Cleavage of 4,6-*O*-Benzylidene Acetal Using Sodium Hydrogen Sulfate Monohydrate

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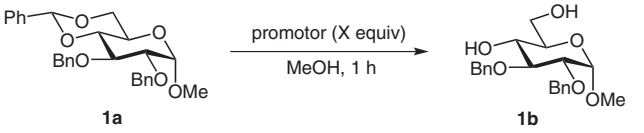
Abstract: The use of protecting groups is an important protocol in carbohydrate synthesis. Among protecting groups, benzylidene acetals are generally more stable than other acetals; therefore, strong conditions are often required for deprotection. We report the deprotection of 4,6-*O*-benzylidene derivatives using sodium hydrogen sulfate monohydrate under mild conditions.

Key words: protecting group, benzylidene acetal, cleavage, sodium hydrogen sulfate monohydrate

There have been increasing interests in protecting groups in the field of carbohydrate synthesis.[1] Acetals are widely used as protecting groups for diols because of their high stability under basic conditions. 4,6-*O*-Benzylidene acetals are frequently employed because they are more stable than other acetals. In particular, the partial and regioselective cleavage to benzyl ethers has been well studied, because of its utility in oligosaccharide synthesis.[2] In these reactions, hydride reagents, such as sodium cyanoborohydride and borane–trimethylamine, have been used. On the other hand, full deprotection of 4,6-*O*-benzylidene acetals leading to 4,6-diols is also an important process in natural product synthesis. The most common methods for cleaving benzylidene acetals are solvolysis under acidic conditions,[3] reduction by hydrogen/palladium on carbon,[4] and Birch reduction.[5] For example, Kim and Salmon used aqueous sulfuric acid for the deprotection of a 4,6-*O*-benzylidene acetal in the synthesis of halichondrin B.[6] Other methods include the use of silica gel supported sodium hydrogen sulfate[7] and phosphomolybdic acid.[8] Alternative methods using inorganic salts such as sodium hydrogen sulfate are also attractive because the catalyst can be easily removed by extraction or filtration. Sodium hydrogen sulfate has moderate acidity, which is sufficient to cleave benzylidene acetals. However, it is less soluble in organic solvents. In order to promote solvolysis efficiently, the solubility of sodium hydrogen sulfate must be increased.

Herein, we report the cleavage of 4,6-*O*-benzylidene acetals using sodium hydrogen sulfate monohydrate ($NaHSO_4 \cdot H_2O$). We found that sodium hydrogen sulfate monohydrate efficiently promoted the deprotection of methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**1a**) to afford the corresponding diol **1b**. All reactions were carried out at 23–26 °C for one hour. The amount of sodium hydrogen sulfate monohydrate was optimized. (Table 1) and the mixtures were filtered through Celite to remove undissolved salts. At first, the filtrate was concentrated in vacuo and purified by silica gel column chromatography to give the diol product **1b** only in 22% yield (entry 1). This low yield was attributed to production of starting material **1a** in of the presence of acid in the concentration step. To avoid this reverse reaction, we added potassium carbonate to the filtrate in order to neutralize the reaction mixture giving **1b** in 87% yield (entry 2). Addition of three equivalents of sodium hydrogen sulfate monohydrate gave **1b** in 99% yield (entry 3). It was also found that sodium hydrogen sulfate monohydrate exhibited better performance than dry sodium hydrogen sulfate as the catalyst (entry 4). During the course of the reaction, we observed insoluble sodium hydrogen sulfate. Therefore, we weighted the amount of dry sodium hydrogen sulfate from the filtrate after evaporation. Figure 1 showed sodium hydrogen sulfate monohydrate has higher solubility than sodium hydrogen sulfate in methanol. The difference in solubility may be the reason why sodium hydrogen sulfate monohydrate promoted deprotection of benzylidene acetals more efficiently than sodium hydrogen sulfate.

