Supporting Information

Selective protection of secondary alcohols by using formic acid as a mild and efficient deprotection reagent for primary TBDMS ethers

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**General Methods**

Commercial solvents and starting materials were used as received. NMR spectra was recorded in Bruker 400 MHz at room temperature. Trimethyl silane (TMS) or the residual CDCl₃ (7.26 ppm) was used as an internal standard for the peak assignment. Desilylation kinetics was analyzed by Hitachi Elite Lachrom HPLC system. HPLC conditions were: Gemini C18 4.6x50 mm column, flow rate 1 mL/min. Isocratic elution with 50% acetonitrile and 10% 40 mM KH₂PO₄ was used for the compound separation. In these conditions, TBDMS glycolate methyl ester elutes at 3.2 min and TBDMS lactate elutes at 3.5 min. The peaks of desilylation products glycolate methyl ester and lactate methyl ester elute at void volume of the column and overlap with corresponding acids: formic acid, acetic acid or TFA. For the reaction progress analysis, the same amount of the silylated alcohol (reaction at time zero) was injected and used as a control. UV was recorded by a photodiode detector at 210 nm for the detection of the carbonyl group. The rate of the primary TBDMS desilylation at different conditions was calculated by integrating area under the curve at different time points of reaction by using Ezchrom Elite software.

**General procedure for silylation**

To 1 equivalent alcohol and 2 equivalent imidazole dissolved in DMF, was added 1.5-2 equivalents of TBDMSCl under nitrogen. The reaction was stirred overnight (16 h) at room temperature and quenched by adding water. Volatiles were removed by an oil-free rotary evaporator at 60°C for 20 minutes. The corresponding TBDMS ether was extracted with ethyl acetate. The organic phase was combined, washed with 4x20 ml water and dried with Na₂SO₄. The corresponding mono- and di-TBDMS ether was obtained in nearly quantitative yield after removing the solvent by rotary-evaporation at 60°C for 1 h.

**General procedure for desilylation**

Three different concentrations of formic acid, acetic acid and trifluoroacetic acid were prepared by mixing the respective acid in acetonitrile containing 15% water. The reaction was started by mixing the TBDMS ether and a desilylation cocktail in 1:10 ratio by volume. For model compounds TBDMS lactate methyl ester and TBMS glycolate methyl ester, a small amount was taken out at different time points, quenched by adding NaHCO₃ and injected in HPLC for kinetic analysis. For other TBDMS ethers, 10% formic acid was used as a desilylation reagent that was prepared by mixing MeCN: formic acid: water in 15:2:3 ratio. Reactions were carried out at room temperature for 4 h with continuous stirring, quenched by 2 equivalents of NaHCO₃ (dissolved in water and added), extracted, and dried as above procedure.
**TBDMS glycolate methyl ester**

Methyl glycolate 0.9 g (10 mmol, Alfa Aesar 98%) was dissolved in 5 ml dry DMF, followed by adding 1.36 g (20 mmol, imidazole (Alfa Aesar 99%). TBDMSCl (Chem impex international 99%, 2.4 g, 16 mmol) was added under nitrogen and stirred overnight at room temperature. The reaction was quenched by adding 2 ml water. It was then extracted with 2x10 ml ethyl acetate. The organic phase was collected, washed with 4x20 ml water, dried by 5g Na₂SO₄. Solvent was removed under reduced pressure at 60°C. It yielded 1.93 g (95%) clear oil. ¹H NMR (Chloroform-d) δ 4.14 (s, 2H), 3.63 (s, 3H), 0.81 (s, 9H), 0.02 (s, 6H).

**TBDMS lactate methyl ester**

Methyl (s)-(−)lactate 1.05 g (10 mmol, Alfa Aesar 97%) was dissolved in 2.5 ml dry DMF and added 1.36 g (20 mmol) imidazole. TBDMSCl (2.4 g, 16 mmol) was added under nitrogen and stirred overnight at room temperature. The reaction was quenched by adding 2 ml water. It was then extracted with 2x 10 ml ethyl acetate. The organic phase was collected, washed with 4x20 ml water, dried by 5 g Na₂SO₄. Solvent was removed under reduced pressure at 60°C. Yield – 2.04 g (94%) clear oil. ¹H NMR (Chloroform-d) δ 4.24 (q, J = 6.8 Hz, 1H), 3.62 (s, 3H), 1.30 (d, J = 6.7 Hz, 3H), 0.81 (s, 9H) 0.02 (s, 6H).

