Pergamon

Tetrahedron Letters 39 (1998) 9143–9146

TETRAHEDRON LETTERS

Synthesis of Dimeric Lewis X Antigenic Determinant with azido-type spacer arm by a Sequence of Regioselective Glycosylation Steps

Santiago Figueroa-Pérez and Vicente Verez-Bencomo

Laboratory of Synthetic Antigens, Facultad de Química, Universidad de la Habana, Ciudad Habana, CUBA 10400

Received 29 June 1998; revised 29 September 1998; accepted 30 September 1998

Abstract: A new regioselective glycosylation strategy was used to develop a highly efficient synthesis of the dimeric Lewis X determinant linked to an azido type spacer arm. Regioselective galactosylation of 3,4 glucosamine diols **2** and **3** with galactose donor **4**, followed by fucosylation provided two trisaccharide building blocks **9** and **10**. The final condensation involved a 3b-regioselective glycosylation of the 2b,3b trisaccharide diol **11** in good yields. © 1998 Elsevier Science Ltd. All rights reserved.

A series of glycosphingolipids expressing extended polyfucosylated type-2 oligosaccharide sequences (Le^y-Le^x, Le^x-Le^x, Le^x-Le^x-Le^x) have been shown to accumulate in several adenocarcinoma cells.[1] The carbohydrate epitopes represented by these complex structures have been found to display higher degree of tumor-association than simpler parent structures such as Le^x or Le^y. The increasing interest and demand of these types of compounds for cancer immunodiagnosis and immunotherapy is one of the leading driving forces for the development of highly efficient oligosaccharide synthesis.

The protection-deprotection strategy for the synthesis of acceptors containing only a single free hydroxyl group is still a long and tedious process. Indeed for medium to large oligosaccharides, like dimeric Le^x determinant, it becomes, to a certain degree, the limiting factor,[2] despite the enormous progress achieved through the implementation of new more effective donors, coupling procedures and concepts such as the armed-disarmed strategy.

Regioselective glycosylation strategies are currently used to minimize the protecting group manipulations, and are based in the differential reactivity of the unprotected hydroxyl groups in a sugar moiety. This old concept is now attracting a renewed interest, because the factors influencing the outcome of the reaction can be manipulated to increase or even reverse the usual regioselectivity. The hydroxyl group reactivity pattern usually depends upon the nature of the surrounding protecting group substitution. Furthermore, the absent of a protective group in a neighbor position generally induces an improvement in the coupling yields.

In the present paper we outline a very straightforward strategy for the synthesis of dimeric Le^x hexasaccharide **1** (figure 1) that make use of regioselective glycosylation process at crucial steps.

PII: S0040-4039(98)02104-2

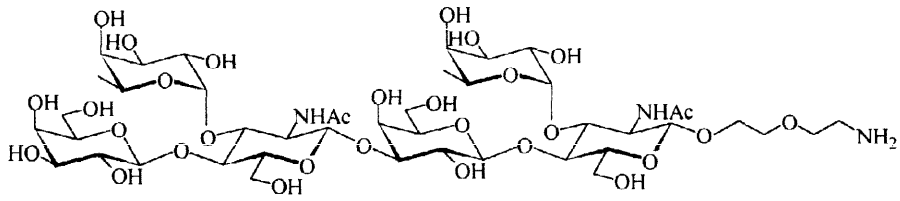

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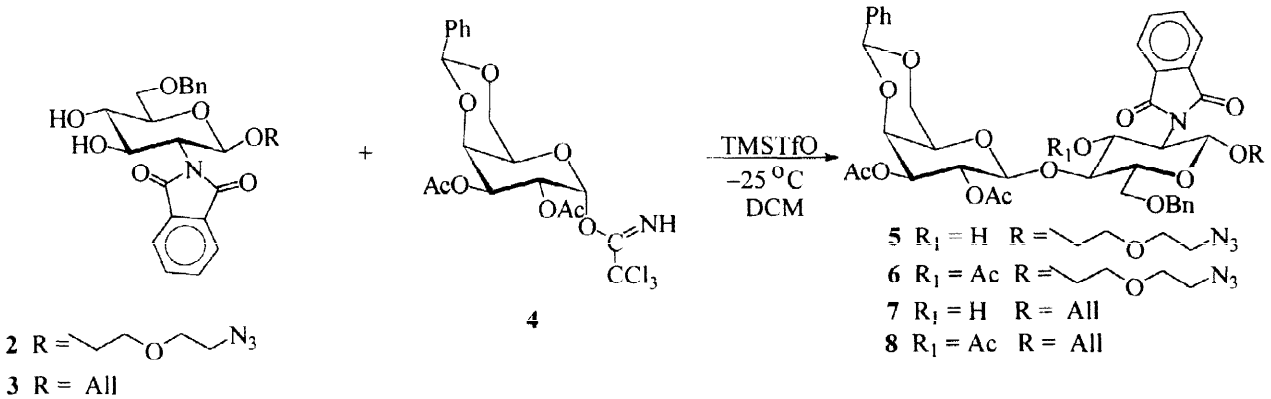
Figure 1: Amino-spacered dimeric Le^x hexasaccharide.

