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D-Gulonolactone as a Synthon for L-Noviose: First Preparation of 4-*O*-Demethyl-L-noviofuranose and Related Derivatives†

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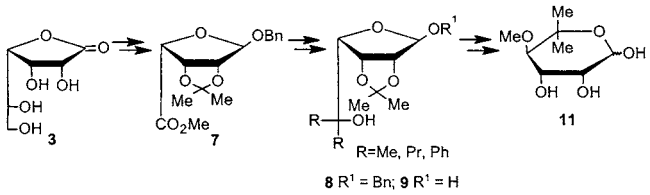
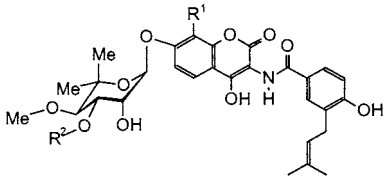
ABSTRACT



A new synthesis of L-noviose (11), a sugar moiety of novobiocin, is presented. D-Gulonolactone was initially converted in a few steps to the key ester derivative 7 [1-*O*-benzyl methyl 2,3-*O*-(1-methylethylidene)-α-L-lyxofuranosiduronate]. An appropriate selection of protecting groups enabled transformation of 7 under mild reaction conditions to 4-*O*-demethyl-L-noviofuranose 9a and related 9b–c. Derivatives 9 were further converted either to L-lyxopyranoses (10a and 10b) or to methyl L-lyxofuranoside 12.

DNA gyrase is a type II topoisomerase that catalyzes the negative supercoiling of DNA in prokaryotes with no direct counterpart in mammalian cells.[1] For this reason, it is an attractive target for the development of new antimicrobial agents.[2,3] The active gyrase molecule (from *Escherichia coli*) is an A_2B_2 tetramer, where the bigger subunit A possesses DNA breakage−reunion domain and the smaller subunit B contains the ATP binding site. DNA gyrase inhibitors may act either on the subunit A (e.g., quinolones)[4] or on the subunit B (e.g., cyclothialidines and coumarins).[5] Novobiocin (**1**) and chlorobiocin (**2**) are the most known representatives of the coumarin-derived antibiotics isolated from a culture broth of *Streptomyces* species. Poor pharmacokinetic properties have prevented their pharmaceutical application, but their activity against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* strains (MRSA), has attracted renewed attention. As a consequence, intensive efforts have been directed in recent years toward different structural modifications of **1** or **2** (and related coumermycin).[6,7]

Our research in this field was first oriented to the synthesis of 4-deoxynovobiocin-like coumarin glycosides,[8] but its extension toward L-noviosyl glycosides led us to the preparation of commercially unavailable noviose.



† Dedicated to Professor Branko Stanovnik, University of Ljubljana, Slovenia, on the occasion of his 65th birthday.

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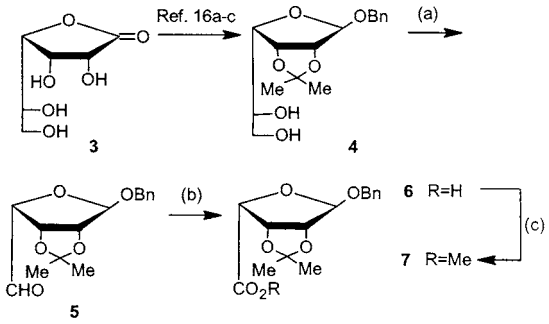
L-Noviose (**11**), which can be found not only in the coumarin antibiotics but also (in modified form) in lipiarmycin,[9] was the subject of many synthetic approaches. It was made as an enantiomerically pure compound starting from D-glucose,[10] L-arabinose,[11] L-rhamnose,[12] and D-ribose[13] and from a sugar building block (obtained from furfural).[14] On the other side, noviose was obtained as a racemic mixture from 2-acetylfuran as a nonsugar starting material.[15]

We have chosen commercially available D-gulonolactone **3** as a starting material and transformed it by the known reaction sequence to isopropylidene derivative **4**[16] (Scheme 1). Periodate cleavage[17] of **4** in a mixture of water and

Scheme 1[a]

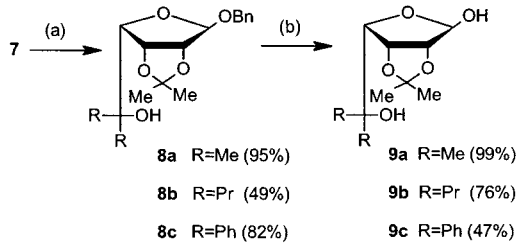


[a] Reagents and conditions: (a) $NaIO_4$, MeOH, H_2O (73%); (b) $AgNO_3$, KOH, EtOH, H_2O (92%); (c) CH_2N_2 in ether (99%).

methanol gave an aldehyde **5**, which was oxidized with Ag_2O[17] into the acid **6**. A subsequent esterification with diazomethane in diethyl ether[17b,18] resulted in the formation of the key intermediate **7** (an enantiomer of the previously described α-D-lyxofuranosiduronic acid derivative[17b]); it was prepared in 66% overall yield for the last three steps.

The ester **7** was treated with a variety of Grignard reagents and transformed to the tertiary alcohols **8a**−**c** (Scheme 2).

Scheme 2[a]



[a] Reagents and conditions: (a) RMgCl, Et_2O; (b) H_2, 10% Pd/C, Et_2O.