**1,3-Bis(tert-butyldimethylsiloxy) butane**

Butane-1,3-diol 0.45 g (5 mmol, Aldrich 98%) was dissolved in 5 ml dry DMF and added 1.36 g (20 mmol) imidazole. TBDMSCl 2.51 g (17 mmol) was added under nitrogen and stirred overnight at room temperature. The reaction was quenched by adding 2 ml water. It was then extracted with 2x 10 ml ethyl acetate. The organic phase was collected, washed with 4x20 ml water, dried by 5 g Na₂SO₄. Solvent was removed under reduced pressure at 60°C. Yield – 1.52 g (96%) colorless oil. ¹H NMR (Chloroform-d) δ 3.94 – 3.89 (m, 1H), 3.68 – 3.56 (m, 2H), 1.69 – 1.46 (m, 3H), 1.10 (d, J = 6.2 Hz, 4H), 0.85 (s, 18H), 0.08 (s,12H).

**3-diethylamino-1,2-bis(tert-butyldimethylsiloxy) propane**

To 1.21 g (8 mmol) 3-diethylamino-1,2 propane (Alfa Aesar 97%) was added 4 ml dry DMF, 2.82 g (40 mmol) imidazole, and TBDMSCl 4.15 g (27 mmol) under nitrogen and stirred overnight at room temperature. The reaction was quenched by adding 4 ml water next morning. It was then extracted with 2x 20 ml ethyl acetate. The organic phase was collected, washed with 4x25 ml water, dried by 5 g Na₂SO₄. Solvent was removed under reduced pressure at 60°C. Yield – 2.73 g (91%) light yellowish oily liquid. ¹H NMR (Chloroform-d) δ 3.69 – 3.60 (m, 1H), 3.58 (dd, J = 10.1, 4.7 Hz, 1H), 3.45 (dd, J = 10.1, 5.7 Hz, 1H), 2.53 – 2.41 (m, 4H), 2.26 (dd, J = 13.6, 5.3 Hz, 1H), 0.94 (t, J = 7.1 Hz, 6H), 0.90 – 0.78 (s, 18H), 0.05 (s, 12H).

**3-phenoxy-1,2-bis(tert-butyldimethylsiloxy)propane**
To 0.34g (2 mmol) 3-phenoxy 1,2 propanediol (TCI America) was added 2 ml dry DMF, 0.68 g (10 mmol) imidazole. TBDMSCl 1.2 g (8 mmol) was added under nitrogen and stirred overnight at room temperature. The reaction was quenched by adding 2 ml water. It was then extracted with 2x10 ml ethyl acetate. The organic phase was collected, washed with 4x20 ml water, dried by 5 g Na$_2$SO$_4$. Solvent was removed under reduced pressure at 60 $^\circ$C. Yield – 0.76 g (96%) clear oily liquid. $^1$H NMR (Chloroform-d) $\delta$ 7.22 – 7.12 (m, 2H), 6.87 – 6.76 (m, 3H), 4.02 – 3.92 (m, 2H), 3.80 – 3.71 (m, 1H), 3.57 – 3.50 (m, 2H), 0.97 – 0.62 (m, 30H).

3-(2-Methoxyphenoxy)-1,2-bis(tert-butyldimethylsiloxy) propane

To 0.40 g (2 mmol) 3-(2-methoxyphenoxy)-1,2 propanediol (Alfa Aesar 97%) was added 2 ml dry DMF, 0.68 g (10 mmol) imidazole. TBDMSCl 1.22 g (8 mmol) was added under nitrogen and stirred overnight at room temperature. The reaction was quenched by adding 2 ml water. It was then extracted with 2x10 ml ethyl acetate. The organic phase was collected, washed with 4x20 ml water, dried by 5 g Na$_2$SO$_4$. Solvent was removed under reduced pressure at 60 $^\circ$C. Yield –0.79 g colorless oil (94%). $^1$H NMR (Chloroform-d) $\delta$ 6.92 – 6.70 (m, 4H), 4.11 – 3.92 (m, 2H), 3.73 (s, 3H), 3.60 – 3.52 (m, 2H), 0.91 – 0.72 (m, 30H).