Table 1 Optimization of the Reaction Conditions for the Cleavage of 4,6-*O*-Benzylidene Acetal **1a**



1a **1b**

Entry[a]	Promoter	X equiv	Yield[b] (%)
1	$NaHSO_4 \cdot H_2O$	1	22
2[c]	$NaHSO_4 \cdot H_2O$	1	87
3[c]	$NaHSO_4 \cdot H_2O$	3	99
4[c]	$NaHSO_4$	3	70

[a] Reaction conditions: promoter was added to a mixture of **1a** (0.5 mmol), MeOH (6.0 mL), stirring, 23–26 °C, 1 h.
[b] Isolated yield after column chromatography (silica gel).
[c] The filtrate was neutralized with K_2CO_3.

Next, we examined the reactivity of other pyranoside derivatives (Table 2). All reactions were carried out using 0.5 mmol of substrates **1a**–**9a** and 1.5 mmol of sodium hy-

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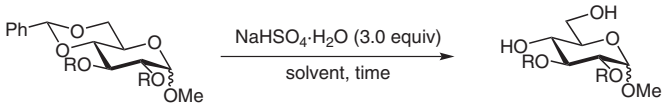
drogen sulfate monohydrate. The reaction with methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-glucopyranoside (**2a**) as a substrate at room temperature provided diol **2b** in 96% yield (entry 2). It should be noted that product **2b** was easily purified by recrystallization from dichloromethane–hexane without silica gel column chromatography. Debenzylidenation of substrate **3a**, which contained an epoxy moiety, proceeded smoothly without cleavage of the epoxide (entry 3). Methyl 4,6-*O*-benzylidene-2,3-di-*O*-tosyl-α-D-glucopyranoside (**4a**), and methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactopyranoside (**9a**) were converted into the corresponding diols in 72% and 68% yield (entries 4 and 9). Methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-β-D-glucopyranoside (**6a**) was converted into the corresponding diol without anomerization and methyl 2,3-di-*O*-benzyl-4,6-*O*-*p*-methoxybenzylidene-α-D-glucopyranoside (**8a**) showed excellent reactivity (entries 6 and 8). In the case of compounds **5a** and **7a**, deacetylation and debenzoylation products were obtained in small amounts, which led to a decrease in the yields of the desired products (49% and 52%, respectively).

Table 2 Deprotection of 4,6-*O*-Benzylidene Acetals[a]



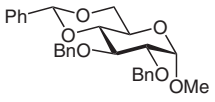
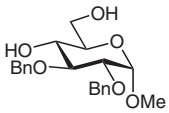
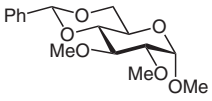
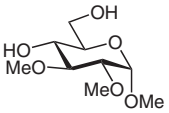
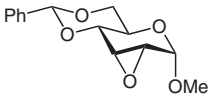
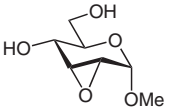
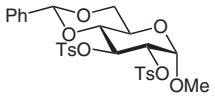
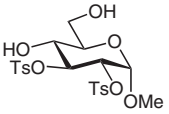
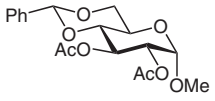
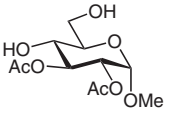
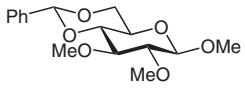
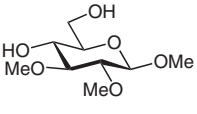
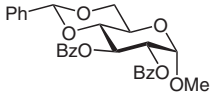
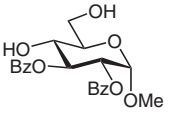
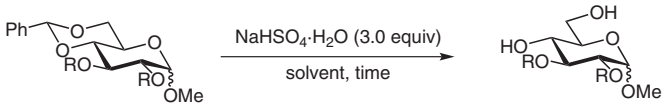
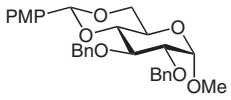
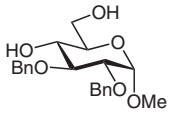
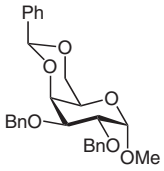
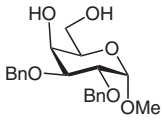
Entry	Substrate	Product	Solvent	Time	Yield[b] (%)
1	 **1a**	 **1b**	MeOH (6 mL)	6 h	99
2	 **2a**	 **2b**	MeOH (3.5 mL)	45 min	96[c]
3	 **3a**	 **3b**	MeOH (2 mL)–CH_2Cl_2 (1 mL)	1 h	74
4[d]	 **4a**	 **4b**	MeOH (0.5 mL)–CH_2Cl_2 (0.5 mL)	24 h	72
5	 **5a**	 **5b**	MeOH (6 mL)	1 h	49
6	 **6a**	 **6b**	MeOH (1 mL)	80 min	71
7	 **7a**	 **7b**	MeOH (1 mL)	1 h	52

