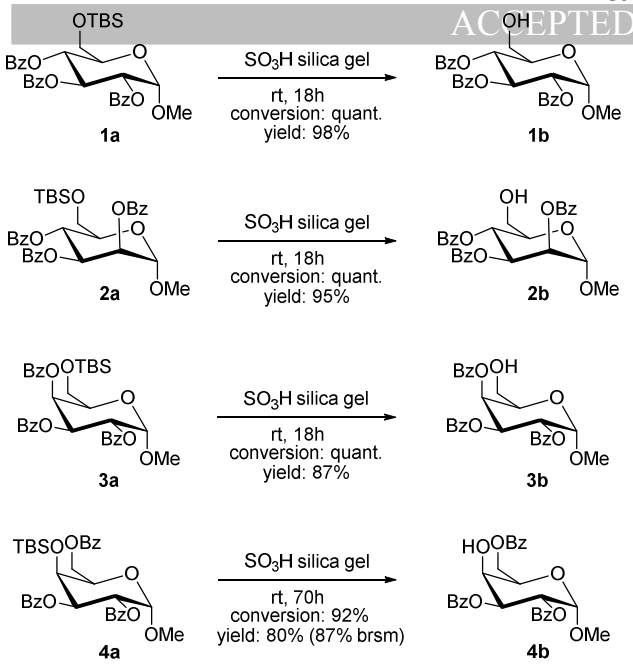


Scheme 1. The deprotection of silyl ethers using SO_3H silica gel.

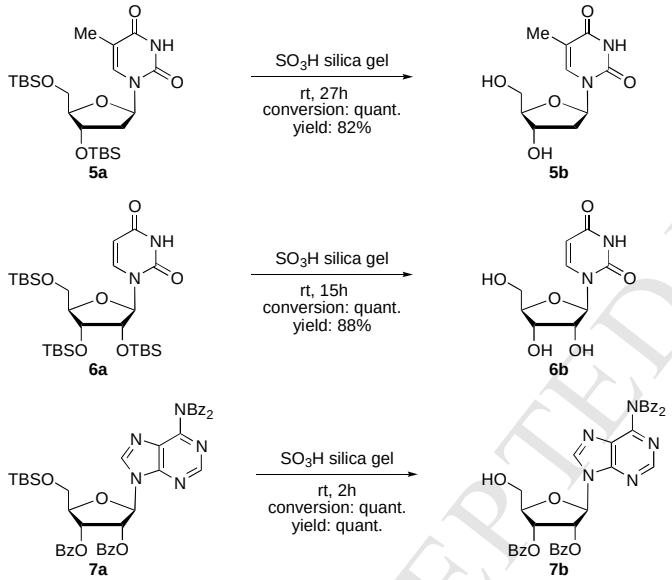
2. Results and Discussion

2.1. Deprotection of silyl ethers in sugar derivatives

We attempted to apply our desilylation procedure to sugar derivatives. Glucose, mannose, and galactose derivatives **1a**–**3a** were selected as silylated sugars. The treatment of **1a**–**3a** with SO_3H silica gel provided the desilylated compounds **1b**–**3b** in excellent yields (Scheme 2). It was possible to use various solvents in this procedure, although we have reported that heptane was optimal.[2] Desilylation of **1a** using heptane gave the desilylated product **1b** in 98% yield (Scheme 2), whereas the product **1b** was obtained in 92% and 95% yield in the experiments using toluene and dichloromethane, respectively. It is noteworthy that neither cleavage of the glycosyl bond nor epimerization were observed under these reaction conditions,



Scheme 2. Desilylation of silylated sugar derivatives.



