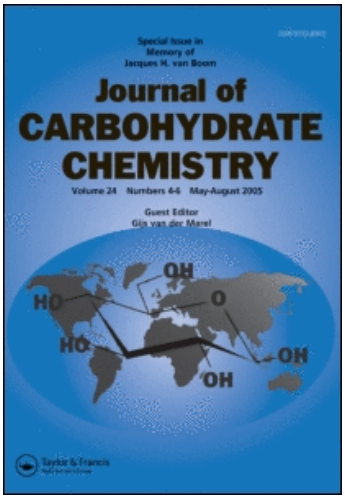

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Efficient Synthesis of "Star-like" Surfactants via "Click Chemistry" (3 + 2) Copper (I)-catalyzed Cycloaddition

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We report an efficient synthesis of tetra- and hexa-substituted carbohydrate-coated compounds, which we have named "star-like" surfactants, starting from either α-methylglucose or *myo*-inositol as a central core. The synthesis explores a new approach to such multipolar compounds using [3 + 2] copper (I)-catalyzed cycloadditions to attach the respective building blocks.

Keywords Surfactant, Carbohydrate, "Click chemistry"

Nonionic surfactants have sparked a growing interest in the last decades. Such compounds prepared from renewable resources, in particular carbohydrate-based surfactants, can have desirable environmental, biodegradation, nontoxicity, and dermatological properties.[1,2] These compounds are made of a water-soluble head derived from a carbohydrate linked by different functional groups to a hydrophobic part. Variations in the nature of sugar and hydrocarbon tails determine the self-organization properties and therefore applications of the resulting surfactant. In this context, the generation of a new class of amphiphilic surfactants using a multidentate carbohydrate scaffold could have much promise.

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The synthesis design uses a reaction known as "click chemistry." The unique aspects of this method arises from the near-perfect reliability of copper (I)-catalyzed 1,3-dipolar cycloaddition of a terminal alkyne to an organic azide. "click chemistry" ligation, as initially reported by Sharpless et al.[3] and Meldal et al.,[4] is highly selective and gives a 1,4-disubstituted-1,2,3-triazole regioisomer exclusively (Sch. 1).

Our attention turned to "click chemistry" reactions since it gives high yields and employs simple reaction conditions (no protecting steps), which are not sensitive to the presence of either oxygen or water. It also requires only stoichiometric amounts of starting materials, and does not generate by-products. Therefore, such chemistry seemed a convenient approach to binding carbohydrate building blocks to a core unit readily and regioselectively.

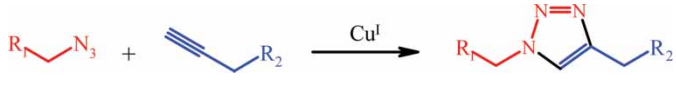
Herein we report for the first time an efficient and simple approach to the synthesis of tetra- and hexavalent carbohydrate-coated surfactants, represented by **8**, **9**, and **11**, that we have given the general name of "star-like" surfactants. To apply the "click chemistry" concept to multipolar materials, we chose to synthesise multibranched core units with either azide or alkyne chain-end groups and attach them to carbohydrates suitably functionalized in the anomeric position.