Table 2 Deprotection of 4,6-*O*-Benzylidene Acetals[a] (continued)



Entry	Substrate	Product	Solvent	Time	Yield[b] (%)
8	 **8a**	 **1b**	MeOH (8 mL)	1 h	98
9[d]	 **9a**	 **9b**	MeOH (0.7 mL)–$CHCl_3$ (1 mL)	23 h	68

[a] Reaction conditions: substrate (0.5 mmol), $NaHSO_4·H_2O$ (1.5 mmol), solvent, 21–28 °C; the filtrate from the reaction was neutralized with K_2CO_3.
[b] Isolated yield after column chromatography (silica gel) unless otherwise noted.
[c] Isolated yield after recrystallization.
[d] Reaction was carried out at 50 °C.

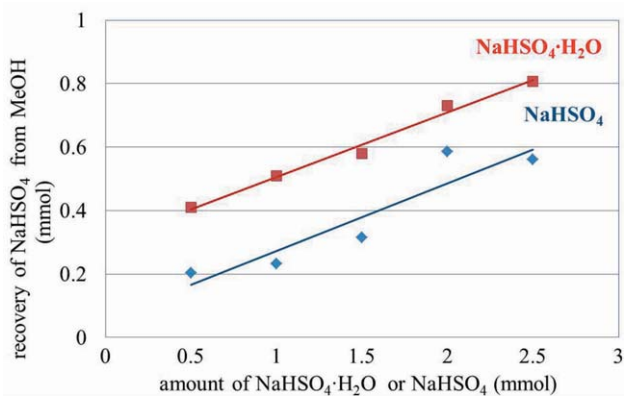


Figure 1 Solubility of sodium hydrogen sulfate monohydrate and sodium hydrogen sulfate in methanol (6.9 mL) at 23–26 °C

In summary, deprotection of 4,6-*O*-benzylidene pyranose derivatives was achieved using sodium hydrogen sulfate monohydrate under mild conditions. The present method has advantages compared to previous methods in view of operational simplicity and mild conditions. It should be mentioned that commercially available sodium hydrogen sulfate monohydrate has appropriate acidity in methanol without destroying other functional groups. Strict adjustment of acidity is necessary if normal Brønsted acids, such as hydrochloric acid and sulfuric acid, are used to maintain other functional groups.

All reactions were carried out in well-cleaned and oven-dried glassware with magnetic stirring. All starting materials were obtained from commercial sources and used without further purification. ^{1}H and ^{13}C NMR spectra (400 and 100.6 MHz respectively) were recorded on a Jeol JNM-LA 400 instrument using TMS as an internal standard. FT-IR spectra were recorded using Thermo Scientific, Nicolet iS5, iD5 ATR instrument. Mass spectra were measured using Thermo Quest LCQ DECA plus. Optical rotations were measured on a Horiba SEPA-300 polarimeter for a soln in a 1-dm cuvette. TLC was carried out on Merk 25 TLC aluminum sheets silica gel 60 F_{254}.

Glucopyranosides 1b–9b; General Procedure

A mixture of methyl 4,6-*O*-benzylidene acetal **1a–9a** (0.5 mmol), $NaHSO_4·H_2O$ (1.5 mmol) and solvent was stirred for the time indicated in Table 2, followed by filtration through Celite and addition of K_2CO_3 (100 mg) to the filtrate for neutralization. After filtration of K_2CO_3 through Celite, the filtrate was concentrated and the residue was purified by column chromatography (silica gel) or recrystallization to give the product.

