Direct Methylenation of Partially Benzyl-Protected Sugar Lactones by Dimethyltitanocene

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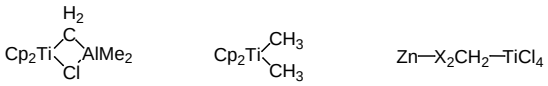
Abstract: Mono- and disaccharidic *exo*-methylenesugars containing an unprotected hydroxy group were conveniently prepared by the direct methylenation of the corresponding mono- and disaccharidic lactones using dimethyltitanocene.

Key words: sugar lactone, methylenation, dimethyltitanocene, *exo*-methylenesugar

exo-Methylenesugars are useful precursors for synthesizing *C*-glycosides[1] and other *C*-glycosyl derivatives,[2] and can also be used as glycosidase inhibitors.[3] *exo*-Methylenesugars protected with a various of groups have been prepared by several procedures, such as a multiple step process ultimately with an elimination reaction,[4] the Meyers' variant of the Ramberg–Backlund rearrangement of *S*-glycoside dioxides,[5] and methylenation of sugar lactones by Tebbe's reagent (**I** in Figure 1)[1a,6] or dimethyltitanocene (Cp_2TiMe_2, **II** in Figure 1).[1b,7] However, few report on the direct synthesis of the partially protected *exo*-methylenesugar has been published, although 3,4,6-tri-*O*-benzyl-1-*exo*-methylenesugars were prepared by an indirect procedure involving multiple sequence with the last step of dehydrohalogenation.[1d,8] We disclosed in this communication a simple preparation of partially benzyl-protected *exo*-methylenesugars by the direct methyleneation of sugar lactones with dimethyltitanocene.

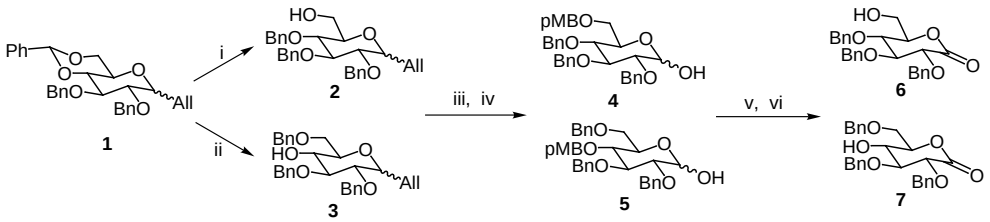
Tebbe's reagent (**I**) and its alternative **II** were effective and useful reagents for the olefination of carbonyl compounds especially for the direct conversion of carboxylic esters to enol ethers.[9–11] The successful application of these reagents to the methylenation of sugar lactones[1a,b,6,7] gave a more direct and convenient access to *exo*-methylenesugars. Concerning the different reactivity of the reagents **I**, **II** and **III**,[12] it has been reported that the highly reactive Tebbe's reagent (**I**) could methylenate the carbonyl group of aldehydes, ketones, esters, and amides. However, the reagent **I** must be sensitive to acidic hydrogens such as those in hydroxy or carboxylic groups.[9] Although the reagent **III** can selectively react with ketones and aldehydes even in the presence of hydroxy[12a,b] or carboxylic[12c] groups, it showed low reactivity to esters.[13] With the consideration of the reasonable stability and the relatively high reactivity of the reagent (**II**),[9,11] we selected dimethyltitanocene (**II**) as the methylenation reagent in our attempt.



I II III

Figure 1

The required partially benzyl-protected monosaccharidic lactones **6** and **7** were prepared by a sequence of reactions as shown in Scheme 1. The disaccharidic lactones **8**, **12** and **13**, and the tetrasaccharidic lactone **14** were synthesized by the procedures shown in Scheme 2 and Scheme 3.



Scheme 1 *Reagents and conditions*: (i) $LiAlH_4$, $AlCl_3$, Et_2O/CH_2Cl_2, reflux; (ii) $BH_3{\cdot}NMe_3$, $AlCl_3$, THF, r.t.; (iii) NaH, *p*MBCl (*p*-methoxybenzyl chloride), THF, r.t; (iv) $PdCl_2$, NaOAc, $HOAc/H_2O$, r.t.; (v) DMSO, OAc_2, r.t.; (vi) DDQ, CH_2Cl_2/H_2O, r.t.

