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Efficient Synthesis of *lactoneo* Series Antigens H, Lewis X (Le^x), and Lewis Y (Le^y)[1]

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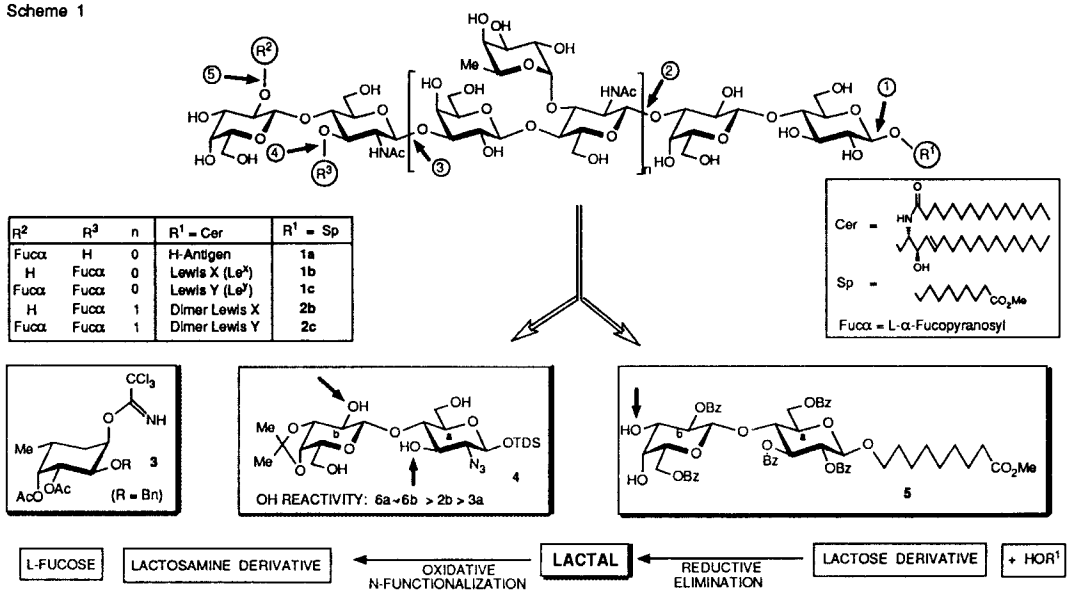
Abstract: Regioselective 6a,6b-di-O-benzoylation of azidolactose **4** furnished derivative **6** which permitted ensuing regioselective 2b-O-fucosylation, 2b,3a-di-O-fucosylation, or regioselective 2b-O-benzoylation and then 3a-O-fucosylation, respectively, thus providing directly H, Le^y, and Le^x antigen building blocks **8a-c**. The derived trichloroacetimidates **9a-c** offered regio- and β-selective glycosylations of partially O-protected acceptors **5** and **13**, affording spacer-linked H, Le^x, Le^y, dimer Le^x and Le^y intermediates **12a-c** and **14b,c**, respectively, which could be readily transformed into target molecules **1a-c** and **2b,c**. Thus, a most straightforward and efficient synthesis of this antigen series is exhibited.

Prominent tumor associated antigens are the Lewis X (Le^x) and Lewis Y (Le^y) determinants[2]; these glycosphingolipids, including the important sialyl Le^x epitope[3], are members of the *lactoneo* family, i.e. *lacto* series type 2 chain. Syntheses of Le^x and Le^y antigens have employed various strategies, various building blocks and/or protecting group patterns[4-14]. We would like to report here on a very efficient synthesis of spacer-linked antigens H, Le^x, Le^y, dimer Le^x, and dimer Le^y (Scheme 1, **1a-c, 2b,c**) which is based on lactal derived azidolactose[14-16] as outlined in the retrosynthetic strategy (Scheme 1); lactal is obtained from lactose *via reduc-*

