CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: int. code + (44) 1223-336033; e-mail: deposit@chemcrys.cam.ac.uk).

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Synthetic *Shigella* Vaccines: A Carbohydrate – Protein Conjugate with Totally Synthetic Hexadecasaccharide Haptens**

Vince Pozsgay*

Carbohydrate-based antibacterial vaccines are among the most successful carbohydrate pharmaceuticals.[1] The basis of using carbohydrates as vaccine components is that the capsular polysaccharides (CPs) and the O-specific polysaccharides (O-SPs) on the surface of pathogenic bacteria are both essential virulence factors and protective antigens, and that serum antibodies raised against these polysaccharides may provide immunity by killing the inoculum.[1] This principle led to the development of CP vaccines against Pneumococci and other Gram-positive bacteria. The inability of polysaccharides to elicit protective levels of anti-carbohydrate antibodies in infants could be overcome by their covalent attachment to proteins that conferred T-cell dependent properties.[2] This principle led to the construction of vaccines against *Haemophilus influenzae* b (Hib),[3] and in countries where these vaccines are routinely used, meningitis and other diseases caused by Hib have been virtually eliminated.[4] Extension of the conjugate technology to the O-SPs of Gram-negative bacteria provided a new generation of glycoconjugate vaccines that are undergoing various phases of clinical trials.[5]

While the immunogenicity and the efficacy of the glycoconjugate vaccines are established, their structural requirements are not well defined. Further improvement of the immunologic properties of conjugate vaccines requires the knowledge of the optimal size of the saccharide, the preferred method of its attachment to the protein, and the saccharide/protein ratio necessary for optimal immunogenicity. Success in this area will depend on the availability of well-defined saccharides that are representative of the native polysaccharides.[6]

Here we describe our approach to a hexadecasaccharide fragment[7] of the O-SP (**A**) of *Shigella dysenteriae* type 1,[8] a human pathogen that is a major causative organism of endemic and epidemic dysentery worldwide.[9]

→3)-α-L-Rha*p*-(1→2)-α-D-Gal*p*-(1→3)-α-D-Glc*p*NAc-(1→3)-α-L-Rha*p*-(1→
A

The target saccharide is equipped with a spacer as the aglycon portion. A heterobifunctional linker unit was appended to this end of the saccharide assembly for covalent attachment to human serum albumin (HSA) as a model carrier protein. The single-point attachment leaves the entire saccharide chain available for interaction with B cell receptors. The average number of saccharide chains attached to HSA is defined by matrix-assisted laser desorption ionization time of flight (MALDI-TOF) mass spectrometry.

The overall strategy to the target **21** (see below) called for the assembly of a tetrasaccharide repeating unit (**12**, **14,** see Scheme 1) in a form that may be used in an iterative fashion for blockwise construction of higher oligosaccharides.[10] In this endeavor we relied on our previous experience in synthesizing related compounds.[7, 11] Of particular importance was the realization that for the iterative building of a saccharide of this size, the tetrasaccharide frame along the polysaccharide chain should correspond to that shown by formula **A**. We also found that

1) the tetrasaccharide block can be most conveniently assembled in a stepwise fashion,
2) the Gal and the Rha synthons should be installed in a prefabricated form which allows the attachment of the subsequent residue after only one deprotecting step, and that
3) the use of a prefabricated synthon for the GlcN unit has no advantage on the overall yield.

Furthermore, we concluded that intermediates with multiple azide groups should be avoided because of the difficulties that may arise in their conversion to acetamido functions.[12]

The principles established in previous studies led to the selection of four monosaccharide building blocks **1**, **2**, **7**, and **11** that were prepared as reported for related synthons.[7, 11, 13] The assembly of the tetrasaccharide **12** started with the condensation of the rhamnose derivative **1** with the chloride **2** (Scheme 1, Table 1). The nonparticipating azido group of **2**

[*] Dr. V. Pozsgay
Laboratory of Developmental and Molecular Immunity
National Institute of Child Health and Human Development
National Institutes of Health
6 Center Drive MSC 2720, Bethesda, MD 20892-2720 (USA)
Fax: Int. code + (1) 301 402-9108
e-mail: vipo@helix.nih.gov

