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The trimethylsilyl xylyl (TIX) ether: a useful protecting group for alcohols

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Abstract—A new protecting group for alcohols, the *p*-trimethylsilyl xylyl (TIX) group has been developed. The TIX group is used to protect various alcohols under acidic as well as basic conditions. The protected ethers thus formed had noteworthy chemoselectivity upon deprotection in the presence of other benzyl ethers and commonly used protecting groups. The stability of the TIX group towards various reagents has also been examined.

1. Introduction

Protection and deprotection are inevitable requirements of a lengthy synthetic sequence leading to natural products, fine chemical intermediates, or important industrial or pharmaceutical organic materials. Protecting groups exist for various functional moieties and have their own pattern of chemoselectivity during deprotection. In molecules with multiple, discrete, simultaneous protections, a careful strategy exists for specific removal and modification of the exposed functionality. Thus, elaborately protected, highly functional templates can serve as total synthetic intermediates. In addition, such templates bound to solid support can lead to diversity upon chemoselective deprotection of various functional groups with subsequent elaboration of the liberated functional group. To date, a remarkable variety of protecting groups have been reported and their preparation, attachment and deprotection strategies under a variety of conditions have been summarized nicely.[1]

Among hydroxyl protecting groups, benzyl ethers are highly robust and are often employed so that they can be removed at later stages in a synthetic sequence. Thus, benzyl ethers are often employed as 'long-term' protecting groups carried through multiple steps in a synthetic sequence. On the other hand, substituted benzyl ethers are deliberately less stable, can be cleaved easily, and are employed as temporary protecting groups that can be removed conveniently at earlier stages of the synthesis when more delicate functionality is present.

A number of esoterically substituted benzyl ethers have been reported in the literature including methoxy, nitro, halo, cyano, azido benzyl ethers, etc.[1,2] Among these, the *p*-methoxy benzyl (PMB) group has found frequent application in natural product synthesis, and can be removed oxidatively in a selective manner.[3] However, the sensitivity of this group to acid[4] severely restricts its synthetic utility. Recently, *p*-substituted benzyl ethers with acetoxy, SEM and halo substituents have been reported.[5] Although these groups offer some advantages, the cleavage conditions are incompatible with either base-sensitive or acid-sensitive groups or functionalities. The development of a benzyl protecting group that is stable to both acidic and basic conditions is certainly a useful addition to the existing substituted benzyl ethers.

In this direction, we envisioned a new protecting group, the trimethylsilyl xylyl ether (TIX), which can be attached to a hydroxyl group efficiently and selectively removed in the presence of other groups under mild conditions. Furthermore, as one procedural iteration involves a polymer-supported reagent during preparation of the reagent **2** for protection, it can also be beneficially applied to solution-phase parallel chemistry using solid-phase reagents during generation of parallel libraries.

Keywords: Trimethylsilyl xylyl; Protecting groups; Ethers.
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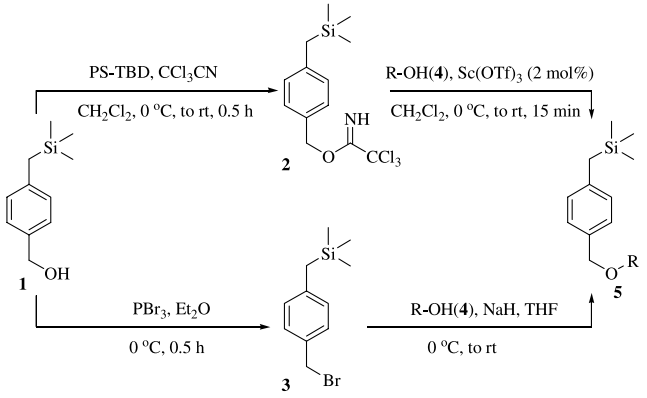
2. Results and discussion

Hence, the TIX group was easily introduced onto a hydroxyl moiety using a one-pot trichloroacetimidate protocol.[6] The known silyl alcohol **1**[7] was initially converted to its trichloroacetimidate derivative **2** using literature precedent in which Cl_3CCN, the alcohol **1**, and DBU were combined.

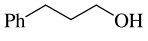
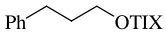
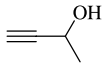
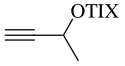
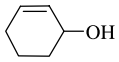
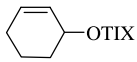
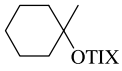
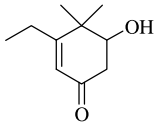
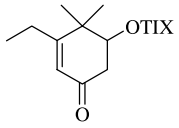
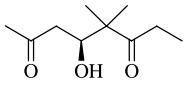
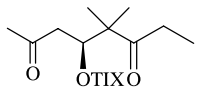
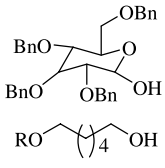
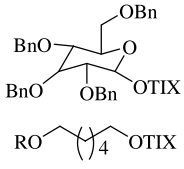


Scheme 1.

