

This article was downloaded by:

On: 23 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713617200>

Novel Selectivity in Carbohydrate Reactions III. Selective Deprotection of *p*-Methoxybenzyl (PMBn) Ethers of Carbohydrates by Tin(IV)Chloride

K. P. Ravindranathan Kartha^a; Makoto Kiso^b; Akira Hasegawa^b; H. J. Jennings^a

^a Institute for Biological Sciences, National Research Council Canada, Ottawa, Canada ^b Department of Applied Bioorganic Chemistry, Gifu University, Gifu, Japan

To cite this Article Kartha, K. P. Ravindranathan, Kiso, Makoto, Hasegawa, Akira and Jennings, H. J. (1998) 'Novel Selectivity in Carbohydrate Reactions III. Selective Deprotection of *p*-Methoxybenzyl (PMBn) Ethers of Carbohydrates by Tin(IV)Chloride', *Journal of Carbohydrate Chemistry*, 17: 4, 811 – 817

To link to this Article: DOI: 10.1080/07328309808002353

URL: <http://dx.doi.org/10.1080/07328309808002353>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

COMMUNICATION

**NOVEL SELECTIVITY IN CARBOHYDRATE REACTIONS III.
SELECTIVE DEPROTECTION OF *p*-METHOXYBENZYL (PMBn)
ETHERS OF CARBOHYDRATES BY TIN(IV)CHLORIDE¹**

K.P. Ravindranathan Kartha,*^{a,2} Makoto Kiso,^b Akira Hasegawa^b and H. J. Jennings^a

^aInstitute for Biological Sciences, National Research Council Canada,
Ottawa K1A 0R6, Canada.

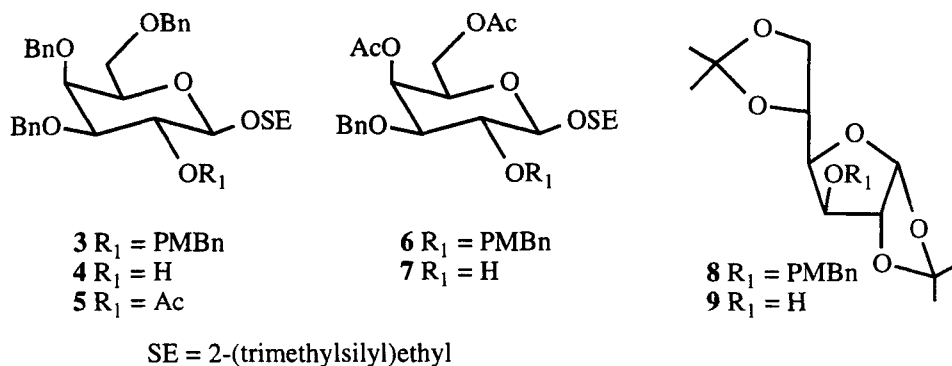
^bDepartment of Applied Bioorganic Chemistry, Gifu University, Gifu 501-11, Japan

Final Form February 23, 1998

In multi-step syntheses involving polyhydroxylated natural products such as carbohydrates that are variously derivatized at different positions, orthogonal removal of one or another type of protecting group is of vital importance. Discrimination of different classes of protecting groups, such as ethers, esters, etc., is often possible with a great degree of success, as for example, selective removal of an *O*-acetyl by catalytic transesterification in the presence of an ether protecting group, or hydrogenolytic removal of a benzyl ether protection in the presence of ester groups such as acetates.³ Differentiation of different types of protecting groups within a given class of protecting groups has also been similarly achieved with great success, as for example, hydrogenolytic removal of a benzyl ether group in the presence of a methyl ether.³ However, the situation becomes more challenging when the same protecting group is used to mask more than one position in a polyfunctional molecule and their preferential partial deprotection is required. Selective unmasking of one or more of such protecting groups has been achieved in some cases.⁴ Of particular interest to us was the regioselective deprotection of the 2-*O*-benzyl group of per-*O*-benzylated 1,6-anhydromannopyranose mediated by SnCl₄ (**1**) and TiCl₄ (**2**). Considering the greater susceptibility of *p*-methoxybenzyl (PMBn) ethers to Lewis acid catalysts⁵ and the complexation of benzyl ethers with **1**^{4b} and **2**^{4b,6} we decided to

