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Stereoselective synthesis of 5-monoalkyl and 5,5-dialkylsubstituted noviose derivatives

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Abstract

The stereoselective synthesis of 5-monosubstituted and 5,5-dialkylsubstituted noviose derivatives has been achieved starting from L-arabinose. These noviose derivatives could be used as useful building blocks in probing structure–activity relationships (SAR) of coumarin antibiotics that are inhibitors of DNA gyrase.

Keywords: antibiotics; Grignard reaction; Grignard reagents; stereoselection; structure–activity.

Novobiocin (**1**),[1a] clorobiocin (**2**)[1b] and closely related synthetic analogues (**3**)[2] are coumarin-containing antibiotics possessing a broad spectrum of Gram-positive antibacterial activity, including methicilin-resistant strains of the staphylococci species, MRSA and MRSE,[3] which are currently one of the major concerns in treatment of bacterial infections. These coumarins have been shown to inhibit the ATPase activity of subunit B of DNA gyrase,[4] a tetrameric A_2B_2 enzyme that belongs to a family of enzymes known as topoisomerase. These ubiquitous enzymes play an important role in resolving topological problems that arise during the various processes of DNA metabolism, including transcription, recombination, replication and chromosome partitioning during cell division.[5]

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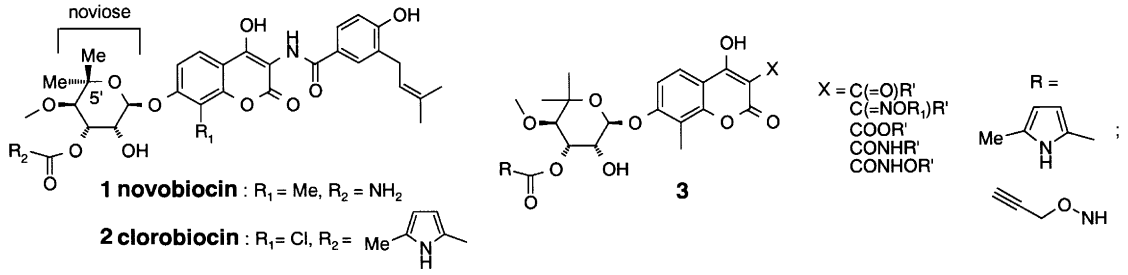
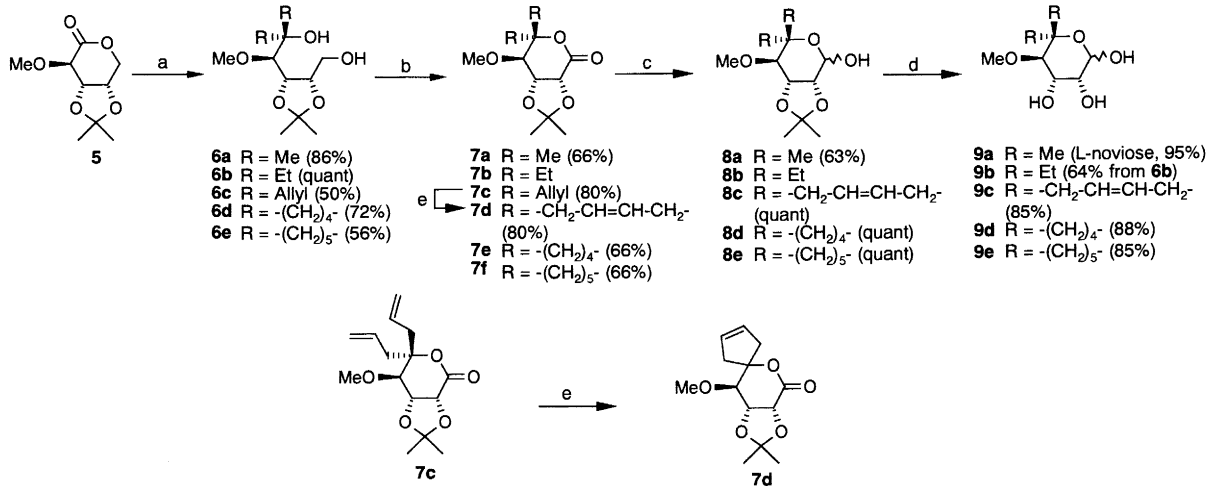