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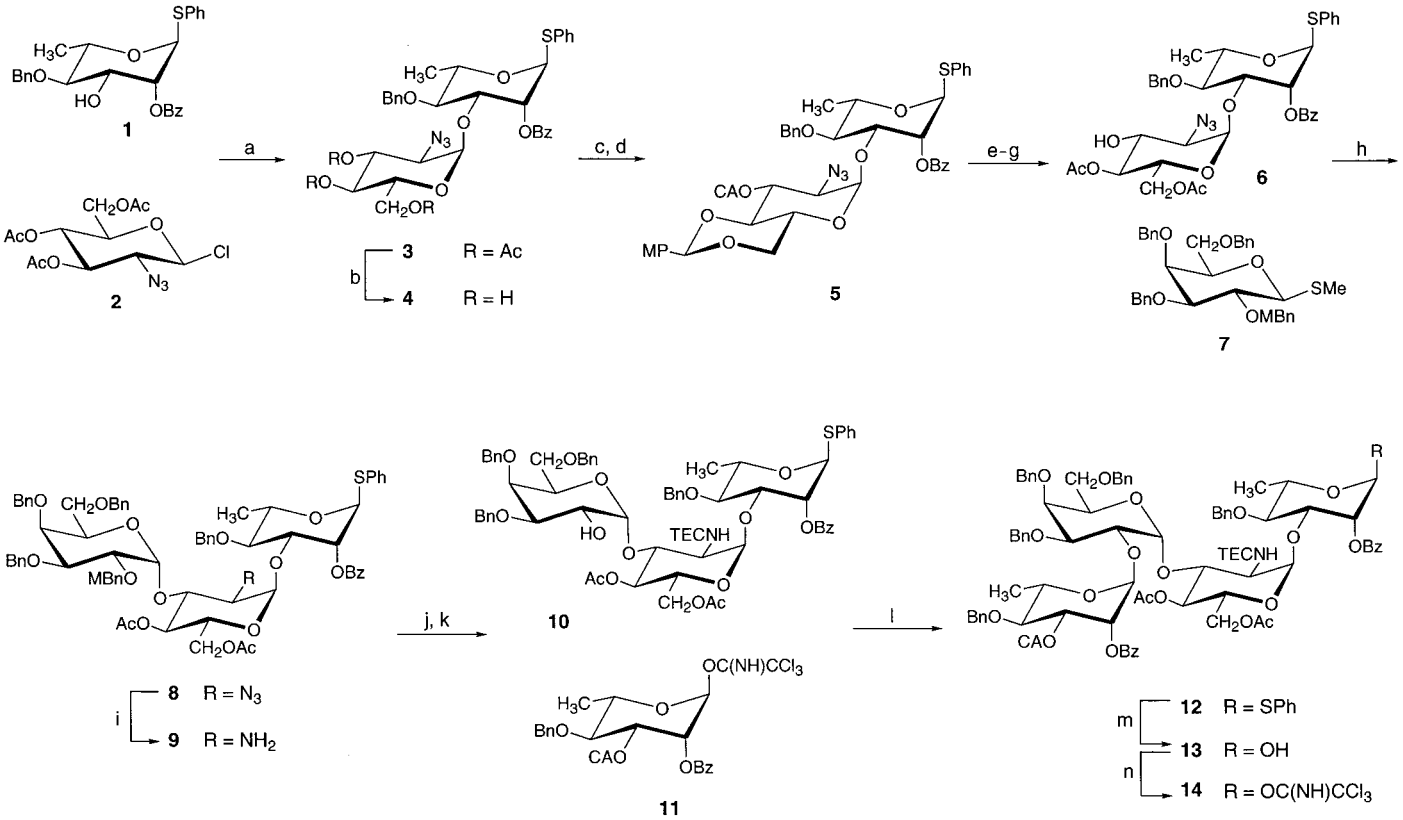

Scheme 1. a) **1** (1.6 equiv) CF_3SO_2OAg (1.5 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (0.9 equiv), CH_2Cl_2, 0 °C, 2 h, 64 %; b) $HBF_4 \cdot Et_2O$, MeOH, 23 °C, 72 h, 79 %; c) 4-methoxybenzaldehyde dimethylacetal (5.4 equiv), 10-camphorsulfonic acid (CSA) (cat), CH_2Cl_2, 23 °C, 20 min; d) $(ClCH_2CO)_2O$ (2.2 equiv), C_5H_5N, 0 °C, 10 min, 92 % for two steps; e) $HBF_4 \cdot Et_2O$, MeOH/CH_2Cl_2, 0 → 23 °C, 30 min; f) Ac_2O, C_5H_5N, 4-dimethylaminopyridine (cat), 0 → 23 °C, 1 h; g) thiourea (5.5 equiv), DMF/C_5H_5N, 23 °C, 24 h, 71 % for three steps; h) **7** (1.4 equiv), CF_3SO_2OMe (1.7 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (2.9 equiv), Et_2O, 23 °C, 66 h; i) PPh_3 (2.2 equiv), CH_2Cl_2, 35 – 40 °C, 48 h, then H_2O, 35 – 40 °C, 24 h, 58 % for three steps; j) $CCl_3CH_2OC(O)Cl$ (5.8 equiv), $NaHCO_3$, acetone/H_2O, 0 °C, 3 min; k) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2.0 equiv), CH_2Cl_2/H_2O, 23 °C, 3 h, 82 % for two steps; l) **11** (3.5 equiv), $BF_3 \cdot Et_2O$ (0.33 equiv), CH_2Cl_2, 0 °C, 2 h, 89 %; m) $Hg(OCOCF_3)_2$ (2.0 equiv), CH_2Cl_2/H_2O, 30 min, 93 %; n) CCl_3CN (9.7 equiv), DBU (0.5 equiv), CH_2Cl_2, 23 °C, 1 h, 85 %. Bn = benzyl, Bz = benzoyl, CA = monochloroacetyl, MBn = 4-methoxybenzyl, MP = 4-methoxyphenyl.

