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4-(*tert*-Butyldimethylsilyloxy)benzylidene acetal: a novel benzylidene-type protecting group for 1,2-diols

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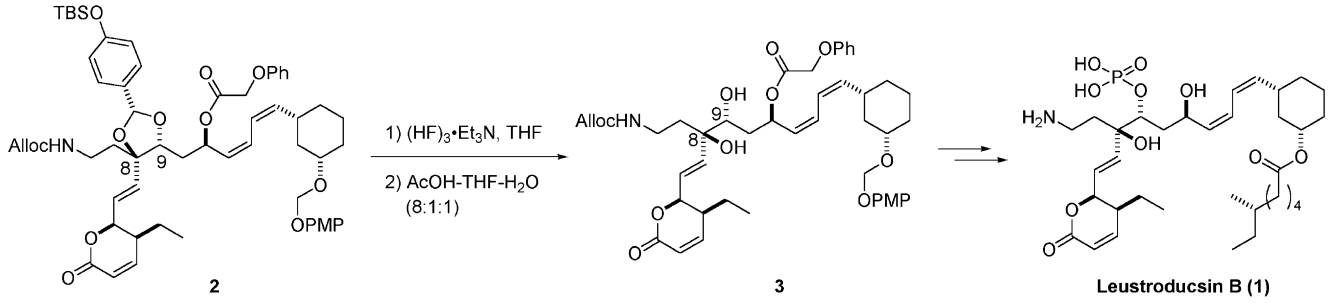
Abstract—A novel 1,2-diol-protecting group, *p*-silyloxybenzylidene group, has been developed. In addition to the stepwise deprotection conditions including desilylation and the subsequent acidic hydrolysis of the *p*-hydroxybenzylidene group in AcOH–THF–H_2O, we have established the one-pot deprotection under basic conditions [K_2CO_3 (5 equiv), $NH_2OH{\cdot}HCl$ (5 equiv), and CsF (1 equiv) in MeOH–H_2O].

Protection and deprotection of functional groups play the critical role in successful synthesis of multifunctional complex molecules. Because of synthetic versatility of 1,2-diols, a variety of protecting groups have been developed to date.[1] Among them, the most frequently used groups are cyclic acetals and ketals. However, since their deprotection generally requires strongly acidic conditions, these protecting groups are generally incompatible with acid labile functional groups. During the course of synthetic studies on leustroducsin B (**1**),[2] we have experienced such difficulties. While the advanced synthetic intermediate **2** was successfully constructed by protecting the sterically hindered C8–C9 diol with acetonide or *p*-methoxybenzylidene group, deprotection of these groups at the later stage of the synthesis was relatively difficult and required too harsh acidic conditions to cause significant isomerization of the conjugated *Z,Z*-diene moiety. To circumvent this problem, we devised a novel benzylidene-type protecting group, *p*-silyloxybenzylidene group, which could be deprotected smoothly by a two-step sequence without affecting other functional groups (Scheme 1). Thus, treatment of the substrate with $(HF)_3{\cdot}Et_3N$ to remove TBS group, followed by subjection to weakly acidic conditions such as AcOH–THF–H_2O to obtain the corresponding 1,2-diol. We report herein details of the



Scheme 1.

Keywords: Protecting group; Benzylidene acetal; Diol; Deprotection under basic conditions; Hydroxylamine.
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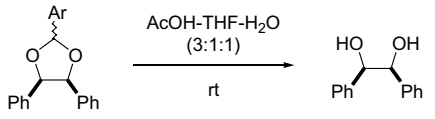
Table 1. Acidic hydrolysis of the benzylidene acetals



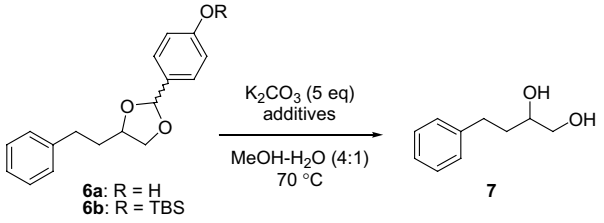
Entry	Ar	Time (h)	Yield (%)
1	Ph (**4a**)	2.5	96
2	*p*-MeO–C_6H_4 (**4b**)	2.0	98
3	*p*-TBSO–C_6H_4 (**4c**)	2.5	96
4	*p*-HO–C_6H_4 (**4d**)	1.0	93

scope and the general applicability of the novel *p*-silyloxybenzylidene protecting group with respect to appropriate conditions for protection and deprotection of various 1,2-diols.[3]