investigate the action of **1** on PMBn ethers of some carbohydrates. We expected the methoxy substituent on the phenyl group in the PMBn moiety to enhance complexation with **1**, possibly resulting in a facile reaction under mild conditions. Since **1** is a strong Lewis acid, the need to use chlorotrimethylsilane and anisole, as in the tin(II)chloride-chlorotrimethylsilane-anisole system for deprotection of PMBn ethers, can be eliminated. Moreover, the complex formation in the case of **1** presents possibilities for unusual regioselectivity in partial de-*O-p*-methoxybenzylation reactions, a problem that has not been addressed in reports on the oxidative cleavage of PMBn ethers by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),⁷ ceric ammonium nitrate (CAN),⁸ *N*-bromosuccinimide (NBS)⁸ or bromine.⁸

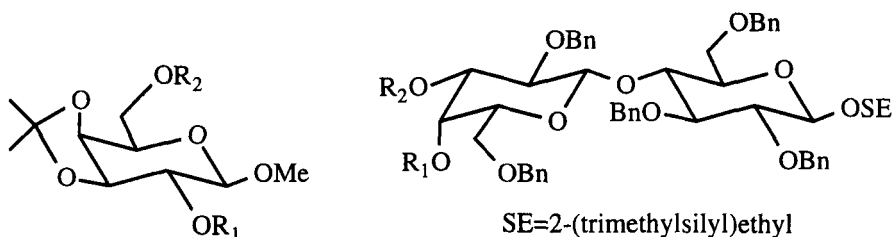
As benzyl ethers are shown to be susceptible to **1** from the work of Hori and coworkers,^{4b} the first compound we examined was the mono-*O*-PMBn ether derivative **3** containing a Lewis/protic acid-sensitive group at the anomeric centre⁹ and benzyl ether protection at the 3-*O*-, 4-*O*- and 6-*O*- positions. This compound, after deprotection of the PMBn group, served as a valuable intermediate in the synthesis of oligosaccharide fragments corresponding to the Type II Group B *Streptococcal* polysaccharide antigen.¹⁰



Indeed, treatment of **3** with **1** (0.1 mol equiv) in dichloromethane (DCM) at 20 °C for 5-8 min followed by an aqueous work up and flash chromatography, gave a product **4** in 95% yield. The structure of **4** was confirmed by NMR. The signals corresponding to the PMBn group [cf. compound **3**, ¹H NMR (CDCl₃) δ 3.78 (s, 3H, OCH₃); ¹³C NMR (CDCl₃) δ 55.24, OCH₃] were absent in the NMR spectrum of **4**. Importantly the benzyl groups [¹H NMR (CDCl₃) δ 4.40-5.00 (2d and 2q, 6H, CH₂Ph)] and the 2-(trimethylsilyl)ethyl group [¹H NMR (CDCl₃) δ 0.02 (s, 9H, SiMe₃), 1.02 (m, 2H, CH₂SiMe₃)] were unaffected. The structure of **4** was further confirmed by conversion to its crystalline mono-*O*-acetyl derivative **5** [mp 66-68 °C; ¹H NMR (CDCl₃) δ 5.42 (dd, 1H, J_{1,2} = 8.1 Hz and J_{2,3} = 9.8 Hz, H-2), 2.10 (s, 3H, OAc); Anal. Calcd for

$C_{34}H_{44}O_7Si$ (592.803): C, 68.89, H, 7.48; Found: C, 68.96, H, 7.52] by treatment with acetic anhydride in pyridine. When the reaction was extended to **6**,¹¹ which is also a valuable intermediate in the above oligosaccharide synthesis, **7**^{10,11} could be isolated in 95% yield. Acetyl groups remained unaffected. Compound **8** bearing an extremely acid sensitive isopropylidene acetal function likewise gave **9**¹² in 90% yield when treated with **1** (0.1 mol equiv, 20 °C, 50 min), demonstrating the wider applicability of this method in multi-step oligosaccharide syntheses.

