Regio- and Stereoselective Synthesis of 1→5-Linked α-L-Arabinofuranosyl Oligosaccharides

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Dedicated to Prof. Pierre Sinaÿ on the occasion of his 62nd birthday.

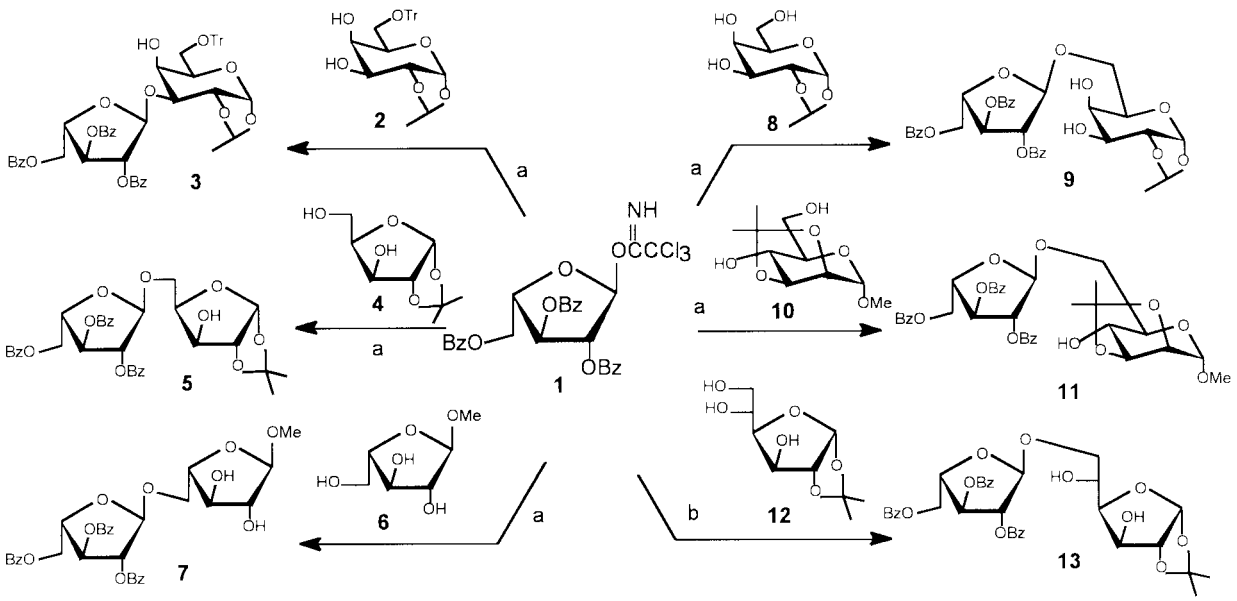
Abstract: Regio- and stereoselective synthesis of furanosyl oligosaccharides in moderate to very good yields using arabinofuranosyl trichloroacetimidates as glycosyl donors and unprotected or partially protected glycosides as acceptors was described. A convergent synthesis of 1→5-linked α-L-arabinofuranosyl octamer was presented.

Key words: imidate, regio- and stereoselective synthesis, furanosyl oligosaccharide, arabinose

The biological significance of glycocojugates has stimulated much synthetic activity in glycoside synthesis in the past years.[1] The specific structural constraints in glycosidic bond-formation often lead to laborious synthetic transformation, complex protecting group manipulations, and tedious intermediate isolations, which complicate the overall synthetic process and decrease synthetic efficiency.