assured sufficient stereocontrol to provide the disaccharide **3** in an acceptable yield. Treatment[11c] of **3** with HBF_4 chemoselectively removed the acetyl groups (→**4**), while the benzoate at O-2 of the rhamnose moiety survived this treatment. Next, the triol **4** was transformed to the diacetate **6**. First the 4-OH and 6-OH groups of the GlcN unit were temporarily protected to allow a monochloroacetyl group to be installed at O-3 of this residue (→**5**). Subsequent mild acid hydrolysis followed by O-acetylation and selective removal of the chloroacetyl group afforded **6** (71 % overall yield from **5**). The Gal-GlcN-Rha trisaccharide was prepared by selective activation of the methylthio galactoside[11c, d] **7** with MeOTf[14] (Tf = F_3CSO_2) in the presence of the phenylthio glycoside **6** to provide **8** in a highly stereoselective reaction. The latter was converted to the amino derivative **9** by the Staudinger reaction using PPh_3 and subsequent hydrolysis providing a 58 % overall yield for three steps. Next, the free amino group in **9** was protected with a 2,2,2-trichloroethoxycarbonyl (TEC) group[15] followed by oxidative removal[16] of the 4-methoxybenzyl group to afford the trisaccharide **10** in 82 % overall yield for two steps. The synthesis of the fully protected tetrasaccharide repeating unit was completed by reaction of **10** with the rhamnose donor **11** under $BF_3 \cdot Et_2O$ activation to afford **12** in 89 % yield.

Experience gained with a tetrasaccharide donor similar to **12** having an anomeric phenylthio group as the leaving group indicated that while such a compound can be successfully coupled with a reactive primary alcohol under I_2/TfOH activation,[17] the method is unsatisfactory for the planned iterative chain elongation. More favorable observations were arrived at with the imidate method.[18] Therefore, the phenylthio glycoside **12** was hydrolyzed with $Hg(OCOCF_3)_2$[19] to afford the hemiacetal **13** as a mixture of the α and β anomers in 93 % yield, which was converted to the imidate **14** as the α anomer, by using CCl_3CN and a catalytic amount of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU)[18b] in 85 % yield.

As the first step in the iterative condensation sequence, the tetrasaccharide donor **14** was treated with an excess of the aglycon moiety **15** under Schmidt conditions[18] to provide the tetrasaccharide glycoside **16** in 68 % yield (Scheme 2, Table 1). The subsequent step involved the removal of the chloroacetyl group under essentially neutral conditions to afford the acceptor **17** in 96 % yield for the subsequent iterations. Three repetitive cycles involving glycosylation with the tetrasaccharide donor **14** and dechloroacetylation gave the desired target compound **19** in a protected form. Sequential deblocking that involved replacement of the TEC groups by acetyl groups (Cd/AcOH, then Ac_2O),

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Table 1. Selected ^{1}H (300 MHz) and ^{13}C NMR data (75 MHz) of **1**, **3**–**6**, **9**–**14**, **16**–**19** (in $CDCl_3$), and **21** (in D_2O).

1: ^{1}H NMR: $\delta = 5.60$ (d, 1H, $J = 3.4$ Hz), 5.54 (d, 1H, $J = 1.7$ Hz), 4.88, 4.75 (2d, 2H, $J \approx 11$ Hz), 4.29 (dq, 1H), 4.20 (ddd, 1H), 3.56 (t, 1H, $J = 9.4$ Hz), 1.40 (d, 3H, $J = 6.2$ Hz); ^{13}C NMR: $\delta = 85.8$, 81.6, 75.1, 74.8, 70.9, 68.7, 18.0