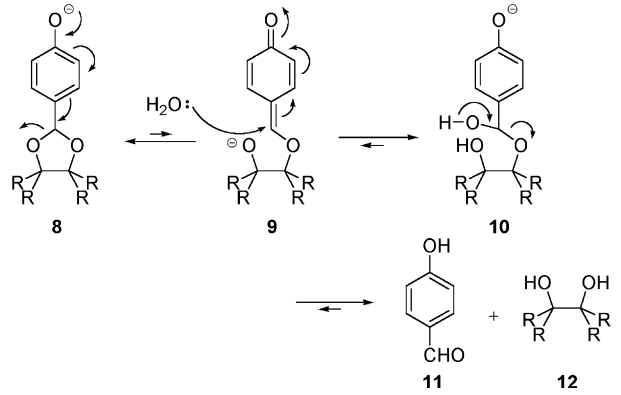
At the outset of this research, relative rates of the deprotection of several benzylidine-type protecting groups in weakly acidic media (AcOH–THF–H_2O, 3:1:1) were compared using model substrates **4a**–**d** (Table 1). Deprotection of the parent benzylidene (**4a**), *p*-methoxybenzylidene (**4b**), and *p*-silyloxybenzylidene group (**4c**) took almost the same reaction time (2–2.5 h) although we had anticipated a faster removal of *p*-silyloxybenzylidene group (**4c**) owing to the electron donating nature of the silyloxy group (entries 1–3). However, the stepwise procedure mentioned above have proved quite effective. Thus, *p*-hydroxybenzylidene acetal **4d**, which was derived from **4c** by treatment with TBAF, was deprotected more easily than any other acetals tested (entry 4).

More significantly, we have found that this newly developed acetal group, *p*-silyloxybenzylidene group, could be deprotected under basic conditions. Upon treatment of **6b** with TBAF, a trace amount of diol **7** was obtained along with the desired *p*-hydroxybenzylidene acetal **6a**. With this observation we considered a possibility of the deprotection under basic conditions. Thus, treatment of the *p*-hydroxybenzylidene acetal **6a** with K_2CO_3 in MeOH–H_2O at 70 °C gave diol **7** in 97% yield (Table 2, entry 1). A plausible reaction mechanism

Table 2. Basic hydrolysis of the benzylidene acetals



Entry	R	Additives	Time (h)	Yield (%)
1	H	No additive	9.0	97
2	H	NH_2OH·HCl (5 equiv)	2.5	91
3	TBS	NH_2OH·HCl (5 equiv)	2.5	97
4	TBS	NH_2OH·HCl (5 equiv) CsF (1 equiv)	1.3	93



Scheme 2.

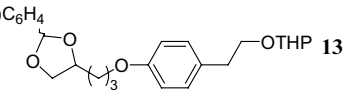
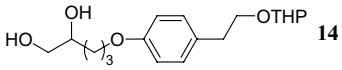
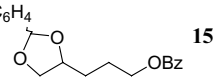
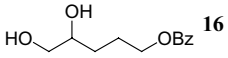
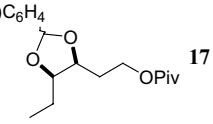
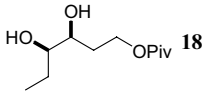
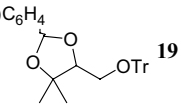
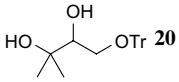
is depicted in Scheme 2. In basic media, a C–O bond of the acetal **8** would be cleaved by electrons provided by the phenoxide anion to give **9**.[4] After addition of water, the resultant hemiacetal **10** would release the diol **12**. At this point, we considered an effectively capturing the resultant *p*-hydroxybenzaldehyde (**11**) would accelerate the deprotection process under equilibrium. As expected, addition of 5 equiv of NH_2OH·HCl shortened the time to 2.5 h and the desired diol was obtained in 91% yield along with the oxime of **11** (entry 2). Under these conditions, the silylated substrate **6b** could be converted to the corresponding diol **7** in one-pot (entry 3). Furthermore, addition of 1 equiv of CsF was effective and reduced the reaction time to 1.3 h (entry 4).

Having established the basic deprotection conditions of *p*-silyloxybenzylidene group, we next applied this method for a variety of substrates. As shown in Table 3, basic deprotection generally proceeded smoothly while sterically hindered acetal **19** required prolonged reaction time (entry 4). In particular, these deprotection conditions are advantageous for substrates bearing acid labile functionalities. For example, THP group remained unaffected during the deprotection (entry 1). While benzoyl ester could not tolerate under these basic conditions, more robust pivaloyl ester survived (entries 2 and 3).