Scheme 3. Desilylation of silylated nucleoside derivatives.

even though the glycosyl bond is generally cleavable under the acidic conditions *via* the oxocarbenium ion. The fact that no 1-epimers of **1b**–**3b** were obtained strongly suggested that the corresponding oxocarbenium ion may not be formed at all during the desilylation. Galactose derivative **4a**, which had the secondary hydroxy group protected by a TBS group, was successfully converted into deprotected compound **4b**. Although this conversion required a long reaction time, only the starting compound **4a** was recovered in 8% and no anomerization was observed. The steric constraint around the secondary siloxy group would retard the progression of the deprotection. One of the features of our desilylation method was that no purification process was required because silyl residues produced during the reaction were captured by the silanol groups on the surface of the silica gel. These phenomena were observed by the solid phase ^{29}Si NMR experiments.[2] In all cases of silylated sugars, no silyl residue was detected in the crude products.

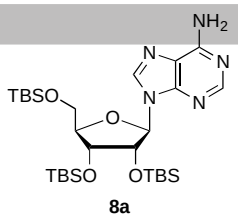
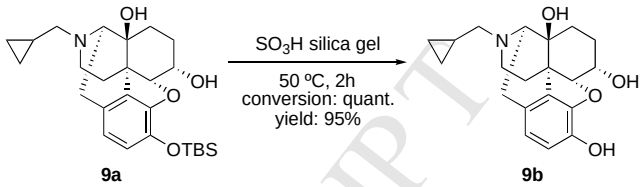
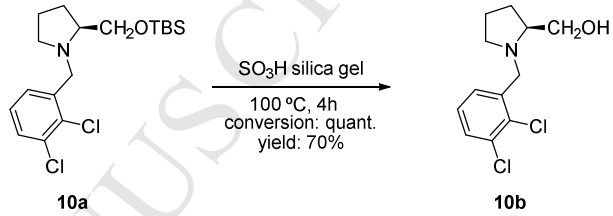


Figure 1. Structure of an adenosine derivative **8a**.



Scheme 4. Desilylation of a morphinane derivative.[2]



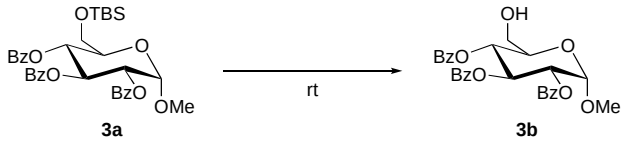
Scheme 5. Desilylation of a silylated proline derivative.

2.2. Deprotection of silyl ethers in nucleoside derivatives

We next attempted desilylation of nucleoside derivatives **5a-8a**. Ethyl acetate was used as a solvent due to the solubility of nucleoside derivatives **5a** and **6a**. Even though the C-N bond in the nucleosides is also labile under strong acid conditions, the desilylated compounds thymidine (**5b**) and uridine (**6b**) were obtained in excellent yields without the cleavage of the C-N bond (Scheme 3). No mono- and/or di-silyl derivatives were detected after the indicated reaction time. The crude products of these reactions contained no silyl residue. In the case of compound **7a**, chloroform was used as solvent (Scheme 3). The primary siloxy group was cleaved effectively under our conditions to afford alcohol **7b** in quantitative yield. These results suggested that a primary siloxy group could be cleaved for short reaction time whereas the cleavage of a secondary siloxy group required longer reaction time. Indeed, the progress of the deprotection of the silylated adenosine derivative **8a**[5] bearing two secondary siloxy groups and a primary one (Fig. 1) was slow. The starting material **8a** was disappeared after a while, which suggested the desilylation of a primary siloxy group would be complete, but mono- and di-silyl derivatives were observed even after 24 hours. The prolongation of the reaction time (72 hour) furnished the decomposition of the compounds. It is not clear at present why silylated adenosine **8a** withstood our desilylation conditions, but the observed decomposition of the compounds was not unnatural because it is known that purine bases are better leaving groups than pyrimidine bases.

