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The 2-(allyloxy) phenyl acetyl ester as a new relay protecting group for oligosaccharide synthesis

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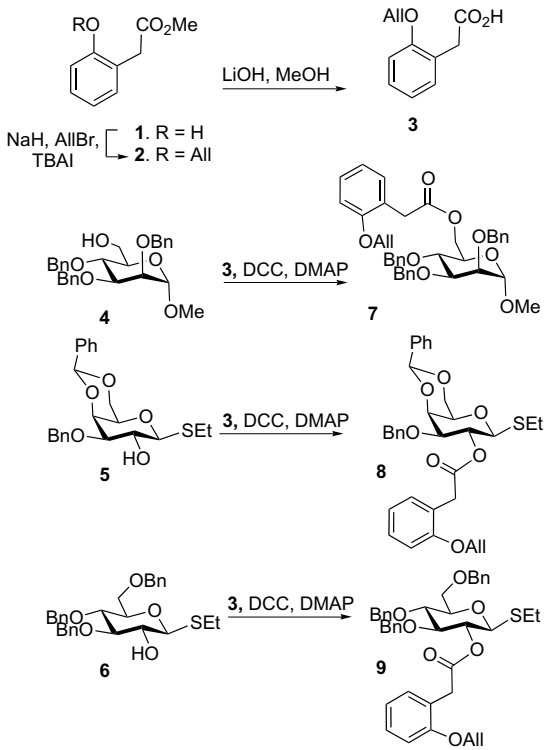
Abstract—The 2-(allyloxy) phenyl acetyl group can be removed by a relay approach using $Pd(PPh_3)_4$ in combination with proton sponge, conditions that do not affect acetyl, benzoyl and levulinoyl esters. On the other hand, the acetyl and levulinoyl ester could be cleaved without removal of the 2-(allyloxy) phenyl acetyl group. The new protecting group is compatible with glycosylations and can perform efficiently neighboring group participation leading to the exclusive formation of 1,2-*trans* glycosides. © 2001 Elsevier Science Ltd. All rights reserved.

Recent developments in oligosaccharide chemistry focus on the preparation of compound libraries either by parallel synthesis or by a mix and split approach.[1] In particular, the use of monosaccharide building blocks that are substituted with orthogonal protecting groups proved to be attractive for parallel synthesis of collections of oligosaccharides. For example, Wong and co-workers reported[2] that chloroacetyl (ClAc), *p*-methoxybenzyl (PMB), levulinoyl (Lev), and *tert*-butyldiphenylsilyl (TBDPS) are a set of orthogonal protecting groups. Recently, we reported[3] that the Fmoc, Lev and diethylisopropylsilyl (DEIPS) are an attractive set of orthogonal hydroxyl protecting groups for amino sugars. The cleavage conditions of these protecting groups did not affect the base sensitive amino protecting group trichloroethoxycarbonyl (Troc).

Although these sets of protecting groups allow the synthesis of a wide range of oligosaccharides, the sensitivity of esters such as ClAc and Fmoc imposes limitations.

Here we present the 2-(allyloxy) phenyl acetyl (APAC) as a new protecting group for oligosaccharide synthesis, which is orthogonal with the levulinoyl and acetyl ester and is capable of controlling the anomeric selectivity of glycosylations by neighboring group participation. The new protecting group can be removed by relay deprotection[4] whereby the phenolic allyl ether is cleaved by treatment with a transition metal followed by intramolecular ester cleavage by nucleophilic attack of the revealed hydroxyl.

2-(Allyloxy) phenyl acetic acid (**3**) was prepared by treatment of methyl 2-hydroxyl phenylacetic acid (**1**)[5] with allyl bromide in the presence of sodium hydride and tetra-*n*-butyl ammonium iodide, followed by



Scheme 1.