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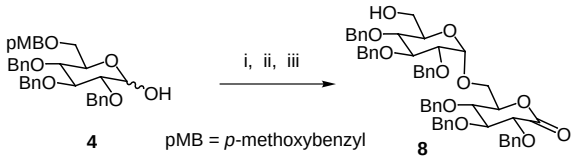

Scheme 2 *Reagents and conditions*: (i) CCl_3CN, K_2CO_3, CH_2Cl_2, r.t.; (ii) **6**, TMSOTf (0.1 equiv), MS 4A, CH_2Cl_2, r.t; (iii) DDQ, CH_2Cl_2/H_2O, r.t.

The methylenations were performed by the reaction of the partially benzyl-protected sugar lactones **6**–**8**, **12**, and **13** with 4.0 molar equivalent of dimethyltitanocene in toluene at 70 °C under argon and afforded the corresponding *exo*-methylenesugars **15**–**19** in good yields[14,15] (Scheme 4). The results are listed in the Table.

As shown in the Table, the methylenation was firstly examined with the sugar lactone **6** using 2.4 equivalents of dimethyltitanocene (**II**) (entry 1). Such molar ratio has been successfully used in the methylenation of the corresponding per benzyl-protected sugar lactones.[2c,7] It was found that the reaction did not complete with remaining unreacted starting material **6**. With increasing amount of dimethyltitanocene (**II**), for example, in the presence of 4.0 molar equivalent of the reagent **II** the reaction gave rise to a good yield of **15** (entry 2). Furthermore, an excess of dimethyltitanocene (5.0 equivalents) did not improve the reaction (entry 3). Under these conditions, the mono- and disaccharidic lactones **7**, **8**, **12** and **13** were methylenated in good yields.[14]

It was also found that a longer reaction time was necessary for the reactions of the disaccharidic lactones **8**, **12** and **13** probably due to the lower reactivity of the lactone group in the big molecule. In addition, an attempt to methylenate the tetrasaccharidic lactone **14** under the same conditions was unsuccessful (entry 8).

Table Methyleneation of Sugar Lactones with Cp_2TiMe_2

Entry	Sugar Lactone	Cp_2TiMe_2 (equiv)	Reaction Time	*exo*-Methylene Sugars (yield)
1[a]	**6**	2.4	14 h	**15** (58.8%)
2	**6**	4.0	14 h	**15** (72.6%)
3	**6**	5.0	14 h	**15** (71.5%)
4	**7**	4.0	14 h	**16** (70.9%)
5	**8**	4.0	24 h	**17** (67.7%)
6	**12**	4.0	24 h	**18** (68.6%)
7	**13**	4.0	24 h	**19** (65.2%)
8	**14**	5.0	24 h	–

[a] The conditions used in the methylenation of per benzyl-protected sugar lactones.[2c,7]

In summary, the methylenations of partially benzyl-protected mono- and disaccharidic lactones with dimethyltitanocene were achieved, providing a direct and convenient method for preparing the *exo*-methylenesugars containing an unprotected hydroxy group.