The possibility for regioselective de-*O-p*-methoxybenzylation was then explored using the di-*O*-PMBn derivative **10**¹³ as a substrate. Thus when **10** (1 mmol) was treated with **1** (0.25 mmol) in DCM (10 mL) at -20 °C for 8 min the mono-*O*-PMBn ether **11**¹³ (further characterised as its mono-*O*-acetyl derivative **12**¹³) was obtained in 70% yield after work up and purification by chromatography. Selective removal of the 2-*O*-PMBn group in



10 $R_1 = R_2 = \text{PMBn}$

11 $R_1 = \text{H}, R_2 = \text{PMBn}$

12 $R_1 = \text{Ac}, R_2 = \text{PMBn}$

13 $R_1 = R_2 = \text{H}$

14 $R_1 = R_2 = \text{PMBn}$

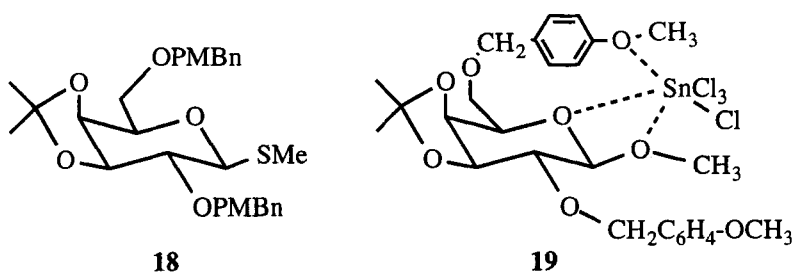
15 $R_1 = \text{H}, R_2 = \text{PMBn}$

16 $R_1 = \text{Ac}, R_2 = \text{PMBn}$

17 $R_1 = R_2 = \text{H}$

10 is contrary to the selectivity observed in acetolysis of benzyl ethers catalyzed by Lewis acids^{4c} in that the rate of acetolysis of a primary benzyl ether is significantly greater than that of a secondary benzyl ether. When the same reaction was carried out using 0.1 mmol of SnCl_4 at 20 °C for 4.5 h an 85% yield of the diol **13**¹⁴ was obtained. Encouraged by this reverse order of reactivity for the selective removal of *O*-PMBn group in **10**, we extended the reaction to **14**,¹⁶ which is easily accessible from its diol precursor **17**,¹⁵ to examine the possibility for the preparation of the valuable disaccharide acceptor **15**. Indeed, reaction of **14** (0.25 mmol) with **1** (0.25 mmol) in DCM (10 mL) at 0 °C for 3 min gave **15**¹⁶ (further characterized as the mono-*O*-acetyl derivative **16**¹⁶) in 73% yield after chromatography. Optimisation of the reaction conditions for the complete deprotection of the PMBn groups showed that by using 0.2 mol equiv of **1** and allowing the reaction mixture to slowly warm to 10 °C, and continuing the reaction for 5 h, (or, alternatively, 0.5 mol equiv of **1**, 20 °C, 1 h) the parent diol **17** could be recovered in 90% yield.

Addition of **1** to a solution of **10** in DCM resulted (as did **3**, **6**, **8** and **14**) in the formation of a purple coloured complex with absorption maxima in the region of 443 and 523 nm. Increasing the quantity of **1** was accompanied by an increase in the colour-intensity of the complex, and an exponential increase in the reaction rate. Thus at 20 °C while formation of **13** took 4.5 h at a concentration of 0.1 mol of **1**/mol of **10** for completion of the reaction (see above), it was complete in a few seconds (with the concomitant separation of **13** as crystals) when the reaction was carried out in the presence of 1 mol of **1**/mol of **10**. Continued reaction resulted in the partial hydrolysis of the isopropylidene acetal. Interestingly, the 1-thio- analogue of **10**, namely **18**, failed to react with SnCl₄ under the above conditions.



