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Removal of Acid-Labile Protecting Groups on Carbohydrates Using Water-Tolerant and Recoverable Vanadyl Triflate Catalyst

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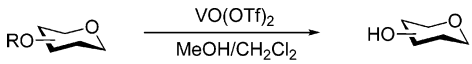

Acetal, trityl, and TBDMS protecting groups on saccharides were subjected to alcoholysis using a catalytic amount of vanadyl triflate in an MeOH−CH_2Cl_2 solvent system. The configuration at the anomeric positions of saccharides was retained, and no glycosidic bond cleavage and oxidation of sulfides were observed. The presented method was easily implemented, compatible with diverse functional groups, and regioselective in some cases.

The protection and deprotection steps are critical to many synthetic schemes,[1] such as the synthesis of complex carbohydrate. Acetal,[2] trityl,[3] and *tert*-butyldimethylsilyl (TBDMS) groups[4] are effective protecting groups in organic and carbohydrate chemistry and are acid-labile protecting groups. The most extensively adopted methods for deprotecting these protecting groups involve the use of protic acids[5] and Lewis acids.[6] Although normal acidic catalysts such as HCl, HBr, TFA, and AcOH are satisfactory reagents[1,7] for selectively deprotecting the acetonide and benzylidene on primary/secondary hydroxyl groups, the strong acidity and free protons can also hydrolyze acid-sensitive groups.[8]

The synthetic use of vanadium-containing complexes has been extensively investigated. They are utilized as reagents or catalysts for redox-type C−C bond formation[9,10] in the presence of suitable co-oxidants.[11] Over the past years, many water-tolerant vanadyl and other oxometallic species have been developed as recoverable, amphoteric catalysis and used in nucleophilic acyl substitution,[12] benzylidenation,[13] and isopropylidenation.[14] This paper describes the use of vanadyl triflate as a Lewis acid catalyst in the deprotection of various acid-labile protecting groups on saccharides. The advantage of using vanadyl triflate is that this catalyst can be recovered by extraction with water and is reusable and, thus, more environmentally friendly.

The 4,6-*O*-benzylidene-protected monosaccharides and the corresponding debenzylidenation products are important precursors in the synthesis of complex carbohydrates.[15] Therefore, 4,6-*O*-benzylideneglucose derivative **1** was selected as an example (Table 1) to investigate the catalytic alcoholysis by vanadyl triflate ($VO(OTf)_2$) in the presence of MeOH. As shown in Table 1, increasing the amount of $VO(OTf)_2$ and the reaction temperature enhanced the reaction rate in methanol/dichloromethane cosolvent system (entries 1−4). Our earlier work demonstrated that the reactivity of vanadyl triflate in catalyzing benzylidenation[13] and isopropylidenation[14] was enhanced using acetonitrile as the solvent. Thus, the methanol/acetonitrile cosolvent was tested. Although the de-benzylidenation rate was increased, the benzoyl migration product was also observed (entries 5 and

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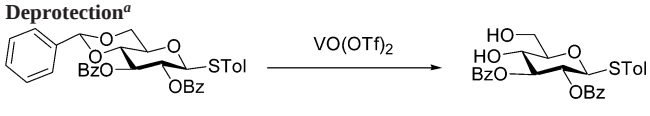
TABLE 1. Survey of Reaction Conditions of Benzylidene Deprotection[a]

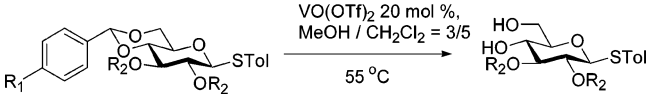


1 **2**

entry	solvent	$VO(OTf)_2$ (mol %)	reaction temp (°C)	reaction time (h)	yield (%)
1	$MeOH/CH_2Cl_2 = 3/5$	5	25	144	62[b]
2	$MeOH/CH_2Cl_2 = 3/5$	20	25	48	81
3	$MeOH/CH_2Cl_2 = 3/5$	5	55	60	80
4	$MeOH/CH_2Cl_2 = 3/5$	20	55	12	80
5	$MeOH/CH_3CN = 1/3$	5	25	24	82[c]
6	$MeOH/CH_3CN = 1/3$	20	25	16	84[c]

[a] Tol = *p*-methylphenyl. [b] About 27% of **1** was recovered. [c] About 9% of benzoyl migration product was observed.