3: ^{1}H NMR: $\delta = 5.88$ (dd, 1H), 5.57 (d, 1H, $J = 1.6$ Hz), 5.44 (dd, 1H, $J = 10.5$, $J = 9.3$ Hz), 5.36 (d, 1H, $J = 3.6$ Hz), 5.00 (dd, 1H, $J = 9.6$), 4.93, 4.81 (2d, 2H), 4.37 (dq, 1H), 3.72 (t, 1H, $J = 9.6$), 3.31 (dd, 1H), 2.10, 2.02, 1.89 (3s, 9H), 1.45 (d, 1H); ^{13}C NMR: $\delta = 93.1$, 86.1, 79.6, 75.9, 70.1, 69.3, 68.9, 68.0, 67.5, 61.6, 60.5, 20.7, 20.6, 20.5, 17.9

4: ^{1}H NMR: $\delta = 5.84$ (d, 1H, $J = 3.1$ Hz), 5.53 (d, 1H, $J = 1.6$ Hz), 5.20 (d, 1H, $J = 3.8$ Hz), 4.81, 4.62 (2d, 2H, $J \approx 11$ Hz), 4.30 (dq, 1H), 4.20 (dd, 1H), 3.12 (dd, 1H, $J = 10.3$ Hz), 1.32 (d, 1H, $J = 6.2$ Hz); ^{13}C NMR: $\delta =$ 93.7, 85.8, 79.5, 75.8, 73.2, 71.3 (2C), 69.9, 69.3, 69.0, 62.2, 61.0, 17.8

5: ^{1}H NMR: $\delta = 5.90$ (d, 1H, $J = 3.2$ Hz), 5.63 (t, 1H, $J = 10.0$ Hz), 5.56 (d, 1H, J = 1.6 Hz), 5.43 (s, 1H), 5.38 (d, 1H, $J = 3.6$ Hz), 4.97, 4.70 (2d, 2H, $J \approx 11$ Hz), 4.37 (dq, 1H), 3.22 (dd, 1H, $J = 10.3$ Hz), 1.30 (d, 1H, $J =$ 6.2 Hz); ^{13}C NMR: $\delta = 101.6$, 93.9, 85.9, 79.8, 78.7, 76.6, 73.0, 70.6, 69.3, 68.8, 68.4, 62.9, 61.0, 55.3, 40.5, 17.8

6: ^{1}H NMR: $\delta = 5.87$ (dd, 1H), 5.56 (d, 1H, $J = 1.6$ Hz), 5.29 (d, 1H, $J =$ 3.9 Hz), 4.84 (dd, 1H, $J = 9.3$ Hz), 4.83, 4.75 (2d, 2H), 4.35 (dq, 1H), 4.26 (dd, 1H, $J = 3.2$, 9.5 Hz), 4.18–3.93 (m, 4H), 3.69 (t, 1H), 3.24 (dd, 1H, $J =$ 10.2 Hz), 2.11, 1.99 (2s, 6H), 1.41 (d, 1H, $J = 6.2$ Hz); ^{13}C NMR: $\delta = 93.0$, 86.0, 79.7, 75.5, 73.0, 70.8, 70.2, 69.2, 69.0, 67.5, 63.0, 61.7, 20.8, 20.7, 17.9

9: ^{1}H NMR: $\delta = 5.83$ (dd, 1H), 5.55 (d, 1H, $J = 1.4$ Hz), 5.13 (d, 1H, $J =$ 3.7 Hz), 5.06 (dd, 1H, $J = 9.1$, 9.4 Hz), 4.88 (2H), 4.75, 4.70, 4.65, 4.58, 4.53, 4.48 (7d, 8H), 3.72 (s, 3H), 2.93 (dd, 1H, $J = 9.5$ Hz), 2.10, 1.74 (2s, 6H), 1.44 (d, 1H, $J = 6.2$ Hz); ^{13}C NMR: $\delta = 99.2$, 95.5, 86.1, 83.0, 79.8, 78.7, 76.3, 75.7, 75.3, 74.6, 73.3 (3C), 72.8, 70.3, 69.8, 69.2, 68.9, 68.8, 67.7, 62.0, 55.5, 55.2, 20.8, 18.0

10: ^{1}H NMR: $\delta = 6.05$ (m, 1H), 5.80 (dd, 1H, $J = 3.2$ Hz), 5.46 (d, 1H, $J =$ 1.6 Hz), 5.30 (d, 1H, $J = 3.2$ Hz), 5.11 (dd, 1H, $J \approx 9.2$ Hz), 4.34 (dq, 1H), 2.92 (dd, 1H, $J = 9.8$ Hz), 2.11, 1.92 (2s, 6H), 1.43 (d, 1H, $J = 6.1$ Hz); ^{13}C NMR: $\delta = 99.4$, 95.8, 92.9, 86.2, 79.8, 79.5, 75.4, 74.2, 73.9, 73.5, 73.2, 73.1, 73.0, 72.4, 70.6, 69.8, 69.4, 69.3, 68.9, 68.1, 61.6, 54.2, 20.8, 20.7, 17.9