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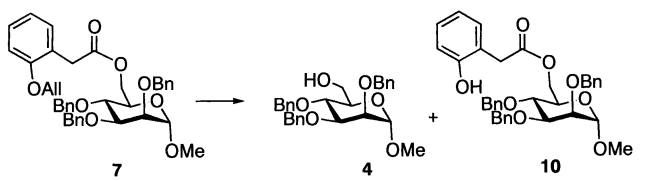
saponification of the ester moiety of the resulting **2** with lithium hydroxide in methanol/water (Scheme 1). The hydroxyls of **4**,[6] **5**,[7] and **6** could be protected as an APAC ester to give **7**, **8** and **9** by reaction with **3** in the presence of DCC and DMAP in DCM. In each case, the ester was isolated in an almost quantitative yield. Several conditions were examined for removal of the APAC ester (Table 1). Thus, treatment of **7** with $PdCl_2$ in MeOH at 60°C gave, after a reaction time of 1 h, the required alcohol **4** together with a small amount of deallylated derivative **10**. Intermediate **10** could be converted into the alcohol **4** by treatment with triethyl amine or imidazole but this approach was deemed less attractive than a one-pot cleavage reaction. The use of $Pd(PPh_3)_4$ and Et_3N in ethanol/H_2O gave a higher yield of alcohol **4**, but also in this case the product was contaminated with **10**. Fortunately, the application of $Pd(PPh_3)_4$ in combination with proton sponge in refluxing ethanol/water gave, after a reaction time of 2 h, **4** in almost quantitative yield.

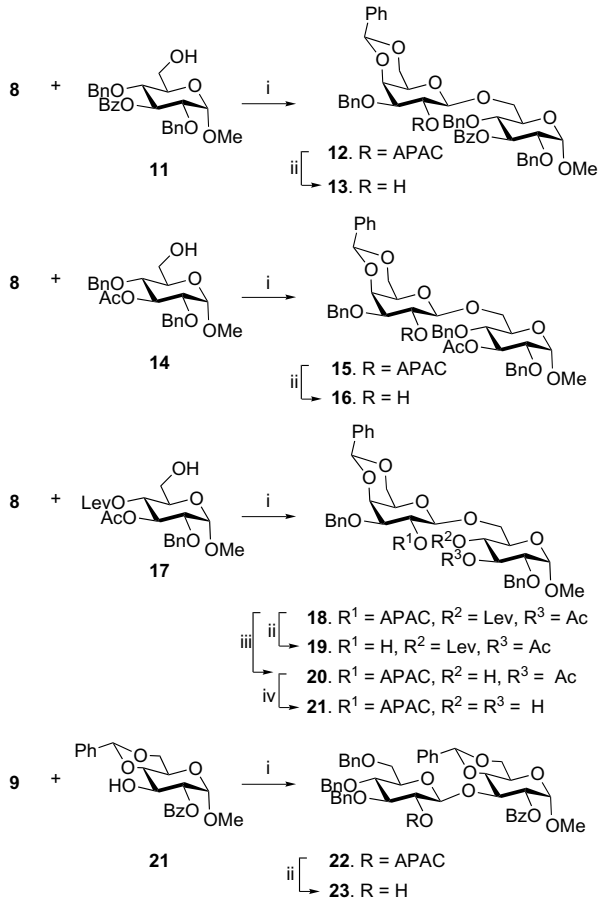
Having established mild conditions for the introduction and removal of the APAC protecting group, attention was focussed on the employment of APAC protected glycosyl donors. Furthermore, its ability to perform neighboring group participation was explored. NIS/TMSOTf-mediated glycosylations of glycosyl donor **8** with acceptors **11**, **14**,[8] and **17** gave disaccharides **12**, **15** and **18**[9] in yields of 76, 67 and 81%, respectively (Scheme 2). As expected, in each case only the β-anomer was formed. Glycosylation of **9** with the less reactive acceptor **21**[10] was also successful and in this case **22** was isolated in a yield of 71% as exclusively the β-anomer. In each case, the APAC protecting group of disaccharides **12**, **15**, **18** and **22** could be removed using standard conditions to give **13**, **16**, **19** and **23** in good yields. It is important to note that the acetyl, benzoyl, and levulinoyl esters of **12**, **15**, **18** and **22** were not affected when the APAC protecting group was removed.

Finally, the orthogonality of the APAC protecting group with the Lev and acetyl ester was explored. Treatment of **18** with hydrazine acetate in DCM resulted in clean removal of the Lev ester without affecting the APAC or acetyl ester to give **20** in a quantitative yield. Furthermore, the acetyl ester of **20** could be selectively removed by guanidine in methanol[11] to furnish diol **21**. The latter two deprotections demonstrate that the APAC is a robust ester functionality that is more stable towards base treatment than the Lev and acetyl ester.

