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Single Step Syntheses of Lactosylated Clusters by Telomerizations

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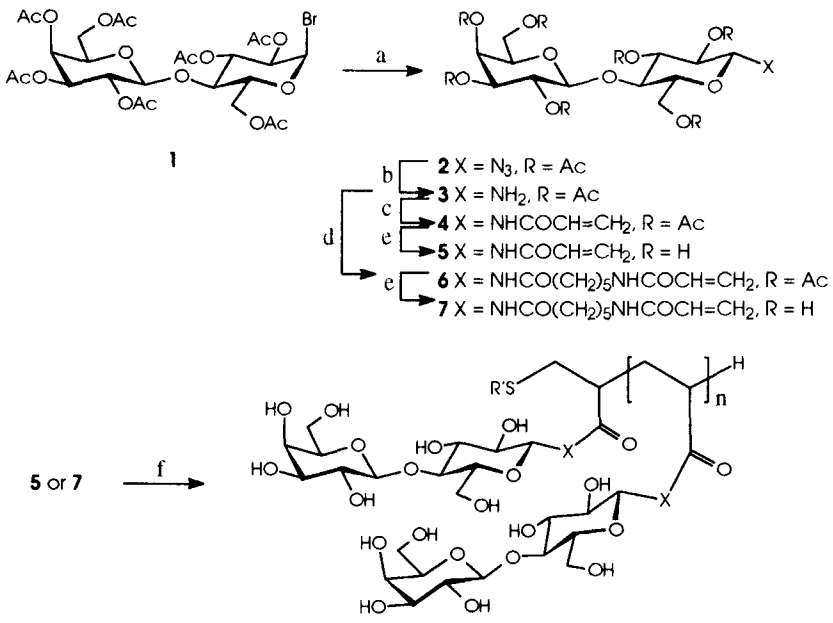
Abstract: N-Acryloylated lactoside derivatives containing spacer arms of different length were polymerized in the presence of thiols acting as radical scavengers to provide small oligomeric clusters (telomers) in a single step. *t*-Butyl mercaptan and methyl 3-mercaptopropionate, chosen as chain transfer reagents, were used for further attachment to L-lysine methyl ester.

Mammalian hepatic asialoglycoprotein receptors (ASGP-R) constitute cell surface lectins exhibiting high specificities toward non-reducing β-D-galactopyranosyl or 2-acetamido-2-deoxy-β-D-galactopyranosyl (Gal-GalNAc) residues present on glycoproteins and glycolipids.[1] These carbohydrate-protein interactions have been extensively studied in terms of carbohydrate specificities and requirements for multivalencies.[2] This last phenomenon, referred to as "glycoside cluster effect" [3] is of paramount importance to achieve subnanomolar binding constants necessary for tight bindings. The routing of D-galactose-bearing clusters for the purpose of liver-specific drug delivery has been envisaged as viable anticancer and antiviral therapies.[4] Furthermore, lactosylated clusters composed of galactoside residues were shown to be potent inhibitors of lung colonization by metastatic cancer cell lines.[5]

As previous lactosylated cluster syntheses were tedious and required multisteps,[3, 6-9] we describe herein a direct, single step access to families of lactosylated clusters which depends on the polymerizations of N-acryloylated lactoside derivatives in the presence of thiols used as radical scavengers. Such process, called telomerizations,[10] allows the chain propagation step to be quenched at an early stage to favor the formation of small repeating units (telomers). High molecular weight glycopolymers-bearing lactosides have been previously described.[11,12]

Reduction of β-D-lactosyl azide **2**, obtained in 98% yield under stereospecific phase transfer catalysis (PTC)[13,14] from α-acetobromolactose **1**, afforded anomerically unstable lactosylamine **3** which was immediately treated with acryloyl chloride or with 6-N-acrylamidohexanoic acid and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) in ethanol to provide protected monomer precursors **4** (85%) and **6** (73%) respectively. After Zemplén de-O-acetylation (NaOMe, MeOH) each resulting monomer **5** and **7** was telomerized in refluxing MeOH in the presence of 2,2'-azobisisobutyronitrile (AIBN) and *tert*-butyl mercaptan (*t*-BuSH) as first chain transfer reagent (telogen) in various molar ratios (Scheme 1). The reactions provided, in one single step, families of low molecular weight lactosylated telomers **8-9** which were readily separated by size exclusion chromatography on Bio-Gel P-2 column using water as eluent. In the case

of monomer **5**, average number lactoside residues in the crude telomer mixtures (500 MHz ^{1}H-NMR) ranged from 2-190 (by integration of the anomeric protons at 5.10 and 4.55 ppm relative to that of the *t*-butyl signal at 1.42 ppm) when using from 10-0.1 equivalents of *t*-BuSH. In a typical run with 10 equivalents of *t*-BuSH per monomer **5** (50 mg, 0.127 mmol) in 0.57 ml MeOH containing 0.2 mg AIBN (5 h, reflux), monoadduct **8** (n=0, 29.4%), dimer **8a** (n=1, 15.8%), trimer **8b** (n=2, 8.4%), tetramer **8c** (n=3, 5.8%) and higher telomers **8d** (n≥4, 41%) were obtained. Using 5.5 equivalents of *t*-BuSH per monomer **7**, monoadduct **9** (26.6%), dimer **9a** (13.9%), trimer **9b** (1%) and higher telomers **9c-9d** (45%) were also obtained in a total yield of 86.5%.