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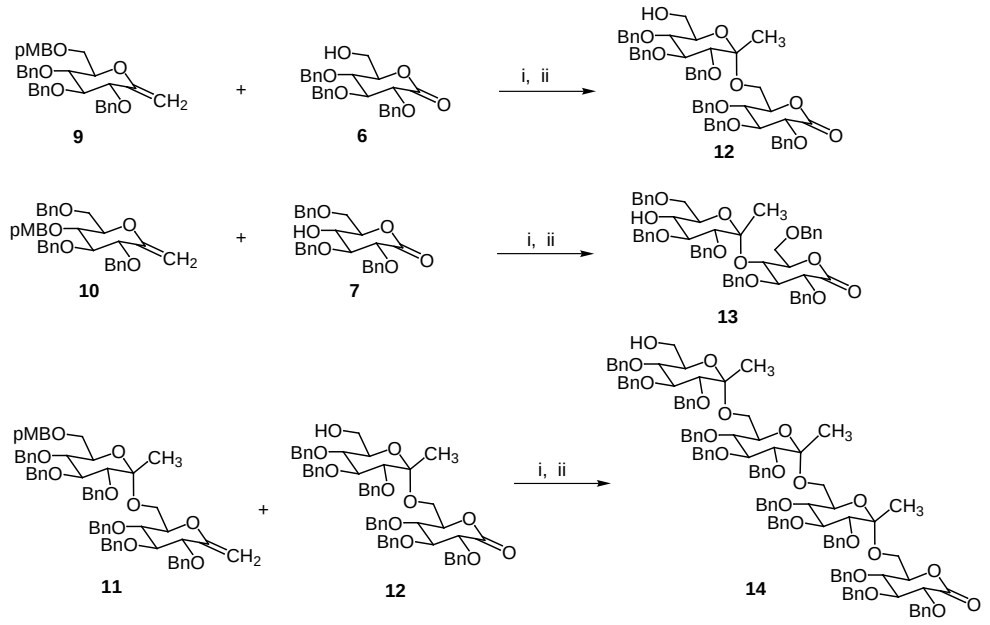
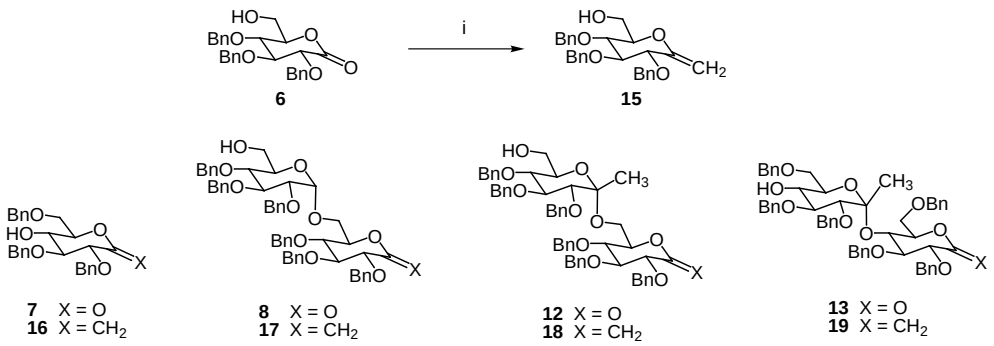


Scheme 3 *Reagents and conditions*: (i) TfOH (0.15 equiv), MS 4A, CH_2Cl_2, –78 °C; (ii) DDQ, CH_2Cl_2/H_2O, r.t.



Scheme 4 *Reagents and conditions*: (i) Cp_2TiMe_2 (4.0 equiv), Toluene, 65–70 °C.

References

(1) (a) Rajan Babu, T. V.; Reddy, G. S. *J. Org. Chem.* **1986**, *51*, 5458. (b) Johson, C. R.; Johons, B. A. *Synlett* **1997**, 1406. (c) Cipolla, L.; Nicotra, F.; Vismara, E.; Guerrini, M. *Tetrahedron* **1997**, *53*, 6163. (d) Vidal, T.; Haudrechy, A.; Langois, Y. *Tetrahedron Lett.* **1999**, *40*, 5677.

(2) (a) Campbell, A. D.; Paterson, D. E.; Raynham, T. M.; Taylor, R. J. K. *Chem. Commun.* **1999**, 1599. (b) Bartolozzi, A.; Capozzi, G.; Falciani, C.; Menichetti, S.; Nativi, C.; Bacialli, A. P. *J. Org. Chem.* **1999**, *64*, 6490. (c) Li, X. L.; Ohtake, H.; Takahashi, H.; Ikegami, S. *Tetrahedron* **2001**, *57*, 4283. (d) Li, X. L.; Takahashi, H.; Ohtake, H.; Shiro, M.; Ikegami, S. *Tetrahedron* **2001**, *57*, 8053. (e) Nishikawa, T.; Ishikawa, M.; Wada, K.; Isobe, M. *Synlett* **2001**, 945.

(3) For reviews, see: (a) Legler, G. In *Adv. Carbohydr. Chem. Biochem.*, Vol. 48; Tipson, R. S.; Horton, D., Eds.; Academic Press Inc.: San Diego, **1990**, 319. (b) Hehre, E. J. In *Adv. Carbohydr. Chem. Biochem*, Vol. 55; Horton, D., Ed.; Academic Press Inc.: San Diego, **1999**, 265.

(4) (a) Brockhaus, M.; Lehmann, J. *Carbohydr. Res.* **1977**, *53*, 21. (b) Lehmann, J.; Knapp, C. *Carbohydr. Res.* **1978**, *63*, 257. (c) Lancelin, J. M.; Pougny, J. R.; Sinay, P. *Carbohydr. Res.* **1985**, *136*, 369.