Protection of 1,2-diols was carried out by two methods A and B (Table 4). The conventional acid-mediated acetalization conditions (method A) provided protected 1,2-diols in high yields, whereas sterically hindered 1,2-diols required somewhat stronger acid and higher temperature (entries 1–3). On the other hand, TMSOTf mediated acetalization reaction reported by Noyori and co-workers[5] (method B) provided the corresponding acetals under mild conditions (entries 4 and 5). The required reagents for the protection (**21** and **22**) are readily prepared from 4-hydroxybenzaldehyde (**11**) (Scheme 3).[2]

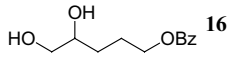
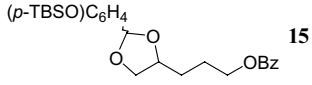
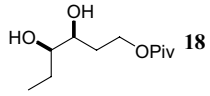
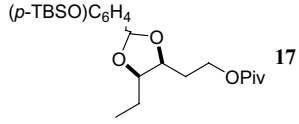
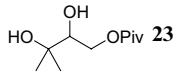
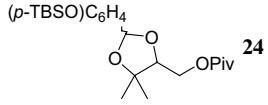
In conclusion, we have developed a novel 1,2-diol protecting group, *p*-silyloxybenzylidene group. The deprotection could be performed under not only weakly acidic conditions but also basic conditions in the presence of hydroxylamine. To the best of our knowledge, this is the first example of acetal-type protecting group, which is

Table 3. Selective removal of the protecting group[a]

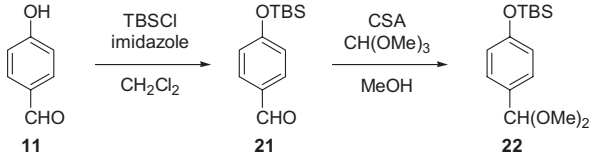
Entry	Substrate	Product	Time (h)	Yield (%)
1	 **13**	 **14**	2.5	93
2	 **15**	 **16**	1.5	29[b]
3	 **17**	 **18**	3.5	92
4	 **19**	 **20**	21	91

[a] Conditions: K_2CO_3 (5 equiv), $NH_2OH{\cdot}HCl$ (5 equiv), CsF (1 equiv), MeOH–H_2O (4:1), 70 °C.
[b] Hydrolysis of benzoyl group occurred.

Table 4. Protection of diols[a]

Entry	Method	Diol	Conditions	Product	Yield (%)
1	A	 **16**	**22**, PPTS (10 mol%) DMF, rt, 3.5 h	 **15**	96[b]
2	A	 **18**	**22**, CSA (5 mol%) DMF, rt, 4.0 h	 **17**	84[c]
3	A	 **23**	**22**, CSA (5 mol%) DMF, 50 °C, 3.0 h	 **24**	93[c]
4	B	**18**	(1) TMSCl, imidazole, CH_2Cl_2 0 °C, 5 min (2) **21**, TMSOTf (1 mol%) CH_2Cl_2, −78 °C, 5 min	**17**	91[d]
5	B	**23**	(1) TMSCl, imidazole CH_2Cl_2, 0 °C, 5 min (2) **21**, TMSOTf (20 mol%) CH_2Cl_2, −78 °C, 30 min	**24**	94[e]

[a] Typical experimental procedures for methods A and B are described in the text.
[b] 1:1 Diastereomeric mixture.
[c] 3:1 Diastereomeric mixture.
[d] 10:1 Diastereomeric mixture.
[e] 2:1 Diastereomeric mixture.



Scheme 3.

removed under basic conditions. We believe that this protecting group would find a niche for the synthesis of multifunctional compounds bearing acid sensitive functionalities.

Typical experimental procedure for protection (method A: Table 4, entry 2): To a stirred solution of diol **18** (57.5 mg, 0.26 mmol) and **22** (148.8 mg, 0.53 mmol) in DMF (2 mL) under Ar atmosphere was added CSA (3.1 mg, 0.013 mmol) at room temperature. After the solution was stirred for 4 h, it was poured into satd $NaHCO_3$ and extracted with ether. The extract was washed with 5% NaCl, dried over $MgSO_4$, filtered, and

evaporated under reduced pressure. The residue was purified by flash column chromatography (2–10% AcOEt in hexane) on silica gel to give **17** (96.2 mg, 84%) as a colorless oil.[6]