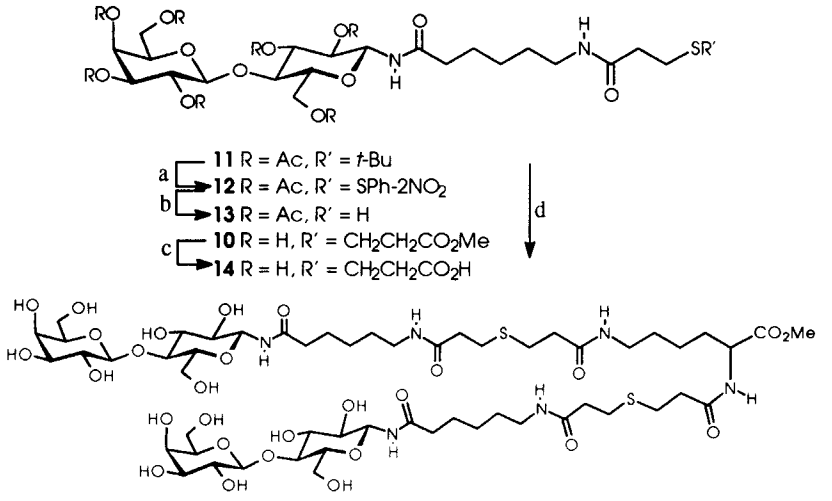
8 R' = *t*-Bu, X = NH, n = 0 (monomer), **8a** n = 1, **8b** n = 2, **8c** n = 3, **8d** n>3
9 R' = *t*-Bu, X = NHCO(CH$_2$)$_5$NH, n = 0, **9a** n = 1, **9b** n = 2, **9c** n = 3, **9d** n>3
10 R' = CH$_2$CH$_2$CO$_2$Me, X = NHCO(CH$_2$)$_5$NH, n = 0, **10a** n = 1, **10b** n = 2, **10c** n =3, **10d** n >3

Scheme 1. *a*: PTC, NaN_3, TBAHS, ETOAc, 1M Na_2CO_3, 30 min, 98%; *b*: H_2, Pd-C, EtOAc, o.n., 94%; *c*: CH_2=CHCOCl, pyridine, EtOAc, 45 min, 85%; *d*: $HO_2C(CH_2)_5$-NH-CO-CH=CH_2, EEDQ, EtOH, r.t., 16 h, 73%; *e*: NaOMe, MeOH, r.t., 3 h, 98% (**5**) and 91% (**7**); *f*: *t*-BuSH (or $HSCH_2CH_2CO_2Me$), AIBN, MeOH, reflux, 5h.

It is also worthy of mention that noticeable level of diastereoselectivities (ca. 2:1, as seen from the ^{1}H-NMR of **8a**) were observed during the telomerizations of **5**. This was not surprising because the monomer **5**, which is deprived of spacer arm, was actually serving as chiral auxiliary to provide telomer tacticities.[15]

Similarly, when monomer **7** was telomerized with 0.43 equivalents of methyl 3-mercaptopropionate, monoadduct **10** (26%), dimer **10a** (22%), trimer **10b** (12.3%), tetramer **10c** (7%) and higher telomers **10d** (n≥4, 30.8%) were obtained.

To further exploit the usefulness of lactosylated telomers for drug attachment and dendrimer syntheses,[16] model experiments with modified monomers **10** and **11** were examined independently. Peracetylated monomer **11**, was obtained as a single product (84%) when **6** was treated with a fifty fold molar excess of *t*-BuSH and a catalytic amount of AIBN in refluxing MeOH. Attempts to prepare **11** by nucleophilic attack of t-BuSH in the presence of triethylamine (Michael addition) failed. Successful deprotection of *t*-butyl thioether in **11** was accomplished in a two step process with 2-nitrobenzenesulfenyl chloride (2-NO_2-PhSCl)[17] in acetic acid to afford S-(2-nitrophenyl)sulfenyl derivative **12** in 84% yield. Disulfide reduction with 2-mercaptoethanol gave **13** (60%). The thiol **13** is suitably functionalized and can be covalently attached to N-chloroacetylated poly-L-lysine dendrimers.[16] Treatment of methyl ester **10** with 0.05M NaOH provided acid **14** (quant). Preparation of a family of telomers related to **14** directly from **6** and 3-mercaptopropionic acid were hampered by difficulties in separation. Treatment of **14** (2 equiv) with lysine methyl ester and EEDQ as above afforded divalent lactosylated cluster **15** (50%) and its monomeric adduct (15%). Works are now in progress to conjugate each individual telomer with dendritic poly-L-lysine[16] and other polyamines to provide rapid access to complex multivalent "dendritic telomers."



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Scheme 2: a: 2-NO_2-Ph-SCl, HOAc, r.t., 3h, 84%; b: $HSCH_2CH_2OH$, MeOH, r.t., 3h, 60%; c: 0.05M NaOH, r.t., 3h, quant; d: **13**, LysOMe, EEDQ, EtOH, DMF, 50%

Preliminary inhibition experiments with peanut lectin from *Arachis hypogaea* and telomers **8** deprived of spacer showed no improved binding properties as compared to those of lactose.[18] On the other hand, trimer **10b** was twice as potent as lactose.

Other model studies with galactosides containing N-acrylamidohexanoic acid as spacer arm provided analogs similar to **9**. Using thiolacetic acid as radical scavenger gave complex telomer mixtures.

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