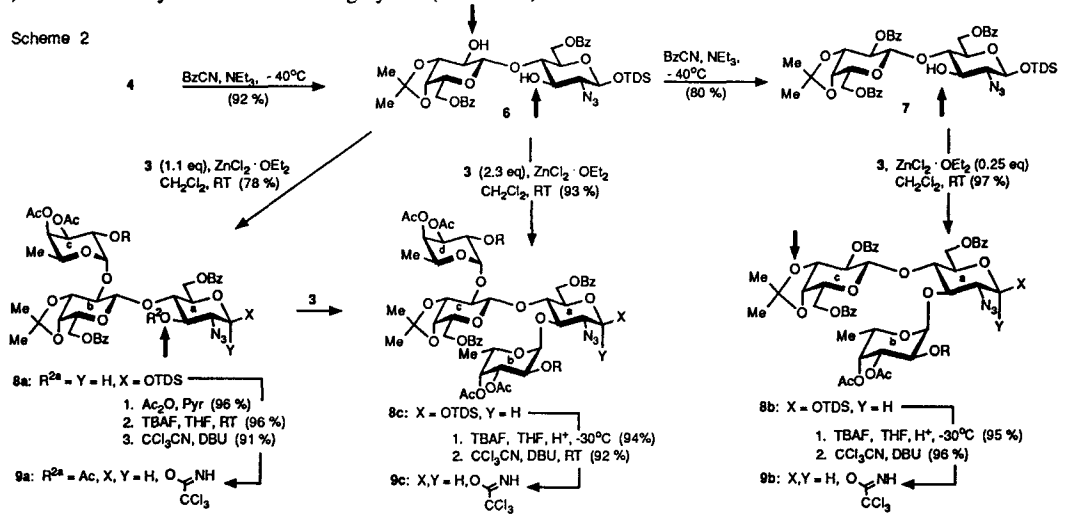
Scheme 1



R^2	R^3	n	R^1 = Cer	R^1 = Sp
Fucα	H	0	H-Antigen	1a
H	Fucα	0	Lewis X (Le^x)	1b
Fucα	Fucα	0	Lewis Y (Le^y)	1c
H	Fucα	1	Dimer Lewis X	2b
Fucα	Fucα	1	Dimer Lewis Y	2c

tive elimination. The retrosynthesis exhibits that starting from lactal, the sequence *oxidative azide introduction*, regioselective O-protection, anomeric carbon activation, glycoside bond formation, and deprotection is closely related to the sequence regioselective lactal protection, *oxidative nitrogen introduction*, anomeric carbon activation via aziridine formation and concomitant glycoside bond formation, and then deprotection, which has been reported recently[10].

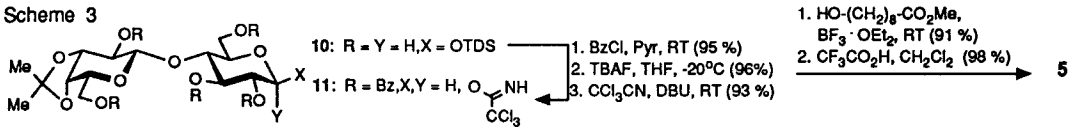
The decisive building blocks in our approach are O-(3,4-O-acetyl-2-O-benzyl-L-fucopyranosyl)-trichloroacetimidate (**3**), readily available from L-fucose[15], thexyldimethylsilyl (TDS) 2a-azido-2a-deoxy-3b,4b-O-isopropylidene-lactoside **4**, readily available from lactal[15,16], and spacer-linked penta-O-benzoyl-lactoside **5**, readily available from lactose, as shown below. An important aspect is regioselective O-benzoylation of **4** which was found to exhibit an 6a ~ 6b > 2b > 3a reactivity order[15]. Thus, regioselective O-benzoylation of **4** with 2.2 equivalents of benzoyl cyanide in the presence of triethylamine at -40°C afforded 6a,6b-di-O-benzoyl derivative **6** in high yield (Scheme 2).



6 can be directly fucosylated with 1.1 equivalents of **3** in the presence of $ZnCl_2 \cdot OEt_2$ as the catalyst to afford regioselectively 2b-O-fucosyl derivative **8a** required for H antigen construction; however, when 2.3 equivalents of **3** are employed in this reaction, practically exclusively **8c** the 2b,3a-di-O-fucosyl derivative of **6** is obtained, which is the building block for Le^y antigen construction. The reactivity difference of 2b-OH over 3a-OH in **6** can be also employed for the regioselective 2b-O-benzoylation. Thus, with an additional equivalent of benzoyl cyanide/triethylamine at -40°C 2b,6a,6b-tri-O-benzoyl derivative **7** is obtained in high yield; then fucosylation with **3** in the presence of $ZnCl_2 \cdot OEt_2$ as the catalyst (0.25 equivalents) afforded trisaccharide **8b**, constituting an Le^x antigen building block. Intermediates **8a-c** were readily transformed into the corresponding trichloroacetimidates **9a-c** required as glycosyl donors.