The above observations strongly indicate that the reaction is not a simple Lewis acid catalyzed hydrolysis. When **1** (0.1-1.0 mol equiv) was added to a solution of PMBn chloride (PMBnCl) in DCM (1 mL/mmol) a coloured complex with several absorption maxima in the range 420-570 nm was instantly formed. The intensity of the coloured complex thus formed increased rapidly with time, the rate of increase being higher in the initial stages of addition. This process was also accompanied by variations in the absorption maxima, indicating a state of flux. A λ_{max} of 524 nm was obtained in an hour. Further, the coloured complex gave bright blue fluorescence on TLC and had slightly lower mobility (ethyl acetate-hexane, 1:8) than PMBnCl. Benzyl chloride on the other hand did not produce a coloured complex with **1**. These observations indicate the possibility of a charge transfer complex in the **1**-PMBnCl system. The initial preferential removal of the 2-*O*-PMBn group in **10** can be rationalised if a complex of structure **19** is assumed to be formed initially. However, with the release of PMBnCl into the solution formation of a new complex (cf. **1**-PMBnCl complex) with it becomes possible, thereby freeing the 6-*O*-PMBn group for further reaction. It is noteworthy that fluorescence as noted for the **1**-PMBnCl system is obtained in all the de-*O*-*p*-methoxybenzylation reactions described here with the release of some PMBnCl into the reaction mixture. Inability of **1** to react with **18** confirms the involvement of the anomeric oxygen atom in the complex. In the case of

formation of **15** from **14** it appears that the complexation of **1** involves the benzyl groups on the galactose residue and the interglycosidic oxygen in **14**. Proximity of the axial PMBn group along with the steric factor may be responsible for its preferential removal. Although the tin complex formed in some of the reactions described above has been isolated at the end of the reaction and obtained as a solid, preliminary X-ray crystallography showed it to be an amorphous compound. Elucidation of the precise nature of the complexes in these and other situations¹⁷ and the reaction mechanism, therefore, must await further studies.

In conclusion, tin(IV)chloride has been found to be an extremely efficient reagent for the selective deprotection of PMBn ethers of carbohydrates.¹⁹ The reactions described in this paper unravel possibilities for selectivities that are otherwise unusual in Lewis acid catalyzed acetolysis and that haven't been achieved in other methods for the deprotection of PMBn ethers.

ACKNOWLEDGEMENTS

We thank Dr. R. A. Field, School of Chemistry, University of St Andrews, St Andrews, Scotland, for his interest and critical comments on the manuscript.

REFERENCES AND NOTES

1. For Part II see K. P. R. Kartha and H. J. Jennings, *J. Carbohydr. Chem.*, accepted (this issue).
2. Present address and address for correspondence: School of Chemistry, The Purdie Building, University of St Andrews, St Andrews KY16 9ST, Scotland.
3. T. W. Green, *Protective Groups in Organic Synthesis*, John Wiley & Sons Publishers, New York, 1980, p 10.
4. For selected examples of regioselective deprotection reactions see:
a) for de-*O*-acetylation: M. Avalos, R. Babiano, P. Cintas, J. L. Jimenez, J. C. Palacios and C. Valencia, *Tetrahedron Lett.*, **34**, 1359 (1993) and references cited therein; b) for de-*O*-benzylation: H. Hori, Y. Nishida, H. Ohruji and H. Meguro, *J. Org. Chem.*, **54**, 1346 (1989) and references cited therein; c) for acetolysis of benzyl groups: K. P. R. Kartha and R. A. Field, *Tetrahedron*, **53**, 11753 (1997) and references cited therein.
5. T. Akiyama, H. Shima and S. Ozaki, *Synlett*, 415 (1992).
6. S. Koto, N. Morishima, R. Kawahara, K. Ishikawa and S. Zen, *Bull. Chem. Soc. Jpn.*, **55**, 1092 (1982).
7. Y. Oikawa, T. Yoshioka and O. Yonemitsu, *Tetrahedron Lett.*, **23**, 885 (1982).
8. B. Classon, P. J. Garegg and B. Samuelsson, *Acta Chem. Scand.*, **B 38**, 419 (1984).
9. K. Jansson, S. Ahlfors, T. Frejd, J. Kihlberg and G. Magnusson, *J. Org. Chem.*, **53**, 5629 (1988); K. P. R. Kartha and H. J. Jennings, *Tetrahedron Lett.*, **31**, 2537 (1990); K. Jansson, G. Noori and G. Magnusson, *J. Org. Chem.*, **55**, 3181 (1990); K. Jansson, T. Frejd, J. Kihlberg and G. Magnusson, *Tetrahedron Lett.*, **29**, 361 (1988).
10. K. P. R. Kartha and H. J. Jennings, Unpublished results.

