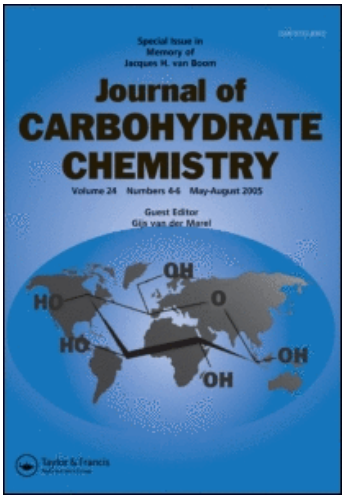

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COMMUNICATION

ALLYLOXYCARBONYL GROUP AS A PROTECTIVE GROUP FOR THE HYDROXYL GROUP IN CARBOHYDRATES

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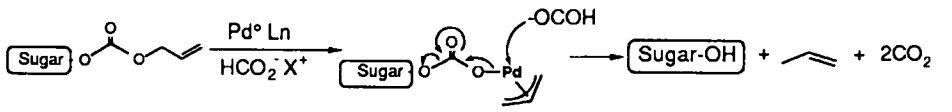
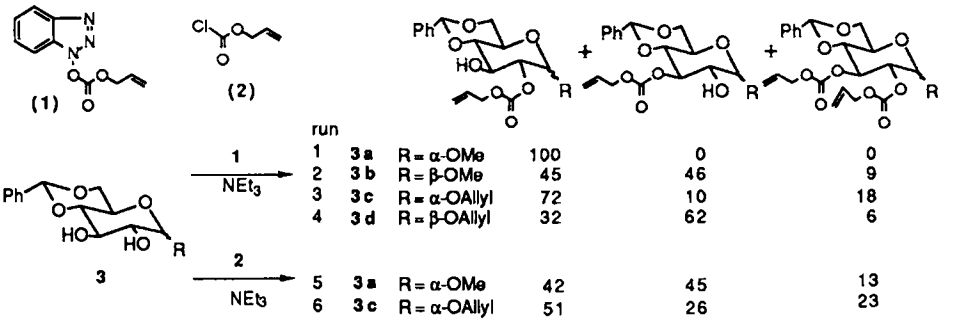
In a carbohydrate synthesis, protective and deprotective operations occupy many of the required steps. Therefore, considerable efforts have been directed toward the development of the protecting groups for carbohydrates.[1] A desirable protecting group must fulfill certain requirements: a) it must be introduced regioselectively; b) it should be stable under various glycosylation conditions; and c) it should be removed chemoselectively with easy separation of protective group byproducts from products. Allyloxycarbonyl (AOC) groups have served as efficient protective groups of the amino functions for the synthesis of the peptides,[2a] nucleotides[2b-d] and amino sugars,[2e,f] and of the phenol function.[2g] These studies suggest that AOC groups are stable under a variety of reaction conditions and can be chemoselectively removed by a palladium-catalyzed reaction under mild condition. Moreover, as the AOC group decomposes into carbon dioxide and propene,[3] accompanied by a small amount of palladium reagents, the deprotected sugars can be easily isolated by simple filtration (Scheme 1).

Those characteristics suggest that the AOC group may satisfy the conditions b) and c) mentioned above. However, with such ideal features of the AOC group, there has been no systematic study on the application of AOC as a protecting group for hydroxyl groups of carbohydrates. We report here such an application.