2.3. Deprotection of silyl ethers in alkaloid derivatives

We have recently reported that a siloxy group of a morphinan derivative was effectively cleaved under our deprotection method (Scheme 4).[2] As another alkaloid derivative, we chose proline derivatives. Proline derivatives are useful compounds because they are used not only as organic catalysts,[6] but also as



3a **3b**

1.14 g	SO_3H silica gel (935 mg)	835 mg (90%)
62.1 mg[a]	SO_3H silica gel (500 mg)	48.3 mg (87%)

Scheme 6. Desilylation of **3a** in a gram scale. [a] This experiment was shown in scheme 2.

physiologically active compounds. For example, some derivatives possessing the proline (substituted pyrrolidine) unit were reported as nicotinic acetylcholine receptor ligands,[7] modulators of G-glycoprotein,[8] and so on.[9] We attempted to synthesize compound **10b**, which was a possible intermediate for synthesis of a modulator of G-glycoprotein (Scheme 5).[8] Compound **10a**, which was prepared from TBS ether of prolinol by benzylation, was treated with SO_3H silica gel using methanol as a solvent to give **10b** in 70% yield. As the desilylation of **10a** was not complete at 50 ˚C, higher reaction temperature was required for reaction completion. One of the features of our desilylation method was no silyl residue in the crude product. However, in the desilylation of alkaloids, some amount of silyl residue remained in the crude product. Since alkaloids are basic compounds, SO_3H groups immobilized on the silica gel surface might be partly neutralized to retard the trapping of silyl residues by silanols.

2.4. Gram scale experiments

A large scale reaction sometimes brings troublesome issues and often requires further optimization of the reaction conditions. Therefore, we attempted desilylation of a gram scale of **3a** (Scheme 6). To a solution of **3a** (1.14 g) in heptane (4.6 mL) was added SO_3H silica gel (935 mg), which was about a tenth of the amount of SO_3H silica gel compared to the amount of SO_3H silica gel using the other reactions shown in this report. After shaking for 1 min, the resulting powder was left to stand at ambient temperature for 24 h. The reaction successfully proceeded to give desilylated product **3b** in 90% yield. In a gram scale experiment, it was possible to monitor the progress of the reaction by picking up a small amount of the silica gel. No silyl residue was observed in a crude product.

3. Conclusion

The desilylation of sugar, nucleoside, and alkaloid derivatives using the SO_3H silica gel successfully proceeded to provide the corresponding desilylated compounds. In the reactions of sugar and nucleoside derivatives, no silyl residue was detected, but the crude products of the reaction of alkaloids contained small amounts of silyl residues. Even though sugar and nucleoside derivatives had a labile glycosyl bond and C-N bond, respectively, these bonds tolerated the reaction conditions. These outcomes suggested that the desilylation procedure using SO_3H silica gel would be applicable to the deprotection of various types of compounds protected by silyl groups. In a gram scale experiment, the desilylation procedure successfully proceeded without the observation of any silyl residue in the crude product.

4. Experimental section

4.1. General

All reagents and solvents were obtained from commercial suppliers and were used without further purification. Infrared (IR) spectra were recorded on a JASCO FT/IR-460Plus. Nuclear magnetic resonance (NMR) spectra were recorded on an Agilent Technologies VXR-400NMR for ^{1}H NMR and ^{13}C NMR. Chemical shifts were reported as δ values (ppm) reference to tetramethylsilane. Mass spectra (MS) were obtained on JMS-AX505HA, JMS-700 MStation, or JMS-100LP instrument by applying an electrospray ionization (ESI) method. The progress of the reaction was determined on Merck Silica Gel Art. 5715 (TLC). Silica gel was purchased from Fuji Silysia (CHROMATOREX® PSQ 60B (60 μm) and SCAVENGER SO_3H SILICA).

