Application of the 2,5-Dimethylpyrrole Group as a New and Orthogonal Amine-Protecting Group in Oligosaccharide Synthesis

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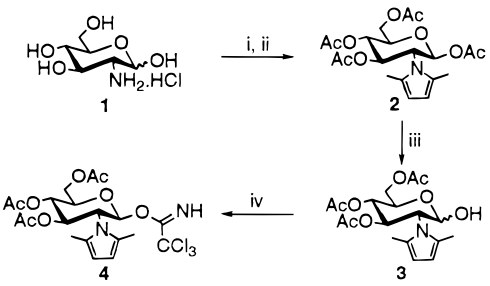
Amino sugars are widely distributed in living organisms and occur as constituents of glycoproteins, glycolipids, bacterial lipopolysaccharides, proteoglycans, and nodulation factors associated with leguminous plants.[1] Glucosamine is the most common amino sugar and is generally found as an N-acetylated and β-linked glycoside. Among the bioactive amino sugars listed above, their N-function can also be derivatized with fatty acids and sulfates, and several polyamino oligosaccharides possess variously differentiated *N*-acyl residues.

The chemical synthesis of complex oligosaccharides containing amino sugars is the focus of extensive research[1,2] and requires amino protecting groups that are compatible with common protecting group manipulations and glycosylations whereby they can be removed or exchanged readily and chemoselectively under mild conditions.

Over the years, 2-deoxyphthalimido-protected glycosyl donors have been the method of choice for the preparation of 1,2-*trans*-glycosides of 2-amino-2-deoxyglycosides. The *N*-phthalimido group can be readily installed by reaction with phthalic anhydride[1] and cleaved with hydrazine,[3] butylamine,[4] hydroxylamine,[5] $NaBH_4$,[6] or with alkyldiamines immobilized on polystyrene beads.[7] Recently, the tetrachlorophthalimido,[8] dichlorophthalimido,[9] *N*-pentenoyl,[8a,10] dithiosuccinoyl,[11] and *N*,*N*-diacetyl[12] groups have been proposed as alternatives to the *N*-phthalimido group and can be removed under milder reaction conditions. Despite many attractive features of these protecting-groups, they are rather base sensitive and incompatible with many protecting group manipulations.

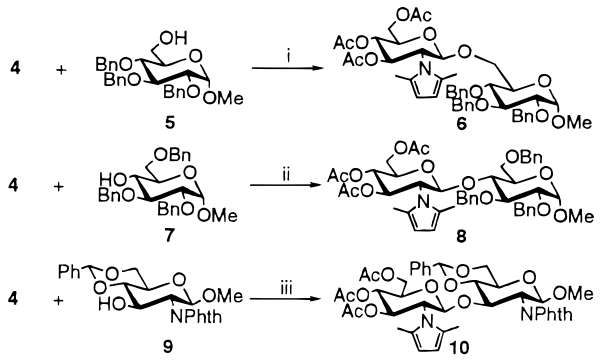
In this paper, we report that the 2,5-dimethylpyrrole[13−15] functionality is a versatile amino protecting group that is compatible with many protecting-group manipulations commonly employed in oligosaccharide chemistry. Interestingly, it can be cleaved by treatment with hydroxylamine hydrochloride but is stable to conditions applied for cleavage of the *N*-phthalimido group. Furthermore, glycosyl trichloroacetimidates derived from 2-deoxy-2,5-dimethylpyrrole glycosides perform well in Lewis acid-mediated glycosylations leading selectively to 1,2-*trans*-glycosides.

Scheme 1[a]



[a] Reagents and conditions: (i) 2,5-hexanedione (1 equiv), Et_3N (1 equiv), MeOH, then (ii) Ac_2O, pyridine, 4 h, 51% (two steps); (iii) hydrazine acetate (1.2 equiv), DMF, 50 °C, 30 min 30%; (iv) CCl_3CN (13 equiv), DBU (0.2 equiv), CH_2Cl_2, 1 h, 78%.

Scheme 2[a]



[a] Reagents and conditions: (i) TMSOTf (0.2 equiv), CH_2Cl_2, −25 °C, 15 min 78%; (ii) TMSOTf (0.2 equiv), CH_2Cl_2, −25 °C, 15 min, 68%; (iii) TMSOTf (0.3 equiv), CH_2Cl_2, −25 °C, 30 min, 62%.

The dimethylpyrrole protecting group is readily installed by treatment of an amine with 2,5-hexanedione in the presence of triethylamine in methanol. When glucosamine hydrochloride (**1**) (Scheme 1) was reacted under these conditions, followed by O-acetylation with acetic anhydride and pyridine, the fully protected sugar **2** was obtained in a yield of 51%. Compound **2** could easily be converted into the analogues trichloroacetimidate **4** via a two-step procedure. Thus, selective anomeric O-deacetylation with hydrazine acetate[16] gave **3** in 93% yield, which was treated with trichloroacetonitrile in the presence of DBU[17] to afford **4** exclusively as the β-anomer. As can be seen in Scheme 2, compound **4** proved to be an efficient glycosyl donor in TMSOTf-mediated glycosylations and gave in each case exclusive formation of a β-glycoside. Although the pyrrole group is highly electron rich and somewhat acid sensitive, the yields of the glycosylations were generally high for both primary and secondary alcohols, and the modest yield of **10** was due to the concurrent formation of trimethylsilylated