11. Selected NMR data: Compound **6**, ^1H NMR (CDCl_3) δ 0.10 (s, 9H, SiMe_3), 1.05 (q, 2H, CH_2SiMe_3), 2.04 and 2.11 (2s, 6H, OAc), 3.77 (s, 3H, OMe), 4.15 (dd, 2H, H-6a and H-6b), 4.35 (d, 1H, $J_{1,2} = 7.4$ Hz, H-1), 4.45-4.85 (2d and q, 4H, CH_2Ph and $\text{CH}_2\text{Ph-}p\text{-OMe}$), 5.46 (near d, 1H, H-4) and 6.75-7.35 (d and m, 9H, H_{Ar}); ^{13}C NMR (CDCl_3) δ -1.53 (SiMe_3), 20.71 and 20.84 (OCOCH_3), 55.20 ($\text{Ph-}p\text{-OCH}_3$) and 103.21 (C-1); Compound **7**, ^1H NMR (CDCl_3) δ 0.10 (s, 9H, SiMe_3), 1.05 (m, 2H, CH_2SiMe_3), 2.05 and 2.10 (2s, 6H, OAc), 3.45 (uu, 1H, $J_{3,4} = 3.3$ Hz, $J_{2,3} = 9.8$ Hz, H-3), 3.58 and 3.96 (2m, 2H, $\text{CH}_2\text{CH}_2\text{SiMe}_3$), 4.12 (m, 2H, H-6a and H-6b), 4.29 (d, 1H, $J_{1,2} = 7.7$ Hz, H-1), 4.48 and 4.77 (2d, 2H, CH_2Ph), 5.47 (d, 1H, H-4) and 7.21-7.36 (m, 5H, H_{Ar}); ^{13}C NMR (CDCl_3) δ -1.46 (SiMe_3), 20.78 (OCOCH_3), and 102.46 (C-1)
12. K. P. R. Kartha, *Tetrahedron Lett.*, **27**, 3415 (1986).
13. Analytical data: Compound **10**, $[\alpha]_{\text{D}} +19.1^\circ$ (c 1.41, CH_2Cl_2); ^1H NMR (CDCl_3) δ 7.29, 7.27, 6.89, 6.86 (4d, 8H, H_{Ar}), 4.75, 4.70, 4.58, 4.49 (4d, 4H, 11.2-11.5 Hz, CH_2Ph), 4.22 (d, 1H, $J_{1,2} = 8.1$ Hz, H-1), 4.11-4.15 (m, 2H, H-3 and H-4), 3.88 (m, 1H, H-5), 3.80, 3.79 (2s, 6H, PhOMe), 3.56 (s, 3H, OMe), 1.35, 1.32 (2s, 6H, Me); Anal. Calcd for $\text{C}_{26}\text{H}_{34}\text{O}_8$ (474.550): C, 65.81, H, 7.22; Found: C, 65.90, H, 7.23; Compound **11**, $[\alpha]_{\text{D}} -1.33^\circ$ (c 1.50, CH_2Cl_2); ^1H NMR (CDCl_3) δ 7.28, 6.88 (2d, 4H, H_{Ar}), 4.53 (2d, 2H, CH_2Ph), 4.16 (dd, 1H, $J_{3,4} = 5.3$ Hz, $J_{4,5} = 2.0$ Hz, H-4), 4.09 (d, 1H, $J_{1,2} = 8.2$ Hz, H-1), 4.04 (dd, 1H, H-3), 3.95 (m, 1H, H-5), 3.80, s, 3H, PhOMe), 3.55 (s, 3H, OMe), 1.51, 1.34 (2s, 6H, Me); IR (film) 3300-3600 (OH) cm^{-1} ; Anal. Calcd for $\text{C}_{18}\text{H}_{26}\text{O}_7$ (354.399): C, 61.00, H, 7.39; Found: C, 61.05, H, 7.42; Compound **12**, $[\alpha]_{\text{D}} +2.56^\circ$ (c 2.73, CH_2Cl_2); ^1H NMR (CDCl_3) δ 7.28, 6.89 (2d, 4H, H_{Ar}), 4.96 (dd, 1H, $J_{1,2} = 8.1$ Hz, $J_{2,3} = 7.0$ Hz, H-2), 4.54 (dd, 1H, 11.5 Hz, CH_2Ph), 4.25 (d, 1H, $J_{1,2} = 8.1$ Hz, H-1), 4.12-4.21 (m, 2H, H-3 and H-4), 3.95 (m, 1H, H-5), 3.80 (s, 3H, PhOMe), 3.48 (s, 3H, OMe), 2.09 (s, 3H, OAc), 1.55, 1.33 (2s, 6H, Me); Anal. Calcd for $\text{C}_{20}\text{H}_{28}\text{O}_8$ (396.436): C, 60.60, H, 7.12; Found: C, 60.64, H, 7.14.