The imidate **2**, thus formed, would then be purified by chromatography or distillation. However, in our hands, this imidate was insufficiently stable to silica gel chromatography, so we opted to proceed without further purification. Thus **1**, after reaction with DBU, was treated with the alcohol followed by a slight excess (with respect to DBU) of *p*-toluenesulfonic acid (*p*TSA) or its pyridinium salt (PPTS). The yields in these cases were moderate to good, but unreacted alcohols (**1** and ROH) were present, undoubtedly due to the presence of traces of water or other contaminants associated with the combining of reaction steps.

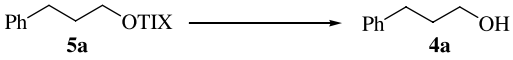
To forestall lengthy low-yielding purifications of imidate **2**, we took advantage of solid-supported chemistries now readily available. Thus, reaction of **1** with a commercially available polymer-supported base related to DBU, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PS-TBD), in the presence of Cl_3CCN in dichloromethane at 0 °C followed by a simple filtration furnished essentially pure imidate **2**. For catalysis of the ensuing ether formation with ROH **4**, because no DBU was present to contend with, harsh, hygroscopic sulfonic acids could be eliminated and a catalytic amount of

Table 1. TIX protection of alcohols[a]

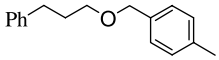
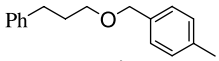
Entry	Alcohol		Product		Isolated yield (%)
1		**4a**		**5a**	81, 80[b]
2		**4b**		**5b**	82
3		**4c**		**5c**	88
4		**4d**		**5d**	76, 78[b]
5		**4e**		**5e**	91
6		**4f**		**5f**	79
7		**4g**		**5g**	80
8		**4h**		**5h**	92
9	R = Bn	**4i**	R = Bn	**5i**	82
10	*p*-xylyl	**4j**	*p*-xylyl	**5j**	91
11	PMB	**4k**	PMB	**5k**	78
12	SEM	**4l**	SEM	**5l**	80
13	Ac	**4m**	Ac	**5m**	82
14	Bz	**4n**	Bz	**5n**	95
15	TBDMS	**4o**	TBDMS	**5o**	85, 87[b]
16	TBDPS	**4p**	TBDPS	**5p**	80
17	MEM	**4q**	MEM	**5q**	80

[a] Conditions: imidate **2**, $Sc(OTf)_3$ (2 mol%), CH_2Cl_2, 0 °C to rt, 15 min.
[b] Yields under basic conditions: bromide **3**, NaH, THF, rt, 2–5 h.

Table 2. Removal of TIX group under various conditions



5a **4a**

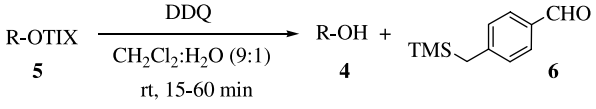
Entry	Reagent	Solvent/temp (°C)	Time (h)	Product	Isolated yield (%)
1	TFA (20 equiv)	CH_2Cl_2/0	0.25	**4a**	52
2	*n*-BU_4NF	THF/rt	0.5	 **4a′**	94
3	CsF	DMF/90[a]	2.5	 **4a′**	88
4	HF-pyridine	THF/rt	4	No reaction	—
5	$BF_3 \cdot Et_2O$	CH_2Cl_2/rt	2	No reaction	—
6	$ZnCl_2$	CH_2Cl_2/rt	2	No reaction	—
7	$MgBr_2$–Et_2O, Me_2S	CH_2Cl_2/rt	3	No reaction	—
8	CAN	THF–H_2O (9:1)/rt	0.5	**4a**	62
9	DDQ	CH_2Cl_2–H_2O (9:1)/rt	0.25	**4a**	91

[a] No reaction at rt.

a mild Lewis acid such as scandium triflate could be usefully employed instead to furnish the protected compound **5** in good to excellent yields. Since acid sensitive groups are unstable under the above reaction conditions for the protection of alcohols, we have also prepared the bromide **3** and used it to protect the hydroxyl group as the TIX ether **5** under basic conditions using NaH (Scheme 1).

To check for generality and functional group compatibility, the protection reaction was performed on a variety of alcohols, for example, 1, 2, 3°, benzylic, allylic and anomeric, bearing functionalities such as a β-keto group, an enone, olefin, acetylenic unit, or a variety of other protecting groups. To examine the issue of the chemoselectivity of these protection conditions, 1,6-hexanediol was differentially protected on one side with TBDMS, TBDPS, SEM, benzyl, PMB, ester, etc., while the remaining hydroxyl group was subjected to the protection protocol.

Table 3. Removal of TIX group using DDQ[a]



Entry	TIX ether	Alcohol	Isolated yield (%)
1	**5a**	**4a**	91
2	**5b**	**4b**	82
3	**5c**	**4c**	74
4	**5d**	**4d**	84
5	**5e**	**4e**	71
6	**5f**	**4f**	81
7	**5g**	**4g**	83
8	**5h**	**4h**	87
9	**5i**	**4i**	92
10	**5j**	**4j**	93
11	**5l**	**4l**	90
12	**5m**	**4m**	89
13	**5n**	**4n**	92
14	**5o**	**4o**	93
15	**5p**	**4p**	91
16	**5q**	**4q**	88

[a] Aldehyde **6** could be isolated in each case.