Recently, we reported structure–activity relationships of a series of coumarin inhibitors of DNA gyrase wherein the L-noviosyl sugar portion was replaced by L-rhamnose. These are noviose analogues bearing a 5′-hydrogen atom instead of the 5′-methyl axial group.[6] As this novel series provided interesting biological activity, we decided to expand SAR around this part of the molecule by varying the size of alkyl substituents. We disclose herein a stereoselective synthesis of 5-monoalkyl and 5,5-dialkyl substituted noviose analogues starting from L-arabinose.

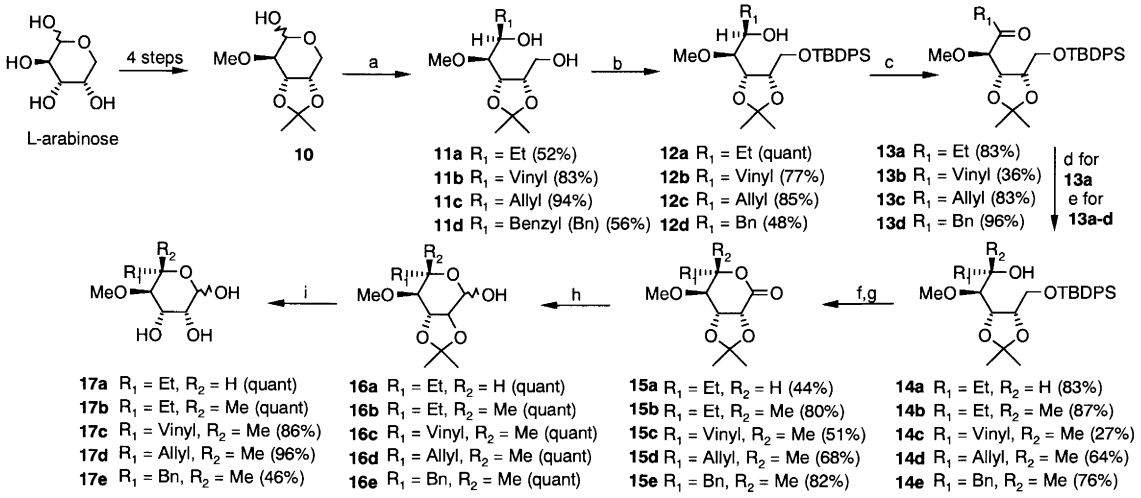
The preparation of 5,5-dialkyl noviose derivatives is outlined in Scheme 1. Lactone **5**, readily available from L-arabinose in five steps,[2a] was reacted with different alkyl Grignards in THF to provide the diols **6a**–**e**.[7] These were oxidatively cyclised to the corresponding lactones **7a**–**c**, **7e**,**f** with $PySO_3$ (2 equiv.) in the presence of DMSO/Et_3N and then reduced with DIBALH to lactols **8a**–**e** in quantitative yield. Acid-catalysed deprotection of the acetonides with H_2SO_4 afforded 5,5-dialkyl noviose analogues **9a**,**b** and **9d**,**e**. 5,5-Diallyl lactone **7c** was subjected to ring-closing metathesis in the presence of Grubbs ruthenium catalyst[8] in dichloromethane to give the spirocyclopentene lactone **7d** in 80% yield, which was further transformed to spirocyclopentene noviose **9c**, as described.



