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The efficient synthesis of amphiphilic oximes of galactose and glucosamine

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ABSTRACT

New amphiphilic oximes of galactose and glucosamine have been synthesized and characterized. The oxime functionality has been introduced to the first and sixth positions of a nonionic surfactant, consisting of a sugar polar head and a lipophilic side chain. The compounds are soluble in pyridine and sparingly soluble in other polar organic solvents and water.

Oximes are an important structural feature and are present in several biologically active compounds. As nucleophiles they are used as antidotes for organophosphate poisoning, with examples being pralidoxime and obidoxime.[1] In addition, they are also found as the artificial sweetener perillartine, as inhibitors of low density lipoprotein oxidation to prevent atherosclerotic diseases or, taken more broadly, as inhibitors of lipid peroxidation induced by different oxidizing agents.[2] The mechanism of their antioxidant activity is not completely understood, however it is possibly due to their scavenging of different reactive species and may also be related to their metal-chelating properties.[3] It has been shown that oximes protect active ingredients susceptible to oxidation against oxidative degradation in complex dosage forms, such as microemulsions.[4] Oximes are used as intermediates in organic chemistry for the synthesis of amines, amides, isoxazoles and are important ligands in the formation of metal complexes.[5] They are usually prepared by the reaction of a carbonyl compound with hydroxylamine or its salt. An efficient microwave-assisted synthesis of oximes, using $BF_3{\cdot}OEt_2$ as the catalyst has been described.[6] Other methods include the oxidation of amines[7] and reduction of nitro compounds.[8]

Surfactants are compounds commonly used in everyday life and in industry as detergents, emulsifiers, solubilizers, or wetting agents. Nonionogenic surfactants with sugar derivatives as a polar group have several advantages over cationic and anionic surfactants.[9] They are physiologically acceptable, relatively nontoxic and less irritant than ionogenic surfactants. Surfactants containing a sugar moiety may form H-bonds with the surrounding water molecules, which prevent their dehydration and enhance their thermostability.[10] The results presented in this Letter are a continuation of our studies on the design, synthesis, and evaluation of glycolipids[11] and amphiphilic oximes.[4]

The design of the target molecules was based on amphiphilic oximes composed of a nonionic polar bulky head consisting of a monosaccharide moiety with one or two oxime functionalities. The nonpolar part consists of medium- or long-chain alkyl groups attached to the sugar in the form of ethers or amides. We focused our attention on the synthesis of derivatives of two monosaccharides, D-galactose and D-glucosamine.

To synthesize the derivatives of D-galactose, the synthetic strategy presented in Scheme 1 was used. Following the preparation of acetonide **1** according to known procedures,[12] the lipophilic chain was introduced to the remaining 4′-hydroxy group at ambient temperature using various alkyl bromides and imidazole and 15-Crown-5 as catalysts. In the next two steps the protecting groups were removed with 75% TFA and the oxime formed at C-1′ of **3** with hydroxylamine in pyridine. Pyridine was used as the solvent since compounds of series **3**[13] and **4** were soluble predominantly in pyridine, but only sparingly soluble in other polar organic solvents and water.

Derivatives of glucosamine were synthesized as shown in Scheme 2. The lipophilic acyl group was introduced to the starting compound D-glucosamine by selective N-acylation with acyl chlorides in a mixture of 1,4-dioxane/aqueous $NaHCO_3$ at room temperature.[14] The primary 6′-hydroxy group in **5**[15] was substituted with the bulky triphenylmethyl group, while the other hydroxy groups were acetylated. The trityl group was selectively removed with an aqueous solution of ferric chloride[16] and the resulting hydroxy group of **8** oxidized to the corresponding aldehyde with Dess–Martin periodinane (DMP).[17] Compounds **9** exist in two