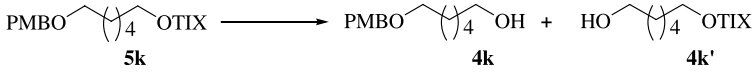
The TIX group was installed without generally affecting the other protecting groups (Table 1).

After developing the new protecting group, its removal was investigated. Accordingly, 3-phenyl-1-propanol TIX ether **5a** was initially treated with TFA leading to the formation of the deprotected alcohol **4a** in low yields. Furthermore, removal of contaminants was found to be quite difficult. Among the by-products were high-R_f aromatic compounds that presumably resulted from facile polymerization of *p*-quinone dimethide (*p*-xylylene).[8] We also used certain fluoride reagents, Lewis acids and oxidizing agents, the results of which are summarized in Table 2. Among these, DDQ provided a mild and chemoselective oxidative cleavage of the TIX moiety in the presence of other functionalities and protecting groups. Entry 7 demonstrates that the deprotection of **5g** occurred with the retention of stereochemistry to produce the **4g** in 83% yield. This deprotection method resulted in high yields, adding an advantage to the use of this protecting group compared to its removal under acidic conditions (Table 3).

Since the cleavage of the TIX group is similar to the PMB group, we were interested in studying the stability of the TIX ether over the PMB ether (Table 4). We subjected **5k** to typical PMB ether deprotection conditions and observed that in most cases the TIX group was stable. Using $ZrCl_4$ in CH_3CN, the PMB group could be selectively removed in the presence of TIX in 95% yield. Furthermore, the TIX group in PMBO–$(CH_2)_6$–OTIX **5k** could be selectively cleaved with DDQ at −10 °C leaving the PMB in place, giving PMB–$(CH_2)_6$–OH **4k** in 74% yield. The TIX group is stable under commonly used basic conditions such as LDA and *n*-BuLi (Tables 2 and 4). As expected, cleavage of both PMB and TIX occurs under catalytic hydrogenation conditions.

Mechanistically, cleavage of the TIX group by DDQ is likely to be similar to that of the PMB group; for, in all the cases, we could isolate *p*-trimethylsilylmethyl benzaldehyde **6** as a by-product. As shown in Scheme 2, the silyl group enhances the rate of benzyl ether cleavage relative to a

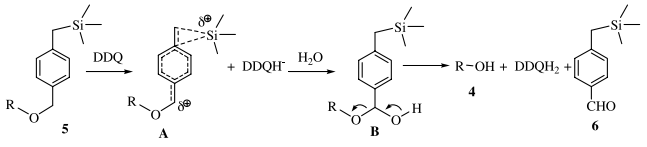
Table 4. Stability of the TIX ether over the PMB ether



Entry	Reagent	Solvent/temp (°C)	Time (h)	Product	Isolated yield (%)
1	5% TFA[4a]	CH_2Cl_2/0	0.5	**4k′**	80[a]
2	$LiBF_4$ (10 mol%)	CH_3CN/reflux	2	**4k′**	90
3	$ZrCl_4$ (20 mol%)[4b]	CH_3CN/rt	0.75	**4k′**	94
4	$CeCl_3 \cdot 7H_2O$, NaI[4c]	CH_3CN/reflux	15	**4k′**	76[a]
5	AcOH[4d]	—/90	0.5	**4k′**	78
6	LDA	THF/−30 to rt	5	No reaction	—
7	BuLi	THF/0 to rt	6	No reaction	—
8	DDQ	CH_2Cl_2–H_2O (9:1)/−10	0.25	**4k**	74
9	H_2–Pd/C	EtOH/rt	2	HO 4 OH	48

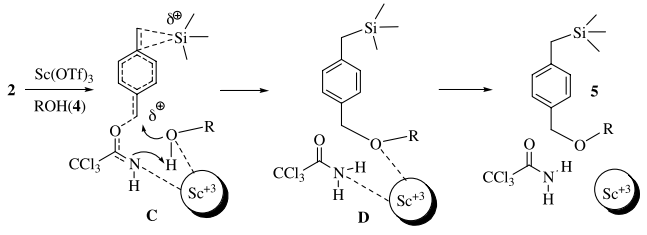
[a] 5–10% of **4k** also observed.

non-silylated version (i.e., the *p*-xylyl benzyl ether **5j** or simple benzyl ether **5i**, Table 1) by stabilization of **A** and/or by the transition state leading to **A**. The resultant intermediate **A** is then captured by water to furnish a hemiacetal **B** that undergoes reversal to aldehyde **6** and the desired deprotected alcohol **4**. The exact mechanism by which DDQ accepts the benzylic proton of **5**, leading to **A** is a matter of debate.[9]



Scheme 2.