Methyl 2,3-Di-*O*-benzyl-α-D-glucopyranoside (1b)

White solid; yield: 185 mg (99%); mp 73–75 °C (Lit.[8] 74–76 °C); $[\alpha]_D^{24}$ +19.3 (*c* 1.0, $CHCl_3$) [Lit.[8] $[\alpha]_D^{30}$ +18.1 (*c* 1.5, $CHCl_3$)].

IR (KBr): 696, 735, 754, 1000, 1023, 1044, 1057, 1119, 3200–3600 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.97 (br s, 1 H, OH), 2.33 (br s, 1 H, OH), 3.38 (s, 3 H, OMe), 3.4–3.6 (m, 2 H, H2, H4), 3.6–3.7 (m, 1 H, H5), 3.7–3.8 (m, 3 H, H3, H6, H6′), 4.59 (d, *J* = 3.2 Hz, 1 H, H1), 4.66 (d, *J* = 12.0 Hz, 1 H, OCH_2Ph), 4.70 (d, *J* = 12.0 Hz, 1 H, OCH_2Ph), 4.74 (d, *J* = 12.0 Hz, 1 H, OCH_2Ph), 5.03 (d, *J* = 12.0 Hz, 1 H, OCH_2Ph), 7.3–7.4 (m, 10 H, H_{Ph}).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.2, 62.4, 70.3, 70.6, 73.1, 75.4, 76.7, 79.7, 81.2, 98.1, 127.9, 128.0, 128.1, 128.5, 128.6, 137.9, 138.6.

HRMS (ESI$^-$): *m/z* [M – H]$^-$ calcd for $C_{21}H_{25}O_6$: 373.1651; found: 373.1644.

Anal. Calcd for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 66.99; H, 6.83.

Methyl 2,3-Di-*O*-methyl-α-D-glucopyranoside (2b)
White solid; yield: 106 mg (96%); mp 78–80 °C (Lit.[9] 83–85 °C); $[\alpha]_D^{27}$ +151.5 (*c* 1.0, H_2O) [Lit.[9] $[\alpha]_D^{23}$ +146.4 (*c* 1.0, H_2O)].

IR (KBr): 699, 755, 1072, 3100–3770 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.07 (br s, 1 H, OH), 2.18 (br s, 1 H, OH), 3.23 (dd, *J* = 9.2, 3.2 Hz, 1 H, H2), 3.4–3.6 (m, 8 H, 2 OMe, H3, H4), 3.6–3.7 (m, 4 H, OMe, H5), 3.81 (dd, *J* = 11.6, 4.0 Hz, 1 H, H6), 3.87 (dd, *J* = 11.6, 4.0 Hz, 1 H, H6′), 4.86 (d, *J* = 3.2 Hz, 1 H, H1).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.3, 55.5, 61.3, 62.4, 76.7, 81.9, 82.7, 97.5,

HRMS (ESI^-): *m*/*z* $[M - H]^-$ calcd for $C_9H_{17}O_6$: 221.1025; found: 221.1025.

Methyl 2,3-Anhydro-α-D-glucopyranoside (3b)
White solid; yield: 65 mg (74%); mp 109 °C (Lit.[10] 103–105 °C); $[\alpha]_D^{33}$ +144.8 (*c* 0.17, $CHCl_3$).

IR (KBr): 616, 750, 793, 840, 894, 911, 964, 981, 1026, 1040, 1051, 1074, 1105, 1306, 1366, 2920, 2964, 3000–3500 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.46 (s, 3 H, OMe), 3.49 (dd, *J* = 4.2 Hz, 1 H, H3), 3.57 (dd, *J* = 3.1, 4.2 Hz, 1 H, H2), 3.6–3.7 (m, 1 H, H5), 3.80 (d, *J* = 3.9, 11.7 Hz, 1 H, H6), 3.86 (d, *J* = 3.9, 11.7 Hz, 1 H, H6′), 3.99 (d, *J* = 8.8 Hz, 1 H, H4), 4.91 (d, *J* = 3.1 Hz, 1 H, H1).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 54.1, 55.5, 55.7, 62.2, 65.9, 69.0, 94.6.