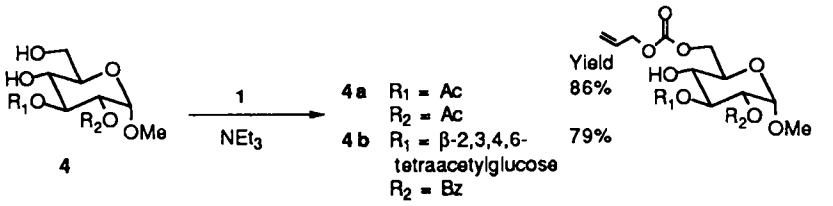
At first, regioselective introduction of allyloxycarbonyl groups to the glucopyranosides, 1) alkyl 4,6-*O*-benzylidene-D-glucopyranoside **3a, 3b, 3c, 3d** (Scheme 2a) and 2) methyl 2,3-diprotected α-D-glucopyranoside **4a, 4b** (Scheme 2b)



Scheme 1



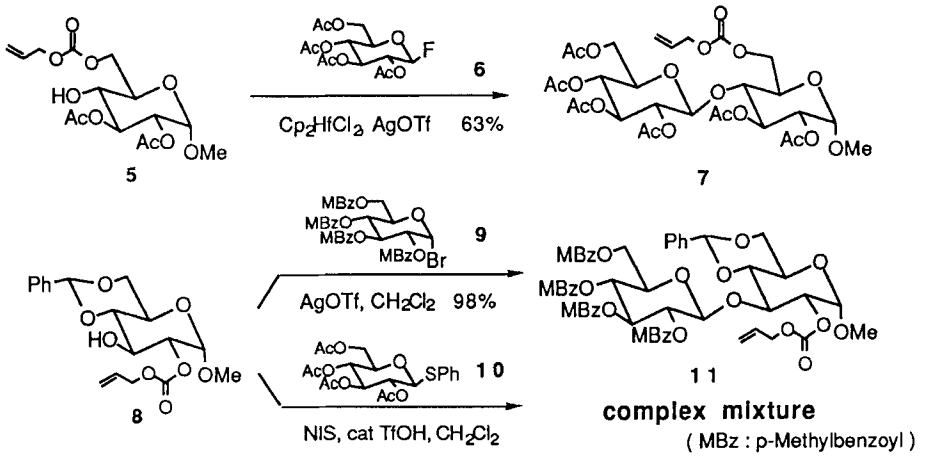
Scheme 2a



Scheme 2b

with two typical reagents, allyl 1-benzotriazoyl carbonate (**1**)[4] and allyl chloroformate (**2**), was examined.[5] The allyl 1-benzotriazoyl carbonate **1** proved to be effective for the selective protection of 2-OH group of α-D-glucopyranosides,[6] but not for the protection of β-D-glucopyranosides (runs 1, 2, 4). By changing α-methyl glucoside into α-allyl glucoside, a decrease in regioselectivity was observed (run 3). In contrast, allyloxycarbonylation of α-D-glucopyranosides with allyl chloroformate **2** showed no selectivity to 2- and 3- OH (runs 5, 6).

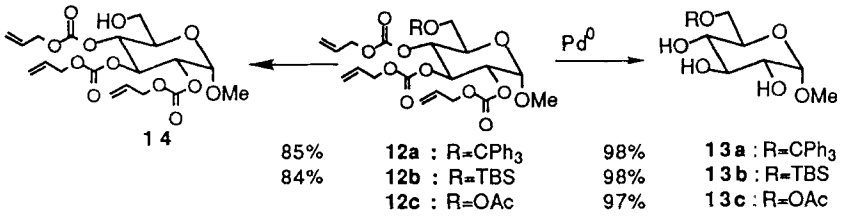
Selective protection of 6-OH of the glucose derivative **4** was achieved with both allyl 1-benzotriazoyl carbonate and allyl chloroformate. No significant differences in selectivity were observed between **1** and **2**.



