A Highly Efficient and Useful Synthetic Protocol for the Cleavage of *tert*-Butyldimethylsilyl (TBS) Ethers Using a Catalytic Amount of Acetyl Chloride in Dry Methanol

Abu T. Khan,* Ejabul Mondal

Department of Chemistry, Indian Institute of Technology, North Guwahati, Guwahati-781039, Assam, India
Fax +91(361)2690762; E-mail: atk@postmark.net

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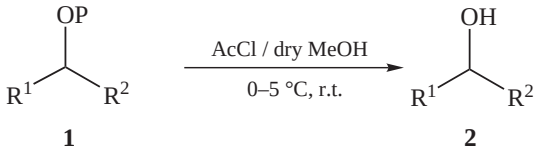
Abstract: A wide variety of *tert*-butyldimethylsilyl (TBS) ethers as well as *tert*-butyldiphenylsilyl (TBDPS) ethers **1** can be easily deprotected to the corresponding parent hydroxyl compounds **2** by employing catalytic amounts of acetyl chloride in dry MeOH at 0 °C to room temperature in good yields. Some of the major advantages are mild conditions, high efficiency, high selectivity, high yields, easy operation, and also compatibility with other protecting groups. Furthermore, no acetylation nor chlorination takes place under the experimental conditions.

Key words: deprotection, *tert*-butyldimethylsilyl (TBS) ethers, *tert*-butyldiphenylsilyl (TBDPS) ethers, acetyl chloride

Protection-deprotection strategy is a very common tactics in polyfunctional natural product and non-natural product syntheses. As far as hydroxyl group protection is concerned, silyl ethers play a pivotal role in carbohydrate and nucleoside chemistry due to their easy installation and inherent stability under basic and mild acidic conditions, with *tert*-butyldimethylsilyl (TBS) ether[1] and *tert*-butyldiphenylsilyl (TBDPS) ether[2] being two of the most important examples. Though a wide variety of reagents have been developed[3] for their removal, still there is a need to develop better alternatives, which might work under mild conditions. For this purpose, a variety of fluoro compounds[4] have been developed over the years in order to facilitate such deprotection. Similarly, deprotection of TBS ethers are also known using various bromo compounds.[5] Likewise, some methods have also been devised by employing chloro compounds for their cleavage such as cerium(III) chloride in combination with sodium iodide,[6a] cerium(III) chloride,[6b] LiCl in DMF,[6c] and TMSCl in H_2O.[6d] Moreover, a few methods are also reported recently by using TMSOTf,[7a] $Sn(OTf)_3$,[7b] I_2,[7c] Oxone in aqueous methanol,[7d] and DDQ.[7e] Unfortunately, some of the methods mentioned as above have some drawbacks such as harsh reaction conditions, failure to deprotect aryl *tert*-butyldimethylsilyl ethers, long reaction times, involvement of expensive reagents, incompatibility with other protecting groups such as a thio group at the anomeric position of the carbohydrate compounds,[5f] over oxidation,[7e] unwanted product such as acetate instead of alcohol,[5c] and requirement a large excess of reagents.[6a–c] Consequently, what is needed is a methodology, which might work under mild conditions by involving economically cheaper reagents. During the development of new methodologies for protection and deprotection of organic functional groups particularly carbonyl group as dithioacetals and oxathioacetals,[8] we have observed that acetyl chloride in methanol can be used as a source for generating dry hydrochloric acid in situ, which can be utilized for protection of various carbonyl compounds as dithioacetals or dithioketals.[9] This result prompted us to look whether acetyl chloride in combination with methanol can be used also for deprotection of *tert*-butyldimethylsilyl (TBS) ethers or not. In this communication, we would like to report our successful results for deprotection of various *tert*-butyldimethylsilyl (TBS) ethers and *tert*-butyldiphenylsilyl (TBDPS) ethers by using catalytic amounts of acetyl chloride in dry methanol (Scheme 1).