*4.2. Preparation of silylated sugar derivatives **1a**–**4a***

*4.2.1. General procedure for the preparation of methyl 2,3,4-tri-O-benzoyl-6-O-(tert-butyl)dimethylsilyl-α-D-pyranosides **1a**–**3a***

Methyl 6-*O*-(*tert*-butyl)dimethylsilyl-α-D-glucopyranoside, methyl 6-*O*-(*tert*-butyl)dimethylsilyl-α-D-mannopyranoside and methyl 6-*O*-(*tert*-butyl)dimethylsilyl-α-D-galactopyranoside were prepared as a starting material according to the literature procedures.[10,11,12] To a solution of the starting material (500 mg, 1.62 mmol) in pyridine (8 mL) was added benzoyl chloride (0.94 mL, 8.10 mmol) at 0 °C. After stirring for 18 h at ambient temperature, the solution was poured into a mixture of 1 M HCl and EtOAc, and extracted with EtOAc. The combined organic layer was washed with successively with brine, saturated aqueous $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* followed by column chromatography (silica gel, hexane/EtOAc = 10/1) provided the indicated product.

*4.2.1.1. Methyl 2,3,4-tri-O-benzoyl-6-O-(tert-butyl)dimethylsilyl-α-D-glucopyranoside (**1a**)*

A colorless oil. Yield: 75%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.02 (s, 3H), 0.03 (s, 3H), 0.88 (s, 9H), 3.47 (s, 3H), 3.81 (d, *J* = 4.4 Hz, 2H), 4.11 (ddd, *J* = 10.0, 8.4, 4.0 Hz, 1H), 5.22–5.25 (m, 2H), 5.51 (t, *J* = 10.0 Hz, 1H), 6.13 (m, 1H), 7.26–7.30 (m, 2H), 7.36–7.44 (m, 5H), 7.49–7.53 (m, 2H), 7.85–7.88 (m, 2H), 7.93–7.99 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ –5.52, –5.45, 18.2, 25.8, 55.2, 62.5, 69.4, 70.4, 70.7, 72.2, 77.2, 96.7, 128.1, 128.28, 128.29, 129.0, 129.1, 129.3, 129.6, 129.7, 129.8, 132.9, 133.15, 133.21, 165.1, 165.8. HR-MS (ESI): Calcd for $C_{34}H_{40}O_9SiNa$ $[M+Na]^+$: 643.2339. Found 643.2343. IR (neat): 2953, 1730, 1280, 1252, 1108, 709 cm^{-1}.

*4.2.1.2. Methyl 2,3,4-tri-O-benzoyl-6-O-(tert-butyl)dimethylsilyl-α-D-mannopyranoside (**2a**)*

A colorless oil. Yield: 91%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.00 (s, 3H), 0.02 (s, 3H), 0.90 (s, 9H), 3.52 (s, 3H), 3.82–3.90 (m, 2H), 4.11 (m, 1H), 4.97 (d, *J* = 2.0 Hz, 1H), 5.66 (dd, *J* = 3.2, 1.6

Hz, 1H), 5.70 (dd, *J* = 10.4, 3.6 Hz, 1H), 5.95 (t, *J* = 10.4 Hz, 1H), 7.24–7.28 (m, 2H), 7.36–7.42 (m, 3H), 7.45–7.53 (m, 3H), 7.60 (m, 1H), 7.82–7.85 (m, 2H), 7.94–7.97 (m, 2H), 8.09–8.12 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ –5.52, –5.48, 18.2, 25.8, 55.2, 62.3, 66.9, 70.5, 70.6, 71.4, 98.5, 128.2, 128.4, 128.5, 129.2, 129.42, 129.43, 129.66, 129.72, 129.9, 133.0, 133.2, 133.4, 165.3, 165.52, 165.54. HR-MS (ESI): Calcd for $C_{34}H_{40}O_9SiNa$ $[M+Na]^+$: 643.2339. Found: 643.2339. IR (neat): 2953, 1731, 1279, 1261, 1107, 710 cm^{-1}.