The usual reactivity of a 3,4-diol in a glucosamine acceptor has been shown[3] to be reversed in a glycosylation reaction by the use of the phthalimido function at C-2. This reaction, that afford a mixture of products with a strong predominance of a β1-4 compound, has been fixed to give only the desired β1-4 isomer by changing the phthalimido protecting group by the bulkier tetrachlorophthalimido.[4] In our current studies, we also attained a complete regiospecific galactosylation of similar diol acceptors **2**[5] and **3**[6] bearing a phthalimido-protecting group, by using a 4,6-benzylidene galactosyl donor. The presence of a cis-decalin bicyclic system has shown to have a profound effect on the donor properties.[7]

The β1→4 disaccharides **5** and **7** were obtained in a 81 % yield (Scheme 1) with complete regio- and stereoselectivity, using a slight excess of the galactosyl imidate (1.2 eq) **4**[8] under trimethylsilyl trifluoromethanesulfonate (TMSTfO) catalysis. The 1-3 isomer was not detected neither in the TLC analysis of the reaction mixture, nor in the NMR spectrum of the crude product. The structures were firmly established by NMR characterization of compound **5** and **7** and also of their acetylated derivatives **6** and **8**.[9]

Scheme 1



2 R = $\sim\!\sim\!O\!\sim\!\sim N_3$

3 R = All

4

5 R_1 = H R = $\sim\!\sim\!O\!\sim\!\sim N_3$

6 R_1 = Ac R = $\sim\!\sim\!O\!\sim\!\sim N_3$

7 R_1 = H R = All

8 R_1 = Ac R = All

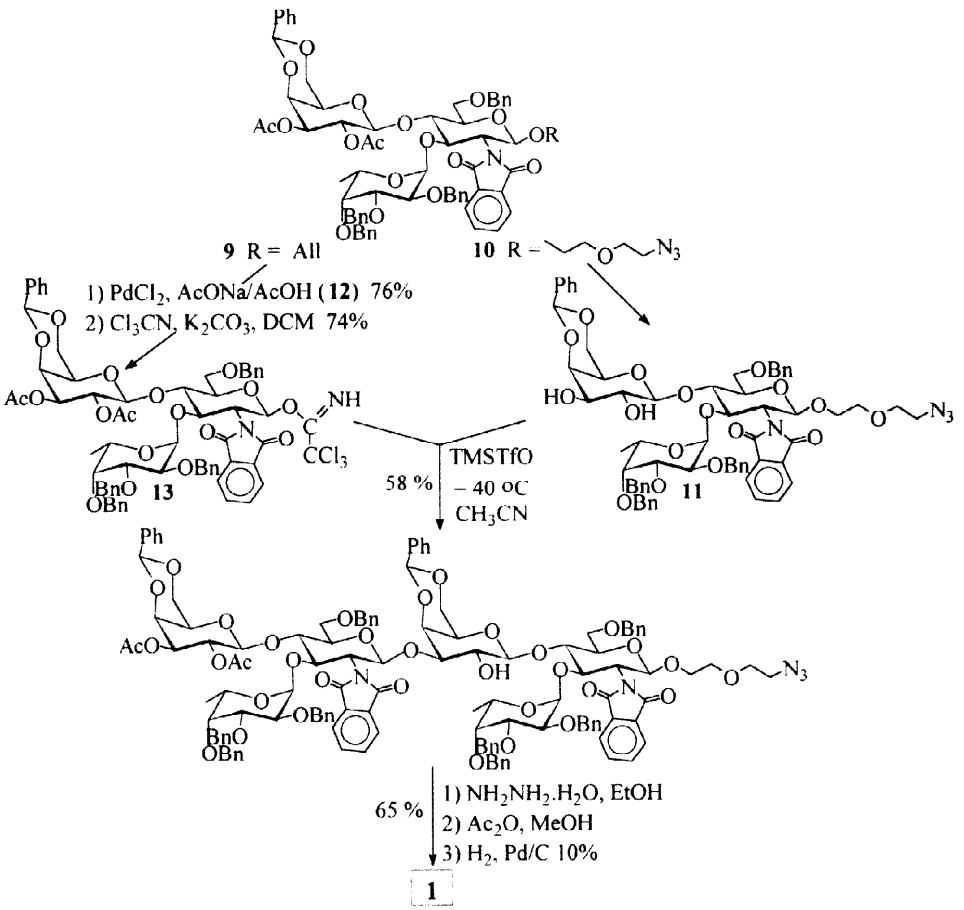
Bromide ion catalyzed fucosylation[10] of disaccharides **5** and **7** proceeded with excellent yields (78 and 82 %) and stereoselectivity (Scheme 2) to provide the trisaccharides building blocks **9** and **10**.