To verify our assumption, we prepared a wide variety of *tert*-butyldimethylsilyl (TBS) ethers as well as *tert*-butyldiphenyl-silyl (TBDPS) ethers by following the reported procedure.[1,2] First, we attempted the reaction of *tert*-butyldimethylsilyl ether of 1-octanol (**1a**) with 0.15 equivalents amounts of acetyl chloride in dry methanol at 0–5 °C. After 5 min, usual work-up of the reaction mixture provided the corresponding desired alcohol **2a** in 98% yield. Similarly, *tert*-butyldimethylsilyl ether of 1-dodecanol (**1b**) was deprotected smoothly to the corresponding alcohols **2b** by following identical reaction conditions.[10] It is important to mention that no acetylation occurs during the experimental conditions. Next, we observed that various *tert*-butyldiphenylsilyl ethers **1c**–**e** can be deprotected easily to the corresponding alcohols **2c**–**e** in very good yields, on treatment with 0.15 equivalents amount of acetyl chloride in methanol on stirring at room temperature. We have noticed that it requires relatively longer reaction times for deprotection of TBDPS ethers than TBS ethers.



1 **2**

R^1 = aryl / alkyl / sugar residue / nucleoside
R^2 = H / alkyl; P = TBS / TBDPS

Scheme 1

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Art Id.1437-2096,E;2003,0,MM,0694,0698,ftx,en;G00703ST.pdf.

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Table 1 Deprotection of Various TBS Ethers (**1**) to the Parent Hydroxyl Compounds (**2**) Using Catalytic Amounts of CH_3COCl in Dry MeOH

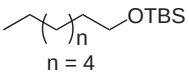
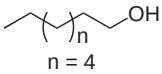
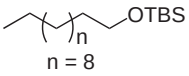
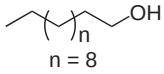
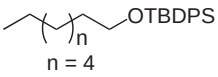
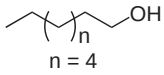
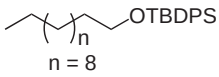
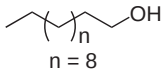
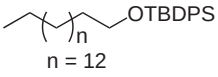
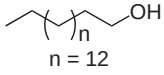
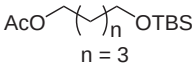
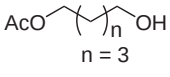
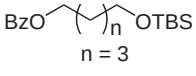
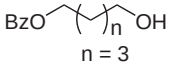
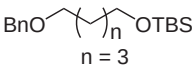
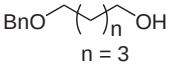
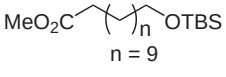
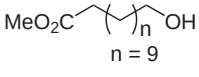
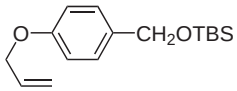
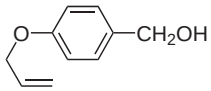
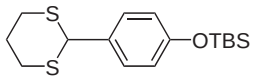
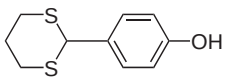
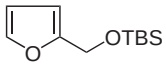
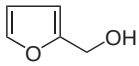
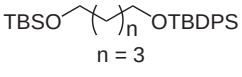
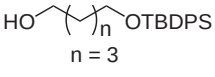
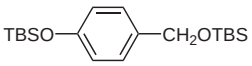
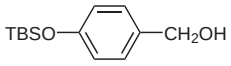
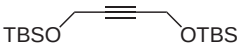
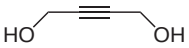
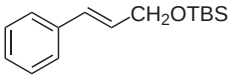
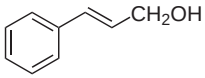
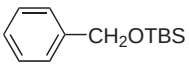
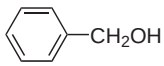
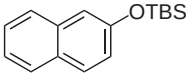
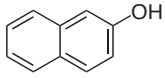
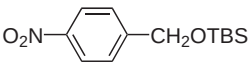
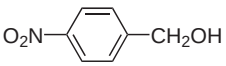
Entry	Substrate	Time min (h)	Product[a]	Yield[b] (%)
a		5		98
b		7		97
c		(2.0)		97
d		(4.0)		95
e		(2.3)		96
f		2		80
g		2		82
h		5		87
i		3		98
j		8		96
k		(5)		95
l		35		85
m		4		86
n		45		80
o		7		87
p		10		94
q		(5)		93
r		15		89
s		5		85

Table 1 Deprotection of Various TBS Ethers (**1**) to the Parent Hydroxyl Compounds (**2**) Using Catalytic Amounts of CH_3COCl in Dry MeOH (continued)