SYNTHESIS OF TETRASUBSTITUTED "STAR-LIKE" COMPOUNDS

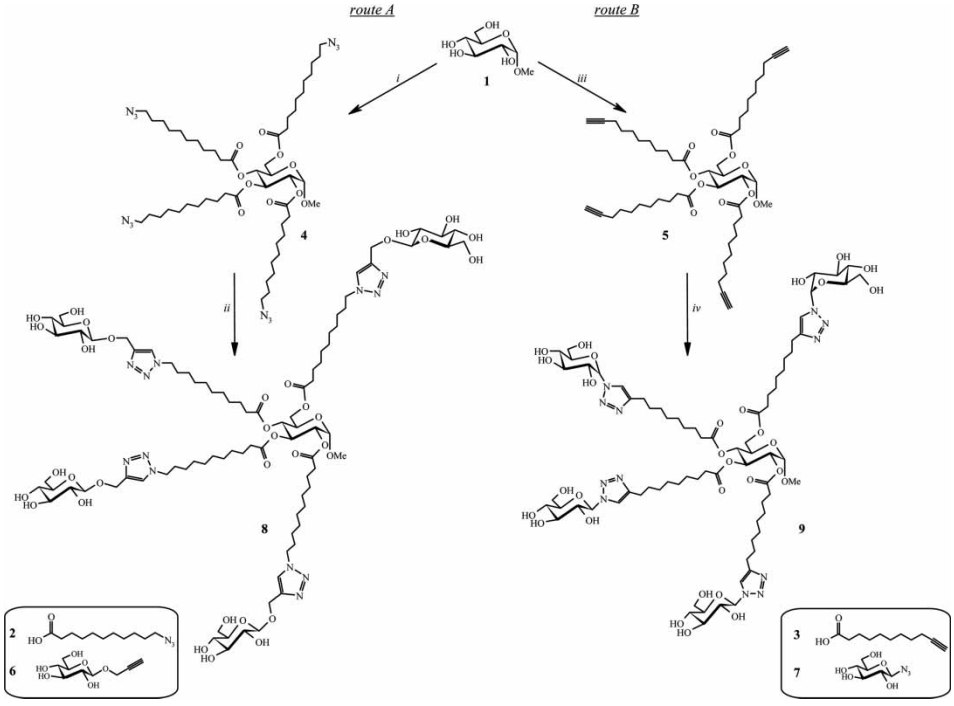
Two different compounds (*routes A* and *B* in Sch. 2) were studied to create the tetravalent "star-like" compounds. In both cases attachment to the hydroxyl groups of α-methylglucopyranoside, acting as the central core, was achieved by esterification of long-chain functionalized carboxylic acids substituted accordingly by either a terminal azide or acetylenic group to be coupled, by copper (I)-catalyzed cycloaddition to the corresponding unprotected glucose residues suitably derivatized in the anomeric position.

Thus, the two different tetrasubstituted building blocks **4** and **5** were synthesized via esterification of the α-D-methylglucopyranoside core by a carboxylic acid with terminal azide (*route A*) and terminal acetylenic (*route B*), respectively. The 11-azidoundecanoic acid precursor **2** was obtained quantitatively by azidation of 11-bromoundecanoic acid with an excess of sodium azide in DMAc. The 10-undecynoic acid derivative **3** is commercially available.

The tetra-azido precursor **4** was obtained by esterification of α-D-methylglucopyranoside with 12 eq. of 11-azidoundecanoic acid **2** in the presence of



Scheme 1: General procedure of "click chemistry" copper (I)-catalyzed cycloaddition.



Scheme 2: General procedure for synthesis of tetrasubstituted glucosidic "star-like" precursors. (*i*) 12 eq. of **2**, 12 eq. TsCl, DMAc, 80°C, 3 d, 82%; (*ii*) 11.5 eq. of **6**, 2 eq. $Cu(OAc)_2$, 2.6 eq. sodium ascorbate, THF/water 1:1, 40°C, 9 d, 47%; (*iii*) 8 eq. of **3**, 6 eq. TsCl, DMAc, 80°C, 7 d, 62%; (*iv*) 6 eq. of **7**, 0.7 eq. $Cu(OAc)_2$, 0.82 eq. sodium ascorbate, tBuOH/water 1:1, 40°C, 4 d, 30%.

12 eq. of tosyle chloride, in DMAc at 80°C over 3 d. After purification by chromatography over silica gel ($CHCl_3$/EtOH 79:1), the four-armed azido compound **4** was isolated in 82% yield. Similarly, acetylenic four-armed precursor was obtained starting from 8 eq. of 10-undecynoic acid derivative **3** in the presence of 6 eq. of tosyl chloride, in DMAc at 80°C for 7 d. Esterification afforded purified compound **5** in 62% yield (silica gel, $CHCl_3$/EtOH 99:1).