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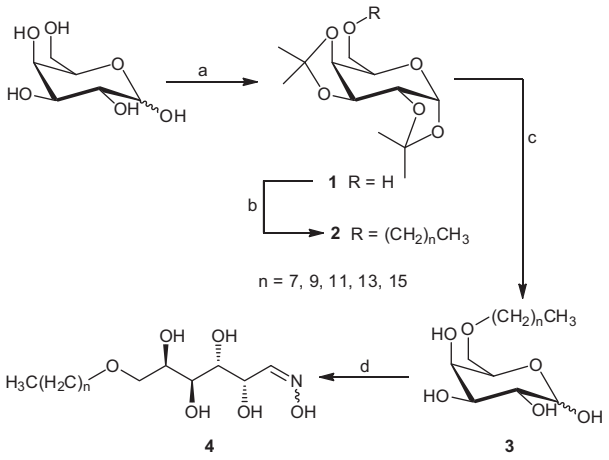
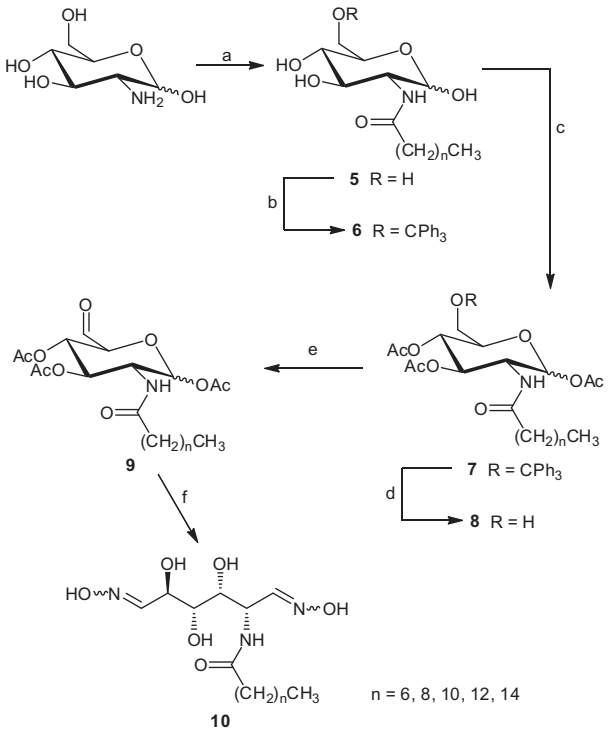
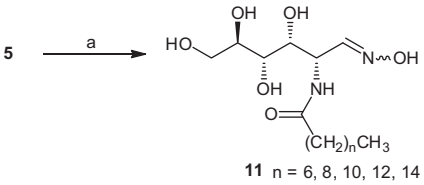


Scheme 1. Reagents and conditions: (a) acetone, $CuSO_4$ (2.4 equiv), H_2SO_4 (0.35 equiv), rt, 24 h, then $Ba(OH)_2$ (0.35 equiv), (**1**, 72%); (b) $CH_3(CH_2)_nBr$ (n = 7, 9, 11, 13, 15; 1.5 equiv), NaH (1.5 equiv), 15-Crown-5 (0.02 equiv), imidazole (0.01 equiv), 1,4-dioxane, 0 °C → rt, 24 h (**2a**, 41%; **2b**, 65%; **2c**, 65%; **2d**, 55%; **2e**, 45%); (c) 75% TFA, H_2O, 0 °C → rt, 1.5 h (**3a**, 84%; **3b**, 90%; **3c**, 95%; **3d**, 92%; **3e**, 97%); (d) NH_2OH (5 equiv), pyridine, 40 °C, 48 h (**4a**, 52%; **4b**, 68%; **4c**, 72%; **4d**, 71%; **4e**, 70%).



Scheme 2. Reagents and conditions: (a) $CH_3(CH_2)_nCOCl$ (n = 6, 8, 10, 12, 14; 1.1 equiv), $NaHCO_3$ (2 equiv), H_2O, 1,4-dioxane, rt, 24 h (**5a**, 54%; **5b**, 36%; **5c**, 54%; **5d**, 55%; **5e**, 60%); (b) Ph_3CCl (1.7 equiv), DMAP (0.05 equiv), pyridine, 75 °C, 2 h; (c) Ac_2O (6 equiv), pyridine, 0 °C → rt, 12 h (**7a**, 50% from **5a**; **7b**, 42% from **5b**; **7c**, 52% from **5c**; **7d**, 46% from **5d**; **7e**, 41% from **5e**); (d) $FeCl_3$ (2 equiv), H_2O, CH_2Cl_2, rt, 2 h (**8a**, 44%; **8b**, 55%; **8c**, 56%; **8d**, 53%; **8e**, 67%); (e) DMP (1.2 equiv), CH_2Cl_2, rt, 1.5 h, then work-up with $Na_2S_2O_{3(aq)}$ (**9a**, 49%; **9b**, 62%; **9c**, 84%; **9d**, 82%; **9e**, 75%); (f) NH_2OH (7 equiv), EtOH, 40 °C, 48 h (**10a**, 99%; **10b**, 76%; **10c**, 84%; **10d**, 81%; **10e**, 86%).

forms, as the aldehyde and geminal diol; the ratio was determined by NMR spectroscopy. Both compounds reacted with hydroxylamine in pyridine to yield the final products with two oxime functionalities, at C-1′ and C-6′. Compounds with only one oxime group at position C-1′ were prepared directly from **5** as shown in Scheme 3.[18]



Scheme 3. Reagents and conditions: (a) NH_2OH (5.6 equiv), pyridine, 40 °C, 48 h (**11a**, 43%; **11b**, 64%; **11c**, 65%; **11d**, 76%; **11e**, 68%).

In conclusion, we have synthesized new amphiphilic oximes of galactose **4** and glucosamines **10** and **11** from inexpensive starting materials. These compounds may lead to a new group of sugar-based excipients combining amphiphilic (surfactants) and antioxidant properties. Some of these are under technological investigation as potential antioxidants for semi-solid pharmaceutical formulations.

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Supplementary data

Supplementary data (experimental procedures and data for representative new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.086.

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