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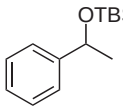
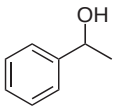
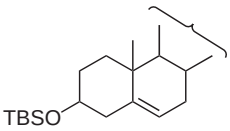
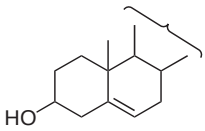
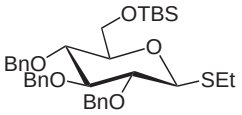
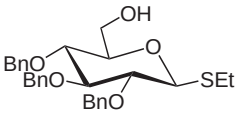
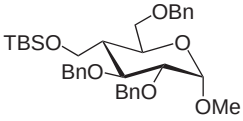
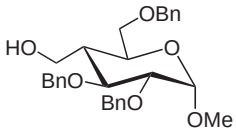
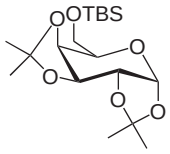
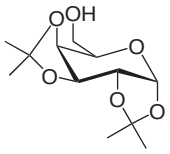
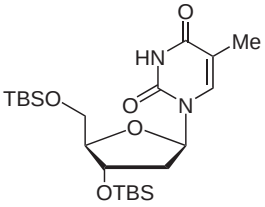
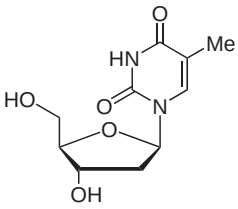
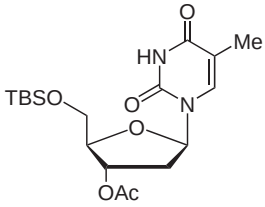
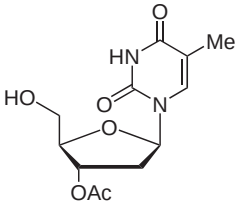
t		35		82
u		(4.0)		90
v		8		88
w		40		90
x		40		87
y		(2.5)		90
z		(1)		95

[a] All final products were characterized by IR, ^1H NMR, ^{13}C NMR and elemental analysis.
[b] Isolated yield.

Various TBS ethers **1f–l** were transformed smoothly into the corresponding alcohols **2f–l** in good yields under identical reaction conditions. These results show that our protocol can be employed in the presence of other protecting groups such as acetyl, benzoyl, benzyl, ester, allyl and thioketal. Remarkably, a highly acid sensitive group such as ester functionality (for instance **1i**) remains unaffected under the reaction conditions. Moreover, a highly acid sensitive substrate **1l** can also be deprotected into the corresponding hydroxy compound **2l**. It is also important to highlight that a TBS ether containing a thioketal group (entry **1k**) might be difficult to cleave by other reported methods.[6d,9] Interestingly, our protocol can be further extended for chemoselective deprotection of TBS ethers (entry **1m** and **1n**) in the presence of TBDPS ether and aryl TBS ether due to reactivity difference. By following the above procedure, TBS ethers **1o** and **1p** were also deprotected into the corresponding compound **2o** and **2p** in good yield without chlorination either at the double or triple bond. By following our methodology, various TBS ethers **1q–u** were transformed into the corresponding deprotected alcohols **2q–u** in good yields. The results are summarized in Table 1 and the structures of the deprotected products were confirmed by usual spectroscopic techniques and elemental analysis.[11] It is pertinent to mention that the deprotection of TBS ether **1u** to the corresponding alcohol **2u** required longer reaction times[5d] than our method.

Lastly, we had turned our attention to the deprotection of various TBS ethers of carbohydrates and nucleosides. The TBS ethers **1v**–**x** were converted into the respective parent hydroxy compounds **2v**–**x** in good yields under similar reaction conditions. Importantly, a thio group at the anomeric position is unaffected under the experimental conditions, whereas it is usually affected by the earlier reported procedure.[5f] It is also noteworthy to mention that OMe ether group at the anomeric position as well as highly acid sensitive isopropylidene group did also survive under the reaction conditions. Likewise, the silyl ethers of nucleosides **1y**–**z** were deprotected smoothly to the parent nucleosides in good yields. All these hydrolyzed products were characterized by ^{1}H NMR, ^{13}C NMR, elemental analyses and in full agreement with the expected products.