3-(4-Chlorophenoxy)-1,2-bis(tert-butyldimethylsiloxy) propane

To 0.41 g (2 mmol) 3-(4-chlorophenoxy)-1,2 propanediol (Alfa Aesar 99%) was added 3 ml dry DMF, 0.68g (10 mmol) imidazole. TBDMSCl 1.2 g (8 mmol) was added under nitrogen and stirred overnight at room temperature. The reaction was quenched by adding 2 ml water. It was then extracted with 2x10 ml ethyl acetate. The organic phase was collected, washed with 4x20 ml water, dried by 5 g Na$_2$SO$_4$. Solvent was removed under reduced pressure at 60 $^\circ$C. Yield – 0.80 g clear oily liquid (93%). $^1$H NMR (Chloroform-d) $\delta$ 7.19 – 7.12 (m, 2H), 6.79 – 6.73 (m, 2H), 4.04 – 3.93 (m, 2H), 3.80 – 3.75 (m, 1H), 3.62 – 3.50 (m, 2H), 0.83 (s, 18H), 0.08 (s, 12H).

2-Ethyl-1,3-bis(tert-butyldimethylsiloxy) hexane

To 0.73 g (5 mmol) 2-Ethyl-1,3-hexane (TCI America) was added 3 ml dry DMF, 1.71 g (25 mmol) imidazole. TBDMSCl 3.05 g (20 mmol) was added under nitrogen and stirred overnight at room temperature. The reaction was quenched by adding 2 ml water. It was then extracted with 2x10 ml ethyl acetate. The organic phase was collected, washed with 4x20 ml water, dried by 5 g Na$_2$SO$_4$. Solvent was removed under reduced pressure at 60 $^\circ$C. Yield – 1.77 g clear liquid (95%). $^1$H NMR (Chloroform-d) $\delta$ 3.79 (ddq, $J$ = 6.7, 5.6, 3.6 Hz, 1H), 3.59 – 3.40 (m, 2H), 1.67 – 1.07 (m, 8H), 0.90 – 0.85 (s, 18H), 0.84 (m, 6H), 0.08 (s,12H).

3-(tert-butyldimethylsiloxy)-1-butanol

To 0.32 g 1,3-Bis(tert-butyldimethylsiloxy)butane dissolved in 7.5 ml MeCN, was added 1.5 ml water and 1 ml formic acid. Cloudy white suspension appeared after adding water but turned clear as the reaction progressed. The reaction was stirred at room temperature for 4 h and quenched by adding 3 ml 1 M NaHCO$_3$. The product was then extracted by 2x10 ml ethyl
acetate. The organic phase was combined, washed with 4x20 ml water and dried by 5 g Na₂SO₄. Solvent was removed under reduced pressure at 60°C. Yield – 0.16 g clear liquid (78%). ¹H NMR (Chloroform-d) δ 3.94 (dddd, J = 9.4, 8.4, 6.3, 3.2 Hz, 1H), 3.81 (dt, J = 10.2, 4.7 Hz, 1H), 3.78 – 3.69 (m, 1H), 3.30 (s, 1H), 1.66 – 1.48 (m, 3H), 1.11 (d, J = 6.2 Hz, 4H) 0.83 (s, 9H), 0.08 (s, 6H).

3-diethylamino-2- (tert-butyldimethylsiloxy)-1-propanol

To 0.37 g 3-diethylamino-1,2-bis(tert-butyldimethylsiloxy)propane dissolved in 7.5 ml MeCN, was added 1.5 ml water and 1 ml formic acid. Cloudy white suspension was appeared after adding water but turned clear as the reaction progressed. The reaction was stirred at room temperature for 4 h and quenched by adding 3 ml 1 M NaHCO₃. The product was then extracted by 2x10 ml ethyl acetate. The organic phase was combined, washed with 4x20 ml water and dried by 5 g Na₂SO₄. Solvent was removed under reduced pressure at 60°C. Yield – 0.21 g clear liquid (81%). ¹H NMR (Chloroform-d) δ 3.63 – 3.49 (m, 3H), 2.58 – 2.51 (m, 2H), 2.48 – 2.29 (m, 4H), 0.95 (t, J = 7.1 Hz, 6H), 0.83 (s, 9H), 0.08 (s, 6H).

