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A novel synthesis of noviose and its C-(4) epimer

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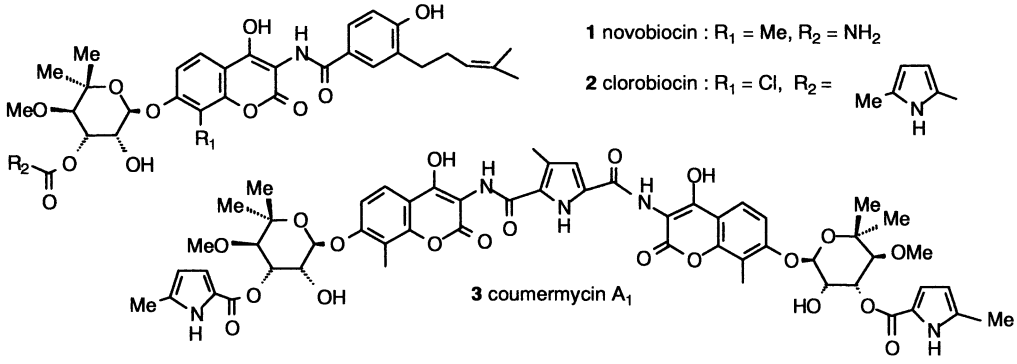
Abstract—An efficient and stereoselective synthetic route has been developed to both noviose and its C-(4) epimer, thus providing a platform for the investigation of the structure–activity relationships (SAR) involving the methoxy group of noviose.

DNA gyrase is a member of an essential class of proteins known as type II topoisomerases and plays a major role in DNA replication, recombination and the control of gene expression.[1] Since it is a crucial enzyme in prokaryotes and is not found in eukaryotes, it is an attractive target for drug design. DNA gyrase is made up of two proteins, A and B, with the active molecule being an A_2B_2 heterotetramer.[2] The gyrase B protein, containing the ATP binding site,[3] is targeted by the coumarin antibiotics of which novobiocin, **1**, clorobiocin, **2** and coumermycin A_1, **3**, are members.[4]

These coumarins are naturally occurring compounds originally isolated from *Streptomyces* species that have been shown to be active against Gram-positive bacteria. As potential pharmaceuticals, they suffer from numerous shortcomings including poor solubility in water, toxicity and side effects, as well as the rapid development of coumarin-resistant organisms,[5] and thus have not found widespread use. In order to overcome these shortfalls, numerous derivatives of novobiocin have been synthesised, the modifications being focused on the C-3 amino-position of the coumarin as well as the C-3′ amino-position and the C-5′ position of the sugar noviose.[6]

The crystal structure of the complex between novobiocin and a 24 kD N-terminal fragment of DNA gyrase B protein has been solved[7] and reveals that the 5′,5′-methyl groups of the sugar component of novobiocin sit in a pocket close to hydrophobic amino acid residues. The 4′-methoxy group sits in a similar hydrophobic cleft.[7b] The important role played by the 5′,5′-methyl groups in the antibacterial activity of coumarin antibiotics has been reported,[8] but little appears to be documented on the interaction between the 4′-OCH_3 of noviose and gyrase B. In order to study this interaction a novel divergent route to noviose as well as its C-(4) epimer has been developed and is the subject of this communication.

Previously, noviose has been synthesised in enantiomerically pure form from D-glucose,[9] L-rhamnose[10] and L-arabinose[11] as well as from (1*S*,4*R*)-4-acetoxy-5,5-



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dimethyl-2-cyclopenten-1-ol.[12] None of these routes, however, directly accesses the C-4 epimer of noviose. This has now been achieved by employing D-ribose as the chiral starting material with a diastereoselective reduction using K-Selectride® as a key step.

The synthesis of the C-4 epimer of noviose is outlined in Scheme 1. D-Ribose was converted to methyl-2,3-*O*-isopropylidene-D-ribofuranose by treatment with excess methanol in the presence of concentrated sulfuric acid, followed by addition of acetone to the reaction mixture.[13] Subsequent oxidation using $RuO_2{\cdot}H_2O$ and $NaIO_4$,[14] followed by esterification using K_2CO_3 and MeI yielded the known ester, **2**, $[\alpha]_D$ −67.8 (*c* 1.28, $CHCl_3$) {lit.[15] $[\alpha]_D$ −72.7 (*c* 2.0, $CHCl_3$)} in 88% yield over the two steps.