TABLE 2. Deprotection of Benzylidene Monosaccharides by $VO(OTf)_2$[a]



entry	substrate	R_1	R_2	time (h)	yield (%)	product
1	**1**	H	Bz	12	80	**2**
2	**3**	CH_3	Bz	16	92	**2**
3	**4**	OMe	Bz	2.5	91	**2**
4	**5**	NO_2	Bz	16	NR	
5	**6**	Cl	Bz	36	76[b]	**2**
6	**7**	OAc	Bz	36	68[c]	**2**
7	**8**	Cl	Bn	40	90	**10**
8	**9**	OAc	Bn	40	87	**10**

[a] Tol = *p*-methylphenyl. [b] 9% of the benzoyl group migration was observed. [c] 13% of the benzoyl group migration

6). According to these results, the reaction conditions in entry 4 were employed as standard reaction conditions because the reaction time is short and the yield of the desired product is good.

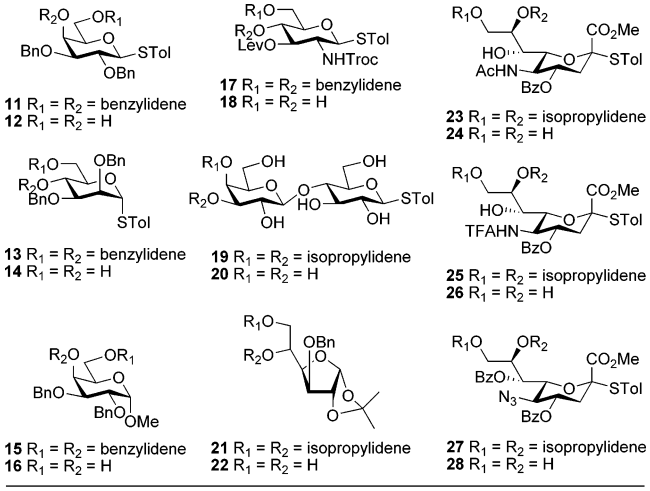
Table 2 refers to the deprotection of benzylidene glucosyl derivatives under the standard reaction conditions. The deprotection of glucosyl derivatives **3** and **4** (entries 2 and 3), which have the electron-donating group at the para positions of the aryl groups, proceeded at a faster deprotection rate than that of the unsubstituted benzylidene protected glucose **1** (entry 1). The presence of electron-withdrawing group at benzylidene reduced the deprotection rate (entries 4−6 vs 1). As expected, the presence of a strong electron-withdrawing group, such as NO_2, prevented the reaction. Notably, although the deprotection of glucosides **6** and **7** (entries 5 and 6), which have weaker electron-withdrawing groups on benzylidene, can proceed, the migration of benzoyl groups becomes a serious side reaction. The catalyst was recovered by extraction with water and reactivated by heat (∼60 °C) under vacuum. In the case of debenzylidenation of **1**, more than 95% of catalyst was recovered with activity lost less than 5% (based on the product formation under the same reaction conditions).

The successful deprotection of glucosyl benzylidenes motivated a study of the generality of the developed method on other benzylidene- or isopropylidene-protected carbohydrates, as presented in Table 3. The deprotection of the benzylidene group on various saccharides was achieved with good product yields (entries 1−4). The developed method also performed very well in the deprotection of isopropylidene (entries 5−9). The terminal

TABLE 3. Deprotection of Benzylidene or Isopropylidene Groups from Saccharides[a]

entry	substrate	time (h)	product	yield (%)
1	**11**	16	**12**	92
2	**13**	16	**14**	93
3	**15**	16	**16**	87
4	**17**	16	**18**	85
5	**19**	17	**20**	85
6	**21**	17	**22**	78
7	**23**	16	**24**	85
8	**25**	18	**26**	83
9	**27**	16	**28**	88

[a] Tol = *p*-methylphenyl.



isopropylidene of diisopropylidene-protected furanose **21** was regioselectively deprotected to yield product **22** (entry 6). The protecting group of amine at the C-5 position of the neuraminic acid (NeuAc) has been reported to affect the reactivities of both NeuAc donor and acceptor in glycosylation[16] and the rate of desilylation.[7c−d] However, the C-5 protecting group of NeuAc did not observably influence the deprotection of terminal isopropylidene using a catalytic amount of $VO(OTf)_2$ (entries 7−9).