Scheme 1. *Reagents and conditions*: (a) for **6a** MeMgBr, THF, 0°C, 86%; for **6b** EtMgBr, THF, 0°C; for **6c** CH_2=CH–CH_2MgBr, THF, 0°C; for **6d** BrMg-$(CH_2)_4$-MgBr,[9] THF, 0°C; for **6e** BrMg-$(CH_2)_5$-MgBr, THF, 0°C 56%; (b) $PySO_3$, TEA, DMSO, CH_2Cl_2; (c) DIBALH, THF, 0°C (d) H_2SO_4, H_2O, 65°C (e) $RuCl_2(CHPh)[P(C_6H_{11})_3]_2$ cat, CH_2Cl_2, rt, 80%

Facing the more challenging problem of stereoselective introduction of the 5-equatorial alkyl substituents while keeping the methyl group or the hydrogen atom in the 5-axial position, we modified the above described methodology for preparation of our new targets, as depicted in Scheme 2. The nucleophilic addition of various Grignard reagents (~4 equiv.) to a protected arabinolactol **10** proceeded stereoselectively in THF affording as major products *(4S,5R)*-diastereomers **11a**–**d**.[10] However, this

configuration was not the desired one as was proven by oxidative cyclisation of the diol **11a** with $PySO_3$/DMSO/Et_3N to give the lactone **18**. The NOE experiments performed on **18** (Fig. 1) indicated *cis*-4H,5H orientation. The NOE between the *endo*-methyl group of acetonide and 5H and $J_{4H–5H}$=1.5 Hz coupling constant indicated a boat conformation of the six-membered lactone ring. In contrast, in lactone **15a** (vide infra), NOE and $J_{4H–5H}$=10 Hz clearly establishes *trans*-diaxial orientation of 4H,5H atoms as observed with L-rhamnose derivative **19**.[11]



Scheme 2. *Reagents and conditions*: (a) for **11a** EtMgBr, THF, 0°C; for **11b** CH_2=CH–MgBr, THF, 0°C; for **11c** CH_2=CH–CH_2–MgBr, THF, 0°C; for **11d** $PhCH_2MgCl$, THF, 0°C; (b) *t*$BuPh_2SiCl$, Im, DMF, rt; (c) PCC, CH_2Cl_2, molecular sieves 4 Å, rt; (d) for **13a** $Zn(BH_4)_2$, Et_2O, THF, 0°C; (e) for **13a**–**d** MeMgBr, THF, 0°C; (f) Bu_4NF, THF, rt; (g) $PySO_3$, DMSO, TEA, CH_2Cl_2, rt; (h) DIBALH, THF, 0°C; (i) H_2SO_4, H_2O, 65°C

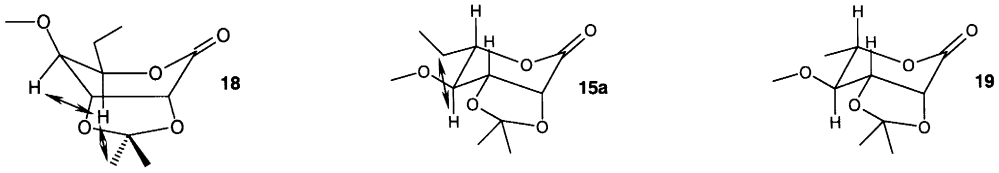
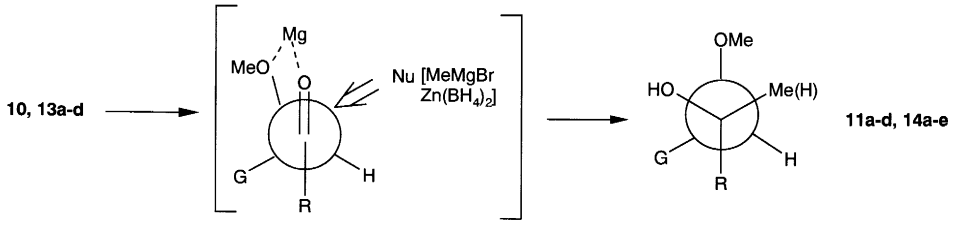