HRMS (ESI^-): *m*/*z* $[M - H]^-$ calcd for $C_7H_{11}O_5$: 175.0606; found: 175.0603.

Methyl 2,3-Di-*O*-tosyl-α-D-glucopyranoside (4b)
White solid; yield: 181 mg (72%); mp 55 °C; $[\alpha]_D^{29}$ +59.6 (*c* 1.0, $CHCl_3$) [Lit.[11] $[\alpha]_D$ +58.5 (*c* 3.1, $CHCl_3$)].

IR (KBr): 564, 664, 732, 811, 830, 907, 972, 995, 1036, 1173, 1190, 1360, 2927, 3000–3600 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, CH_3), 2.46 (s, 3 H, CH_3), 3.27 (s, 3 H, OMe), 3.40 (d, *J* = 3.3 Hz, 1 H, OH), 3.6–3.7 (m, 1 H, H5), 3.77 (dd, *J* = 9.2, 9.1 Hz, 1 H, H4), 3.8–3.9 (m, 2 H, H6, H6′), 4.30 (dd, *J* = 3.5, 9.4 Hz, 1 H, H2), 4.76 (d, *J* = 3.5 Hz, 1 H, H1), 4.85 (dd, *J* = 9.4, 9.1 Hz, 1 H, H3), 7.29 (d, *J* = 7.6 Hz, 2 H, PhCH_2), 7.34 (d, *J* = 7.6 Hz, 2 H, PhCH_2), 7.66 (d, *J* = 8.4 Hz, 2 H, PhCH_2), 7.77 (d, *J* = 8.4 Hz, 2 H, PhCH_2).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.70, 21.75, 55.5, 61.7, 69.2, 70.7, 75.5, 80.4, 97.0, 128.0, 128.3, 129.81, 129.84, 132.3, 132.9, 145.3, 145.4.

HRMS (ESI^+): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{26}O_{10}S_2Na$: 525.0865; found: 525.0865.

Methyl 2,3-Di-*O*-acetyl-α-D-glucopyranoside (5b)
Colorless oil; yield: 68 mg (49%); $[\alpha]_D^{29}$ +149.2 (*c* 0.46, $CHCl_3$) [Lit.[12] $[\alpha]_D^{19}$ +127 ($CHCl_3$)].

IR (KBr): 604, 755, 918, 1029, 1223, 1370, 1742, 2932, 3000–3500 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.68 (br s, 1 H, OH), 2.10 (s, 3 H, CH_3COO), 2.11 (s, 3 H, CH_3COO), 2.94 (br s, 1 H, OH), 3.41 (s, 3 H, OMe), 3.7–3.8 (m, 2 H, H4, H6), 3.8–3.9 (m, 2 H, H5, H6′), 4.84 (dd, *J* = 10.3, 3.3 Hz, 2 H, H2), 4.91 (d, *J* = 3.3 Hz, 1 H, H1), 5.2–5.3 (m, 1 H, H3).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.8, 20.9, 55.3, 62.0, 69.9, 70.7, 71.1, 73.4, 96.8, 170.3, 172.0.

HRMS (ESI^+): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{18}O_8Na$: 301.0899; found: 301.0899.

Methyl 2,3-Di-*O*-methyl-β-D-glucopyranoside (6b)
White solid; yield: 79 mg (71%); mp 42 °C (Lit.[13] 62–64 °C); $[\alpha]_D^{32}$ –41.3 (*c* 1.0, $CHCl_3$) [Lit.[13] $[\alpha]_D$ –47.8 ($CHCl_3$)].