Following the success of the deprotection of benzylidene and isopropylidene, the effectiveness of the selective cleavage of the trityl group in sugar derivatives by the developed protocol was examined (Table 4). Detritylation of 6-trityl glucosides **29** and **33** with a benzyl or a benzoyl group as the protecting group of other hydroxyls (entries 1 and 3) was successfully performed to obtain the desired products **30** and **34**. However, the acyl migration product was observed when the acetyl group was used as the protecting group of other hydroxyls (entry 2**)**. Notably, chemoselective deprotection of the trityl group was achieved in the presence of acetonide (entry 5). Moreover, the $VO(OTf)_2$-catalyzed detritylation efficiently deprotected trityl groups of nucleoside **41** and amino acid **39** without cleaving the glycosidic bond[17] or transesterification (entries 7 and 6). However, TBDMS

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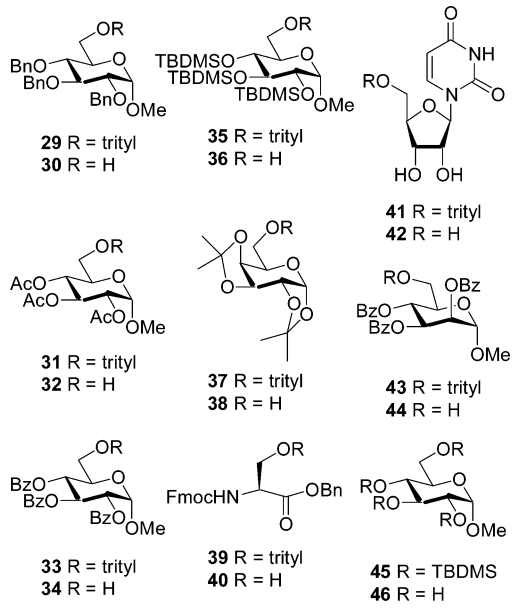
TABLE 4. Deprotection of Trityl or TBDMS Groups from Saccharides[a]

entry	substrate	time (h)	product	yield (%)
1	**29**	16	**30**	92
2	**31**	18	**32**	34[b]
3	**33**	16	**34**	96
4	**35**	38	**46**	91
5	**37**	16	**38**	88
6	**39**	16	**40**	85
7	**41**	16	**42**	92
8	**43**	16	**44**	96
9	**45**	40	**46**	88

[a] Tol = *p*-methylphenyl. [b] 45% of the acyl group migration product was observed.



group did not survive, resulting in full deprotection under the standard $VO(OTf)_2$ conditions, as indicated in entries 4 and 9.

In conclusion, benzylidene, isopropylidene, trityl, and TBDMS protecting groups on saccharides were hydrolyzed using a catalytic amount of vanadyl triflate in a MeOH−CH_2Cl_2 solvent system. The configuration at the anomeric positions was retained and no glycosidic bond cleavage or oxidation of sulfides was observed. This developed method was easy to implement, compatible with diverse functional groups, and regioselective in some cases. In combination with our previously reported method,[13,14] $VO(OTf)_2$ can be used as a catalyst either in the formation or cleavage of benzylidene and isopropylidene. Remarkably, the water-tolerant catalyst was recovered easily from the aqueous layer following the removal of water. The catalyzes of the current and various vanadyl complexes augured well for their potential applications in organic and carbohydrate chemistry.

Experimental Section

Compounds **2**, **10**, **22**, **30**, **32**, **34**, **38**, **40**, and **44** have been previously characterized and their NMR spectral data were in good agreement with the literature data. References for the reported compounds are cited in the Supporting Information.