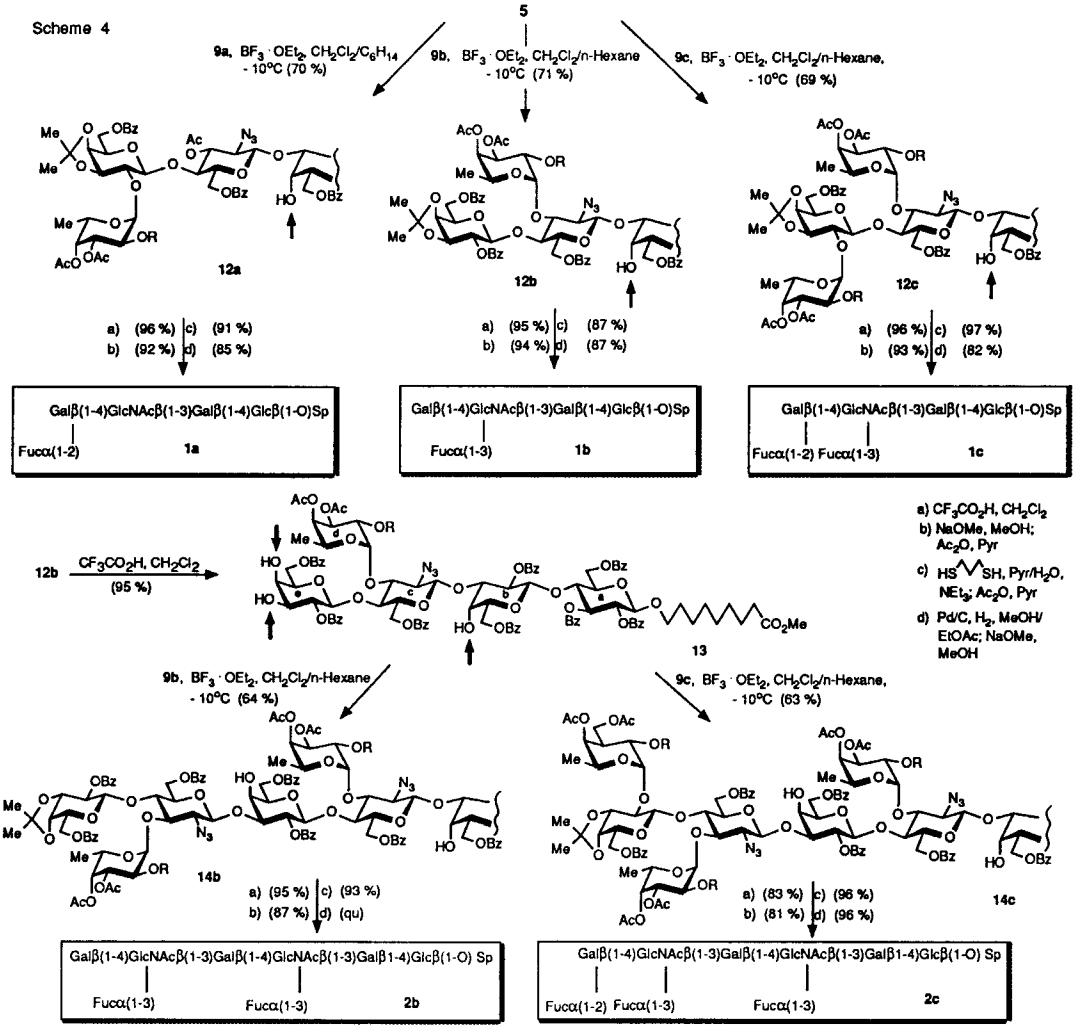
Spacer-linked lactose building block **5** was obtained from lactose derivative **10**[15] via per-O-benzoylation, TDS group removal with tetra-*n*-butylammonium fluoride (TBAF), and trichloroacetimidate formation with CCl_3CN/DBU (→ **11**, Scheme 3). Glycosylation of the Lemieux spacer with **11** in the presence of $BF_3 \cdot OEt_2$ as the catalyst and then de-O-isopropylidenation afforded **5** in very high overall yield.

Scheme 3



The combination of the building blocks of Schemes 2 and 3 for obtaining the target molecules turned out to be very straightforward. Reaction of glycosyl donors **9a-c** with acceptor **5** in CH_2Cl_2/*n*-hexane at -10°C in the presence of $BF_3 \cdot OEt_2$ as the catalyst afforded the H, X, and Y antigen intermediates **12a-c** in good yields, thus exhibiting the expected regioselective reaction at 3-OH of the galactose moiety of **5** (Scheme 4). Intermediates **12a-c** were transformed by the same highyielding four step sequence (consisting of acid catalyzed isopropylidene group removal, deacylation and per-O-acetylation, azide group reduction and N-acetylation, and hydrogenolytic debenzylation and O-deacetylation) into the desired target molecules **1a-c**[17].