(5) (a) Griffin, F. K.; Murphy, P. V.; Paterson, D. E.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 8179. (b) Alcaraz, M.-L.; Griffin, F. K.; Paterson, D. E.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 8183.

(6) Wilcox, C. S.; Long, G. W.; Suh, H. *Tetrahedron Lett.* **1984**, *25*, 395.

(7) Csuk, R.; Glänzer, B. I. *Tetrahedron* **1991**, *47*, 1655.

(8) Martin, O. R.; Xie, F. *Carbohydr. Res.* **1994**, *264*, 141.

(9) For a review, see: Pine, S. H. In *Organic Reactions*, Vol. 43; Paquette, L. A., Ed.; John Wiley and Sons Inc.: New York, **1993**, 1.

(10) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270.

(11) (a) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392. (b) Petasis, N. A.; Bzowej, E. I. *J. Org. Chem.* **1992**, *57*, 1327.

(12) (a) Furber, M.; Mander, L. N. *J. Am. Chem. Soc.* **1988**, *110*, 4084. (b) Oppolzer, W.; Cunningham, A. F. *Tetrahedron Lett.* **1986**, *27*, 5467. (c) Shimada, J.; Hashimoto, K.; Kim, B. H.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1759.

(13) We found that the reaction of perbenzyl-protected sugar lactone and the reagent **III** in the presence of *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA) did not proceed well, although this protocol has been used to the methylenation of some esters and lactones. See: (a) Okazoe, T.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 4410. (b) Barrett, A. G. M.; Bezuidenhoudt, B. C. B.; Metcher, L. M. *J. Org. Chem.* **1990**, *57*, 5196.

(14) **General procedure for the Methylenation**: To a solution of 449 mg (1.0 mmol) of **6** in 10 mL of dry toluene was added 832 mg (4.0 mmol, 4.0 equiv) of dimethyltitanocene under argon. The solution was heated with stirring in the dark at 70 °C (oil bath) for 14 hours. After removing the most part of toluene in vacuo, the residue was applied on a silica gel column using EtOAc : Hexane (1:10) containing 1% Et_3N as the eluent to afford the product **15** (324.2 mg, 72.6%).

(15) Characterization data: **15**: ^{1}H NMR ($CDCl_3$): δ = 1.83 (dd, 1 H, *J* = 7.93 Hz, *J* = 5.49 Hz, OH), 3.68–3.77 (m, 4 H), 3.88 (dd, 1 H, *J* = 9.46 Hz, *J* = 5.18 Hz), 3.93 (d, 1 H, *J* = 6.51 Hz), 4.57–4.84 (m, 8 H, $CH_2Ph \times 3$, CH_2=), 7.26–7.35 (m, 15 H, ArH); ^{13}C NMR ($CDCl_3$): δ = 61.98, 72.35, 73.99, 74.26, 77.43, 78.23, 78.58, 84.33, 94.61, 127.71, 127.80, 127.86, 127.97, 128.39, 128.44, 137.74, 137.92, 138.15, 155.67. **16**: ^{1}H NMR ($CDCl_3$): δ = 2.63 (d, 1 H, *J* = 6.11 Hz, OH), 3.65 (dd, 1 H, *J* = 9.77 Hz, *J* = 6.50 Hz), 3.76 (dd, 1 H, *J* = 9.77 Hz, *J* = 3.05 Hz), 4.14–4.22 (m, 4 H), 4.40–4.68 (m, 8 H, CH_2Ph, CH_2=), 7.28–7.35 (m, 15 H, ArH); ^{13}C NMR ($CDCl_3$): δ = 67.90, 69.94, 71.72, 72.33, 73.53, 80.08, 81.15, 82.45, 86.94, 127.74, 127.81, 127.88, 128.00, 128.41, 128.48, 128.52, 137.41, 137.58, 138.00, 159.55. **17**: ^{1}H NMR ($CDCl_3$): δ = 1.69 (s, br, 1 H, OH), 3.54–3.58 (m, 2 H), 3.68 (d, br, 1 H), 3.72–3.77 (m, 3 H), 3.84–3.86 (m, 1 H), 3.88–3.94 (m, 4 H), 4.05 (t, 1 H, *J* = 9.35 Hz), 4.58 (d, 1 H, *J* = 11.55 Hz, CH_2Ph), 4.62 (s, br, 1 H), 4.67–4.77 (m, 7 H, CH_2Ph, CH_2=), 4.84–4.86 (m, 2 H, CH_2Ph), 4.89 (d, 1 H, *J* = 11.55 Hz, CH_2Ph), 4.93 (d, 1 H, *J* = 11.00 Hz, CH_2Ph), 5.02 (d, 1 H, *J* = 11.00 Hz, CH_2Ph), 5.09 (d, 1 H, *J* = 3.85 Hz, 1'-H), 7.27–7.41 (m, 30 H, ArH); ^{13}C NMR ($CDCl_3$): δ = 61.81, 65.85, 70.85, 72.35, 72.56, 74.16, 74.40, 74.94, 75.50, 77.33, 77.41, 78.19, 78.82, 80.21, 81.47, 84.65, 94.51, 97.18, 127.50, 127.54, 127.65, 127.66, 127.68, 127.75, 127.82, 127.83, 127.88, 127.94, 127.99, 128.30, 128.34, 128.39, 128.41, 128.43, 137.80, 138.15, 138.25, 138.35, 138.74, 155.69. **18:** ^{1}H NMR ($CDCl_3$): δ = 1.28 (s, 3 H, CH_3), 1.68 (s, br, 1 H, OH), 3.30 (d, 1 H, *J* = 9.46 Hz), 3.49–3.63 (m, 4 H), 3.69–3.83 (m, 4 H), 3.90–3.93 (m, 2 H), 4.13 (s, 1 H, *J* = 9.46 Hz), 4.55–4.95 (m, 14 H, $CH_2Ph \times 6$, CH_2=), 7.21–7.35 (m, 30 H, ArH); ^{13}C NMR ($CDCl_3$): δ = 21.05 (CH_3), 60.93, 61.89, 71.77, 72.40, 73.96, 74.06, 74.49, 75.11, 75.28, 77.42, 78.09, 78.26, 78.70, 82.55, 84.45, 84.52, 94.46, 100.58, 127.47, 127.55, 127.60, 127.65,