To further assess the role of the silyl group in both protection and deprotection steps, we prepared a few representative *p*-methylbenzyl (xylyl) ethers. Surprisingly, while *p*-methylbenzyl alcohol readily underwent imidate formation, it was reluctant to undergo acid-catalyzed ether formation with comparable, or even marginally similar, efficacy compared to the TIX group. This fact implied that the protection step was promoted by the presence of the 1,6-silyl group and presumably by a mechanism reminiscent of the deprotection step outlined in Scheme 2. Thus, the fact that *p*-methylbenzyl ethers would not form in acceptable yields or at acceptable rates with either 0.02 or even 0.10 mol equiv of scandium triflate, while imidate **2** reacted rapidly and cleanly with 0.02 mol equiv (entry 10, Table 1), strongly implicated a silyl-assisted transition state for the protection step (Scheme 3).



Scheme 3.

Furthermore, DDQ was quite selective for the rapid removal of the TIX group in the presence of a *p*-methylbenzyl group as had been the case for the benzyl ether (entries 8–10 in Table 3).

3. Conclusion

We expect that the TIX group will prove to be a new 'PMB-like' versatile protecting group for hydroxyl functions in natural product synthesis and carbohydrate chemistry. It can be introduced under both acidic and basic reaction conditions and removed with DDQ, even in the presence of other commonly used protecting groups. The stability of the TIX group towards acidic as well as basic conditions is an added advantage.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere, unless otherwise stated. Thin layer chromatography (TLC) was performed on precoated silica gel G and GP Uniplates. The plates were visualized with a 254-nm UV light, iodine chamber, or charring with acid. Flash chromatography was carried out on silica gel 60 (particle size 32–63 μm, pore size 60 Å). ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz, respectively. The chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane, and *J*-values are in Hz. IR spectra were recorded on FT-IR spectrometer on a germanium crystal plate as neat solids or liquids. The high-resolution mass spectra (HRMS) were recorded on a Waters/Micromass Q-TOF Micro mass spectrometer with ESI lock spray source. Dry dichloromethane was prepared by distilling it over calcium hydride. Commercially available polystyrene-bound 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PS-TBD), trichloroacetonitrile and scandium (III) triflate were used directly without further purification. The trimethylsilyl alcohol **1** was prepared in two steps starting from the commercially available 4-bromobenzyl bromide using the literature procedure.[7]

4.2. General procedure for the TIX protection of the alcohols

PS-TBD (250 mg/mmol of **1**) was suspended in dry dichloromethane (5 mL/mmol of **1**) under argon at 0 °C, to which silyl alcohol **1** (1 mol equiv) was added. After stirring for 5 min at 0 °C, trichloroacetonitrile (1 mol equiv) was added. The reaction mixture was brought to room temperature and stirred for 15 min. The organic solution was separated from the polymer beads, and the clear dichloromethane solution of **2** was then cooled to 0 °C. One molar equivalent of a representative alcohol **4** was added followed by scandium triflate (0.02 mol equiv). The reaction mixture was stirred at room temperature for 15 min and diluted with dichloromethane (15 mL/mmol). The organic layer was washed with water and brine, dried (anhydrous Na_2SO_4), and concentrated. Simple purification was accomplished by flash column chromatography over silica gel using EtOAc/hexanes, providing the TIX ethers **5** in good yields (Table 1).

4.2.1. 4-[(Trimethylsilyl)methyl]benzyl 2,2,2-trichloroethanimidoate (2). Colorless oil which upon standing at room temperature to give colorless crystals, mp 32–35 °C; ^{1}H NMR ($CDCl_3$): δ 8.41 (bs, 1H), 7.32 (d, 2H, J=7.9 Hz), 7.05 (d, 2H, J=7.9 Hz), 5.32 (s, 2H), 2.13 (s, 2H), 0.04 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 162.7, 140.9, 130.9, 129.2, 128.1 (2C), 127.9 (2C), 71.0, 27.0, −1.9 (3C); IR (neat): 645, 841, 1074, 1294, 1662, 2953 cm^{-1}.

4.2.2. Trimethyl{4-[(3-phenylpropoxy)methyl]benzyl}silane (5a). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.32–7.21 (m, 7H), 7.01 (d, J=7.6 Hz, 2H), 4.47 (s, 2H), 3.51 (t, J=6 Hz, 11.6 Hz, 2H), 2.74 (t, J=7.6, 15.2 Hz, 2H), 2.10 (s, 2H), 1.98–1.94 (m, 2H), 0.02 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 142.3, 140.1, 134.2, 128.7 (2C), 128.5 (2C), 128.3 (2C), 128.1 (2C), 126.0, 73.2, 69.6, 32.7, 31.6, 27.0, −1.66 (3C); IR (neat): 851, 1099, 1246, 2921, 2951 cm^{-1}; HRMS (ESI): calcd for $C_{20}H_{28}OSi$, 335.1801 $(M+Na)^+$, found 335.1803.