*4.2.1.3. Methyl 2,3,4-tri-O-benzoyl-6-O-(tert-butyl)dimethylsilyl-α-D-galactopyranoside (**3a**)*

A colorless oil. Yield: 99%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ –0.04 (s, 3H), 0.01 (s, 3H), 0.85 (s, 9H), 3.48 (s, 3H), 3.73–3.80 (m, 2H), 4.28 (br t, *J* = 6.8 Hz, 1H), 5.28 (d, *J* = 3.6 Hz, 1H), 5.61 (dd, *J* = 10.0, 3.6 Hz, 1H), 5.95–5.99 (m, 2H), 7.22–7.26 (m, 2H), 7.35–7.39 (m, 2H), 7.42 (m, 1H), 7.47–7.53 (m, 3H), 7.61 (m, 1H), 7.78–7.80 (m, 2H), 7.97–7.99 (m, 2H), 8.06–8.08 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ –5.7, –5.6, 18.1, 25.7, 55.5, 61.3, 68.6, 69.1, 69.4, 69.7, 97.5, 128.1, 128.3, 128.5, 129.26, 129.34, 129.6, 129.7, 129.77, 129.81, 132.9, 133.2, 165.4, 165.5, 166.1. HR-MS (ESI): Calcd for $C_{34}H_{40}O_9SiNa$ $[M+Na]^+$: 643.2339. Found 643.2347. IR (neat): 2951, 1730, 1282, 1265, 1108, 839, 711 cm^{-1}.

*4.2.2. Methyl 2,3,6-tri-O-benzoyl-4-O-(tert-butyl)dimethylsilyl-α-D-galactopyranoside (**4a**)*

Under an Ar atmosphere, to a solution of methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside (253 mg, 0.5 mmol) and 2,6-lutidiene (0.12 mL, 1.0 mmol) in CH_2Cl_2 (1 mL, 0.5 M) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.12 mL, 0.5 mmol) at 0 °C. After stirring at ambient temperature for 18 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution, and extracted with EtOAc. The combined organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* followed by column chromatography (silica gel, hexane/EtOAc = 10/1) provided the title compound (237 mg, 76%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ –0.09 (s, 3H), 0.03 (s, 3H), 0.96 (s, 9H), 3.45 (s, 3H), 4.33–4.43 (m, 2H), 4.54–4.59 (m, 2H), 5.19 (d, *J* = 4.0 Hz, 1H), 5.65 (dd, *J* = 10.8, 2.8 Hz, 1H), 5.80 (dd, *J* = 10.8, 3.6 Hz, 1H), 7.32–7.37 (m, 4H), 7.44–7.51 (m, 4H), 7.60 (m, 1H), 7.95–7.99 (m, 4H), 8.06–8.08 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ –4.7, –4.6, 18.2, 25.8, 55.3, 63.7, 68.49, 68.51, 69.4, 71.8, 97.6, 128.30, 128.34, 128.5, 129.48, 128.53, 129.6, 129.7, 129.8, 133.1, 133.16, 133.24, 166.1, 166.2, 166.4. HR-MS (ESI): Calcd for $C_{34}H_{40}O_9SiNa$ $[M+Na]^+$: 643.2339. Found: 643.2346. IR (neat): 2952, 1723, 1273, 1104, 711 cm^{-1}.

4.3. General procedure for the desilylation of the sugar derivatives

To a solution of silylated sugar derivatives (**1a–4a**) (0.1 mmol) in heptane (0.25 mL, 0.4 M) was added SO_3H silica gel (500 mg). After shaking for 1 min, resulting powder was left to stand at ambient temperature. After the indicated reaction time, the powder was put on the glass filter and eluted with MeOH (50 mL). The obtained elute was evaporated *in vacuo* followed by column chromatography (silica gel, hexane/EtOAc = 2/1 (**1b**–**3b**) or 4/1 (**4b**)) provided the desilylated sugar derivatives **1b**–**4b**.