127.67, 127.73, 127.84, 127.91, 127.96, 128.25, 128.31, 128.36, 128.43, 137.88, 138.15, 138.17, 138.39, 138.49, 138.68, 155.69. **19**: ^{1}H NMR ($CDCl_3$): δ = 1.34 (s, 3 H, CH_3), 2.47 (d, 1 H, *J* = 2.75 Hz, OH), 3.22 (d, 1 H, *J* = 9.46 Hz), 3.51 (dd, 1 H, *J* = 10.07 Hz, *J* = 4.58 Hz), 3.57 (dd, 1 H, *J* = 9.77 Hz, *J* = 4.58 Hz), 3.64 (dd, 1 H, *J* = 9.46 Hz, *J* = 2.75 Hz), 4.04 (s, br, 1 H), 3.92 (dd, 1 H, *J* = 10.37 Hz, 1.83 Hz), 3.98–4.06 (m, 4 H), 4.18 (d, 1 H, *J* = 12.21 Hz, CH_2Ph), 4.24–4.28 (m, 1 H), 4.32 (d, 1 H, *J* = 12.21 Hz, CH_2Ph), 4.33 (d, br, 1 H, *J* = 8.55 Hz), 4.41–4.46 (m, 3 H, CH_2Ph), 4.50–4.54 (m, 3 H, CH_2Ph and CH_2=), 4.61 (t, 2 H, *J* = 10.99 Hz, CH_2Ph), 4.74 (dd, 1 H, *J* = 8.85 Hz, *J* = 3.05 Hz), 4.88–4.95 (m, 3 H, CH_2Ph), 7.00–7.03 (m, 2 H, ArH), 7.20–7.37 (m, 28 H, ArH); ^{13}C NMR ($CDCl_3$): δ = 21.23, 69.23, 69.93, 69.96, 70.44, 70.74, 71.58, 73.04, 73.31, 73.63, 75.33, 75.35, 80.16, 80.82, 81.29, 82.72, 84.54, 86.44, 101.53, 127.16, 127.21, 127.33, 127.49, 127.59, 127.60, 127.64, 127.69, 127.74, 127.78, 127.80, 127.82, 127.84, 127.87, 128.12, 128.18, 128.25, 128.33, 128.37, 128.39, 128.44, 128.46, 128.55, 137.80, 138.04, 138.20, 138.59, 138.62, 138.99, 159.82.