IR (KBr): 614, 890, 955, 996, 1025, 1061, 1085, 1103, 3000–3700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.28 (br s, 1 H, OH), 2.89 (br s, 1 H, OH), 3.00 (dd, *J* = 9.2, 7.8 Hz, 1 H, H2), 3.14 (dd, *J* = 9.1, 9.0 Hz, 1 H, H4), 3.3–3.4 (m, 1 H, H5), 3.51 (dd, *J* = 9.2, 9.1 Hz, 1 H, H3), 3.56 (s, 3 H, OMe), 3.58 (s, 3 H, OMe), 3.64 (s, 3 H, OMe), 3.7–4.0 (m, 2 H, H6, H6′), 4.25 (d, *J* = 7.8 Hz, 1 H, H1).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 57.2, 60.2, 60.9, 62.5, 70.1, 74.7, 83.6, 95.6, 104.6.

HRMS (ESI^-): *m*/*z* $[M - H]^-$ calcd for $C_9H_{17}O_6$: 221.1025; found: 221.1025.

Methyl 2,3-Di-*O*-benzoyl-α-D-glucopyranoside (7b)
White solid; yield: 105 mg (52%); mp 63–65 °C; $[\alpha]_D^{28}$ +178.2 (*c* 1.0, $CHCl_3$) [Lit.[14] $[\alpha]_D^{19}$ +165.6 ($CHCl_3$)].

IR (KBr): 696, 739, 961, 1028, 1045, 1094, 1194, 1275, 1354, 1453, 1722, 2928, 3000–3500 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.72 (br s, 1 H, OH), 2.16 (br s, 1 H, OH), 3.43 (s, 3 H, OMe), 3.86 (ddd, *J* = 6.7, 6.7, 3.1 Hz, 1 H, H5), 3.9–4.0 (m, 3 H, H4, H6, H6′), 5.12 (d, *J* = 3.9 Hz, 1 H, H1), 5.23 (dd, *J* = 3.9, 9.5 Hz, 1 H, H2), 5.74 (dd, *J* = 10.3, 9.5 Hz, 1 H, H3), 7.3–7.4 (m, 4 H, H_{Ph}), 7.5–7.6 (m, 2 H, H_{Ph}), 7.9–8.0 (m, 4 H, H_{Ph}).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.4, 62.1, 69.6, 71.3, 71.5, 74.3, 97.1, 128.4, 129.08, 129.15, 129.87, 129.88, 133.3, 133.5, 166.0, 167.5.

HRMS (ESI^-): *m*/*z* $[M - H]^-$ calcd for $C_{21}H_{21}O_8$: 401.1236; found: 401.1237.

Methyl 2,3-Di-*O*-benzyl-α-D-galactopyranoside (9b)
Colorless oil; yield: 128 mg (68%); $[\alpha]_D^{29}$ +46.9 (*c* 0.67, $CHCl_3$) [Lit.[15] $[\alpha]_D^{30}$ +43.0 (*c* 0.74, $CHCl_3$)].

IR (KBr): 686, 706, 991, 1025, 1068, 1094, 1275, 1451, 1720, 2933, 3000–3500 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.46 (br s, 1 H, OH), 2.78 (br s, 1 H, OH), 3.37 (s, 3 H, OMe), 3.7–3.9 (m, 5 H, H2, H3, H5, H6, H6′), 4.0–4.1 (m, 1 H, H4), 4.67 (d, 1 H, PhCH_2), 4.69 (d, *J* = 11.9 Hz, 1 H, PhCH_2), 4.70 (d, *J* = 3.2 Hz, 1 H, H1), 4.81 (d, *J* = 11.9 Hz, 2 H, PhCH_2), 7.3–7.4 (m, 10 H, H_{Ph}).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.3, 63.0, 68.8, 69.1, 72.9, 73.5, 75.6, 98.6, 127.8, 127.9, 128.0, 128.4, 128.5, 138.0, 138.2.

HRMS (ESI^-): *m*/*z* $[M - H]^-$ calcd for $C_{21}H_{25}O_6$: 373.1651; found: 373.1650.

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Supporting Information for this article is available online at http://www.thieme-connect.de/ejournals/toc/synthesis. Included are ^1H and ^{13}C NMR spectra for compounds **1b**–**9b**.

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