TOWARDS OLIGOSACCHARIDE ANALOGUES OF CELLULOSE

A dissertation
Submitted to the
SWISS FEDERAL INSTITUTE OF TECHNOLOGY
(ETH) ZURICH
for the degree of Doctor of Natural Sciences

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Zürich 1995
SUMMARY

It is proposed to study the influence of intra- and interresidue H–bonds on the structure and properties of polysaccharides by comparing them to a series of systematically modified oligosaccharide analogues where some or all of the O–C(1) units are replaced by a buta-1,3-diynyl-1,4-diyl group. This group is long enough to interrupt the interresidue H–bonds and chemically versatile; it allows a binomial synthesis.

Several variations of the synthesis of the simplest monomeric unit that is required for the synthesis of one of the cellulose analogues are described. In the first variant, treatment of the epoxide 105 with LiMe3Si=C=Cl/Et2AlCl according to a known procedure gave the desired alkyne 106 besides 107, resulting from a neighboring group participation of the MeOCH20 group. Using Me3Al instead of Et2AlCl increased the yield and selectivity of the ring opening. Deprotection of 106 (→ 111), dibenzylation (→ 115), and acetolysis led to the diacetate 116 which was partially deacetylated (→ 117) and oxidised to the lactone 118. Addition of (Me3SiC≡Cl)/TiCl4 afforded the anomeric hemiketals 119 (α-D/β-D = 3:2) which were deoxygenated to the dialkyne 120. This synthesis of the monomers was shortened by treating the hydroxyacetal 129 (from 106) with (Me3Si-C≡C)3Al (Scheme 30); formation of the alkyne 130 (70%) by retentive alkynylation acetal cleavage is rationalised by postulating a participation of HOC(3). The synthesis was further improved by substituting the MeOCH20 by the (iPr)3SiO group (Scheme 32); the epoxide 131 from 104 yielded 85% of the alkyne 132 which was transformed, on the one hand, via 133 into the dibenzyl ether 115 and, on the other hand, after C-de-silylation (→ 134) into the dialkyne 135. Finally, combined alkynylation opening of the oxirane and the 1,3-dioxolane rings of 131 with excess
Et₂AlC≡CSiMe₃ led directly to the monomer 137 which is thus available in two steps and 77% yield from 104 (Scheme 33).

The Me₃Si-C(1) bond of the bis-trimethylsilylethynylated anhydroalditol 137 was regioselectively cleaved with BuLi to yield 144/145, while AgNO₂/KCN in MeOH cleaved the Me₃Si-C(2') bond, leading to 135. Both Me₃Si groups were removed with NaOH in MeOH (→ 147), the (i-Pr)₃Si group was selectively cleaved with HCl in aq. MeOH (→ 146); all silyl substituents were removed with Bu₄NF (→ 148). Oxidative dimerisation of either 144 or 135, or of a mixture of 144/146 yielded only the homodimers 149 and 150; treatment of 150 with AgNO₂/KCN yielded 151, deprotection proceeding much more slowly than the cleavage of the C(2')Me₃Si group of 137.

The iodoalkyne 154, required for the cross coupling with 135 according to Cadiot-Chodkiewicz and Wityak-Chan, was prepared by deprotection of 144/145 to 152, methoxymethylation (→ 153), and iodination. Cross-coupling yielded mostly 156, besides the homodimer 155. Similarly, cross coupling of 154 and 159 (obtained from 145) led to 160 and 155. The structure of 160 was established by X-ray analysis, showing a C(6)–C(5') distance of 5.2 Å. The conditions for desilylating 137 were applied to 156, and led regioselectively to 161 (AgNO₂/KCN), 162 (aq. NaOH), 164 (Bu₄NF), and 163 (HCl/MeOH). Attempted deprotection of the propargylic ether moiety with BuLi, however, failed. The dimer 164 was further deprotected to 165.

Cleavage of the benzyloxy groups was then studied. Acetolysis (Ac₂O/Me₃SiOTf) transformed 169 into 174, which was desilylated to 175, while thiolysis of 169 led to a mixture of 171 and 172. The tetraacetate 175 has also been obtained from 169 via 170. Acetolytic debenzylation of the dimer 176, obtained from 170, gave 177 (83%), which was deacetylated to 178. Cross coupling of the alkyne 135 and the bromoalkyne 179, obtained from 170, yielded 180; again, acetolysis proceeded well, leading to 181. The cellobiose derivative 184 was prepared from the lactone 182 via 183. The glycosidic linkage of 184 proved resistant to the conditions of acetolysis, leading to 185. Acetolysis of the benzylated thiophene 186 (from 176 with Na₂S) yielded the octaacetate 187, but proceeded in substantially lower yields (50%). NaSMe in toluene leads to regioselective de-C-
silylation of the bis(trimethylsilyl (Me3Si) ethynyl) saccharide 137, but to decomposition of butadiynes such as 156 or 200.