The introduction of the *gem*-dimethyl groups of noviose was achieved by performing a double Grignard reaction on the ester using MeMgI to afford **3** in 92% yield. The tertiary hydroxyl group of **3** was then protected as its benzyl ether **4** in 92% yield by first refluxing with NaH for 1 h to ensure formation of the anion before adding the BnBr and $^nBu_4NI$. In order to reduce to the ribitol, **4** was completely hydrolysed in aqueous acid and then treated with acetone and concentrated sulphuric acid to reform the 2,3-acetonide in 62% overall yield. Reduction with $LiAlH_4$ afforded a high yield of diol **5**, which underwent chemoselective primary protection to form benzyl ether **6** in 98% yield. Methylation of the remaining secondary hydroxyl group of **6** to form **7** proved to be difficult using standard conditions owing to steric hindrance imposed by the *cis*-relationship between the substituents of the dioxolane ring. Methylation was eventually achieved in high yield by first refluxing a solution of **6** in THF with NaH for 2 h before adding dry MeI. As with the benzylation of **3**, failure to do this resulted in very low yields. The scene was now set for transformation to the pyranose ring.

Double debenzylation proceeded in 99% yield to afford diol **8**, which was then oxidatively cyclised under Swern conditions (2 equiv.) to the lactone **9**, via the lactol. Reduction with DIBAL-H afforded the crystalline β-lactol **10**[16] as the major anomer in 67% yield. Mono-oxidation to the desired lactol was always complicated by over-oxidation to the lactone. A single-crystal X-ray structure determination (Fig. 1) confirmed the $^4C_1$ chair conformation as well as the configuration of the anomeric position as β. Finally, hydrolysis of acetonide **10** using $EtOH:CF_3CO_2H:H_2O$ (90:9:1) afforded the C-(4) epimer of noviose, **11**, as a mixture of anomers, in 95% yield.

The synthesis of noviose is summarised in Scheme 2. Swern oxidation of the free hydroxyl group of **6** afforded ketone **12**, mp 43–45°C (from hexane), $[\alpha]_D$ +31.7 (*c* 1.2, $CHCl_3$) in 85% yield. The diastereoselectivity of the reduction of **12** with various reducing

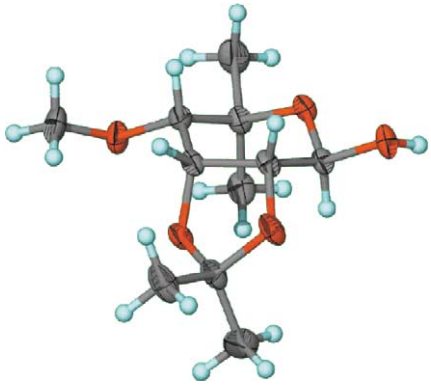
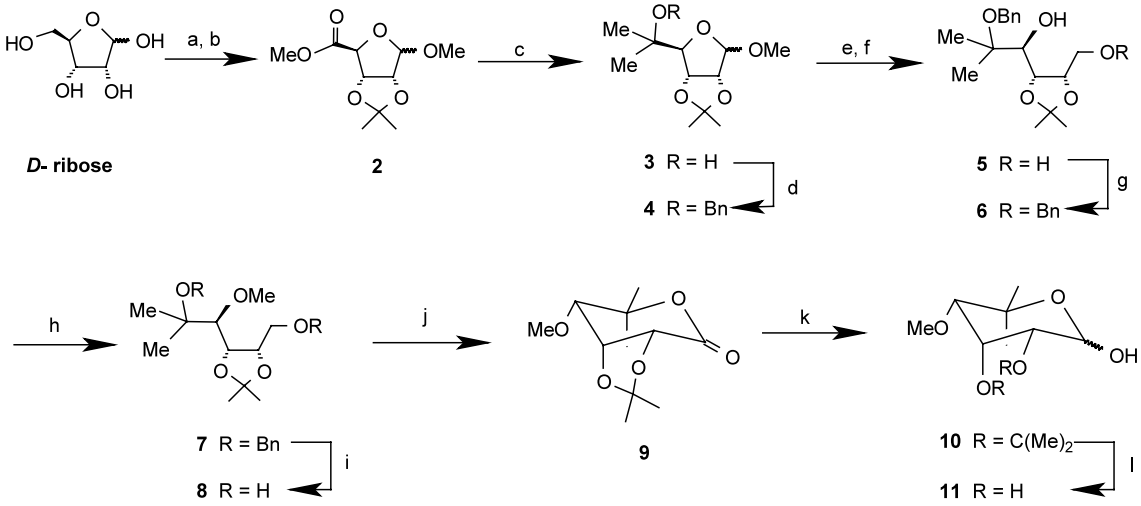
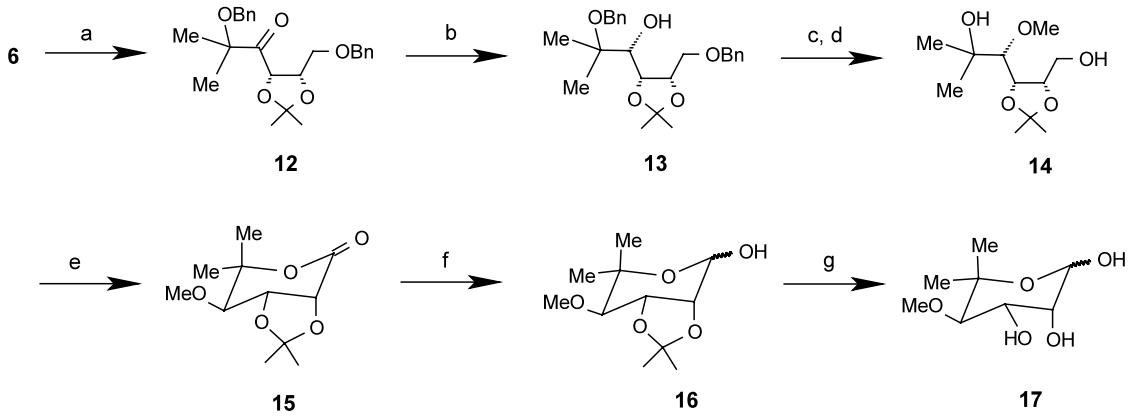