11: ^{1}H NMR: $\delta = 6.32$ (d, 1H, $J = 1.4$ Hz), 5.72 (dd, 1H), 5.52 (dd, 1H, $J =$ 3.1, 9.7 Hz), 4.74, 4.68 (2d, 2H, $J \approx 11$ Hz), 4.13 (dq, 1H), 3.94, 3.85 (2d, 2H, $J \approx 15$ Hz), 3.73 (t, 1H), 1.45 (d, 3H); ^{13}C NMR: $\delta = 94.8$, 77.8, 75.5, 73.6, 70.7, 68.7, 40.6, 18.0

12: ^{13}C NMR: $\delta = 170.8$, 168.9, 165.8, 165.2, 165.0, 153.6, 98.1, 97.4, 95.9, 92.2, 86.1, 79.8, 79.6, 78.5, 75.5, 74.9, 74.1, 73.7, 73.5, 73.3, 72.9, 72.5, 72.3, 71.6, 71.3, 71.0, 70.3, 70.2, 69.4, 69.3, 68.0, 67.9, 62.0, 53.8, 40.6, 20.8, 17.9

13: ^{1}H NMR: $\delta = 5.94$ (d, 1H, $J \approx 10$ Hz), 5.62, 5.58 (2dd, 2H), 5.47 (dd, 1H, $J = 3.2$ Hz, $J = 9.6$ Hz), 5.42 (br. s, 1H), 5.28, 5.13 (2br. d, 2H), 5.24 (t, 1H), 2.06, 1.82 (2s, 6H), 1.41, 1.27 (2d, 2H, $J \approx 6.3$ Hz)

14: ^{1}H NMR: $\delta = 6.26$ (d, 1H, $J =$ 2.0 Hz), 5.99 (d, 1H, $J \approx 9.9$ Hz), 5.74, 5.63 (2dd, 2H), 5.50 (dd, 1H, $J = 3.3$, 9.7 Hz), 5.43 (d, 1H, $J = 1.5$ Hz), 5.32 (t, 1H, $J \approx 9$ Hz), 5.29, 5.14 (2d, 2H, $J \approx 3.5$ Hz), 2.06, 1.82 (2s, 6H), 1.41, 1.27 (2d, 2H, $J \approx 6.3$ Hz)

16: ^{1}H NMR: $\delta = 5.90$ (d, 1H, $J \approx 9$ Hz), 5.62 (dd, 1H, $J = 1.8$, 3.3 Hz), 5.52 (dd, 1H), 5.48 (dd, 1H, $J = 9.6$ Hz), 5.41 (d, 1H), 5.29 (t, 1H, $J \approx 9$ Hz), 5.23, 5.12 (2d, 2H, $J \approx 3.5$ Hz), 4.99, 4.75, 4.70, 4.62, 4.55, 4.49 (6d, 6H), 4.77 (br. s, 1H), 2.32 (t, 2H), 2.06, 1.81 (2s, 6H), 1.36, 1.26 (2d, 6H); ^{13}C NMR: $\delta = 174.0$, 170.7, 168.7, 165.7, 165.2, 153.6, 98.1, 97.5, 97.4, 95.8, 92.5, 79.8, 79.6, 78.5, 75.4, 74.81, 74.0, 73.7, 73.5, 73.2, 72.9, 72.4, 72.2, 71.9, 71.4, 70.7, 70.3, 69.9, 69.3, 68.0, 67.9, 67.8, 67.6, 61.6, 54.0, 51.5, 40.5, 33.8, 28.9, 25.5, 24.5, 20.7, 20.6, 17.9, 17.8

17: ^{1}H NMR: $\delta = 5.89$ (d, 1H, $J \approx 9$ Hz), 3.66 (s, 3H), 2.31 (t, 2H), 2.05, 1.82 (2s, 6H), 1.36, 1.29 (2d, 6H); ^{13}C NMR: $\delta = 97.94$, 97.86, 97.6, 95.8, 92.5, 81.2, 79.8 (2C), 75.5, 75.1, 74.1, 73.7, 73.3, 73.0, 72.9, 72.6, 72.1, 71.8, 70.9, 70.3, 70.1, 70.0, 69.4, 68.1, 67.9 (3C), 67.7, 61.6, 54.0, 51.5, 33.9, 29.0, 25.6, 24.6, 20.9, 20.8, 18.1, 18.0