4.2.3. Trimethyl{4-[(1-phenylethoxy)methyl]benzyl}silane (5b). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.38 (d, 2H), 7.30–7.23 (m, 3H), 7.16 (d, 2H, J=7.6 Hz), 6.97 (d, 2H, J=7.6 Hz), 4.51 (m, 1H), 4.40 (d, 1H, J=11.4 Hz), 4.25 (d, 1H, J=11.6 Hz), 2.07 (s, 2H), 1.48 (d, 3H, J=6.4 Hz), −0.006 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 144.0, 139.8, 133.9, 128.8 (2C), 128.1 (2C); 127.9 (2C); 127.5, 126.5 (2C), 77.2, 70.5, 26.9, 24.4, −1.8 (3C); IR (neat): 760, 845, 1107, 1246, 1511, 2889 cm^{-1}.

4.2.4. Trimethyl(4-{[(1-methylprop-2-yn-1-yl)oxy]methyl}benzyl)silane (5c). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.24 (d, 2H, J=7.6 Hz), 7.01 (d, 2H, J=7.6 Hz), 4.76 (d, 1H, J=11.2 Hz), 4.47 (d, 1H, J=11.2 Hz), 4.25–4.22 (m, 1H), 2.48 (s, 1H), 2.10 (s, 2H), 1.93 (d, 3H, J=6.8 Hz), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 140.1, 133.0, 128.1 (2C), 127.9 (2C), 83.7, 73.0, 70.4, 63.9, 26.7, 22.0, −2.0 (3C); IR (neat): 850, 1103, 1250, 1516, 2962, 3294 cm^{-1}; HRMS (ESI): calcd for $C_{15}H_{22}OSi$, 269.1333 $(M+Na)^+$, found 269.1344.

4.2.5. {4-[(Cyclohex-2-en-1-yloxy)methyl]benzyl}(trimethyl)silane (5d). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.19 (d, J=7.6 Hz, 2H), 6.95 (d, J=8 Hz, 2H), 5.86–5.78 (m, 2H), 4.51 (dd, J=11.6 Hz, 2H), 3.94 (bs, 1H), 2.05 (s, 2H), 1.96–1.72 (m, 6H), 0.03 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 140.0, 134.6, 131.3 (2C), 128.2 (2C), 128 (2C), 72.3, 70.3, 28.6, 27.0, 25.5, 19.5, −1.7 (3C); IR (neat): 845, 1076, 1246, 1504, 2951 cm^{-1}; HRMS (ESI): calcd for $C_{17}H_{26}OSi$, 297.1645 $(M+Na)^+$, found 297.1647.

4.2.6. Trimethyl(4-{[(1-methylcyclohexyl)oxy]methyl}benzyl)silane (5e). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.20 (d, J=7.6 Hz, 2H), 6.95 (d, J=7.6 Hz, 2H), 4.35 (s, 2H), 2.05 (s, 2H), 1.83–1.78 (m, 2H), 1.68–1.62 (m, 2H), 1.46–1.25 (m, 6H), 1.22 (s, 3H), −0.02 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 139.4, 135.6, 128.2 (2C), 127.5 (2C), 74.0, 62.9, 36.8 (2C), 26.9, 26.0, 25.1, 22.5 (2C), −1.7 (3C); IR (neat): 847, 1068, 1123, 1245, 2856, 2921 cm^{-1}; HRMS (ESI): calcd for $C_{18}H_{30}OSi$, 313.1964 $(M+Na)^+$, found 313.1959.

4.2.7. 3-Ethyl-4,4-dimethyl-5-({4-[(trimethylsilyl)methyl]benzyl}oxy)cyclohex-2-en-1-one (5f). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.15 (d, J=8 Hz, 2H), 6.95 (d, J=7.6 Hz, 2H), 5.83 (s, 1H), 4.59 (d, J=11.6 Hz, 1H), 4.36 (d, J=11.2 Hz, 1H), 3.54 (dd, J=4, 8 Hz, 1H), 2.73 (dd, J=4, 16 Hz, 1H), 2.57 (dd, J=8.8, 16.8 Hz, 1H), 2.26 (distorted doublet J=6.8 Hz, 2H), 2.06 (s, 2H), 1.16 (d, J=4.8 Hz, 6H), 1.08 (t, J=7.2, 14.4 Hz, 3H), −0.02 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 197.9, 172.8, 140.3, 133.7, 128.2 (2C), 128.1 (2C), 123.7, 81.3, 71.6, 39.1, 29.9, 27.0, 25.0, 24.6, 21.5, 11.8, −1.70 (3C); IR (neat): 850, 1075, 1245, 1664, 2921, 2951 cm^{-1}; HRMS (ESI): calcd for $C_{21}H_{32}O_2Si$, 345.2250 $(M+H)^+$, found 345.2241.

