Concise and Effective Synthesis of 1→2 α-Linked Mannopyranosyl Oligosaccharides and Related Antigenic Factor 34 and Dominant of Antigenic Factor 13

ZHU, Yu-Liang(朱玉亮) KONG, Fan-Zuo*(孔繁祚)

Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences, Beijing 100085, China

A highly concise and effective synthesis of 1→2 α-linked mannopyranosyl oligosaccharides was achieved *via* TMSOTf promoted condensation of the corresponding benzoylated monosaccharide alkyl orthoester. 1→2 α-Linked mannosyl di, trisaccharide, antigenic factor 34, and dominant of antigenic factor 13 were readily synthesized by the new method.

Keywords Oligosaccharides, orthoester, regio- and stereoselective synthesis

Candida species are opportunistic pathogens of humans which frequently cause severe systemic infections in patients with AIDS,[1] cancer,[2] and burns[3] as well as in those under immunosuppressive or radiation therapy.[4] Many *Candida* species and antigenic factors contain 1→2 α-linked mannopyranosyl oligosaccharides as reducing terminals of the cell wall mannan.[5-8] Synthesis of 1→2 α-linked mannose oligosaccharides has been achieved via multistep selective protection and deprotection using orthogonal masking groups.[9] In continuation of our previous orthoester-based research[10-12] here we report a new effective strategy for highly regio- and stereoselective synthesis of 1→2 α-linked mannopyranosyl oligosaccharides *via* condensation of benzoylated manno-orthoesters.

As outlined in Scheme 1, 2,3,4,6-tetra-*O*-acetyl-α-*D*-mannopyranosyl bromide (**1**) was transformed to the corresponding allyl orthoester in the presence of 2,4-lutidine and allyl alcohol, and subsequent Zemplén deacetylation (→**2**) and benzoylation furnished the orthoester **3**. In the presence of catalytic amount of TMSOTf, **3** was transformed to allyl 2-*O*-acetyl-3,4,6-tri-*O*-benzoyl-α--mannopyranosyl-(1→2)-3, 4, 6-tri-*O*-benzoyl-α-*D*-mannopyranoside (**4**) in a good yield (66%) while the rearrangement product allyl 2-*O*-acetyl-3,4,6-tri-*O*-benzoyl-α-*D*-mannopyranoside was the minor product (18%).[13] Formation of (1→2)-linked mannose disaccharide from acetylated mannose orthoester was firstly reported by Lindhorst.[14] However, the rather low yield (< 30%) and difficulty for further transformation limited the use of this finding. We were gratified to find that replacement of the acetyl of the mannose orthoester with benzoyl made a substantially different result for the TMS promoted transformation of the mannose orthoester, *i.e.* the condensation product disaccharide **4** was obtained as the major product (66%). Owing to the high yield and easy separation, large quantity preparation of **4** was carried out and further transformation of **4** was successfully achieved. Thus deallylation followed by trichloroacetimidation[15] gave the disaccharide donor **5** (82%) while selective deacetylation[16] at C-2 afforded acceptor **6** (93%).

Possible mechanism was shown on Scheme 2. There were two paths for the TMSOTf catalyzed transformation of orthoester: path 1 was the normal rearrangement affording the corresponding monosaccharide, while path 2 was the condensation of two orthoester molecules releasing one molecule of alkyl acetate.