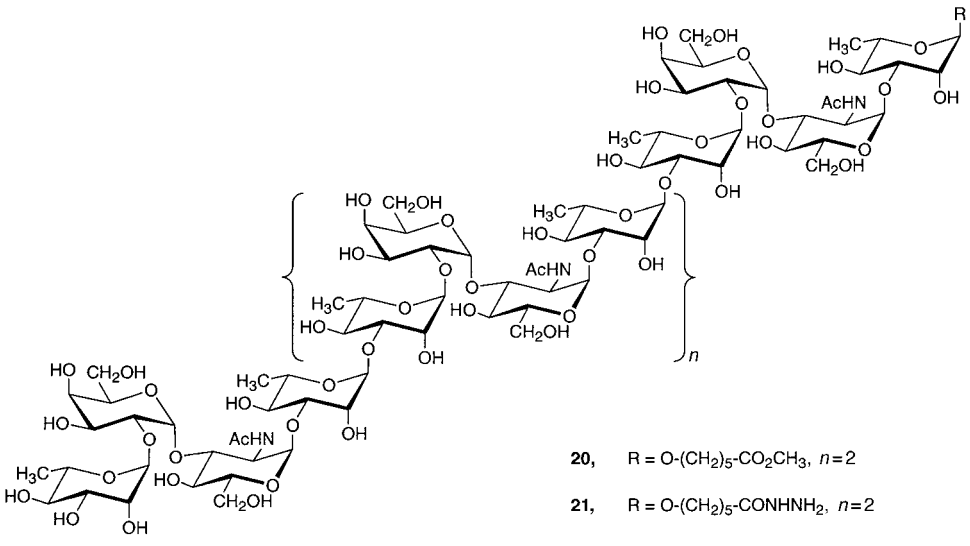
18: ^{13}C NMR: $\delta = 170.7$, 170.5 (2C), 170.43, 170.40, 169.83, 169.80, 169.6, 169.4, 168.87, 168.83 (2C), 165.8, 165.5, 165.4, 165.3, 165.2, 165.1, 164.81, 164.77, 99.5, 99.3 (3C), 98.1, 98.0 (5C), 97.4, 96.1, 94.32, 94.27, 93.9, 61.0, 60.8, 60.7 (2C), 51.6, 51.3, 51.1 (2C), 40.4, 33.8, 28.9, 25.5, 24.5, 23.1, 22.8 (2C), 22.6, 20.92, 20.86 (3C), 20.7, 20.4 (3C)

19: ^{1}H NMR: $\delta = 5.77$, 5.75 (2H), 5.74 (3d, 4H, $J \approx 9$ Hz), 2.32 (t, 2H, $J \approx$ 7.5 Hz), 1.98, 1.84, 1.81, 1.79, 1.72 (9H), 1.71 (6H), 1.59, 1.58, 1.47 (9s, 36H); ^{13}C NMR: $\delta = 174.0$, 170.7, 170.53 (2C), 170.50, 170.3, 169.9, 169.8, 169.7, 169.0, 168.9 (3C), 166.1, 165.5, 165.46, 165.4, 165.3, 165.1, 164.9, 164.8, 99.3 (4C), 98.4, 98.2, 98.1 (5C), 97.5, 95.4, 94.4, 94.3, 94.0, 61.1, 60.7, 60.0 (2C), 51.5, 51.3, 51.2 (2C), 33.9, 29.7, 25.6, 24.6, 23.1, 22.9 (2C), 22.7, 20.98, 20.94, 20.93 (2C), 20.8, 20.4 (3C), 18.1, 18.0 (2C), 17.95, 17.90, 17.74 (2C), 17.7

21: ^{1}H NMR: $\delta = 5.59$ (d, 4H, $J \approx 3.4$ Hz), 5.11 (d, 3H, $J \approx 1.6$ Hz), 5.08 (d, 1H, $J \approx 1.7$ Hz), 5.06 (d, 3H, $J \approx 1.6$ Hz), 5.04 (d, 3H, $J \approx 3.6$ Hz), 5.00 (d, 1H, $J \approx 3.5$ Hz), 4.80 (d, 1H, $J \approx 1.7$ Hz), 2.06 (s, 9H), 2.05 (s, 3H), 1.34 (d, 9H, $J \approx 6.1$ Hz), 1.31 (d, 3H, $J \approx 6.3$ Hz), 1.30 (d, 12H, $J \approx 6.1$ Hz); ^{13}C NMR: $\delta = 102.6$ (3C), 102.2, 102.1 (3C), 98.4 (4C), 94.9 (4C), 61.4 (4C), 61.0 (3C), 60.9, 52.7 (4C), 28.8, 26.1, 25.6, 25.5, 22.8 (4C), 17.6 (3C), 17.4 (4C), 17.3

removal of the acyl protecting groups under Zemplén conditions, and hydrogenolytic cleavage of the benzyl groups afforded the target hexadecasaccharide as the methyl ester **20** from which the hydrazide **21** (Table 1) was obtained by treatment with hydrazine in a combined yield of 26% for four steps from **19**.

