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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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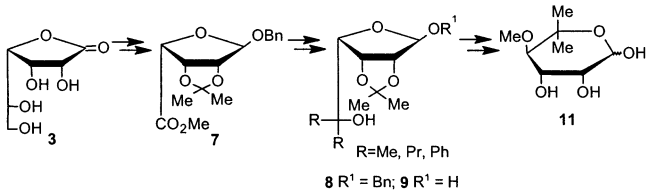
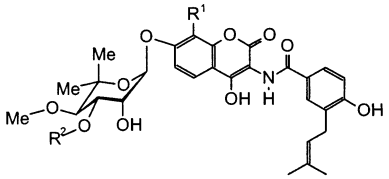
ABSTRACT



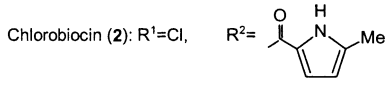
A new synthesis of L-noviose (11), a sugar moiety of novobiocin, is presented. D-Gulonolactone was initially converted in a few steps to the key ester derivative 7 [1-*O*-benzyl methyl 2,3-*O*-(1-methylethylidene)-α-L-lyxofuranosiduronate]. An appropriate selection of protecting groups enabled transformation 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.



Novobiocin (**1**): R^1=Me, R^2=$CONH_2$



Chlorobiocin (**2**): R^1=Cl, R^2=

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

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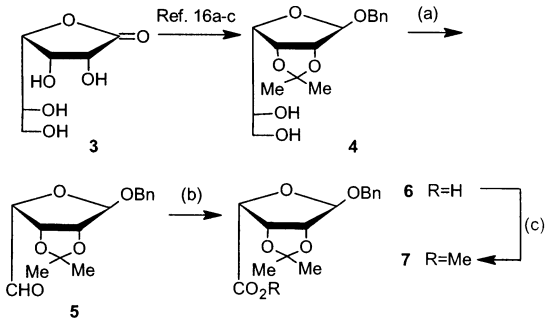
L-Noviose (**11**), which can be found not only in the coumarin antibiotics but also (in modified form) in lipiarmycin,[9] was the subject of many synthetic approaches. It was made as an enantiomerically pure compound starting from D-glucose,[10] L-arabinose,[11] L-rhamnose,[12] and D-ribose[13] and 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]

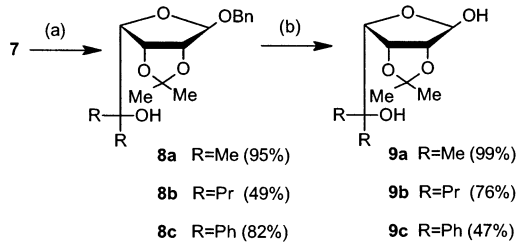


[a] Reagents and conditions: (a) $NaIO_4$, MeOH, H_2O (73%); (b) $AgNO_3$, KOH, EtOH, H_2O (92%); (c) CH_2N_2 in ether (99%).

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

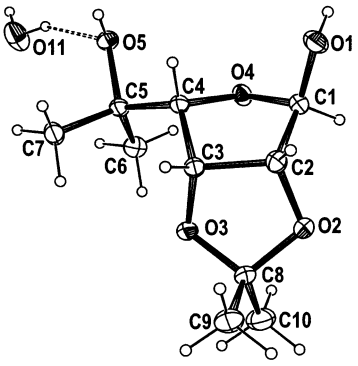


Figure 1. ORTEP plot of 4-*O*-demethyl-L-noviofuranose **9a**.

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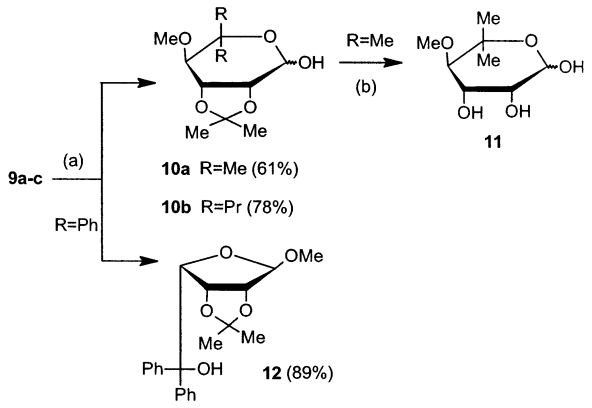
the Supporting Information, so that the work of Klemer and Waldmann is in no way being questioned by these new results.

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.

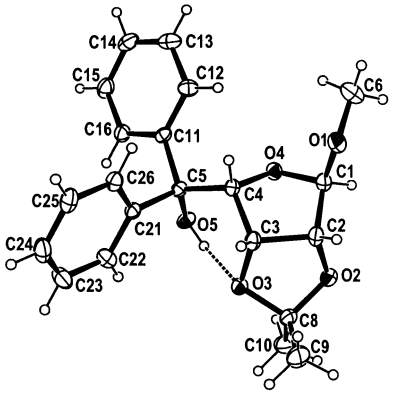


Figure 2. ORTEP plot of diphenyl derivative **12**.

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.

Acknowledgment. We thank the Ministry of Education, Science and Sport of the Republic of Slovenia for financial support (P0-503-103 and P0-511-103). Dr. B. Kralj and Dr. D. Žigon (Centre for Mass Spectroscopy), "Jožef Stefan" Institute, Ljubljana, Slovenia) are gratefully acknowledged for MS measurements.

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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