* E-mail: fzkong@mail.rcee.ac.cn; Fax: 86-10-62923563

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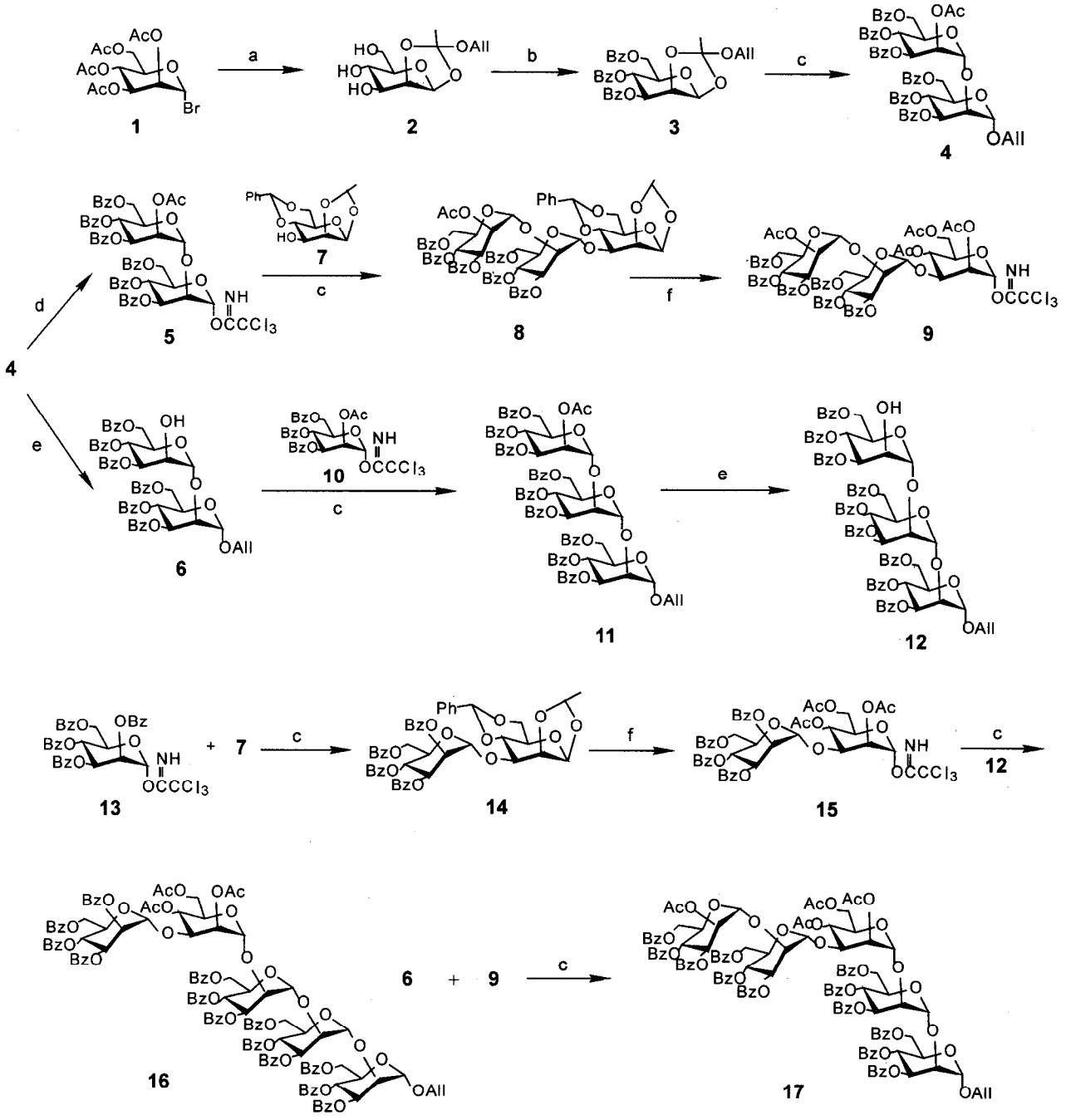
Scheme 1