The acylation of the saccharide hydrazide **21** with the linker moiety[20] **22** was promoted by 1,2-dicyclohexylcarbodiimide (DCC), furnishing the intermediate acetal **23** that was deprotected with AcOH under mild conditions to afford the aldehyde **24**[21] (Scheme 3). Exposure of a solution of the linker-armed hexadecasaccharide and human serum albumin to $NaCNBH_3$ at pH 7[22] afforded the glycoconjugate **25** that was determined by MALDI-TOF mass spectrometry to have



20, R = O-$(CH_2)_5$-CO_2CH_3, $n = 2$

21, R = O-$(CH_2)_5$-$CONHNH_2$, $n = 2$

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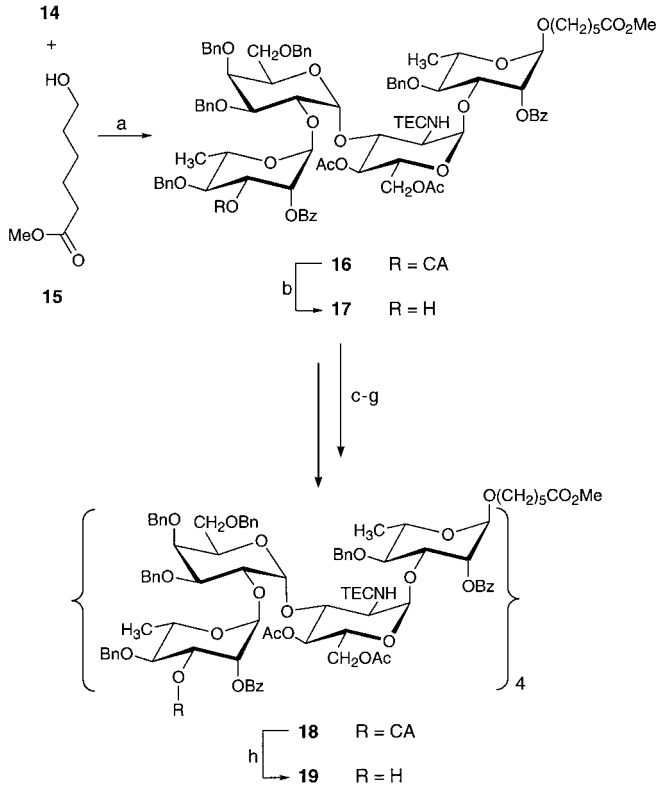
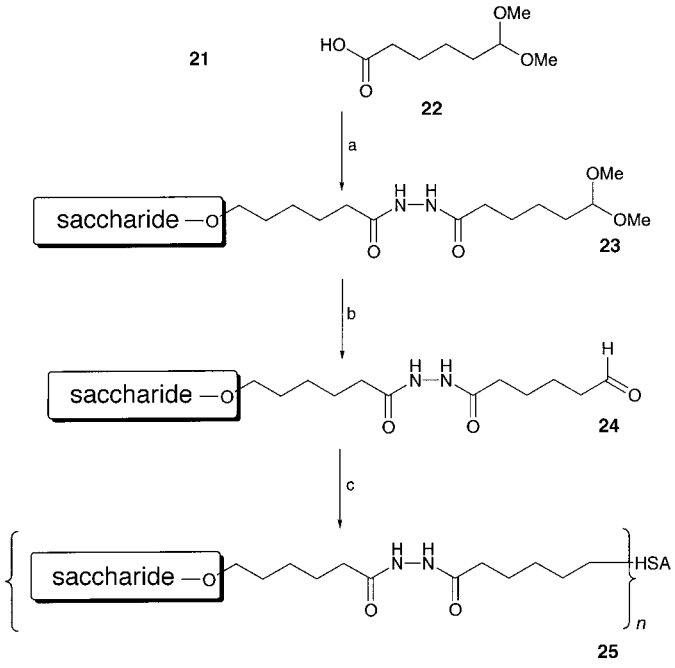


Scheme 2. a) **15** (3.5 equiv), $BF_3 \cdot Et_2O$ (1.4 equiv), CH_2Cl_2, 0 °C, 2 h, 68 %; b) thiourea (45 equiv), DMF/C_5H_5N, 23 °C, 24 h, 96 %; c) **14** (1.5 equiv), $BF_3 \cdot Et_2O$ (3.1 equiv), CH_2Cl_2, 0 °C, 15 min, 91 %; d) thiourea (24 equiv), DMF/C_5H_5N, 23 °C, 24 h, 82 %; e) **14** (2 equiv), $BF_3 \cdot Et_2O$ (4 equiv), CH_2Cl_2, 0 °C, 3 h; f) thiourea (33 equiv), DMF/C_5H_5N, 23 °C, 24 h, 62 % for two steps; g) **14** (3 equiv), $BF_3 \cdot Et_2O$ (10 equiv), CH_2Cl_2, 0 °C, 3 h, 48 %; h) thiourea (120 equiv), DMF/C_5H_5N, 23 °C, 24 h, 82 %.