Complete esterification of the tetrasubstituted precursors **4** and **5** was clearly established by ^{1}H NMR, IR, and mass spectroscopy. The structure of the tetra-azido core **4** was confirmed by the presence of five peaks from 3.25 to 1.29 ppm in the NMR spectrum integrating for 80H, assigned to the four alkyl chains. This observation was supported by IR peaks at 1746 and 2095 cm^{-1} corresponding to C═O and N_3 functional groups, respectively. Similarly, the ^{1}H NMR spectrum of compound **5** showed the appearance of a triplet at 1.94 ppm assigned to the four acetylenic terminal protons, along with glycosyl protons. Furthermore, the IR spectrum showed a weak peak at 2112 cm^{-1} for $\nu_{C\equiv C}$ and another at 3292 cm^{-1} for ≡C-H linkage, confirming thus the four-arm structure with terminal alkyne function. On the other

hand, a strong peak at 1745cm^{-1} for C=O attests the fixation of alkyl chains via an ester linkage. Furthermore, the structure of "star-like" compounds **4** and **5** was confirmed by ESI-MS, showing the $[M + Na]^+$ peak adduct at, respectively, $m/z = 1053.5$ and 873.5.

The following step consisted of anchoring the unprotected glucose residues to the respective scaffolds via "click chemistry" cycloaddition. The glycosyl units were required to be deacetylated before click-linkage because of the instability of the ester linkage to the basic conditions, such as ammonia in methanol, used in this chemistry. Thus, the deprotection of commercially available 2,3,4,6-tetra-*O*-acetylpropynyl-β-D-glucose was carried out with an excess of 7N-ammonia in methanol and gave the acetylenic sugar **6** in quantitative yield. In the same way, the 1-azidoglucose **7** was obtained quantitatively by NH_3 in methanol.

Finally, each building block was linked together. *Route A* was operated with the azido precursor **4** in the presence of 11.5 eq. of propynylglucose **6**, 2 eq. of copper acetate (0.5 eq. per terminal azide), and 2.6 eq. of sodium ascorbate (0.65 eq. per terminal azide) in THF/water 1:1. After 9 d at 40°C and purification by silica gel chromatography, the "star-like" compound **8** was obtained in 47% yield. Alternatively, *route B* used the same procedure, employing the tetra-acetylenic residue **5** in the presence of 6 eq. of azidoglucose **7**, 0.7 eq. of $Cu(OAc)_2$, and 0.82 eq. of sodium ascorbate in *tertio*butanol/water 1:1 at 40°C, over 4 d. After purification, the click-reaction afforded the "star-like" **9** in 30% yield.

The "star-like" structure were confirmed by ^{1}H NMR Compound **8**: ^{1}H NMR (DMSO d_6): δ 1.30 (m, 48H, H-4 to H-9), 1.59 (quint., 16H, $J = 7.6$ Hz, H-3), 1.89 (quint., 16H, $J = 7.0$ Hz, H-10), 2.36 (t, 8H, $J = 7.5$ Hz, H-2), 2.97 (t, 4H, $J = 8.5$ Hz, H-2′*glc*), 3.04 (t, 4H, $J = 9.0$ Hz, H-3′ *glc*), 3.21 (t, 8H, $J = 8.3$ Hz, H-11), 3.30 (s, 3H, OMe), 3.34 (m, 4H, H-5′ *glc*), 3.35 (t, 4H, $J = 8.9$ Hz, H-4′*glc*), 4.04 (dd, 1H, $J = 6.5$, 11.2 Hz, H-6b *glc*), 4.06 (dd, 1H, $J = 6.6$, 9.3 Hz, H-6a *glc*), 3.67 (dd, 4H, $J = 5.3$, 11.9 Hz, H-6′b *glc*), 3.87 (dd, 4H, $J = 1.4$, 11.1 Hz, H-6′a *glc*), 4.18 (t, 1H, $J = 6.4$ Hz, H-5 *glc*), 4.24 (d, 4H, $J = 7.8$ Hz, H-1′β *glc*), 4.39 (t, 8H, $J = 7.1$ Hz, H-1), 4.78 (d, 4H, $J = 12.4$ Hz, H-β *propynyl*), 4.93 (d, 1H, $J = 3.3$ Hz, H-1α *glc*), 4.98 (d, 4H, $J = 12.4$ Hz, H-α *propynyl*), 5.00 (dd, 1H, $J = 3.3$, 10.8 Hz, H-2 *glc*), 5.20 (m, 1H, H-3 *glc*), 5.38 (m, 1H, H-4 *glc*), 8.01 (s, 4H, H-*triazole*). Compound **9**: ^{1}H NMR (DMSO d_6): δ1.26 (m, 36H, H-4 to H-7), 1.47 (m, 8H, H-8), 1.56 (m, 8H, H-3), 2.26 (m, 6H, H-2), 2.38 (t, 2H, $J = 7.5$ Hz, H-2), 2.58 (t, 8H, $J = 7.0$ Hz, H-9), 3.22 (m, 4H, H-5′ *glc*), 3.32 (s, 3H, OMe), 3.37 (m, 4H, H-6′b *glc*), 3.41 (d, 4H, $J = 8.0$ Hz, H-4′ *glc*), 3.45 (m, 4H, H-6′a *glc*), 3.70 (m, 8H, H-2′ *glc* and H-3′ *glc*), 4.04 (dd, 1H, $J = 6.6$, 9.3 Hz, H-6b *glc*), 4.06 (dd, 1H, $J = 6.5$, 11.2 Hz, H-6a *glc*), 4.18 (t, 1H, $J = 6.4$ Hz, H-5 *glc*), 4.63 (se, 4H, OH-*glc6′*), 4.93 (d, 1H, $J = 3.3$ Hz, H-1α *glc*), 5.00 (dd, 1H, $J = 3.3$, 10.8 Hz, H-2 *glc*), 5.13 (de, 4H, $J = 3.1$ Hz, OH-*glc4′*), 5.20 (m, 1H, H-3 *glc*), 5.23 (dd, 4H, $J = 3.2$,