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General Procedure for the Deprotection of Benzylidene, Isopropylidene, Trityl, and TBDMS Groups on Saccharides and the Recovery of Catalyst. In a dry 25-mL round-bottomed flask was placed the protected carbohydrate (1 mmol), and then 10 mL of MeOH/CH_2Cl_2 (ratio 3:5) was added. To the above solution was added vanadyl triflate (0.2 mmol) at ambient temperature, and the resulting mixture was stirred at 55 °C for the indicated time period. After completion of the reaction as monitored by TLC, the reaction mixture was cooled to ambient temperature, and then ice-cold water (10 mL) and CH_2Cl_2 (50 mL) were added. The separated organic layer was dried ($MgSO_4$), filtered, and evaporated. The crude product was purified by column chromatography on silica gel. The product obtained was characterized by spectroscopic methods. The separated aqueous layer was concentrated by rotatory evaporator at 40 °C. Subsequently, the recovered catalyst was dried in vacuo at 60 °C for 24 h to give blue solid (0.19 mmol, 95% recovery).

4-Methyl phenyl 2,3-*O*-dibenzyl-1-thio-β-D-galactopyranoside (12): syrup; ^{1}H NMR (500 MHz, $CDCl_3$) 7.44 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 7.0 Hz, 2H), 7.35−7.27 (m, 8H), 7.08 (d, J = 7.8 Hz, 2H), 4.82 (d, J = 10.3 Hz, 1H), 4.73 (d, J = 10.3 Hz, 1H), 4.68 (s, 2H), 4.56 (d, J = 9.2 Hz, 1H), 4.02 (d, J = 3.1 Hz, 1H), 3.95 (dd, J = 11.8, 6.8 Hz, 1H), 3.76 (dd, J = 11.8, 4.2 Hz, 1H), 3.70 (t, J = 9.2 Hz, 1H), 3.56 (dd, J = 9.2, 3.1 Hz, 1H), 3.45 (dd, J = 6.8, 4.2 Hz, 1H), 2.30 (s, 3H), 1.94 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 138.1, 137.8, 137.5, 132.6, 129.7, 129.6, 128.6, 128.4, 128.2, 128.1, 127.9, 127.8, 87.9, 82.4, 77.9, 77.0, 75.3, 72.3, 67.4, 62.8, 21.1; HRMS (FAB) calcd for $C_{27}H_{31}O_5S$ $[M + H]^+$ 467.1892, found 467.1895.

4-Methyl phenyl 2,3-*O*-dibenzyl-1-thio-α-D-mannopyranoside (14): syrup; ^{1}H NMR (400 MHz, $CDCl_3$) 7.39−7.27 (m, 12H), 7.11 (d, J = 8.0 Hz, 2H), 5.48 (d, J = 1.3 Hz, 1H), 4.65 (d, J = 12.2 Hz, 1H), 4.58 (d, J = 7.2 Hz, 1H), 4.54 (d, J = 7.2 Hz, 1H), 4.46 (d, J = 12.2 Hz, 1H), 4.15−4.06 (m, 2H), 4.00 (dd, J = 3.0, 1.3 Hz, 1H), 3.87 (dd, J = 11.6, 3.1 Hz, 1H), 3.80 (dd, J = 11.6, 4.7 Hz, 1H), 3.69 (dd, J = 8.9, 3.0 Hz, 1H), 2.33 (s, 3H), 2.04 (br, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 137.9, 137.7, 137.6, 132.4, 123.0, 129.9, 128.5, 128.4, 127.9, 127.9, 127.9, 127.8, 86.3, 79.5, 75.5, 73.2, 72.1, 71.7, 67.2, 62.5, 21.1; HRMS (FAB) calcd for $C_{27}H_{30}O_5SNa$ $[M + Na]^+$ 489.1712, found 489.1721.

Methyl 2,3-*O*-dibenzyl-α-D-galactopyranoside (16): syrup; ^{1}H NMR (400 MHz, $CDCl_3$) 7.36−7.25 (m, 10H), 4.79 (d, J = 12.0 Hz, 2H), 4.68 (d, J = 12.0 Hz, 1H), 4.68 (d, J = 3.5 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.03 (d, J = 1.5 Hz, 1H), 3.91−3.82 (m, 3H), 3.77−3.73 (m, 2H), 3.37 (s, 3H), 2.45 (br, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 138.2, 138.0, 128.5, 128.4, 128.0, 128.0, 127.8, 127.8, 98.6, 77.3, 75.6, 73.5, 72.9, 69.1, 68.9, 63.0, 55.3; HRMS (FAB) calcd for $C_{21}H_{26}O_6Na$ $[M + Na]^+$ 397.1627, found 397.1622.