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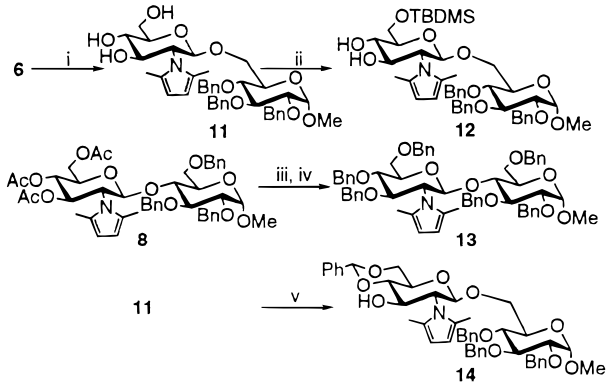
Scheme 3[a]



[a] Reagents and conditions: (i) $Et_3N/H_2O/MeOH$ (2/5/5, v/v), 1 h, 99%; (ii) TBDMSCl (1.5 equiv), Et_3N, pyridine, 5 h, 87%; (iii) Et_3N/H_2O/MeOH (2/5/5, v/v), 1.5 h, quant; (iv) BnBr (4.5 equiv), NaH (4.5 equiv), DMF, 1 h, 92%; (v) benzal bromide (4 equiv), Et_3N, pyridine, reflux, 2.5 h, 58%.

glycosyl acceptor (13%) by its reaction with the activator. The high β-selectivity is also remarkable since the C-2 dimethylpyrrole moiety is electronically a nonparticipating functionality. Probably, the α-face of the glycoside is sterically shielded, forcing the glycosyl acceptor to approach from the β-face. To the best of our knowledge, this type of steric-directed anomeric selectivity has not been reported.

A series of protecting group manipulations were performed to demonstrate the versatility of the pyrrole protecting group. Disaccharide **6** (Scheme 3) was deacetylated with triethylamine in methanol/water to afford triol **11** in a quantitative yield. The primary hydroxyl of **11** could be regioselectively protected by reaction with TBDMSCl and triethylamine in pyridine to give **12**. Surprisingly, in the absence of triethylamine, no product formation was observed. Deacetylation of **8** followed by benzylation with benzyl bromide and NaH in DMF afforded the fully protected disaccharide **13** in a yield of 92%. This reaction is of special significance since many amino-protecting groups are incompatible or perform unpredictably under standard benzylation conditions. Finally, the 4,6-diol of **11** could be protected as a benzylidene acetal by treatment with benzal bromide[18] and triethylamine in boiling pyridine to afford **14** in a yield of 58%.

The pyrrole protecting group can be easily removed by treatment with hydroxylamine hydrochloride (Scheme 4). Low yields of products were obtained when hydroxylamine in refluxing methanol[13] was employed. However, treatment of **11** with an excess of hydroxylamine hydrochloride and triethylamine in 2-propanol/water[15] gave almost quantitative

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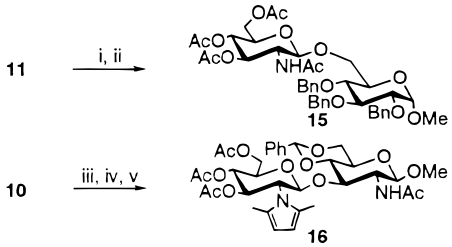
Scheme 4[a]



[a] Reagents and conditions: (i) $NH_2OH{\cdot}HCl$ (15 equiv), Et_3N (10 equiv), $iPrOH/H_2O$, (4/1, v/v), 80 °C, 3 h; (ii) Ac_2O, pyridine, 2 h, 97% (two steps); (iii) Et_3N/H_2O/MeOH (2/5/5, v/v), 1 h, 97%; (iv) hydrazine monohydrate (18 equiv), EtOH, 95 °C, 2 h; (v) Ac_2O, pyridine, 2 h, 78% (two steps).

amine formation, which was converted into the analogues *N*-acetamido derivatives **15** in an overall yield of 97%.

Disaccharide **10** was selected as a model compound to investigate the selective deprotection of the *N*-phthalimido group in the presence of the 2,5-dimethylpyrrole. In a previous experiment (Scheme 1), it was observed that the dimethylpyrrole group is stable to treatment with hydrazine acetate, and therefore, it was anticipated that the *N*-phthalimido group of **10** can be cleaved with hydrazine without affecting the dimethylpyrrole moiety. Indeed, saponification of the acetyl esters of **10** with triethylamine and subsequent treatment with hydrazine monohydrate and O-acetylation with acetic anhydride and pyridine gave **16** in an overall yield of 78%. A tentative explanation for such orthogonal group stability is that the cleavage of the dimethylpyrrole moiety requires protonation, which for example, is delivered from the hydrochloride salt of hydroxylamine. In the absence of a proton source, the pyrrole group is unreactive, and treatment with hydrazine will only result in cleavage of the *N*-phthalimido group.

In conclusion, we have demonstrated that the 2,5-dimethylpyrrole moiety can be used as a protecting group for the amino functionalities of saccharides. The new protecting group can be installed and cleaved under mild conditions but is stable to conditions required for deprotection of an *N*-phthalimido group. Also, a trichloroacetamido 2-deoxy-2,5-dimethylpyrrole glycosyl donor gives high yields and β-anomeric selectivity in TMSOTf-promoted glycosylations. The exploitation of the 2,5-dimethylpyrrole group for the synthesis of complex oligosaccharides is underway and will be reported in due course.

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Supporting Information Available: Detailed experimental procedures including ^1H and ^{13}C NMR spectra for all compounds in this study (28 pages).

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