Trisaccharide **10** was deallylated in 76 % yield using palladium chloride in a mixture of acetic acid and sodium acetate.[11] The reducing trisaccharide **12** was then transformed into the pure trichloroacetimidate donor **13** with good yields (74 %) by reaction with trichloroacetonitrile and potassium carbonate,[12] followed by column chromatogratophy.

Deacetylation of trisaccharide **9** led to the diol-acceptor **11** in only one step. This compound was used to further substantiate the regioselective concept. The reactivity of the hydroxyl group on position 3b is further enhanced by the presence of the vicinal benzylidene group, and therefore would be the preferred site of substitution. The condensation reaction of trisaccharides **13** and **11** was performed in acetonitrile at –40 °C under TMSTfO catalysis,[2e,3a] and did furnish the hexasaccharide **14** with complete regio- and stereoselectivity in good yields (58 %). Two dimensional homo- and heteronuclear NMR spectroscopy unambiguously confirmed the structural identity of the protected hexasaccharide[13]. Classical deprotection of hexasaccharide **14** afforded the target compound **1** in 65 % yield.

In conclusion, the galactosyl donor used in this strategy made it possible to achieve complete regioselective reactions, which provide a very efficient route to access the dimeric Le^x hexasaccharide. The use of this concept for the synthesis of other polyfucosylated tumor-associated antigenic determinants is now being explored.

Scheme 2



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9. Compound **8**: mp 212-213 °C (from hexane/EtOAc); $[\alpha]_D$ +32.5 (c 2.4, EtOAc); ^{1}H-NMR data (250 MHz, $CDCl_3$): δ 7.84, 7.73 (Phth), 7.39 (Ph), 5.62 (dd, $J_{2,3}$ = 9.7 Hz, $J_{3a,4a}$ = 10.6 Hz, H-3a), 5.61 (m, 1H, =C*H*), 5.42 (s, 1H, PhC*H*), 5.09 (m, 2H, =CH_2), 5.40 (d, 1H, $J_{1a,2a}$ = 9.7 Hz, H-1a), 5.18 (dd, 1H, $J_{1b,2b}$ = 8 Hz, $J_{2b,3b}$ = 10.5 Hz, H-2b), 4.77 (dd, 1H, $J_{3b,4b}$ = 3.6, H-3b), 4.65 (AB, 2H, J = 12 Hz, CH_2Ph), 4.51 (d, 1H, $J_{1b,2b}$ = 8 Hz, H-1b), 4.32 (d, $J_{3b,4b}$ = 3.6 Hz,1H, H-4b), 3.66 (m, 1H, H-5a), 3.28 (s, 1H, H-5b), 2.01, 1.99, 1.98 (*CH*$_3$COO), ^{13}C-NMR data (250 MHz, $CDCl_3$): δ 170.6, 170.5, 170.0, 168.9 (C=O), 137.9, 137.1 (ipso Ph), 134.2, 131.3, 123.4 (Phth), 133.6, 117.4 (All), 128.9-127.7 (Ph), 101.0 (*C*HPh) 99.9 (C-1b), 97.1 (C-1a), 75.0 (C-4a), 74.5 (C-5a), 73.4 (*C*H$_2$), 73.0 (C-4b), 71.9 (C-3b), 70.5 (C-3a), 69.9 (C-6a), 68.9 (C-2b), 68.3 (C-6b), 65.9 (C-5b), 54.7 (C-2a), 20.6, 20.5, 20.3 (*C*H$_3$COO).

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13. Compound **13**: $[\alpha]_D$ -100 (*c* 2.2, chloroform); ^{1}H-NMR data (250 MHz, $CDCl_3$): δ 7.86, 7.70 (2m, 8H, Phth), 7.47-7.15 (m, 50H, Ph), 5.52 (s, 1H, CHPh-e), 5.41 (s, 1H, CHPh-d), 5.36 (dd, 1H, $J_{1e,2e}$ = 8.4 Hz, $J_{2e,3e}$ = 9.9 Hz, 1H, H-2e), 5.01 (d, $J_{1a,2a}$ = 7.1 Hz, 1H, H-1a), 4.72, 4.55 (H-1c, 1f), 4.70 (H-1e), 4.32 (H-1b), 2.98 (CH_2-N$_3$), 2.02, 2.00 (2s, 6H, CH_3CO), 1.14 (d, 2H, H-6f), 0.42 (d, 2H, H-6c); ^{13}C-NMR data (250 MHz, $CDCl_3$): δ 170.4, 168.6 (C=O), 139.3-137,5 (ipso Ph), 134.0, 133.9, 131.4, 123.2 (Phth), 128.7-125.7 (Ph), 100.8 (C-1b), 99.5 (C-1e, 2xCHPh), 98.7 (C-1d), 98.3 (C-1a), 97.7, 97.3 (C-1c, f), 78.7 (C-3c, f, C-4c or 4f), 78.4 (C-4f or 4c), 77.5 (C-3b), 56.6, 56.3 (C-2a, 2d), 50.2 (CH_2N_3), 20.7 (2xCH_3), 15.9, 15.6 (C-6c, f).