*4.3.1. Methyl 2,3,4-tri-O-benzoyl-α-D-glucopyranoside (**1b**)*

A colorless oil. Yield: 98%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.69 (dd, *J* = 8.4, 6.0 Hz, 1H), 3.47 (s, 3H), 3.74 (m, 1H), 3.83 (m, 1H), 4.04 (m, 1H), 5.26–5.31 (m, 2H), 5.51 (t, *J* = 10.0 Hz, 1H), 6.23 (t, *J* = 9.6 Hz, 1H), 7.26–7.31 (m, 2H), 7.36–7.44 (m, 5H), 7.49–7.56 (m, 2H), 7.87–7.89 (m, 2H), 7.96–7.99 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 55.6, 61.0, 69.5, 69.8, 70.1, 72.0, 97.1, 128.3, 128.4, 128.5, 128.6, 129.0, 129.2, 129.6, 129.9, 123.0, 165.792, 165.799, 166.4. HR-MS (ESI): Calcd for $C_{28}H_{26}O_9Na$ $[M+Na]^+$: 529.1475. Found: 529.1474. IR (neat): 3537, 2933, 1728, 1281, 1107, 710 cm^{-1}.

*4.3.2. Methyl 2,3,4-tri-O-benzoyl-α-D-mannopyranoside (**2b**)*

A colorless oil. Yield: 95%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.64 (br, 1H), 3.52 (s, 3H), 3.77–3.84 (m, 2H), 4.06 (m, 1H), 5.01 (d, *J* = 1.6 Hz, 1H), 5.68 (dd, *J* = 3.2, 1.6 Hz, 1H), 5.85 (t, *J* = 10.0 Hz, 1H), 5.98 (dd, *J* = 10.0, 3.2 Hz, 1H), 7.24–7.27 (m, 2H), 7.37–7.45 (m, 3H), 7.47–7.55 (m, 3H), 7.61 (m, 1H), 7.81–7.84 (m, 2H), 7.97–8.00 (m, 2H), 8.09–8.12 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 55.5, 61.4, 67.2, 69.6, 70.5, 70.8, 98.7, 128.3, 128.5, 128.6, 128.7, 129.1, 129.3, 129.7, 129.87, 129.89, 133.1, 133.5, 133.6, 165.4, 165.5, 166.5. HR-MS (ESI): Calcd for $C_{28}H_{26}O_9Na$ $[M+Na]^+$: 529.1475. Found: 529.1478. IR (neat) 3533, 2924, 1728, 1283, 1069, 710 cm^{-1}.

*4.3.3. Methyl 2,3,4-tri-O-benzoyl-α-D-galactopyranoside (**3b**)*

A colorless oil. Yield: 87%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.69 (br t, *J* = 7.2 Hz, 1H), 3.48 (s, 3H), 3.65 (m, 1H), 3.79 (m, 1H), 4.33 (br t, *J* = 7.2 Hz, 1H), 5.28 (d, *J* = 3.6 Hz, 1H), 5.72 (dd, *J* = 10.8, 3.6 Hz, 1H), 5.87 (m, 1H), 5.99 (dd, *J* = 10.8, 3.2 Hz, 1H), 7.22–7.26 (m, 2H), 7.36–7.45 (m, 3H), 7.48–7.54 (m, 3H), 7.63 (m, 1H), 7.80–7.83 (m, 2H), 7.99–8.01 (m, 2H), 8.10–8.13 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 55.7, 60.8, 68.4, 69.1, 69.6, 70.1, 97.5, 128.3, 128.4, 128.7, 128.9, 129.1, 129.2, 129.6, 129.8, 130.0, 133.2, 133.4, 133.7, 165.4, 166.1, 166.8. HR-MS (ESI): Calcd for $C_{28}H_{26}O_9Na$ $[M+Na]^+$: 529.1475. Found: 529.1476. IR (neat): 3522, 2934, 1726, 1602, 1069, 712 cm^{-1}.