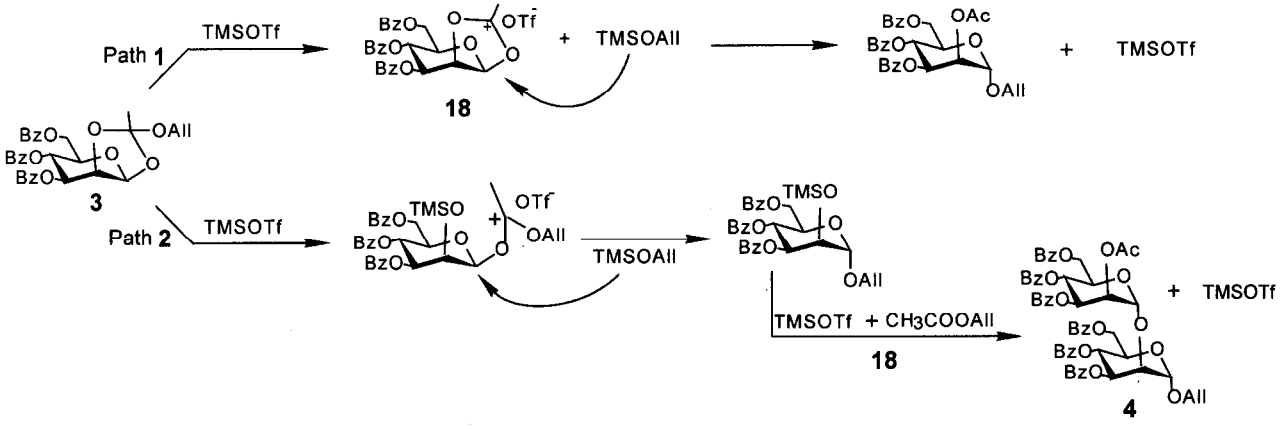


Conditions and reagents: (a) Allyl alcohol (4 equiv), lutidine (1 equiv); MeONa/MeOH; (b) BzCl/pyridine; (c) TMSOTf, CH_2Cl_2, 0.4 nm M.S., −42℃ to r.t.; (d) $PdCl_2$, CH_3COOH/CH_3COONa, r.t.; then CCl_3CN, CH_2Cl_2, DBU, r.t.; (e) CH_3COCl/CH_3OH, r.t.; (f) CF_3COOH (90%); Ac_2O, pyridine; NH_4HCO_3, DMF, r.t.; then CCl_3CN, CH_2Cl_2, DBU, r.t.

Based on the easy preparation of 1→2 α-linked mannose oligosaccharide, the fully protected pentasaccharide (**17**, corresponding to the dominant of antigenic factor 13[17]) was synthesized from coupling of disaccharide acceptor **6** with trisaccharide donor **9**, which was easily prepared from coupling of **5** with **7** followed by debenzylidenation and deethylidenation, then acetylation, selective 1-*O*-deacetylation and trichloroacetim-

idation. Similarly, a pentasaccharide (**16**, corresponding to antigenic factor 34[17]) was synthesized from condensation of the trisaccharide acceptor **12** with the disaccharide donor **15**, which was easily prepared from coupling of **13** with **7** followed by debenzylidenation and deethylidenation, then acetylation, selective 1-*O*-deacetylation and trichloroacetimidation.

Scheme 2



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13 Procedure for the preparation of **4** from **3**: To a stirred solution of **3** (5.74 g, 10 mmol) dissolved in anhydrous dichloromethane (50 mL) TMSOTf (50 μL, 0.03 equiv) was added dropwise at −42℃ with N_2 protection. The reaction mixture was stirred for 1 h, at the end of which time TLC (3/1 petroleum ether/ethyl acetate) indicated that the reaction was complete. Then the mixture was neutralized with triethylamine, concentrated under reduced pressure to dryness. Further purification by column chromatography (3/1 petroleum ether/ethyl acetate) gave **4** (3.79 g, 66%) as a colorless solid.