Scheme 4



The building blocks **9b,c** and **12b** could be also successfully employed for the synthesis of spacer-linked dimer Le^x and Le^y antigens **2b,c**. Removal of the O-isopropylidene group in **12b** with CF_3CO_2H/CH_2Cl_2 afforded 3e, 4b, 4e-O-unprotected derivative **13** in quantitative yield. Glycosylation of **13** with donors **9b** and **9c** under the above described conditions furnished under exclusive 3e-O-attack the protected dimer Le^x and Le^y intermediates **14b,c**, respectively, again in acceptable yields; the same sequence of reactions as described for **12a-c** transformed **14b,c** into target molecules **2b,c**[17] in high overall yield.

In summary, diastereoselective lactal transformation into silyl 3b,4b-O-isopropylidene-2-azidolactoside **4** provides a stereochemically secured starting material which permits highly regioselective reactions at the remaining hydroxy groups, thus furnishing via simple benzoylations and highyielding fucosylations directly the desired H, Le^x, and Le^y antigen building blocks. Their transformation into trichloroacetimidates affords reactive glycosyl donors for regioselective β-glycosylations of the readily accessible partially O-protected acceptors **5** and **13**, thus providing the protected target molecules in very few steps. For deprotection, highyielding standard procedures can be employed.

References and Notes

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17. Values of $[\alpha]_D$ and δ_H: **1a**: $[\alpha]^{20} = -30.0$ (c = 0.5, H_2O) ^{1}H-NMR (250 MHz, D_2O): δ = 4.23 (d, $J_{1,2}$ = 8.7 Hz, 1 H, 1-H), 4.28 (d, $J_{1,2}$ = 8.3 Hz, 1 H, 1-H), 4.35 (d, $J_{1,2}$ = 7.6 Hz, 1 H, 1-H), 4.50 (d, $J_{1,2}$ = 8.2 Hz, 1 H, 1c-H), 5.11 (bs, $J_{1,2}$ < 1 Hz, 1 H, 1e-H). **1b**: $[\alpha]^{20} = -36.0$ (c = 1, H_2O) ^{1}H-NMR (250 MHz, D_2O): δ = 4.24 (d, $J_{1,2}$ = 7.9 Hz, 1 H, 1-H), 4.27 (d, $J_{1,2}$ = 7.7 Hz, 1 H, 1-H), 4.28 (d, $J_{1,2}$ = 8.1 Hz, 1 H, 1-H), 4.51 (d, $J_{1,2}$ = 8.0 Hz, 1c-H), 4.93 (d, $J_{1,2}$ = 3.9 Hz, 1 H, 1d-H). **1c**: $[\alpha]^{20} = -71.0$ (c = 1, H_2O) ^{1}H-NMR (250 MHz, D_2O): δ = 4.23-4.40 (3 d, $J_{1,2}$ = 8.8 Hz, $J_{1,2}$ = 8.4 Hz, $J_{1,2}$ = 8.7 Hz, 3 H, 1a-H, 1b-H, 1e-H), 4.53 (d, $J_{1,2}$ = 8.2 Hz, 1 H, 1c-H), 4.93 (d, $J_{1,2}$ = 3.9 Hz, 1 H, 1d-H), 5.09 (d, $J_{1,2}$ = 2.3 Hz, 1 H, 1f-H). **2b**: $[\alpha]^{20} = -56$ (c = 1, H_2O) ^{1}H-NMR (250 MHz, D_2O): δ = 4.25-4.36 (4 d, $J_{1,2}$ = 7.6 Hz, $J_{1,2}$ = 8.3 Hz, $J_{1,2}$ = 8.2 Hz, $J_{1,2}$ = 8.0 Hz, 4 H, 1a-H, 1b-H, 1e-H, 1h-H), 4.54 (2 d, $J_{1,2}$ = 8.5 Hz, 2 H, 1c-H, 1f-H), 4.95 (d, $J_{1,2}$ = 4.0 Hz, 1 H, 1d-H), 4.97 (d, $J_{1,2}$ = 4.1 Hz, 1 H, 1g-H). **2c**: $[\alpha]^{20} = -68$ (c = 0.5, H_2O) ^{1}H-NMR (250 MHz, D_2O): δ = 4.25-4.36 (4 d, $J_{1,2}$ = 8.2 Hz, $J_{1,2}$ = 8.4 Hz, $J_{1,2}$ = 8.0 Hz, $J_{1,2}$ = 7.9 Hz, 1a-H, 1b-H, 1e-H, 1h-H), 4.55 (2 d, $J_{1,2}$ = 7.9 Hz, 2 H, 1c-H, 1f-H), 4.95 (bs, 2 H, 1d-H, 1g-H), 5.11 (bs, 1 H, 1i-H).

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