Scheme 3. a) **22** (50 equiv), 1,3-dicyclohexylcarbodiimide (50 equiv), MeOH, 23 °C, 24 h; b) AcOH/H_2O, pH 2.7, 23 °C, 4 h; c) human serum albumin, pH 7 borate-phosphate buffer, $NaCNBH_3$ (15 equiv), 23 °C, 3 d, 32 % for three steps.

an average molecular weight of 93 kDa, and a molecular weight range of 83 – 103 kDa.[23] This corresponds to an average incorporation level of 11 saccharide chains per albumin molecule and an overall coupling efficiency of 32 %. We note that the tetra-, octa-, and the dodecasaccharide intermediates were likewise deprotected, equipped with the linker unit, and coupled to HSA, thus affording a series of compositionally related glycoconjugates for immunological studies.

In summary we have prepared the most complex, structurally defined synthetic carbohydrate – protein conjugate yet reported. The syntheses relied mostly on the Schmidt glycosylation, which proved to be highly efficient. This method as tested here offers a challenge against which new glycosylation methods should be evaluated as part of their performance test. Further improvements in the conjugation technology and preclinical evaluation of the synthetic glycoconjugates are in progress.

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Correlation between ^{51}V NMR Chemical Shift and Reactivity of Oxovanadium(v) Catalysts for Ethylene Polymerization**

Michael Bühl*

Olefin polymerization is one of the most important industrial applications of organometallic catalysts.[1] The most widely used catalysts in both homo- and heterogeneous reactions are of the Ziegler type, that is, based on Ti and Zr species along with certain cocatalysts.[2–4] The key step (not necessarily the rate-determining one) is the insertion of the olefin into a metal – carbon bond. Several such reactions and thus many potential catalysts for olefin polymerization are known. Silica-supported vanadium catalysts have attracted some attention in this context.[5] The oxidation state of the active vanadium species is still being debated;[5] low-valent species have been typically assumed, but studies on a soluble model compound have indicated that vanadium in the oxidation state v can also be catalytically active.[6] Upon addition of alkylaluminum reagents the simpler model compound **1** also shows mild catalytic activity for ethylene polymerization.[7] From multinuclear NMR spectroscopy it has been concluded that in the active catalyst, the organoaluminum compound is coordinated to the terminal oxygen atom of **1**.[7]

$[VO(CH_2SiMe_3)_3]$ **1** $[VOMe_3]$ **2** $[V(O\cdots AlH_3)Me_3]$ **3**

Recent calculations for model systems **2** and **3**, employing gradient-corrected levels of density functional theory (DFT), have corroborated this conclusion and have outlined a plausible mechanism for ethylene polymerization by **3** [Eq. (1)].[8] The rate-determining step is ethylene insertion into a V – C bond

$$[V(O\cdots AlH_3)Me_3] + H_2C{=}CH_2 \xrightarrow{\mathbf{3(TS)}} [V(O\cdots AlH_3)(CH_2CH_2Me)Me_2] \quad (1)$$

3

via the transition structure **3(TS)**, which has approximate square – pyramidal coordination about the vanadium center.

The role of the cocatalyst is addressed here in more detail, and the dependence of the computed insertion barrier on the specific Lewis acid is examined. As the latter is also found to affect the chemical shifts of the reactant complex substantially, it is suggested that prospective cocatalysts may be identified by ^{51}V NMR spectra of their adducts with, for example, **1**.

Apart from **3**, model catalysts $[V(O\cdots X)Me_3]$ derived by addition of Lewis acids X have been investigated: none (**2**), Li^+ (**4**), SbF_5 (**5**), and H^+ (**6**). Absolute and zero-point energies[9,10] of reactant minima and transition states, as well as the resulting barriers are collected in Table 1, and the transition structures are displayed in Figure 1. As expected,

[*] Dr. M. Bühl
Organisch-chemisches Institut der Universität
Winterthurerstrasse 190, CH-8057 Zürich (Switzerland)
Fax: Int. code + (41) 1-635 6812
e-mail: buehl@oci.unizh.ch

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