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18 All new compounds gave satisfactory elemental analysis. Selected physical data and ^{1}H NMR (400 MHz, $CDCl_3$) data are as follows: For **4**: m.p. 148—150℃, $[\alpha]_D^{20}$ + 3.0°(*c* 1.3, $CHCl_3$); ^{1}H NMR δ: 8.07—7.33 (m, 30H, ArH), 5.99 (t, *J* = 9.9 Hz, 1H), 5.90—5.85 (m, 4H), 5.70 (dd, *J* = 1.7, 3.0 Hz, 1H, H-2′), 5.28—5.18 (m, 2H, CH_2 = $CHCH_2$), 5.16 (d, *J* = 1.5 Hz, 1H), 5.11 (d, *J* = 1.7 Hz, 1H), 4.61—4.47 (m, 5H), 4.42—4.39 (m, 1H), 4.37 (dd, *J* = 1.5, 2.9 Hz, 1H), 4.15—4.13 (m 1H), 3.95—3.92 (m, 1H), 2.03 (s, 3H, CH_3CO). Anal. Calcd. for $C_{59}H_{52}O_{18}$: C 67.56, H 4.96; Found: C 67.60, H 4.92. For **16**: m.p. 140—143℃, $[\alpha]_D^{20}$ − 8.4° (*c* 1.1, $CHCl_3$); ^{1}H NMR δ: 8.14—7.25 (m, 65H, ArH), 6.35 (t, *J* = 10.0 Hz, 1H), 6.02 (t, *J* = 9.9Hz, 1H), 5.92—5.74 (m, 8H), 5.62 (dd, *J* = 9.9, 3.2 Hz, 1H), 5.58 (dd, *J* = 3.1, 1.5 Hz, 1H), 5.48 (d, 1H,), 5.30 (dd, 1H, CH_2 = $CHCH_2$), 5.27 (s, 1H), 5.22 (dd, 1H, CH_2 = $CHCH_2$), 5.13 (d, *J* = 1.5 Hz, 1H),

5.10 (s, 1H), 5.03 (s, 1H), 4.81—4.75 (m, 2H), 4.71 (dd, J = 3.1, 1.5 Hz, 1H), 4.60—4.40 (m, 8H), 4.47—4.42 (m, 2H), 4.27—4.15 (m, 4H), 3.93—3.85 (m, 2H), 3.82—3.78 (m, 1H), 2.52—3.48 (m, 1H), 2.22 (s, 3H, CH_3CO), 2.06 (s, 3H, CH_3CO), 2.04 (s, 3H, CH_3CO). Anal. Calcd. for $C_{130}H_{114}O_{42}$: C 66.50, H 4.86; Found: C 66.55, H 4.82. For **17**: m.p. 136—139℃, $[\alpha]_D^{20}$ − 9.9°(c 1.2, $CHCl_3$); ^{1}H NMR δ: 8.00—7.25 (m, 60H, ArH), 6.15 (t, J = 9.8 Hz, 1H), 5.97 (t, J = 9.8 Hz, 1H), 5.90—5.82 (m, 6H), 5.79 (dd, J = 9.8, 3.0 Hz, 1H,), 5.70 (dd, J = 9.9, 3.1 Hz, 1H), 5.65 (dd, J = 3.0, 1.5 Hz, 1H), 5.49 (dd, J = 3.0, 1.5 Hz, 1H), 5.36 (s, 1H), 5.32 (s, 1H), 5.26 (dd, J = 17.2, 1.4 Hz, 1H, CH_2 = $CHCH_2$), 5.20 (s, 1H), 5.18 (dd, J = 10.3, 1.4 Hz, 1H, CH_2 = $CHCH_2$), 5.08 (d, J = 1.6 Hz, 1H), 4.80 (s, 1H), 4.69—4.37 (m, 18H), 4.24 (dd, J = 3.0, 1.5 Hz, 1H), 4.17—4.12 (m, 1H), 3.79—3.75 (m, 1H), 2.14 (s, 3H, CH_3CO), 1.99 (s, 6H, $2CH_3CO$), 1.97 (s, 3H, CH_3CO). Anal. Calcd. for $C_{125}H_{112}O_{42}$: C 65.67, H 4.90; Found: C 65.64, H 4.93.

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