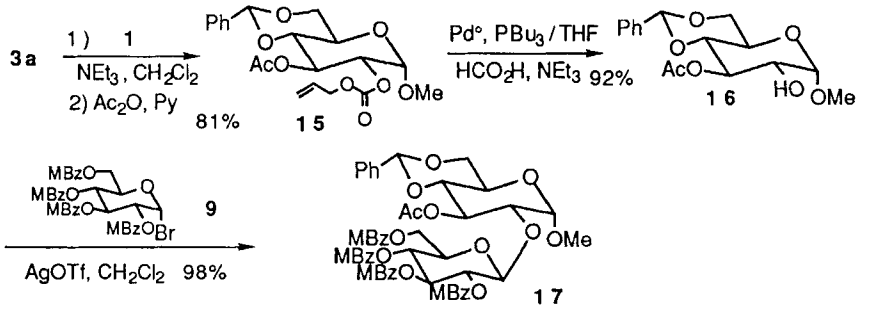
Scheme 3

In order to apply AOC group as a protecting group to oligosaccharide synthesis, the durability under three typical glycosylation conditions was examined (Scheme 3). Reactions between the glycosyl fluoride **6** and the glycosyl acceptor **5** under Suzuki conditions[7] (Cp_2HfCl_2 / AgOTf) gave the disaccharide **7** in 63% yield without damaging the allyloxycarbonyl group. Glycosylation of methyl glucoside **8** with glycosyl bromide **9** under Koenigs-Knorr conditions[8] (AgOTf) afforded the disaccharide **11** in 98% yield. However, the reaction of methyl glucoside **8** with thioglycoside **10** under Fraser-Reid conditions[9] (NIS / cat. TfOH) resulted in a complex reaction mixture. These experimental results indicate that the AOC group could withstand the Lewis acidic conditions, but not conditions with olefin reactive reagents such as NBS and NIS (Scheme 3).

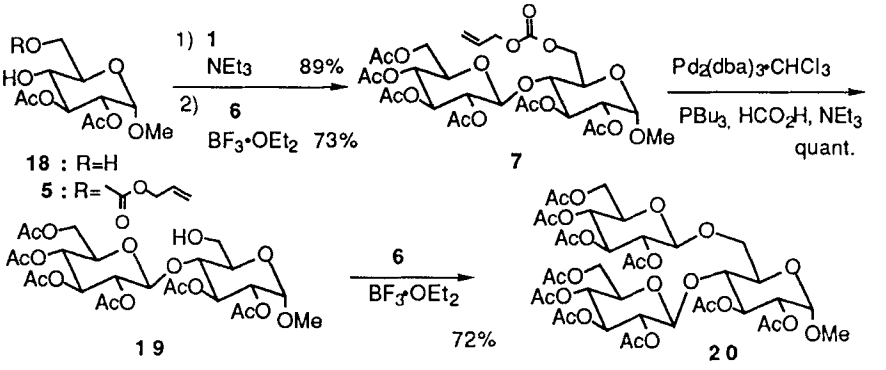
As a number of chemical reagents are employed in usual oligosaccharide synthesis, it is very important to understand the compatibility of a protective group with these reagents. We have examined the chemoselective deprotection of the AOC group in glucose derivatives **12** containing trityl ether, silyl ether or acetate groups and 4,6-*O*-benzylidene acetal groups **15**. Removal of the AOC groups in **12a**, **12b** and **12c** with Pd^0, PBu_3, and HCO_2H/Et_3N[10] gave the corresponding triols **13a**, **13b** and **13c**, respectively, in high yield (>97%). Moreover, the deprotected triol was easily isolated from the reaction mixture by filtration through Florisil and column chromatography. Triphenylmethyl ether, *t*-butyldimethysilyl ether (**12** → **14**) and benzylidene acetal (**3a** → **15**) groups were resistant to the Pd-catalyzed reaction, but were cleaved



Scheme 4



Scheme 5a



Scheme 5b

chemoselectively by 30% HBr / AcOH, HF / Py and 80% acetic acid / H_2O, respectively, in the presence of the AOC group (Scheme 4, 5).