The formation of the product can be rationalized as follows. We believe that acetyl chloride reacts with methanol to generate dry hydrochloric acid, which reacts with silyl ether to provide the parent hydroxy compounds.

In summary, we have described a new, efficient, and regio- as well as chemoselective protocol for deprotection of TBS- and TBDPS ethers using a catalytic amount of acetyl chloride in dry methanol under very mild conditions. The salient features of the present method include: i) the ease of operations ii) high efficiency iii) mild conditions iv) chemoselectivity, which may be used extensively in organic synthesis. In addition, the selective deprotection of alkyl *tert*-butyldimethylsilyl ether can be possible in the presence of aryl-*tert*-butyldimethylsilyl ethers. Moreover, a wide variety of other protecting groups such as acetyl, benzyl, benzoyl, thioketals, esters and isopropylidene survived under the experimental conditions. A similar transformation might be possible by using other acid chlorides, which will be reported in due course.

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References

(1) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(2) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.

(3) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, **1999**, 127–144. (b) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429.

(4) (a) Kelly, D. R.; Roberts, S. M.; Newton, R. F. *Synth. Commun.* **1979**, *9*, 295. (b) Collington, E. W.; Finch, H.; Smith, I. J. *Tetrahedron Lett.* **1985**, *26*, 681. (c) Shimshock, S. J.; Watermire, R. E.; Deshong, P. *J. Am. Chem. Soc.* **1991**, *113*, 8791. (d) Zhang, W.; Robins, M. J. *Tetrahedron Lett.* **1992**, *33*, 1177. (e) Corey, E. J.; Yi, K. Y. *Tetrahedron Lett.* **1992**, *33*, 2289. (f) Ramasamy, K. S.; Averett, D. *Synlett* **1999**, 709. (g) Metcalf, B. W.; Burkhart, J. P.; Jund, K. *Tetrahedron Lett.* **1980**, *21*, 35. (h) Ranu, B. C.; Jana, U.; Majee, A. *Tetrahedron Lett.* **1999**, *40*, 1985.

(5) (a) Lee, A. S.; Yeh, H.; Shie, J. *Tetrahedron Lett.* **1998**, *39*, 5249. (b) Bajwa, J. S.; Vivelo, J.; Slade, J.; Repi, O.; Blacklock, T. *Tetrahedron Lett.* **2000**, *41*, 6021. (c) Oriyama, T.; Oda, M.; Gono, J.; Koga, G. *Tetrahedron Lett.* **1994**, *35*, 2027. (d) Gopinath, R.; Patel, B. K. *Org. Lett.* **2000**, *2*, 4177. (e) Barros, M. T.; Maycock, C. D.; Thomassigny, C. *Synlett* **2001**, 1146. (f) Kartha, K. P. R.; Field, R. A. *Synlett* **1999**, 311.

(6) (a) Bartoli, G.; Bosco, M.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Synlett* **1998**, 209. (b) Ankala, S. V.; Fenteany, G. *Tetrahedron Lett.* **2002**, *43*, 4729. (c) Farras, J.; Serra, C.; Vilarrasa, J. *Tetrahedron Lett.* **1998**, *39*, 327. (d) Grieco, P. A.; Markworth, C. J. *Tetrahedron Lett.* **1999**, *40*, 665.

(7) (a) Hunter, R.; Hinz, W.; Richards, P. *Tetrahedron Lett.* **1999**, *40*, 3643. (b) Oriyama, T.; Kobayashi, Y.; Noda, K. *Synlett* **1998**, 1047. (c) Lipshutz, B. H.; Keith, J. *Tetrahedron Lett.* **1998**, *39*, 2495. (d) Sabitha, G.; Syamala, M.; Yadav, J. S. *Org. Lett.* **1999**, *1*, 1701. (e) Paterson, I.; Cowden, C. J.; Rahn, V. S.; Woodrow, M. D. *Synlett* **1998**, 915.