3-phenoxy-2-(tert-butyldimethylsiloxy)-1-propanol

To 0.39 g 3-phenoxy-1,2-bis(tert-butyldimethylsiloxy)propane dissolved in 7.5 ml MeCN, was added 1.5 ml water and 1 ml formic acid. Cloudy white suspension was appeared after adding water but turned clear as the reaction progressed. The reaction was stirred at room temperature for 4 h and quenched by adding 3 ml 1 M NaHCO₃. The product was then extracted by 2x10 ml ethyl acetate. The organic phase was combined, washed with 4x20 ml water and dried by 5 g Na₂SO₄. Solvent was removed under reduced pressure at 60°C. Yield – 0.24 g colorless oil (86%). ¹H NMR (Chloroform-d) δ 7.23 – 7.18 (m, 2H), 6.87 – 6.81 (m, 3H), 3.93 (d, J = 4.0 Hz, 3H), 3.70 (dd, J = 4.7, 3.2 Hz, 2H), 0.87 – 0.75 (s, 9H), -0.00 (s, 6H).

3-(2-Methoxyphenoxy)-2-(tert-butyldimethylsiloxy)-1-propanol

To 0.42 g 3-(2-methoxyphenoxy)-1,2-bis(tert-butyldimethylsiloxy)propane dissolved in 7.5 ml MeCN, was added 1.5 ml water and 1 ml formic acid. Cloudy white suspension was appeared after adding water but turned clear as the reaction progresses. The reaction was stirred at room temperature for 4 h and quenched by adding 3 ml 1 M NaHCO₃. The product was then extracted by 2x10 ml ethyl acetate. The organic phase was combined, washed with 4x20 ml water and dried by 5 g Na₂SO₄. Solvent was removed under reduced pressure at 60°C. Yield – 0.27 g colorless oil (88%). ¹H NMR (Chloroform-d) δ 6.88 – 6.80 (m, 4H), 3.99 (ddt, J = 10.9, 9.0, 3.9 Hz, 3H), 3.77 (s, 4H), 3.73 – 3.64 (m, 2H), 2.83 – 2.75 (m, 1H), 0.82 (s, 9H), 0.08 (s, 6H).

3-(4-Chlorophenoxy)-2-(tert-butyldimethylsiloxy)-1-propanol
To 0.43 g 3-(4-chlorophenoxy)-1,2-bis(tert-butyldimethylsiloxy)propane dissolved in 7.5 ml MeCN, was added 1.5 ml water and 1 ml formic acid. Cloudy white suspension was appeared after adding water but turned clear as the reaction progresses. The reaction was stirred at room temperature for 4 h and quenched by adding 3 ml 1 M NaHCO₃. The product was then extracted by 2x10 ml ethyl acetate. The organic phase was combined, washed with 4x20 ml water and dried by 5 g Na₂SO₄. Solvent was removed under reduced pressure at 60°C. Yield – 0.27 g (85%). ¹H NMR (Chloroform-d) δ 7.17 – 7.13 (m, 3H), 6.78 (s, 1H), 6.75 (d, J = 1.6 Hz, 1H), 3.94 – 3.87 (m, 4H), 3.68 (dd, J = 4.8, 3.2 Hz, 2H), 2.49 (d, J = 4.6 Hz, 1H), 0.82 (s, 15H)

2-Ethyl-3-(tert-butyldimethylsiloxy)-1-hexanol
To 0.37 g 2-Ethyl-1,3-bis(tert-butyldimethylsiloxy)hexane dissolved in 7.5 ml MeCN, was added 1.5 ml water and 1 ml formic acid. Cloudy white suspension was appeared after adding water but turned clear as the reaction progresses. The reaction was stirred at room temperature for 4 h and quenched by adding 3 ml 1 M NaHCO₃. The product was then extracted by 2x10 ml ethyl acetate. The organic phase was combined, washed with 4x20 ml water and dried by 5 g Na₂SO₄. Solvent was removed under reduced pressure at 60°C. Yield – 0.23 g (90%). ¹H NMR (Chloroform-d) δ 3.86 (dd, J = 10.1, 3.2 Hz, 1H), 3.73 – 3.58 (m, 2H), 1.51 – 1.20 (m, 8H), 0.88 – 0.84 (m, 6H), 0.82 (s, 9H), 0.08 (s, 6H).
NMR spectra of Mono- and Di-TBDMS-Protected Alcohols