We have therefore combined the reagent-controlled, regioselective desilylation of 137 and of 200 (AgNO2/KCN) with a substrate controlled regioselective de-C-silylation, based on C-silyl groups of different size. This combination was studied with the fully protected 188 which was mono-desilylated to 189 or to 159. Triethylsilylation of 159 (→ 195) was followed by removal of the Me3Si group (→ 196). Introduction of a tert.-butyldimethylsilyl (TBDMS) group (→ 197) and removal of the triethylsilyl (TES) group yielded 198; these high-yielding transformations proceed with a high degree of selectivity.

Iodination of 189 gave 190; this was coupled with 159 to the homodimer 199 and the heterodimer 200, which was desilylated to 204. The second building block for the tetramer was obtained by coupling 201 (from 196) with 159, leading to 202 and 203. Removal of the Me3Si group (→ 206) and iodination led to 207 which was coupled with 204 to the homotetramer 208 and the heterotetramer 209. Deprotection of 209 gave 210, which was, on the one hand, iodinated to 211, and, on the other hand, protected as the C-TBDMS alkyne 212. Removal of the TES group and coupling afforded the homooctamer 214 and the heterooctamer 215. Yields of iodination, silylation, and desilylation were consistently high, while heterocoupling proceeded in only 50–64%.

Cleavage of the (iPr3SiO– and MeOCH2O– groups of 199 (→ 216), 202 (→ 217), 208 (→ 218) and 214 (→ 219) proceeded in high yields. Complete deprotection in two steps of the heterocoupling products 203 (→ 220 → 165), 209 (→ 221 → 222), and 215 (→ 223 → 224) gave the unprotected dimer 165, tetramer 222, and octamer 224 in high yields. Only the dimer 165 is soluble in H2O; the 1H-NMR spectra of 165, 222, and 224 in D6-DMSO (relatively low concentration) show no signs of association.
ZUSAMMENFASSUNG

Um den Einfluss von inter- und intramolekularen Wasserstoffbrücken auf die Struktur und die Eigenschaften von Polysacchariden zu untersuchen, wird vorgeschlagen, systematisch modifizierte Oligosaccharidanaloge herzustellen. Dabei sollen Buta-1,3-diy-1,4-diyl-Gruppen einen Teil oder alle der glycosidisch gebundenen Sauerstoffzentren (O-C(1)) ersetzen. Buta-1,3-diyn-1,4-diyl-Gruppen sind lang genug, um die Wasserstoffbrückenbildung zu unterdrücken und können leicht modifiziert werden; im weiteren erlauben sie eine binominale Synthese.

Das bis-trimethylsilylthénylierte Anhydroaldit 137 wurde durch die Einwirkung von BuLi an C(1) regioselektiv zu 144/145 entschützt, während AgNO₂/KCN in MeOH zur komplementär regioselektiven Entfernung der Me₃Si-Gruppe an C(2') führte (→ 135). Beide Me₃Si Gruppen wurden mit NaOH in MeOH (→ 147) entfernt. Die (i-Pr)₃Si Gruppen wurden selektiv mit HCl in aq. MeOH (→ 146) abgespalten. Alle Silylgruppen lassen sich mit Bu₄NF (→ 148) abspalten. Die oxidative Dimerisierung von 144 oder 135, bzw. einem Gemisch von 144 und 146 ergab ausschließlich die Homodimeren 149 und 150. Die Behandlung von 150 mit AgNO₂/KCN führte zu 151; diese Abspaltung der Schutzgruppe verlief bedeutend langsamer als die jene der Me₃Si-Gruppe an C(2') in 137. Die regio-selektive Entsilylierung mit BuLi liess sich nicht auf Butadiyne übertragen.


das Octaacetat 187, allerdings in einer mässigen Ausbeute (50%). NaSMe in Toluol führte zur regioselektiven Ent-C-silylierung des disilylierten Saccharids 137; Butadiyne wie 156 und 200 wurden unter diesen Bedingungen zerstört.