14. A. Stoffyn and P. Stoffyn, *J. Org. Chem.*, **32**, 4001 (1967).
15. A. Hasegawa, T. Nagahama, H. Ohki, K. Hotta, H. Ishida and M. Kiso, *J. Carbohydr. Chem.*, **10**, 493 (1991).
16. Analytical data: Compound **14**, mp 42°C ; $[\alpha]_{\text{D}} = +11.6^\circ$ (c 0.61, CH_2Cl_2); Anal. Calcd for $\text{C}_{68}\text{H}_{80}\text{O}_{13}\text{Si}$ (1133.458): C, 72.06, H, 7.11; Found: C, 72.18, H, 7.15; Compound **15**, $[\alpha]_{\text{D}} +16.27^\circ$ (c 1.29, CH_2Cl_2); ^1H NMR δ 7.25 (m, 27H, H_{Ar}), 6.85 (d, 2H, the remaining H_{Ar}), 3.78 (s, 3H, OMe); IR 3300-3600 (OH) cm^{-1} ; Anal. Calcd for $\text{C}_{60}\text{H}_{72}\text{O}_{12}\text{Si}$ (1013.308): C, 71.12, H, 7.16; Found: C, 71.08, H, 7.19; Compound **16**, $[\alpha]_{\text{D}} +17.44^\circ$ (c 1.55, CH_2Cl_2); ^1H NMR δ : 7.25 (m, 27H, H_{Ar}), 6.80 (d, 2H, the remaining H_{Ar}), 5.55 (d, 1H, $J_{3,4} = 2.4$ Hz, H-4'), 3.78 (s, 3H, OMe), 2.03 (s, 3H, OAc); IR 1750 (C=O) cm^{-1} ; Anal. Calcd for $\text{C}_{62}\text{H}_{74}\text{O}_{13}\text{Si}$ (1055.345): C, 70.56, H, 7.08; Found: C, 70.65, H, 7.10.
17. When 2-(trimethylsilyl)ethyl 2,3,4-tri-*O*-acetyl-6-*O*-*p*-methoxybenzyl- β -D-galactopyranoside (**20**) was treated with **1** (0.25 mol equiv, 0°C , 30 min) the de-*O*-*p*-methoxybenzylated product, 2-(trimethylsilyl)ethyl 2,3,4-tri-*O*-acetyl- β -D-galactopyranoside¹⁸ was obtained in 70% yield after chromatographic purification. The poorer yield obtained in this reaction is due to the fact that a portion of **20** remained unchanged even on prolonged exposure to **1**.
18. K. P. R. Kartha, M. Kiso, A. Hasegawa and H. J. Jennings, *J. Chem. Soc., Perkin Trans. 1*, 3023 (1995).

19. **Typical Procedure:** *Preparation of Compound 11 from 10:* A soln of **1** (250 μ L, 1.0M in DCM) was added, during stirring, to a soln of **10** (474.5 mg, 1 mmol) in anhyd DCM (10 mL) cooled to -20 °C. After 8 min of stirring, aq Na_2CO_3 soln was added to it to quench the reaction. The mixture was then transferred to a separatory funnel and extracted with DCM (3 x 30 mL). The organic layer was then washed successively with aq Na_2CO_3 soln and water, dried (Na_2SO_4), concd to a syrup and chromatographed on a column of silica gel (200 mL) using EtOAc-hexane, 1:3 and 1:1 successively, as eluent to give **11** as a clear syrup (248 mg, 70%).