Fig. 1. Observed NOEs for the lactones **15a** and **18**

In order to correct the undesired diastereoselectivity of Grignard addition, the diols **11a**–**d** were regioselectively protected at a primary hydroxyl group with *t*$BuPh_2SiCl$ under standard silylating conditions, and the secondary alcohols were oxidised with PCC in the presence of molecular sieves (4 Å) to the corresponding ketones **13a**–**d**. Reduction of the ketone **13a** with $Zn(BH_4)_2$[12] in ether or nucleophilic addition of MeMgBr in THF to **13b**–**d** proceeded diastereoselectively [(4*R*,5*S*) for **14a**, (4*S*,5*S*) for **14b**–**d**] to establish the axial orientation of the hydrogen atom or methyl group, respectively.[13] The alcohols **14a**–**d** were smoothly desilylated with Bu_4NF in THF and the resulting diols were subjected to the same reaction sequence as described above and gave the noviose analogues **17a**–**e**. Thus, the above proposed synthetic scheme allows access to noviose derivatives having either 5,5-R_1(eq)/R_2(ax) or 5,5-R_1(ax)/R_2(eq) configuration depending on the order of addition of Grignard reagents to lactol **10** and ketone **13**.

The configurations of the newly formed alcohols were confirmed by X-ray structure analysis[14] or by NOE experiments. The observed stereoselectivity of the nucleophilic addition of Grignard reagents to lactol **10** or with ketones **13b**–**d** as well as the reduction of ketone **13a** with $Zn(BH_4)_2$ follow Cram's

rule.[15] Presumably, the nucleophilic reactions proceed through an α-chelated transition state which is consistent with Still's finding[16] that Grignard reagents in THF solutions prefer α-chelation (Scheme 3).



Scheme 3.

In conclusion, we have described a highly stereoselective approach to 5-monoalkylsubstituted and 5,5-dialkylsubstituted noviose derivatives, as well as a general synthetic approach to 5,5-bisalkyl noviose, including 5,5-spiro analogues. These synthetic intermediates could serve as useful scaffolds in probing SAR related to coumarin antibiotics.

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7. The yields in parentheses refer to isolated yields. Selected data: Compound **15d**: white solid, mp 95–96°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1. 31 (s, 3H), 1.38 (s, 3H), 1.47 (s, 3H), 2.46 (d, 2H, *J*=7 Hz), 3.31 (d, 1H, *J*=6.5 Hz), 3.5 (s, 3H), 4.5 (dd, 1H, *J*=6.5, 8.5 Hz); 4.73 (d, 1H, *J*=8.5 Hz), 5.16 (m, 2H), 5.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 21.0, 24.7, 26.7, 43.2, 58.0, 71.1, 77.2, 81.4, 82.9, 111.0 119.6, 131.6, 168.7; Anal. calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 61.0; H, 7.90; Compound **18**: white solid, mp 75–76°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.04 (t, 3H, *J*=7 Hz), 1. 38 (s, 3H), 1.52 (s, 3H), 1.72 (qdd, 1H, *J*=6, 7, 15 Hz), 1.90 (qdd, 1H, *J*=7, 8.5, 15 Hz), 3.34 (dd, 1H, *J*=1.5, 2.5 Hz), 3.48 (s, 3H), 4.45 (ddd, 1H, *J*=1.5, 6, 8.5 Hz); 4.56 (dd, 1H, *J*=2.5, 7 Hz), 4.65 (d, 1H, *J*=7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 9.9, 23.7, 23.8, 25.9, 58.4, 72.3, 72.7, 76.6, 77.9, 111.1, 167.3; anal. calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.20; H, 7.90.

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10. The ratio of *(*4*S*,5*R)*/(4*S*,5*S*) varied from 10:1 for **11a** to 15:1 for **11c**.
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13. Diastereomeric ratios: (4*R*,5*S*)-**14a**/(4*S*,5*S*)-**14a**=9:1 and 10:1 to 13:1 for (4*S*,5*S*)-**14b**–**d**/(4*R*,5*S*)-**14b**–**d**.
14. Crystallographic data (excluding structure factors) for the structure **15b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No CCDC 137236. Copies of that data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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