*4.3.4. Methyl 2,3,6-tri-O-benzoyl-α-D-galactopyranoside (**4b**)*

A colorless powder. Yield: 80%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.05 (br, 1H), 3.45 (s, 3H), 4.36 (br t, *J* = 6.4 Hz, 1H), 4.44 (br, 1H), 4.59 (dd, *J* = 11.6, 7.2 Hz, 1H), 4.67 (dd, *J* = 11.6, 5.6 Hz, 1H), 5.23 (d, *J* = 3.6 Hz, 1H), 5.73 (dd, *J* = 10.8, 3.2 Hz, 1H), 5.77 (dd, *J* = 10.8, 2.8 Hz, 1H), 7.31–7.37 (m, 4H), 7.41–7.51 (m, 4H), 7.56 (m, 1H), 7.67–8.04 (m, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 55.4, 63.5, 67.7, 68.1, 68.9, 70.8, 97.4, 128.3, 128.36, 128.37, 129.2, 129.3, 129.57, 129.61, 129.7, 129.8, 133.17, 133.18, 133.3, 165.8, 166.1, 166.4. HR-MS (ESI): Calcd for $C_{28}H_{26}O_9Na$ $[M+Na]^+$: 529.1475. Found: 529.1466. IR (neat): 3502, 2020, 1719, 1273, 1105, 706 cm^{-1}.

*4.4. Desilylation of the sugar derivative **3a** (gram scale)*

To a solution of methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(*tert*-butyl)dimethylsilyl-α-D-glucopyranoside (**3a**) (1.14 g, 1.84 mmol) in heptane (4.6 mL, 0.4 M) was added SO_3H silica gel (935 mg). After shaking for 1 min, resulting powder was left to stand at ambient temperature. After 24 h, the powder was put on

the glass filter and eluted with MeOH (500 mL). The obtained elute was evaporated *in vacuo* to yield methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside in a satisfactory level of purity (**3b**) (835 mg, 90%) as a colorless oil.

4.5. General procedure for the desilylation of the nucleoside derivatives

The silylated nucleosides **5a**–**7a** were prepared according to the literature procedures.[13,14,15] A solution of silylated nucleosides **5a**–**7a** (0.4 mmol) in EtOAc (**5a** and **6a**, 1 mL, 0.4 M) or $CHCl_3$ (**7a**, 1 mL, 0.4 M) was treated with SO_3H silica gel (2 g, 0.2 mmol/g) at ambient temperature. After shaking for 1 min, resulting powder was left to stand at ambient temperature for the indicated reaction time. Then, the powder was put on the glass filter and eluted with MeOH. The obtained elute was evaporated *in vacuo* to yield corresponding desilylated Thymidine (**5b**, 88% yield), Uridine (**6b**, 81% yield) or **7b** (quant.). The ^{1}H NMR spectrum of **7b** was identical to that reported in the literature.[16]

4.6. Preparation and desilylation of the alkaloid derivative

*4.6.1. (S)-2-(((tert-Butyldimethylsilyl)oxy)methyl)-1-(2,3-dichlorobenzyl)pyrrolidine (**10a**)*

Under an Ar atmosphere, to a suspension of (*S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)pyrrolidine (prepared according to the literature procedure,[16] 218 mg, 1.01 mmol) and K_2CO_3 (281 mg, 2.04 mmol) in EtOH (8 mL) was added a solution of 2,3-dichlorobenzyl bromide (281 mg, 1.17 mmol) in EtOH (2 mL) at ambient temperature. The reaction mixture was stirred at this temperature for 26 h. Then the excess EtOH was removed *in vacuo* and the residue was dissolved in EtOAc. The organic layer was washed with distillated water and brine, dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* followed by column chromatography (silica gel, hexane/EtOAc = 100/0–4/1) provided the title compound (340 mg, 90%) as a colorless oil. Analytically pure sample was obtained by purification with preparative TLC ($CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.02 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 1.55–1.66 (m, 1H), 1.67–1.81 (m, 2H), 1.88–1.98 (m, 1H), 2.27 (dd, *J* = 7.8, 8.9 Hz, 1H), 2.75–2.84 (m, 1H), 2.96–3.02 (m, 1H), 3.50 (dd, *J* = 10.0, 6.2 Hz, 1H), 3.65 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.67 (d, *J* = 15.1 Hz, 1H), 4.21 (d, *J* = 15.1 Hz, 1H), 7.16 (dd, *J* = 7.6, 7.9 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ –5.3, –5.2, 18.4, 23.3, 26.1 (3C), 28.5, 55.2, 57.5, 65.6, 67.3, 127.0, 128.6 (2C), 131.8, 132.9, 140.6. HR-MS (ESI): Calcd for $C_{18}H_{30}Cl_2NOSi$ $[M+H]^+$: 374.1474. Found: 374.1470. IR (neat): 2954, 2856, 1449, 1421, 1361, 1255, 1097, 837, 755 cm^{-1}.