4.2.8. (−)-4*S*-5,5-Dimethyl-4-({4-[(trimethylsilyl)methyl]benzyl}oxy)octane-2,6-dione (5g). Colorless oil; $[\alpha]_D^{25}$ = −38.76 (c=0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.08 (d, J=8 Hz, 2H), 6.93 (d, J=8 Hz, 2H), 4.42 (dd, J=11.2, 29.6 Hz, 2H), 4.25 (dd, J=3.2, 7.2 Hz, 1H), 2.62 (dd, J=7.6, 17.2 Hz, 1H), 2.54–2.46 (m, 3H), 2.14 (s, 3H), 2.04 (s, 2H), 1.15 (s, 3H), 1.10 (s, 3H), 0.98 (t, J=6.8, 14, 7.2 Hz, 3H), −0.03 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 215.6, 207.5, 140.1, 134.1, 128.1 (2C), 127.8 (2C), 79.7, 73.8, 52.2, 45.9, 31.9, 27.0, 23.9, 21.2, 21.1, 8.07, −1.7 (3C); IR (neat): 847, 1075, 1245, 1705, 2951 cm^{-1}; HRMS (ESI): calcd for $C_{21}H_{34}O_3Si$, 385.2175 $(M+Na)^+$, found 385.2180.

4.2.9. 4-[(Trimethylsilyl)methyl]benzyl 2,3,4,6-tetra-*O*-benzylhexopyranoside (5h). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.31–7.19 (m, 20H), 7.14 (d, J=7.6 Hz, 2H), 6.98 (d, J=7.6 Hz, 2H), 5.03–4.81 (m, 4H), 4.73–4.46 (m, 6H), 4.05 (t, J=9.2, 18.4 Hz, 1H), 3.83–3.56 (m, 6H), 2.1 (s, 2H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 140.4, 139.0, 138.4, 138.3, 138.1, 132.6, 128.8 (2C), 128.5 (8C), 128.1 (4C), 128.05 (4C), 128.0 (4C), 127.8, 127.7, 95.3, 82.3, 79.9, 77.8, 75.8, 75.1, 73.5, 72.8, 70.4, 69.2, 68.5, 26.9, −1.7 (3C); IR (neat): 702, 845, 1078, 1245, 1458, 2892 cm^{-1}; HRMS (ESI): calcd for $C_{45}H_{52}O_6Si$, 739.3431 $(M+Na)^+$, found 739.3394.

4.2.10. [4-({[6-(Benzyloxy)hexyl]oxy}methyl)benzyl](trimethyl)silane (5i). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.36–7.25 (m, 5H), 7.20 (d, J=8 Hz, 2H), 6.98 (d, J=8 Hz, 2H), 4.52 (s, 2H), 4.45 (s, 2H), 3.50–3.45 (m, 4H), 2.08 (s, 2H),

1.66–1.62 (m, 4H), 1.42–1.39 (m, 4H), −0.05 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 140.0, 138.9, 134.8, 128.6 (2C), 128.3, 128.2, 128.0 (2C), 127.9 (2C), 127.7, 73.1 (2C), 70.6, 70.5, 30.0 (2C), 27.0, 26.3 (2C), −1.7 (3C); IR (neat): 847, 1099, 1242, 2853, 2931 cm^{-1}; HRMS (ESI): calcd for $C_{24}H_{36}O_2Si$, 407.2382 $(M+Na)^+$, found 407.2371.

4.2.11. Trimethyl{4-[({6-[(4-methylbenzyl)oxy]hexyl}-oxy)methyl]benzyl}silane (5j). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.23 (d, 2H, J=7.6 Hz), 7.18 (d, 2H, J=7.6 Hz), 7.15 (d, 2H, J=7.6 Hz), 6.97 (d, 2H, J=7.6 Hz), 4.46 (s, 2H), 4.44 (s, 2H), 3.45 (dd, 4H, J=6.4 Hz), 2.34 (s, 3H), 2.07 (s, 2H), 1.60 (m, 4H), 1.38 (m, 4H), −0.02 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 139.8, 137.1, 135.7, 134.1, 129.0 (2C), 128.0 (2C), 127.8 (2C), 127.8 (2C), 72.9, 72.8, 70.3, 70.2, 29.7, 27.1, 26.8, 26.1 (2C), 21.2, −1.8 (3C); IR (neat): 694, 857, 1098, 1245, 1507, 2949 cm^{-1}; HRMS (ESI): calcd for $C_{25}H_{38}O_2Si$, 437.2278 $(M+K)^+$, found 437.2263.

4.2.12. {4-[({6-[(4-Methoxybenzyl)oxy]hexyl}oxy)-methyl]benzyl}(trimethyl)silane (5k). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.29 (d, 2H, J=8.4 Hz), 7.21 (d, 2H, J=7.6 Hz), 6.99 (d, 2H, J=7.6 Hz), 6.90 (d, 2H, J=8.4 Hz), 4.46 (s, 4H), 3.83 (s, 3H), 3.46 (dd, 4H, J=6.4, 13.2 Hz), 2.09 (s, 2H), 1.68–1.60 (m, 4H), 1.42–135 (m, 4H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 159.1, 139.8, 134.0, 130.8, 129.2 (2C), 127.9 (2C), 127.7 (2C), 113.7 (2C), 72.8, 72.5, 70.3, 70.1, 55.3, 29.7 (2C), 26.8, 26.1 (2C), −1.9 (3C); IR (neat): 845, 1099, 1246, 1511, 2856, 2933 cm^{-1}; HRMS (ESI): calcd for $C_{25}H_{38}O_3Si$, 437.2488 $(M+Na)^+$, found 437.2470.