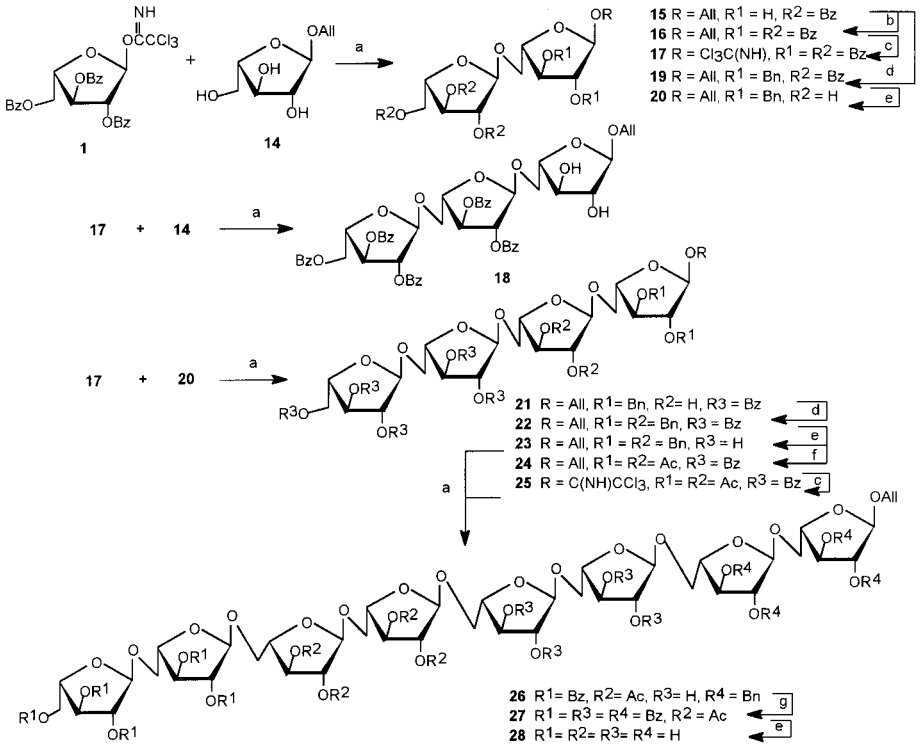
To facilitate the synthesis of oligosaccharides, regiospecific glycosylation of glycosyl donors with unprotected or partially protected sugar acceptors has been taken tremendous efforts. Some of the exciting results have been achieved recently.[2] However, there has been no breakthrough so far in the regio- and stereoselective synthesis of oligofuranose due to the difficulty in the preparation of stable furanosyl donors[3] and lack of efficient protecting strategies in differentiation of hydroxy groups in furanosyl system.[4] The glycosyl imidate donors, initially proposed by Sinaÿ[5] and developed few years later by Schmidt,[6] is so far one of the most powerful alternatives in oligosaccharide synthesis. However, to the best of our knowledge, few examples of furanosyl trichloroacetimidates have been reported[7] and the regioselective glycosylation of oligofuranoses was inconceivably neglected. Herein, we present the use of perbenzoylated arabinofuranosyl trichloroacetimidates as the donors for regio- and stereoselective glycosylation with unprotected or partially protected carbohydrate acceptors. The efficiency of this method was further proved by arabinofuranosyl oligosaccharide syntheses.

Our initial interest was in the preparation of arabinogalactan moiety **3**. We found that coupling of perbenzoylated arabinofuranosyl trichloroacetimidate **1** with galactose residue **2** gave exclusively regioselective product **3**, while



a. TMSOTf , CH_2Cl_2. b. TMSOTf, CH_3CN.

Scheme 1



Convergent synthesis of 1→5-linked α-L-arabinofuranosyl oligosaccharides- a. TMSOTf, CH_2Cl_2, - 42 °C. b. BzCl, Pyr. c. $PdCl_2$, NaOAc, HOAc; then Cl_3CCN, K_2CO_3, CH_2Cl_2. d. $BnOC(NH)CCl_3$, TMSOTf. e. NaOMe, MeOH. f. $Pd(OH)_2$/C, H_2, EtOAc; then Ac_2O, Pyr. g. $Pd(OH)_2$/C, H_2, EtOAc; then BzCl, Pyr.

Scheme 2

the use of peracetylated arabinofuranosyl bromide as the donor gave a mixture of two regioisomers with excessive 1→3-linked product. This result stimulated us to investigate the regioselective coupling of donor **1** with a variety of partially protected acceptors. Thus, **1** was condensed with diol **4** in anhydrous CH_2Cl_2 in the presence of TMSOTf at – 42 °C giving difuranoside **5** in 85% yield. ^1H NMR of acetylated **5** ($J_{1',2'}$ <1 Hz and the chemical shift of H-3 was moved downfield to 5.29 ppm after acetylation) promised α-1→5 linkage in **5**. The same coupling reaction was applied to **1** and triol **6** to furnish **7** in 79% yield. The stereo- and regioselectivity in this process was assured by ^1H-^{13}C COSY of **7**, i.e. the characteristic coupling constant of $J_{1',2'}$ ($J_{1',2'}$ < 1 Hz in this case) indicated α stereoselectivity while C-5 (63.5 ppm in ^{13}C NMR) and downfield H-2, H-3 (5.09, 5.20 ppm, respectively) in its acetylated derivative confirmed 1→5 linkage of **7**.[8] When donor **1** was coupled with D-glucofuranose triol **12** in CH_2Cl_2, a sharply decreased yield was obtained (about 20%) due to the poor solubility of **12** in CH_2Cl_2. The same reaction proceeded in anhydrous CH_3CN gave 53% (corrected yield based on 28% recovered acceptor **12**) 1→6-linked difuranose **13**, together with ~10% by-product. When D-galactopyranose triol **8** and D-mannopyranose diol **10** were glycosylated with **1** in CH_2Cl_2, a very low regioselectivity was found in the formation of **9** while a moderate regioselectivity (3.4:1) was obtained in preference to compound **11**. Although we have no convincing evidence to rationalise the reaction, we thought the intermediate might be a sugar-sugar ortherester which rearranged *in situ* to give 1,2-*trans* linked product.[9]