*4.6.2. (S)-(1-(2,3-dichlorobenzyl)pyrrolidin-2-yl)methanol (**10b**)*

To a solution of **10a** (73.3 mg, 0.196 mmol) in MeOH (5 mL) was added SO_3H silica gel (1.01 g). After shaking for 1 min, resulting powder was left to stand at 100 ºC. After 4 h, the reaction mixture was cooled to ambient temperature. The powder was put on the glass filter and eluted with 2.0 M NH_3 in MeOH. The obtained elute was evaporated *in vacuo* and the residue was dissolved in $CHCl_3$. Filtration through a pad of celite and evaporation *in vacuo* followed by column chromatography (silica gel, hexane/EtOAc = 5/1–1/1) provided the title compound (35.5 mg, 70%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.66–1.76 (m, 2H), 1.82–1.99 (m, 2H), 2.32 (ddd, *J* = 7.2, 9.4, 9.4 Hz, 1H), 2.60 (br s, 1H), 2.76–2.83 (m, 1H), 2.95–2.99 (m, 1H), 3.45 (dd, *J* = 2.3, 11.0 Hz, 1H), 3.52 (d, *J* = 13.7 Hz, 1H), 3.72 (dd, *J* = 3.3, 11.0 Hz, 1H), 4.08 (d, *J* = 13.7 Hz, 1H), 7.17 (dd, *J* = 7.7, 7.9 Hz, 1H), 7.31 (dd, *J* = 1.6, 7.7 Hz, 1H), 7.38 (dd, *J* = 1.6, 7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.7, 27.6, 54.7, 56.8, 62.0, 64.9, 127.1, 128.8, 129.2, 132.4, 133.3, 139.3. HR-MS (ESI): Calcd for $C_{12}H_{16}Cl_2NO$ $[M+H]^+$: 260.0609. Found: 260.0602. IR (neat): 3408, 2959, 1449, 1421, 1184, 1079, 1048, 778 cm^{-1}.

References and notes

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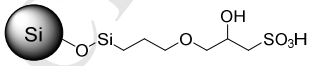
2. Fujii H, Yamada T, Hayashida K, et al. *Heterocycles.* 2012;85:2685–2691.
3. The SO_3H silica gel has already been commercially developed by FUJI SILYSIA CHEMICAL LTD.
   Structure of SO_3H Silica gel and its specification.



   Shape: spherical
   Pore size: 7 nm
   Particle size: 100 mm
   SO3H content: 0.5 mmol/g
   Containing 5% H_2O
   Catalog number: CH27

4. For reuse of the SO_3H silica gel, no special pretreatment such as activation was required. After removing eluent under reduced pressure, the obtained SO_3H silica gel can be used for the next desilylation reaction.
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   (c) BACE inhibitor: Cumming J, Babu S, Huang Y, et al. *Bioorg Med Chem Lett.* 2010;20:2837–2842;
   (d) σ1 lignad: Yu L–F, Zhang H–K, Gunosewoyo H, Kozikowski AP, *ACS Med Chem Lett.* 2012;3:1054–1058;
   (e) falcipain-2 inhibitor: Chakka SK, Kalamuddin M, Sundararaman S, et al. *Bioorg Med Chem.* 2015;23:2221–2240;
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