4-Methyl phenyl 2-deoxy-3-*O*-levulinoyl-2-(2,2,2-trichloroethoxycarbonylamino)-1-thio-β-D-glucopyranoside (18): syrup; ^{1}H NMR (500 MHz, $CDCl_3$) 7.45−7.41 (m, 2H), 7.30−7.26 (m, 3H), 5.55 (d, J = 9.6 Hz, 1H), 5.08 (t, J = 9.6 Hz, 1H), 4.80 (d, J = 9.6 Hz, 1H), 4.75 (s, 2H), 3.91 (dd, J = 12.0, 3.0 Hz, 1H), 3.80 (dd, J = 12.0, 4.6 Hz, 1H), 3.72 (t, J = 9.6 Hz, 2H), 3.49 (ddd, J = 9.6, 4.6, 3.0 Hz, 1H), 2.81 (ddd, J = 18.5, 8.3, 4.7 Hz, 1H), 2.71 (ddd, J = 18.5, 6.2, 4.7 Hz, 1H), 2.58 (br, 2H), 2.55 (ddd, J = 16.6, 8.3, 4.7 Hz, 1H), 2.45 (ddd, J = 16.6, 6.2, 4.7 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 208.3, 173.4, 154.3, 132.8, 132.0, 129.1, 127.9, 95.5, 86.8, 79.3, 76.8, 74.5, 69.4, 62.4, 54.7, 38.3, 29.7, 28.2; HRMS (FAB) calcd for $C_{20}H_{24}O_8NCl_3SNa$ $[M + Na]^+$ 566.0186, found 566.0181.

4-Methyl phenyl (β-D-galactopyranosyl)-(1→4)-1-thio-β-D-glucopyranoside (20): syrup; ^{1}H NMR (500 MHz, MeOD) 7.46 (d, J = 8.1 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H), 4.57 (br, 7H), 4.53 (d, J = 9.8 Hz, 1H), 4.36 (d, J = 7.5 Hz, 1H), 3.89 (dd, J = 12.3, 2.4 Hz, 1H), 3.82 (dd, J = 12.3, 4.6 Hz, 1H), 3.81 (d, J = 3.6 Hz, 1H), 3.77 (dd, J = 11.5, 7.6 Hz, 1H), 3.69 (dd, J = 11.5, 4.5 Hz, 1H), 3.59−3.52 (m, 4H), 3.49 (dd, J = 9.7, 3.2 Hz, 1H), 3.43−3.40 (m, 1H), 3.25 (dd, J = 9.7, 8.8 Hz, 1H); ^{13}C NMR (125 MHz,

$CDCl_3$) 137.5, 132.3, 129.2, 129.1, 103.4, 87.9, 79.0, 78.6, 76.4, 75.6, 73.3, 71.8, 71.0, 68.8, 61.0, 60.5, 19.6; HRMS (FAB) calcd for $C_{19}H_{28}O_{10}S$ $[M + H]^+$ 448.1403, found 448.1408.

Methyl (4-methyl phenyl 5-acetamido-4-*O*-benzoyl-3,5-dideoxy-2-thio-α-D-*galacto*-non-2-ulopyranosid)onate (24): syrup; ^1H NMR (500 MHz, $CDCl_3$) 8.02 (d, $J = 7.5$ Hz, 2H), 7.62 (t, $J = 7.5$ Hz, 1H), 7.47 (t, $J = 7.5$ Hz, 2H), 7.40 (d, $J = 8.0$ Hz, 2H), 7.15 (d, $J = 8.0$ Hz, 2H), 6.45 (d, $J = 10.5$ Hz, 1H), 5.16 (ddd, $J = 12.3$, 10.5, 4.9 Hz, 1H), 4.20 (q, $J = 10.5$ Hz, 1H), 3.90−3.86 (m, 2H), 3.75−3.72 (m, 1H), 3.65 (s, 3H), 3.57 (d, $J = 8.31$ Hz, 1H), 3.44 (d, $J = 10.5$ Hz, 1H), 3.09 (br, 3H), 3.00 (dd, $J = 12.3$, 4.9 Hz, 1H), 2.35 (s, 3H), 2.27 (t, $J = 12.3$ Hz, 1H), 1.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 173.4, 169.4, 167.3, 140.9, 136.7, 134.0, 129.9, 129.7, 128.7, 128.7, 124.6, 86.3, 76.6, 71.0, 70.1, 69.2, 64.1, 53.2, 51.3, 37.3, 22.8, 21.4; HRMS (FAB) calcd for $C_{26}H_{31}O_9NSNa$ $[M + Na]^+$ 556.1617, found 556.1618.