Encourage by the results described above, we turned our attention on the facile synthesis of α-(1→5)-linked L-arabinofuranosyl oligosaccharides which are fragments in arabinogalactan and some of the Chinese Medicines.[10] Direct glycosylation of **1** with unprotected allyl α-L-arabinofuranoside **14** under the promotion of TMSOTf at –42 °C provided **15** regioselectively in 78% yield. Compound **15** was fully benzoylated with BzCl in pyridine, followed by deallylation ($PdCl_2$, NaOAc, HOAc) and activation (Cl_3CCN, K_2CO_3, CH_2Cl_2) to give difuranosyl donor **17** in 70% yield. Glycosylation of **17** with unprotected **14** as described above furnished homo-trisaccharide **18** easily (81%). In another route, **15** was benzylated using benzyl trichloroacetimidate and TMSOTf [11] to give difuranoside **19** which was subjected to Zemplén deacylation furnishing triol **20** (70% from **15**). Reaction of disaccharide donor **17** with triol **20** under the same glycosylation conditions generated homo-tetrasaccharide **21** in 79% yield. **21** was subjected to hydrogenolysis ($Pd(OH)_2$/C, H_2), followed by acetylation (→ **24**), deallylation ($PdCl_2$, NaOAc, HOAc) and activation (Cl_3CCN, K_2CO_3) obtained tetrasaccharide trichloroacetimidate **25** (65% from

21). Convergently, **21** was benzylated under mild acid condition (→ **22**) and then deacylated to give tetrasaccharide acceptor **23** (67% from **21**). 4 + 4 coupling reaction was carried out between **23** and **25** as described for the preparation of **15**, followed by debenzylation (H_2, $Pd(OH)_2/C$), benzoylation (→ **27**) and Zemplén deacylation to finish α-(1→5)-linked L-arabinofuranosyl octamer **28** (71% based on **23**).

In summary, we have shown here a very effective method for regio- and stereoselective synthesis of 1→5-linked α-L-arabinofuranosyl oligosaccharide using benzoylated arabinofuranosyl trichloroacetimidates as the glycosyl donors. The present work may thus open an unexplored route to other furanosyl oligosaccharides with much simplified procedures. Further investigation of the application of this new finding to build bioactive furanosyl oligosaccharides is in process and the biological, chemical and physical properties of the synthesized furanosyl oligomers will be published in due course.

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(8) Typical procedure: Furanosyl trichloroacetimidate (500 mg scale) and 0.95 equiv. of unprotected acceptor were dried together under high vacuum for 2 h, then dissolved in anhydrous CH_2Cl_2 (15 mL). TMSOTf (0.15 equiv.) in anhydrous CH_2Cl_2 (35 mL) was added dropwise at –42 °C with N_2 protection. The reaction mixture was stirred at –42 °C for 40 to 90 min, then neutralized with triethylamine, concentrated under reduced pressure, and purified on silica gel column with EtOAc–petroleum ether. All new compounds gave satisfactory elemental analysis results. Selected ^{13}C NMR (100 MHz, $CDCl_3$) are as follows: **7** 54.9 (C-5'), 63.5 (C-5), 77.5 (C-3), 78.1 (C-2), 79.5 (C-4), 81.8 (C-3'), 82.0 (C-2'), 85.4 (C-4'), 106.1 (C-1), 109.2 (C-1'). **24** 20.5, 20.6, 20.7, 20.9 (*C*H_3CO), 63.5, 65.0, 65.5, 65.9 (C-5^{I-IV}), 67.7 (C=C-*C*-), 104.4, 105.1, 105.7, 105.8 (C-1^{I-IV}), 76.4, 76.8, 77.2, 77.7, 80.9, 81.1, 81.3, 81.4, 81.6, 81.8, 81.9, 82.0 (C-2-4^{I-IV}), 117.4 (*C*=C-C-), 128.2-129.8 (C^{Ar}), 132.9 (C=*C*-C-), 133.2, 133.3, 133.4, 133.5, 133.6 (C^{Ar}), 165.0, 165.1, 165.5, 165.6, 166.1 (5 Ph*C*O), 169.6, 169.8, 170.0, 170.1 (4 CH_3*C*O). **27** 104.8, 105.3, 105.4, 105.7, 105.8, 105.9, 106.2, 106.6 (C-1^{I-VIII}). MALDI-TOF MS Calcd for $C_{142}H_{130}O_{50}$: 2634.7 [M]. Found: 2658.2 [M+Na]. **28** (D_2O): 66.0-66.5 (C-5), 68.1 (C=C-*C*-), 75.7-76.4 (C-3), 80.3-80.6 (C-4), 81.9-82.0 (C-2), 107.0-107.2 (C-1), 108.3 (C-1 on reducing end), 118.1 (*C*=C-C-), 133.1 (C=*C*-C-). ESMS Calcd for $C_{43}H_{70}O_{33}$: 1114.38 [M]. Found: 1115.3 [M+H].

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