4.2.13. 2,2-Dimethyl-15-{4-[(trimethylsilyl)methyl]-phenyl}-5,7,14-trioxa-2-silapentadecane (5l). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.17 (d, J=7.6 Hz, 2H), 6.95 (d, J=7.6 Hz, 2H), 4.65 (s, 2H), 4.42 (s, 2H), 3.60 (t, J=8.4, 16.8 Hz, 2H), 3.52 (t, J=6.8, 13.2 Hz, 2H), 3.45 (t, J=6.8, 13.2 Hz, 2H), 2.06 (s, 2H), 1.61–1.56 (m, 4H), 1.38–1.25 (m, 4H), 0.93 (t, J=8.4, 16.8 Hz, 2H), 0.01 (s, 9H), −0.02 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 140.0, 134.2, 128.2 (2C), 128.0 (2C), 95.0, 73.1, 70.5, 68.0, 65.1, 29.9 (2C), 27.0, 26.3, 26.2, 18.3, −1.2 (3C), −1.7 (3C); IR (neat): 854, 1061, 1106, 12.52, 2863, 2945 cm^{-1}; HRMS (ESI): calcd for $C_{23}H_{44}O_3Si_2$, 447.2727 $(M+Na)^+$, found 447.2726.

4.2.14. 6-({4-[(Trimethylsilyl)methyl]benzyl}oxy)hexyl acetate (5m). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.20 (d, 2H, J=7.6 Hz), 6.99 (d, 2H, J=7.6 Hz), 4.46 (s, 2H), 4.07 (t, 2H, J=6.4 Hz), 3.48 (t, 2H, J=6.4 Hz), 2.09 (s, 2H), 2.06 (s, 3H), 1.70–1.62 (m, 4H), 1.46–1.36 (m, 4H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 171.2, 139.8, 134.0, 128.0 (2C), 127.7 (2C); 72.9, 70.1, 64.5, 29.6, 28.6, 26.8, 25.9, 25.8, 21.0, −1.9 (3C); IR (neat): 854, 1103, 1246, 1740, 2860, 2950 cm^{-1}; HRMS (ESI): calcd for $C_{19}H_{32}O_3Si$, 359.2018 $(M+Na)^+$, found 359.2027.

4.2.15. 6-({4-[(Trimethylsilyl)methyl]benzyl}oxy)hexyl benzoate (5n). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 8.07 (d, 2H, J=7.2 Hz), 7.58 (t, 1H, J=7.6 Hz), 7.46 (t, 2H, J=7.2 Hz), 7.20 (d, 2H, J=7.6 Hz), 6.99 (d, 2H, J=7.6 Hz), 4.47 (s, 2H), 4.34 (t, 2H, J=6.4 Hz), 3.50 (t, 2H, J=6.4 Hz), 2.09 (s, 2H), 1.83–1.76 (m, 2H), 1.70–1.62 (m, 2H), 1.54–1.42 (m, 4H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 166.7, 139.8, 134.0, 132.8, 130.5, 129.6 (2C), 128.5, 128.3, 128.0 (2C), 127.8 (2C), 72.9, 70.2, 65.0, 29.7, 28.7, 26.8, 26.0 (2C), −1.9 (3C); IR (neat): 711, 854, 1107, 1275, 1720, 2856, 2946 cm^{-1}; HRMS (ESI): calcd for $C_{24}H_{34}O_3Si$, 421.2175 $(M+Na)^+$, found 421.2184.

4.2.16. *tert*-Butyl(dimethyl){[6-({4-[(trimethylsilyl)-methyl]benzyl}oxy)hexyl]oxy}silane (5o). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.17 (d, 2H, J=7.6 Hz), 6.96 (d, 2H, J=7.6 Hz), 4.43 (s, 2H), 3.60 (t, 2H, J=6.4 Hz), 3.45 (t, 2H, J=6.4 Hz), 2.07 (s, 2H), 1.3–1.58 (m, 2H), 1.55–1.50 (m, 2H), 1.40–1.31 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H), −0.02 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 140.0, 134.3, 128.2 (2C), 128.0 (2C), 73.1, 70.5, 63.4, 33.1, 30.0, 27.0, 26.2 (3C), 25.9, 25.8, 18.6, −1.7 (3C), −5.0 (2C); IR (neat): 776, 858, 1099, 1250, 2856, 2933 cm^{-1}; HRMS (ESI): calcd for $C_{23}H_{44}O_2Si_2$, 447.2517 $(M+Na)^+$, found 447.2513.