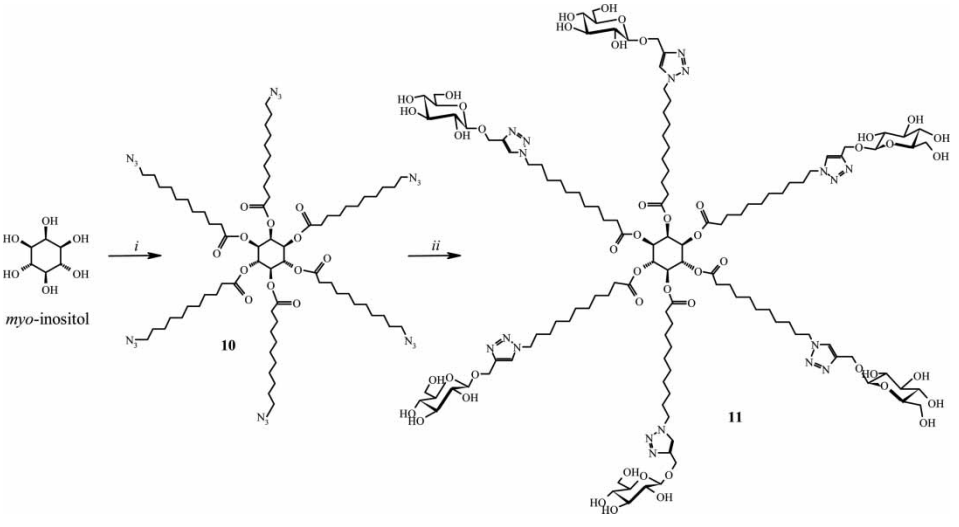
10.8 Hz, OH-*glc3′*), 5.36 (de, 4H, $J = 2.8$ Hz, OH-*glc2′*), 5.38 (m, 1H, H-4 *glc*), 5.44 (d, 4H, $J = 9.2$ Hz, H-1′β *glc*), 7.99 (s, 4H, H-*triazole*) with the presence of glycosyl protons and also by the appearance of a 4H singlet at 8.00 ppm corresponding to the triazole protons, confirming attachment of sugar moieties via the heterocyclic 1,2,3-triazole linkage. In addition, ESI-MS showed, respectively, a $[M + 2Na]^{2+}$ peak at $m/z = 975.0$ and 858.7 for both compounds **8** and **9**, thus validating the structural assignments.