Methyl (4-methyl phenyl 4-*O*-benzoyl-3,5-dideoxy-5-trifluoroacetamido-2-thio-α-D-*galacto*-non-2-ulopyranosid)onate (26): syrup; ^1H NMR (500 MHz, $CDCl_3$) 7.99 (d, $J = 7.3$ Hz, 2H), 7.77 (d, $J = 10.5$ Hz, 1H), 7.60 (t, $J = 7.3$ Hz, 1H), 7.46 (t, $J = 7.3$ Hz, 2H), 7.34 (d, $J = 8.0$ Hz, 2H), 7.12 (d, $J = 8.0$ Hz, 2H), 5.20 (ddd, $J = 12.2$, 10.5, 4.9 Hz, 1H), 4.33 (q, $J = 10.5$ Hz, 1H), 3.85−3.77 (m, 2H), 3.74 (dd, $J = 10.7$, 3.5 Hz, 1H), 3.67 (d, $J = 10.5$ Hz, 1H), 3.61 (d, $J = 8.7$ Hz, 1H), 3.45 (s, 3H), 3.02 (dd, $J = 12.2$, 4.9 Hz, 1H), 2.86 (br, 3H), 2.32 (s, 3H), 2.19 (t, $J = 12.2$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 169.3, 167.0, 159.2 (q, $J = 38.0$ Hz), 141.0, 136.6, 134.0, 129.9, 129.7, 128.7, 128.6, 124.4, 115.5 (q, $J = 285.6$ Hz), 86.3, 75.3, 71.3, 70.2, 68.6, 63.3, 53.1, 50.8, 37.1, 21.3; HRMS (FAB) calcd for $C_{26}H_{29}O_9NF_3S$ $[M + H]^+$ 588.1515, found 588.1512.

Methyl (4-methyl phenyl 5-azido-4,6-*O*-dibenzoyl-3,5-dideoxy-2-thio-α-D-*galacto*-non-2-ulopyranosid)onate (28): syrup; ^1H NMR (500 MHz, $CDCl_3$) 8.18 (d, $J = 7.2$ Hz, 2H), 7.99 (d, $J = 7.2$ Hz, 2H), 7.68 (t, $J = 7.2$ Hz, 1H), 7.59−7.53 (m, 3H), 7.46−7.40 (m, 4H), 7.18 (d, $J = 7.9$ Hz, 2H), 5.48 (dd, $J = 9.2$, 1.8 Hz, 1H), 5.03 (ddd, $J = 11.6$, 10.5, 4.9 Hz, 1H), 4.09 (ddd, $J = 9.2$, 5.9, 2.4 Hz, 1H), 3.81 (s, 3H), 3.76 (dd, $J = 10.5$, 1.8 Hz, 1H), 3.71 (dd, $J = 12.0$, 2.4 Hz, 1H), 3.60 (dd, $J = 12.0$, 5.9 Hz, 1H), 3.54 (t, $J = 10.5$ Hz, 1H), 3.20 (dd, $J = 12.9$, 4.9 Hz, 1H), 2.38 (s, 3H), 2.00 (dd, $J = 12.9$, 11.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 169.3, 165.6, 165.3, 140.9, 136.7, 133.7, 133.6, 130.1, 129.8, 129.7, 129.1, 128.9, 128.7, 128.5, 124.4, 86.3, 74.38, 72.6, 70.5, 70.1, 63.2, 60.0, 53.6, 37.1, 21.4; HRMS (FAB) calcd for $C_{31}H_{31}O_9N_3SNa$ $[M + Na]^+$ 644.1679, found 644.1674.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of deprotected products. This material is available free of charge via the Internet at http://pubs.acs.org.

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