4.2.17. *tert*-Butyl(diphenyl){[6-({4-[(trimethylsilyl)-methyl]benzyl}oxy)hexyl]oxy}silane (5p). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.70 (m, 4H), 7.41 (m, 6H), 7.21 (d, 2H, J=7.6 Hz), 6.99 (d, 2H, J=8.4 Hz), 4.46 (s, 2H), 3.68 (t, 2H, J=6.4 Hz), 3.47 (t, 2H, J=6.4 Hz), 2.09 (s, 2H), 1.67–1.57 (m, 4H), 1.44–1.30 (m, 4H), 1.07 (s, 9H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 140.0, 135.8 (4C), 134.5 (4C), 134.4 (2C), 129.8 (2C), 128.3 (2C), 128.0, 127.9 (2C), 73.2, 70.6, 64.2, 32.8, 30.1, 27.2 (3C), 27.1, 26.3, 26.0, 19.5. −1.6 (3C).; IR (neat): 702, 845, 1107, 1246, 1511, 2852, 2933 cm^{-1}; HRMS (ESI): calcd for $C_{33}H_{48}O_2Si_2$, 571.2830 $(M+K)^+$, found 571.2850.

4.2.18. Trimethyl[4-(2,9,11,14-tetraoxapentadec-1-yl)-benzyl]silane (5q). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.17 (d, 2H, J=7.6 Hz), 6.96 (d, 2H, J=7.6 Hz), 4.70 (s, 2H), 4.42 (s, 2H), 3.68 (t, 2H, J=6.4 Hz), 3.56–3.51 (m, 4H), 3.45 (t, 2H, J=6.4 Hz), 2.06 (s, 2H), 1.61–1.57 (m, 4H), 1.41–1.34 (m, 4H), −0.02 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 139.8, 134.0, 128.0 (2C), 127.7 (2C), 95.5, 72.9, 71.8, 70.3, 67.9, 66.7, 59.0, 29.7, 29.6, 26.8, 26.1, 26.0, −1.9 (3C); IR (neat): 853, 1045, 1106, 1249, 1511, 2933 cm^{-1}; HRMS (ESI): calcd for $C_{21}H_{38}O_4Si$, 421.2176 $(M+K)^+$, found 421.2159.

4.3. General procedure for the deprotection of TIX ethers

The TIX ether (1 mol equiv) was taken in dichloromethane: water (9:1 or 5 mL/mmol). To this well stirred solution was added DDQ (1 mol equiv) at room temperature (generally 15–60 min). After completion of the reaction (as monitored by TLC for disappearance of starting material), the reaction mixture was filtered, and the filtrate was washed with dichloromethane (10 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, brine, dried (anhydrous Na_2SO_4), filtered and concentrated. Purification of the residue was readily achieved by flash column chromatography (silica gel 60, EtOAc/hexanes) affording the alcohols in excellent yields (Table 3).

4.3.1. 1-Methyl-4-[(3-phenylpropoxy)methyl]benzene (4a′). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.36–7.22 (m, 9H), 4.54 (s, 2H), 3.54 (t, 2H, J=6.4 Hz), 2.78 (t, 2H, J=

7.2 Hz); 2.42 (s, 3H); 2.03–1.96 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 142.1, 137.3, 135.6, 129.1 (2C), 128.6 (2C), 128.4 (2C), 127.9 (2C), 125.8, 72.9, 69.4, 32.5, 31.5, 21.3; IR (neat): 702, 845, 1107, 1246, 1511, 2852, 2933 cm^{-1}; HRMS (ESI): calcd for $C_{17}H_{20}O$, 279.4384 $(M+K)^+$, found 279.4388.

4.3.2. 6-[(4-Methylbenzyl)oxy]hexan-1-ol (4j). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.22 (d, 2H, J=7.6 Hz), 7.15 (d, 2H, J=7.6 Hz), 4.45 (s, 2H), 3.62 (t, 2H, J=6.4 Hz), 3.44 (t, 2H, J=6.4 Hz), 2.34 (s, 3H), 2.07 (s, 2H), 1.63–1.54 (m, 4H), 1.43–1.37 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 137.2, 135.4, 129.1 (2C), 127.8 (2C), 72.7, 70.2, 62.6, 32.6, 29.7, 26.0, 25.6, 21.2; IR (neat): 681, 804, 1074, 1262, 2945, 3374 cm^{-1}.

4.3.3. 6-({4-[(Trimethylsilyl)methyl]benzyl}oxy)hexan-1-ol (4k′). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.19 (d, 2H, J=7.6 Hz), 6.98 (d, 2H, J=7.6 Hz), 4.46 (s, 2H), 3.65 (t, 2H, J=6.4 Hz), 3.48 (t, 2H, J=6.4 Hz), 2.08 (s, 2H), 1.63–1.58 (m, 4H), 1.46–1.37 (m, 4H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 139.8, 133.7, 127.9 (2C), 127.7 (2C), 72.8, 70.1, 62.6, 32.5, 29.5, 25.8, 25.5, 25.4, −2.0 (3C); IR (neat): 858, 1107, 1246, 1687, 2856, 2938, 3370 cm^{-1}; HRMS (ESI): calcd for $C_{17}H_{30}O_2Si$, 333.1652 $(M+K)^+$, found 333.1659.

4.3.4. 4a to 4e,[10] 4f and 4g,[11] 4h,[10] 4i,[12] 4k,[13] 4l,[14] 4m,[15] 4n,[16] 4o and 4p,[17] 4q[18] and 6.[19] ^{1}H NMR, IR and mass spectral data of these known compounds were identical with those of authentic samples.

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