This wide compatibility of AOC group with other protective groups enables a flexible synthetic strategy in saccharide synthesis (Scheme 5a). To demonstrate this, we have carried out the synthesis of disaccharide **17**. Selective protection of 2-OH group in diol **3a** with allyl 1-benzotriazoyl carbonate **1**, followed by acetylation gave **15** in 81% yield. After the removal of AOC group by Pd-catalyzed reaction, the glucosyl bromide **9** was reacted under Koenigs-Knorr conditions to give disaccharide **17**. This is more efficient than the reported route.[11]

Based on the above results, synthesis of trisaccharide **20** was undertaken to demonstrate the usefulness of AOC group (Scheme 5b). Selective protection of the 6-hydroxyl group in diol **18** with allyl 1-benzotriazoyl carbonate **1** in the presence of triethylamine gave 6-allyloxycarbonate **5** in 89% yield. Glycosylation of **5** with glycosyl fluoride **6** in the presence of AOC group (BF_3•OEt_2, 73% yield), followed by selective removal of the AOC group in disaccharide **7** ($Pd_2(dba)_3$•$CHCl_3$•PBu_3 / HCO_2H / Et_3N) afforded the 6-hydroxy disaccharide **19** in quantitative yield. Glycosylation of **19** with glycosyl fluoride **6** gave trisaccharide **20** in 72% yield. All the features of AOC (regioselective protection, chemoselective deprotection, durability to acidic conditions) are effectively involved in this scheme.

As a conclusion, we believe that this work has shown the usefulness of AOC as a protecting group for hydroxyl groups. Due to the unique chemical characteristics of AOC, it should serve as a powerful tool in carbohydrate synthesis.

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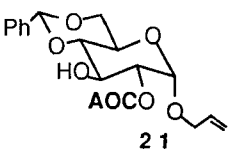
5.



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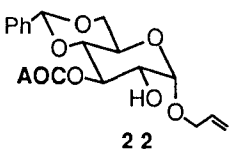

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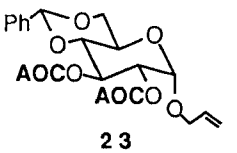

23

21 : ^{1}H NMR (270 MHz, $CDCl_3$) δ : 2.55 (br-s, 1H, OH), 3.58 (dd, 1H, J_{34} = 9.4 Hz, J_{45} = 9.7 Hz, H-4), 3.76 (dd, 1H, $J_{56ax.}$= 10.1 Hz, $J_{6ax.6eq.}$ = 10.2 Hz, H-6ax), 3.92 (ddd, 1H, J_{45} = 9.7 Hz, $J_{56ax.}$ = 10.1 Hz, $J_{56eq.}$ = 4.7 Hz, H-5), 4.04 (dddd, 1H, J = 13.0 Hz, J = 6.1 Hz, J = 1.3 Hz, J = 1.3 Hz, OAllyl), 4.23 (dddd, 1H, J = 13.0 Hz, J = 5.1 Hz, J = 1.5 Hz, J = 1.5 Hz, OAllyl), 4.26 (dd, 1H, J_{23} = 9.4 Hz, J_{34} = 9.4 Hz, H-3), 4.29 (dd, 1H, $J_{56eq.}$ = 4.7 Hz, $J_{6ax.6eq.}$ = 10.2 Hz, H-6eq.), 4.65 (dd, 1H, J_{12} = 3.6 Hz, J_{23} = 9.4 Hz, H-2), 4.67 (ddd, 2H, J = 5.9 Hz, J = 1.5 Hz, J = 1.5 Hz, O-AOC), 5.17 (d, 1H, J_{12} = 3.6 Hz, H-1), 5.56 (s, 1H, benzylidene), 5.19-5.42 (m, 4H, vinyl), 5.82-6.02 (m, 2H, vinyl), 7.35-7.52 (m, 5H, benzylidene). IR (neat) cm^{-1}; 3476, 2922, 2862, 1747, 1453, 1381, 1261, 1152, 1090, 1038, 926, 755, 700.