For protection (method B: Table 4, entry 5): To a stirred solution of diol **23** (206 mg, 0.944 mmol) and imidazole (385 mg, 5.66 mmol) in CH_2Cl_2 (9 mL) was cooled to 0 °C under Ar atmosphere. To this stirred solution was added TMSCl (359 μL, 2.83 mmol). After 5 min, the reaction mixture was poured into satd $NaHCO_3$ and extracted with AcOEt. The extract was washed with brine twice, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography (10% AcOEt in hexane) on neutral silica gel to give bis-TMS ether (337 mg, 98%). A solution of the bis-TMS ether (111 mg, 0.32 mmol) and **21** (151 mg, 0.64 mmol) in CH_2Cl_2 (3 mL) was cooled to −78 °C under Ar atmosphere. To this stirred solution was added TMSOTf (12 μL, 0.064 mmol). After stirring for 30 min, pyridine was added, and allowed to warm to room temperature. The reaction mixture was poured into satd $NaHCO_3$ and extracted with AcOEt. The extract was washed with brine twice, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography (2–10% AcOEt in hexane) on silica gel to give **24** (129 mg, 96%) as a white solid.[6]

For deprotection under basic conditions (Table 3, entry 1): To a stirred solution of **13** (77.5 mg, 0.14 mmol) in MeOH–H_2O (4:1, 1 mL) at room temperature was added CsF (21.7 mg, 0.14 mmol), K_2CO_3 (98.7 mg, 0.71 mmol), and $NH_2OH{\cdot}HCl$ (49.6 mg, 0.71 mmol) in this sequence. The reaction mixture was heated at 70 °C and stirred for 2.5 h. The reaction mixture was cooled to room temperature, and extracted with AcOEt three times. The extracts were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by preparative TLC (60% AcOEt in hexane) to give diol **14** (43.3 mg, 93%) as a white solid.

For preparation of **21**: A 100-mL round-bottom flask was charged with 4-hydroxybenzaldehyde (1.04 g, 8.5 mmol) and dry CH_2Cl_2 (40 mL) at room temperature under Ar atmosphere. To the solution was added TBSCl (1.54 g, 10 mmol) and imidazole (1.45 g, 21 mmol). After the solution was stirred for 15 min, the reaction mixture was diluted with CH_2Cl_2 and washed with brine twice. The organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography (10% AcOEt in hexane) on a silica gel to give **21**[7] (1.84 g, 92%) as a colorless oil.