In the next step, benzyl protection group[19] was removed by the catalytic hydrogenation to give 4-*O*-demethyl-L-noviofuranose derivative **9a** [2,3-*O*-(1-methylethylidene)-5,5-di-*C*-methyl-α-L-lyxofuranose] and related propyl **9b** or phenyl **9c** derivatives. To our knowledge, **9a** is the first example of a noviofuranose derivative containing an unsubstituted anomeric hydroxy group. Namely, it was reported previously that anomeric methoxy group was cleaved under strong acidic conditions to give the corresponding pyranosyl derivative; thus, concomitant ring transformation of the furanoid to the pyranoid form occurred.[12] In our case, under neutral conditions in diethyl ether as a solvent, this ring−ring conversion was not feasible. An X-ray diffraction study of the compound **9a** (Figure 1) revealed its α-L-lyxofuranosyl structure and a

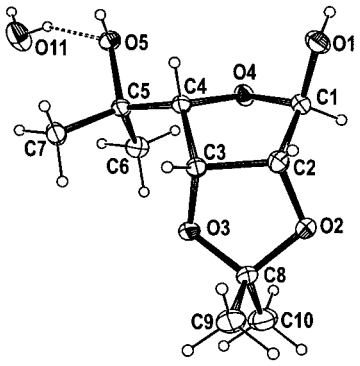


Figure 1. ORTEP plot of 4-*O*-demethyl-L-noviofuranose **9a**.

twist form (with C-4 endo and O exo) of the furanosyl skeleton. We would also like to mention that the pyranose analogue of **9a**, reported in ref 12 (compound **6**), has physical data distinctly different from the data for **9a** described in

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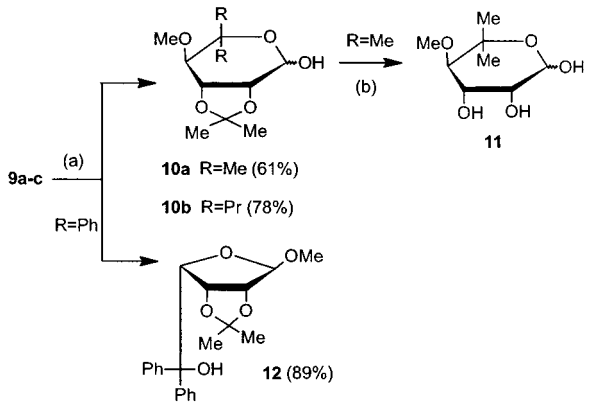
the Supporting Information, so that the work of Klemer and Waldmann is in no way being questioned by these new results.

A phase-transfer methylation[12] of L-noviofuranose **9a** with dimethyl sulfate in a two-phase system (water/toluene and methylene chloride) and in the presence of tetrabutylammonium bromide (as a phase-transfer catalyst) resulted in the formation of L-noviopyranose derivative **10a** (Scheme 3).

Scheme 3[a]



[a] Reagents and conditions: (a) Me_2SO_4, NaOH, H_2O−toluene/CH_2Cl_2, Bu_4NBr; (b) EtOH/CF_3CO_2H/H_2O (ref 12) or DOWEX 50-W/H_2O (ref 14).

This reaction may be explained as follows: in the first step, a transformation of the furanoid sugar form to pyranoid occurs,[12] followed by the methylation of hydroxy groups at the positions 1 and 4. High hydrolytic susceptibility of such 6-deoxysugars caused then a fast hydrolysis of its anomeric methoxy group to give product **10a**. The structure of **10a** (for which α-L-stereochemistry had been previously[12] determined) was confirmed by the ^{1}H NMR spectroscopy and specific rotation ($[\alpha]_D$ −78.7 (*c* 1.56, methanol); lit.[12] $[\alpha]_D$ −79.1). Further hydrolysis under acidic conditions[12,14] can give L-noviose **11** as a desired final product in overall yield for 11 steps of about 12% (with some steps not being completely optimized; ref 14 was used for the last step).

A stereoelectronic influence of substituents at position 5 of the furanose derivatives **9b** and **9c** was investigated under previously mentioned phase-transfer methylation. As we found out, a phase-transfer methylation of the propyl derivative **9b** took place analogously with the methyl derivative leading to **10b** (that exhibits similar ^{1}H NMR spectroscopic characteristics as **10a**). On the other hand, sterically bulky phenyl groups seem to prevent an interconversion of the furanoid form to the pyranoid and as a consequence furanosyl methyl glycoside **12** was isolated. Its structure was also determined by the X-ray diffraction study (Figure 2) revealing an envelope structure (with O out of plane) of the α-L-lyxofuranosyl moiety.

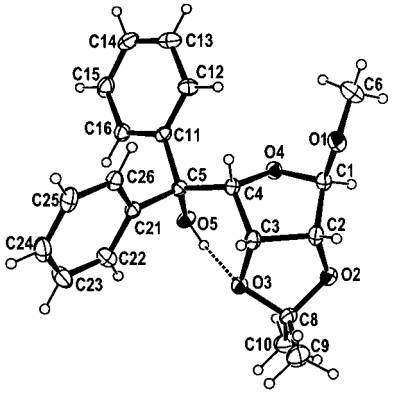


Figure 2. ORTEP plot of diphenyl derivative **12**.

Structures of the products **8b**, **9b**, and **9c** were also determined by the X-ray structural analysis.[20]

In summary, we have developed a new and efficient synthesis of L-noviose via previously unknown L-noviofuranose. We believe that our results have opened up new possibilities for the design of some novel molecules containing furanosyl type of noviose.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **5**, **6**, **7**, **8a**−**c**, **9a**−**c**, **10a**−**b**, and **12**, as well as X-ray data for **9a** and **12**, are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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