22 : ^{1}H NMR (270 MHz, $CDCl_3$) δ : 2.21 (d, 1H, J_{2OH} = 11.5 Hz, OH), 3.63 (dd, 1H, J_{34} = 9.6 Hz, J_{45} = 9.6 Hz, H-4), 3.74 (ddd, 1H, J_{12} = 3.9 Hz, J_{23} = 9.6 Hz, J_{2OH} = 11.5 Hz, H-2), 3.75 (dd, 1H, $J_{56ax.}$ = 10.0 Hz, $J_{6ax.6eq.}$ = 10.2 Hz, H-6ax.), 3.93 (ddd, 1H, J_{45} = 9.6 Hz, $J_{56ax.}$ = 10.0 Hz, $J_{56eq.}$ = 4.7 Hz, H-5), 4.30 (dd, 1H, $J_{56eq.}$ = 4.7 Hz, $J_{6ax.6eq.}$ = 10.2 Hz, H-6eq.), 4.64 (ddd, 2H, J = 5.9 Hz, J = 1.3 Hz, J = 1.3 Hz, O-AOC), 4.97 (d, 1H, J_{12} = 3.9 Hz, H-1), 5.15 (dd, 1H, J_{23} = 9.6 Hz, J_{34} = 9.6 Hz, H-3), 5.50 (s, 1H, benzylidene), 4.03-4.10 (m, 1H, OAllyl), 4.23-4.31 (m, 1H, OAllyl), 5.21-5.38 (m, 4H, vinyl), 5.85-5.99 (m, 2H, vinyl), 7.34-7.48 (m, 5H, benzylidene). IR (KBr) cm^{-1}; 3424, 2912, 2864, 1743, 1453, 1373, 1265, 1090, 1045, 973, 919, 753, 698.

23 : 1H NMR (270 MHz, CDCl3) δ : 3.70 (dd, 1H, J_{34} = 9.7 Hz, J_{45} = 9.7 Hz, H-4), 3.76 (dd, 1H, $J_{56ax.}$ = 10.1 Hz, $J_{6ax.6eq.}$ = 10.2 Hz, H-6ax.), 4.00 (ddd, 1H, J_{45} = 9.7 Hz, $J_{56ax.}$ = 10.1 Hz, $J_{56eq.}$ = 4.9 Hz, H-5), 4.01 (dddd, 1H, J = 13.3 Hz, J = 7.6 Hz, J = 1.4 Hz, J = 1.4 Hz, OAllyl), 4.22 (dddd, 1H, J = 13.3 Hz, J = 5.1 Hz, J = 1.3 Hz, J = 1.3 Hz, OAllyl), 4.30 (dd, 1H, $J_{56eq.}$ = 4.9 Hz, $J_{6ax.6eq.}$ = 10.2 Hz, H-6eq.), 4.77 (dd, 1H, J_{12} = 3.8 Hz, J_{23} = 9.8 Hz, H-2), 5.21 (d, 1H, J_{12} = 3.8 Hz, H-1), 5.46 (dd, 1H, J_{23} = 9.8 Hz, J_{34} = 9.7 Hz, H-3), 5.51 (s, 1H, benzylidene), 4.62-4.66 (m, 2H, O-AOC), 5.02-5.05 (m, 2H, O'-AOC), 5.18-5.40 (m, 6H, vinyl), 5.81-6.21 (m, 3H, vinyl), 7.32-7.47 (m, 5H, benzylidene). IR (neat) cm^{-1}; 2936, 2866, 1755, 1452, 1366, 1268, 1238, 1155, 1093, 1043, 987, 943, 787, 747.

6. A typical procedure for the allyloxycarbonylation with allyl 1-benzotriazoyl carbonate **1** is as follows. To a suspension of diol **3a** and 1.6 eq. of **1** in CH_2Cl_2 was added 4.6 eq of triethylamine and then the reaction mixture was stirred for 2 h. After removal of solvent and triethylamine under vacuum, chromatographic purification gave the 2-allyloxycarbonyl derivative in 92% yield. No formation of the 3-allyloxycarbonyl derivative was detected.
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