(8) (a) Mondal, E.; Bose, G.; Khan, A. T. *Synlett* **2001**, 785. (b) Mondal, E.; Bose, G.; Sahu, P. R.; Khan, A. T. *Chem. Lett.* **2001**, 1158. (c) Khan, A. T.; Boruwa, J.; Mondal, E.; Bose, G. *Indian J. Chem, Sect. B* **2001**, *40*, 1039. (d) Mondal, E.; Sahu, P. R.; Bose, G.; Khan, A. T. *Tetrahedron Lett.* **2002**, *43*, 2843. (e) Mondal, E.; Sahu, P. R.; Khan, A. T. *Synlett* **2002**, 463. (f) Mondal, E.; Sahu, P. R.; Bose, G.; Khan, A. T. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1026. (g) Khan, A. T.; Mondal, E.; Sahu, P. R.; Islam, S. *Tetrahedron Lett.* **2003**, *44*, 919. (h) Khan, A. T.; Mondal, E.; Sahu, P. R. *Synlett* **2003**, 377.

(9) Khan, A. T.; Mondal, E. *unpublished results.*

(10) **A Typical Procedure for Deprotection:** To a stirred solution of silylated compound **1** (1 mmol) in dry MeOH (3 mL) was added AcCl (11 μL, 0.15 mmol) at ice-bath temperature. The reaction mixture was stirred at ice-bath temperature or r.t. depending upon the substrate (see Table 1). After completion of the reaction (monitored by TLC), CH_2Cl_2 was added (20 mL), the reaction mixture was neutralized with 10% $NaHCO_3$ (1 mL) and washed with H_2O (10 mL). Finally, the organic layer was dried (Na_2SO_4) and concentrated in vacuo to give a 'crude' residue, which was purified on silica gel column chromatography. The final desired products were obtained in good to excellent yields.

(11) **Spectroscopic data for compound 1i:** ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.01 [s, 6 H, $Si(CH_3)_2$], 0.85 [s, 9 H, $SiC(CH_3)_3$], 1.19–1.60 (m, 18 H, -CH_2), 2.25 (t, 2 H, *J* = 7.3 Hz, -C*H*$_2$CO$_2$CH$_3$), 3.55 (t, 2 H, *J* = 6.4 Hz, -C*H*$_2$OTBS), 3.62 (s, 3 H, CO_2CH_3). Anal. Calcd for $C_{19}H_{40}O_3Si$: C, 66.22; H, 11.70. Found: C, 66.01; H, 11.65. **For compound 2i:** ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.20–1.70 (m, 18 H, -CH_2-), 1.80 (br s, 1 H, OH, D_2O exchangeable), 2.30 (t, 2 H, *J* = 6.8 Hz, -C*H*$_2$CO$_2$CH$_3$), 3.63 (t, 2 H, *J* = 5.9 Hz, -C*H*$_2$OH), 3.67 (s, 3 H, CO_2CH_3). Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.78; H, 11.38. Found: C, 67.52; H, 11.26. **For compound 1v:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 [s, 3 H, $Si(CH_3)_2$], 0.02 [s, 3 H, $Si(CH_3)_2$], 0.85 [s, 9 H, $SiC(CH_3)_3$], 1.25 (t, 3 H, *J* = 7.3 Hz, SCH_2CH_3], 2.63–2.71 (m, 2 H, SC*H*$_2$CH$_3$), 3.21–3.24 (m, 1 H, H-5), 3.46 (t, 1 H, *J* = 9.0 Hz, H-3), 3.56 (t, 1 H, *J* = 9.3 Hz, H-2), 3.61 (t, 1 H, *J* = 9.0 Hz, H-4), 3.75 (dd, 1 H, *J* = 3.8 Hz, *J* = 11.2 Hz, H-6), 3.80 (dd, 1 H, *J* = 2.0 Hz, *J* = 11.7 Hz, H-6′), 4.38 (d, 1 H, *J* = 9.8 Hz, H-1), 4.62 (d, 1 H, *J* = 10.2 Hz, -OC*H*Ph),