Table 1. Cleavage of APAC protecting group



Cleavage conditions	Yield **4** (%)	Yield **10** (%)
$PdCl_2$, MeOH, 60°C	59	11
$Pd(PPh_3)_4$, Et_3N, EtOH/H_2O, Δ	70	25
$Pd(PPh_3)_4$, proton sponge, EtOH/H_2O, Δ	89	–



Scheme 2. *Reagents and conditions*: (i) NIS, TMSOTf, DCM; (ii) $Pd(PPh_3)_4$, proton sponge, EtOH/H_2O; (iii) NH_2NH_2·AcOH, DCM, guanidine, 0.1 M in MeOH, DCM.

In conclusion, the APAC ester is a robust protecting group that can be cleaved under mild conditions using a relay approach involving cleavage of a phenolic allyl ether followed by cyclization. The new protecting group performs neighboring group participation in glycosylations and is orthogonal with acetyl and Lev esters. We anticipate that the APAC protecting group will be a valuable tool for combinatorial synthesis of oligosaccharide libraries.

Experimental procedure for removal APAC ester: $Pd(PPh_3)_4$ (5 mg) and proton Sponge (0.2 mmol) were added to a solution of the protected sugar (0.2 mmol, **7**, **12**, **15**, **18** or **22**) in ethanol/water (2/1, v/v). The reaction mixture was heated under reflux (2–7 h) until TLC analysis indicated completion of the reaction. The solvents were evaporated under reduced pressure and the crude product purified by silica gel column chromatography.

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9. All new compounds gave satisfactory ^{1}H, ^{13}C, and MS data. Analytical data for compound **18**. $[\alpha]_D^{26}=+69.1$ ($c=3.6$, DCM). ^{1}H NMR ($CDCl_3$) δ 7.50 (m, 2H, CH arom), 7.40–7.15 (m, 15H, CH arom), 6.90–6.78 (m, 2H, CH arom), 6.06–5.90 (m, 1H, 1H, CH= allyl), 5.50–5.34 (m, 4H, OCHO, H-3, H-2′, CH_2= allyl), 5.26–5.16 (dd, 1H, $J=10.4$ Hz, $J=1.5$ Hz, CH_2= allyl), 4.88 (t, 1H, $J=9.7$ Hz, H-4), 4.70–4.44 (m, 8H, H-1, H-1′, $2CH_2Ph$, CH_2O allyl), 4.28 (d, 1H, $J=12.4$ Hz, H-6′^{a}), 4.05 (d, 1H, $J=3.3$ Hz, H-4′), 4.00–3.85 (m, 3H, H-6′^{b}, H-6^{a}, H-5), 3.74 (AX, 2H, CH_2CO), 3.62–3.48 (m, 3H, H-2, H-3′, H-6^{b}), 3.36 (s, 3H, OCH_3), 3.32 (bs, 1H, H-5′), 2.68–2.60 (m, 2H, CH_2), 2.52–2.43 (t, 2H, $J=6.0$ Hz, CH_2), 2.08 (s, 3H, CH_3), 2.01 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 206.3 (CO), 171.7, 170.0 (CO), 156.5 (C arom), 138.1, 137.9, 137.6 (C arom), 133.4 (CH arom), 130.9 (CH= allyl), 128.9, 128.4, 128.3, 128.1, 127.9, 127.8, 127.6, 127.5, 126.4 (CH arom), 123.3 (C arom), 120.6 (CH arom), 117.0 (CH_2=), 111.8 (CH arom), 101.1, 100.9 (OCHO, H-1′), 97.5 (C-1), 77.4, 77.3 (C-2, C-3′), 73.5 (C-4′), 73.0 (CH_2Ph), 71.7 (C-3 or C-2′), 71.3 (CH_2O allyl), 69.9 (C-3 or C-2′), 69.5 (C-4), 68.9 (C-6′), 68.2 (C-5), 66.6 (C-6 and C-5′), 55.4 (OCH_3), 37.7 (CH_2CO lev), 35.5 (CH_2CO), 29.6 (CH_3CO), 28.0 (CH_2CO lev), 20.9 (CH_3CO). MALDI-TOF MS: $m/z=961.5$ (M^++Na), 977.7 (M^++K).
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