Acknowledgements

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6. Spectroscopic data for *p*-silyloxybenzylidene acetals. For **13** (a colorless oil, an inseparable 1:1 diastereomeric mixture): IR (neat, cm^{-1}) 2936, 2859, 1611, 1513, 1254, 1078, 1031, 914, 839; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.34 (m, 2H), 7.15 (d, $J = 8.4$ Hz, 2H), 6.86–6.82 (m, 4H), 5.87 (s, 0.5H), 5.76 (s, 0.5H), 4.60 (t, $J = 3.6$ Hz, 1H), 4.35–4.24 (m, 1.5H), 4.16–4.08 (m, 0.5H), 4.06–3.88 (m, 3H), 3.82–3.72 (m, 1.5H), 3.68–3.56 (m, 1.5H), 3.50–3.44 (m, 1H), 2.86 (t, $J = 7.0$ Hz, 2H), 2.04–1.47 (m, 10H), 0.99 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 156.4, 131.2, 130.9, 130.3, 129.9, 128.0, 127.7, 119.9, 114.3, 104.0, 103.0, 98.7, 77.2, 76.1, 70.9, 69.9, 68.5, 67.4, 62.3, 35.4, 30.6, 30.2, 30.0, 25.6, 25.4, 19.5, 18.2, −4.5; HRMS (FAB^+) calcd for $C_{31}H_{46}O_6Si$ 542.3064 $(M)^+$, found 542.3087. For **15** (a colorless oil, an inseparable 1:1 diastereomeric mixture): IR (neat, cm^{-1}) 2955, 2930, 2857, 1720, 1611, 1514, 1273, 1109, 1071, 914, 840; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, $J = 7.2$ Hz, 2H), 7.56 (t, $J = 7.4$ Hz, 1H), 7.45 (t, $J = 7.6$ Hz, 2H), 7.35 (t, $J = 7.8$ Hz, 2H), 6.84 (d, $J = 8.4$ Hz, 1H), 6.83 (d, $J = 8.4$ Hz, 1H), 5.87 (s, 0.5H), 5.76 (s, 0.5H), 4.40–4.38 (m, 2H), 4.31–4.25 (m, 1.5H), 4.11 (t, $J = 7.2$ Hz, 0.5H), 3.74 (t, $J = 7.2$ Hz, 0.5H), 3.64 (s, 0.5H), 2.06–1.70 (m, 4H), 0.98 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 156.6, 132.9, 130.8, 130.2, 129.5, 128.3, 128.0, 127.7, 120.0, 104.1, 103.1, 76.5, 75.9, 70.7, 69.9, 64.6, 30.2, 30.0, 25.6, 25.3, 25.2, 18.2, −4.5; HRMS (FAB^+) calcd for $C_{25}H_{34}O_5Si$ 442.2176 $(M)^+$, found 442.2166. For **17** (a colorless oil, an inseparable 3:1 diastereomeric mixture): IR (neat, cm^{-1}) 2959, 2932, 2859, 1731, 1611, 1514, 1264, 1163, 1092, 915, 840; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, $J = 8.6$ Hz, 1.5H), 7.31 (d, $J = 8.8$ Hz, 0.5H), 6.83 (d, $J = 8.8$ Hz, 0.5H), 6.82 (d, $J = 8.6$ Hz, 1.5H), 5.99 (s, 0.25H), 5.73 (s, 0.75H), 4.35–4.03 (m, 4H), 1.90–1.78 (m, 2H), 1.71–1.44 (m, 2H), 1.19 (s, 9H), 1.05 (t, $J = 7.2$ Hz, 3H), 0.98 (s, 9H), 0.17 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 156.4, 156.0, 132.3, 130.3, 128.0, 127.3, 119.8, 103.1, 101.4, 80.4, 79.7, 77.2, 75.1, 61.5, 38.6, 29.4, 27.7, 27.1, 25.5, 22.8, 21.8, 18.1, 10.7, 10.5, −4.6; HRMS (FAB^+) calcd for $C_{24}H_{40}O_5Si$ 436.2645 $(M)^+$, found 436.2647. For **19** (a colorless foam, an inseparable 3:1 diastereomeric mixture): IR (neat, cm^{-1}) 2930, 2858, 1514, 1262, 1077, 914, 839; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51–7.42 (m, 6H), 7.36–7.11 (m, 11H), 6.84 (d, $J = 8.6$ Hz, 0.5H), 6.80 (d, $J = 8.6$ Hz, 1.5H), 5.87 (s, 0.25H), 5.82 (s, 0.75H), 4.07–4.03 (m, 1H), 3.60–3.56 (m, 1H), 3.12–3.07 (m, 0.75H), 3.05–3.01 (m, 0.25H), 1.52 (s, 0.75H), 1.41 (s, 2.25H), 1.11 (s, 2.25H), 1.10 (s, 0.75H), 0.97 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 143.9, 131.9, 130.5, 128.6, 128.0, 127.8, 127.7, 127.0, 119.8, 101.7, 101.5, 87.0, 83.3, 81.7, 81.1, 79.9, 62.8, 62.5, 26.6, 26.3, 25.6, 22.9, 19.6, 18.1, −4.5; HRMS (FAB^+) calcd for $C_{37}H_{44}O_4Si$ 580.3009 $(M)^+$, found 580.2997. For **24** (a white solid, an inseparable 2:1 diastereomeric mixture): IR (neat, cm^{-1}) 2959, 2932, 2860, 1735, 1612, 1515, 1264, 1163,

915, 840; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.31 (m, 2H), 6.83 (d, $J = 8.4$ Hz, 2H), 5.98 (s, 0.33H), 5.83 (s, 0.67H), 4.33–4.11 (m, 2H), 4.02–3.98 (m, 1H), 1.47 (s, 1H), 1.44 (s, 2H), 1.31 (s, 3H), 1.22 (s, 9H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 156.7, 156.4, 131.6, 130.1, 128.1, 127.7, 120.0, 102.0, 101.9, 82.0, 80.8, 79.7, 62.9, 62.6, 38.7, 27.2, 26.2, 26.0, 25.6, 23.0, 20.1, 18.2, −4.5; HRMS (FAB$^+$) calcd for $C_{23}H_{39}O_5Si$ 423.2567 $(M+1)^+$, found 423.2571.

7. Spectroscopic data for **21**: IR (neat, cm^{-1}) 2956, 2931, 2887, 2859, 1700, 1599, 1577, 1508, 1472, 1275, 1211, 1156, 909, 842, 800, 784; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.78 (d, $J = 8.4$, Hz, 2H), 6.94 (d, $J = 8.4$ Hz, 2H), 0.99 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 161.2, 131.7, 130.3, 120.3, 25.4, 18.0, −4.6; HRMS (FAB$^+$) calcd for $C_{13}H_{20}O_2Si$ 236.1233 $(M)^+$, found 236.1239. Spectroscopic data for **22**: see Ref. 2.