4.68 (d, 1 H, *J* = 10.2 Hz, OC*H*Ph), 4.79 (dd, 2 H, *J* = 4.6 Hz, *J* = 10.7 Hz, OCH_2Ph), 4.85 (dd, 2 H, *J* = 4.0 Hz, *J* = 10.3 Hz, OCH_2Ph), 7.19–7.33 (m, 15 H, ArH). ^{13}C NMR: δ = –5.37, –5.04, 15.19, 18.30, 24.34, 25.89 (3 C), 62.30, 75.06, 75.46, 75.87, 77.68, 80.03, 81.83, 84.40, 86.62, 127.69, 127.81, 127.93, 128.00, 128.29, 128.38, 128.46, 138.09, 138.32, 138.52. Anal. Calcd for $C_{35}H_{48}O_5SSi$: C, 69.04; H, 7.94, S, 5.26. Found: C, 69.35; H, 7.85; S, 5.01. **For compound 2v:** ^1H NMR (400 MHz, $CDCl_3$): δ = 1.32 (t, 3 H, *J* = 7.3 Hz, SCH_2CH_3), 1.95 (br s, 1 H, OH, D_2O exchangeable), 2.71–2.80 (m, 2 H, SCH_2CH_3), 3.35–3.39 (m, 1 H, H-5), 3.41 (t, 1 H, *J* = 9.3 Hz, H-3), 3.58 (t, 1 H, *J* = 9.3 Hz, H-2), 3.70 (t, 1 H, *J* = 8.8 Hz, H-4), 3.87 (d, 1 H, *J* = 11.5 Hz, -OC*H*Ph), 4.50 (d, 1 H, *J* = 9.8 Hz, H-1), 4.65 (d, 1 H, *J* = 11 Hz, -OC*H*Ph), 4.74 (d, 1 H, *J* = 11 Hz, OC*H*Ph), 4.86 (d, 2 H, *J* = 12.4 Hz, -OCH_2Ph), 4.89 (d, 1 H, *J* = 10.0 Hz, -OC*H*Ph), 4.92 (dd, 2 H, *J* = 6.8 Hz, *J* = 11 Hz, H-6, H-6′), 7.25–7.38 (m, 15 H, ArH). ^{13}C NMR: δ = 15.16, 25.20, 62.15, 75.17, 75.57, 75.74, 75.76, 77.69, 79.27, 81.77, 85.27, 86.47, 127.71, 127.77, 127.89, 127.96, 128.07, 128.29, 128.41, 128.46, 128.52, 137.90 (2 C), 138.41. Anal. Calcd for $C_{29}H_{34}O_5S$: C, 70.42; H, 6.93, S, 6.48. Found: C, 70.20; H, 6.86; S, 6.24. **For compound 1x:** ^1H NMR ($CDCl_3$, 300 MHz) δ = 0.07 [s, 6 H, $Si(CH_3)_2$], 0.90 [s, 9 H, $SiC(CH_3)_3$], 1.33 [s, 6 H, $=C(CH_3)_2$], 1.44 (s, 3 H, $=CCH_3$), 1.54 (s, 3 H, $=CCH_3$), 3.70–3.86 (m, 3 H, H-2, H-3, H-5), 4.30 (dd, 2 H, *J* = 2.3 Hz, *J* = 7.2 Hz, H-4, H-6), 4.60 (dd, 1 H, *J* = 1.6 Hz, *J* = 7.9 Hz, H-6′), 5.52 (d, 1 H, *J* = 4.9 Hz, H-1). Anal. Calcd for $C_{18}H_{34}O_6Si$: C, 57.72; H, 9.15. Found: C, 57.55; H, 9.03. **For compound 2x:** ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.34 [s, 6 H, $=C(CH_3)_2$], 1.46 (s, 3 H, $=CCH_3$), 1.54 (s, 3 H, $=CCH_3$), 2.28 (br s, 1 H, OH, D_2O exchangeable), 3.75 (t, 1 H, *J* = 7.3 Hz, H-4), 3.82–3.90 (m, 2 H, H-2 and H-5), 4.27 (d, 1 H, *J* = 7.9 Hz, H-3), 4.34 (dd, 1 H, *J* = 2.3 Hz, *J* = 4.9 Hz, H-6), 4.62 (dd, 1 H, *J* = 2.3 Hz, *J* = 7.9 Hz, H-6′), 5.57 (d, 1 H, *J* = 5.0 Hz, H-1). Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.48; H, 7.69.