In consideration of the success of this chemistry in achieving attachment of sugar moieties to tetrasubstituted glycosyl scaffolds, it was decided to further exemplify its utility by synthesizing the related hexasubstituted dendrimers.

SYNTHESIS OF A HEXASUBSTITUTED "STAR-LIKE" SURFACTANT

The synthesis of carbohydrate hexa-coated compound requires two types of building blocks, namely a hexavalent core optically active carbocycle, *myo*-inositol, bearing a carbon spacer arm with, at its terminus, a reactive group, which is coupled efficiently to a deprotected glucose unit functionalized in the anomeric position, as shown in Scheme 3.

The six-armed azido core was obtained by esterification of *myo*-inositol by 10 eq. of 11-azidoundecanoic acid **2** in the presence of 12 eq. of tosyl chloride, in DMAc at 60°C for 72 h. After purification by silica gel chromatography, the hexabranched azido core **10** was isolated in 40%. In this approach, the azide-terminated compound was preferred to those involving a terminal alkyne because of



Scheme 3: Convenient route toward hexavalent "star-like" surfactant synthesis. (*i*) 12 eq. of **2**, 12 eq. TsCl, DMAc, 60°C, 72 h, 40%; (*ii*) 10.5 eq. of **6**, 5.4 eq. $Cu(OAc)_2$, 3.7 eq. sodium ascorbate, THF/water 1:1, 40°C, 48 h, 46%.

its better reactivity, according to Rodionov et al.[5] They have reported, for flexible alkynes, that the proximity of the acetylenic functions may coordinatively saturate the Cu^{I} atom through chelation, leading to a failed result.

Finally, with the same conditions as for the four-armed compounds, the click-reaction gave the target hexamer **11** in 46% yield using 10.5 eq. propynylglucose, 5.4 eq. of $Cu(OAc)_2$, and 3.7 eq. of sodium ascorbate in THF/water 1:1 at 40°C, for 48 h. The complete anchoring of glucose residues on the azido-hexamer **10** was unequivocally established by ^{1}H NMR and ESI-MS. Compound **11**: ^{1}H NMR ($CD_3OD + D_2O$): δ 1.25–1.29 (m, 72H, H-4 to H-9), 1.52 (m, 12H, H-3), 1.88 (t, $J = 5.8$ Hz, H-10), 2.25 (d, 12H, $J = 7.4$ Hz, H-2), 3.27 (t, 6H, $J = 8.5$ Hz, H-2′*glc*), 3.41 (m, 6H, H-4′*glc*), 3.44 (t, 6H, $J = 8.8$ Hz, H-3′*glc*), 3.63 (dd, 6H, $J = 7.0$, 14.2 Hz, H-6′a *glc*), 3.71 (dd, 6H, $J = 5.5$, 12.1 Hz, H-5′*glc*), 3.90 (dd, 6H, $J = 1.5$, 12.0 Hz, H-6′b *glc*), 4.39 (t, 12H, $J = 6.9$ Hz, H-11), 4.47 (d, 6H, $J = 7.8$ Hz, H-1′β *glc*), 4.80 (d, 6H, $J = 12.4$ Hz, H-α *propynyl*), 4.97 (m, 6H, H-β *propynyl*), 5.40 (de, 2H, $J = 11.5$ Hz, H-2 and H-6 *inositol*), 5.50 (m, 3H, H-3, H-4 and H-5 *inositol*), 5.66 (te, 1H, $J = 2.7$ Hz, H-1 *inositol*), 8.04 (s, 6H, H-*triazole*). ESI-MS: $[M + Na]^+$ at $m/z = 2766.4$.

CONCLUSION

A highly efficient route to triazole surfactants has been made available resulting from the near-perfect reliability of Cu^{I}-catalyzed ligation of terminal alkynes and azides. Both α-D-methylglucose and *myo*-inositol have served as central cores to "star-like" compounds. It is of interest to note that the recently discovered ability of polydentate 1,4-disubstituted 1,2,3-triazole species[6] to show important biological applications has been an encouragement to the potential of "star-like" multimers being of use in biological processes. These compounds also exhibit original tensioactive properties.

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