Figure 1. X-Ray crystal structure of lactol **10**.



Scheme 1. *Reagents and conditions*: (a) i. MeOH, H_2SO_4, 0°C; ii. acetone, H_2SO_4, 0°C to rt, 80%; (b) i. $RuO_2{\cdot}H_2O$, aq. $NaIO_4$ (10% m/v), acetonitrile/CCl_4 (1:1); ii. K_2CO_3, MeI, DMF, rt, 88%; (c) MeMgI (2 equiv.), ether, reflux, 92%; (d) NaH, BnBr, $^nBu_4NI$, THF, reflux, 92%; (e) i. HCl (1 M), dioxane, 60°C; ii. acetone, H_2SO_4, 0°C, 62%; (f) $LiAlH_4$, THF, 0°C, 84%; (g) NaH (1.1 equiv.), BnBr (1.1 equiv.), THF, rt, 98%; (h) NaH, THF, reflux, then MeI, rt, 97%; (i) Pd/C, H_2, EtOH, 99%; (j) $(COCl)_2$ (2 equiv.), DMSO (4 equiv.), Et_3N, CH_2Cl_2, 72%; (k) DIBAL-H, toluene, −78°C, 67%; (l) $EtOH:CF_3COOH:H_2O$ (90:9:1), 80°C, 95%.



Scheme 2. *Reagents and conditions*: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 85%; (b) K-Selectride®, toluene, 0°C to rt, 72%; (c) NaH, THF, reflux, then MeI, rt, 85%; (d) Pd/C, H_2, EtOH, 94%; (e) TPAP (cat.), NMO, 4 Å sieves, CH_2Cl_2, 91%; (f) DIBAL-H, THF, −78°C, 89%; (g) EtOH:CF_3CO_2H:H_2O (90:9:1), 80°C; 92%.

agents is outlined in Table 1. The desired product was obtained by treating **12** with K-Selectride® in toluene at 0°C and allowing the reaction to warm to room temperature.

The observed stereoselectivity may be rationalised using the Felkin–Ahn model (Fig. 2a) in which the hydride is delivered to the less hindered face of the lowest energy non-chelated conformation. By comparison, reduction with DIBAL-H and L-Selectride® may be explained by Houk's model (Fig. 2b) in which the metal (Al or Li) chelates to the carbonyl prior to the delivery of the hydride.[17]

Table 1. Observed stereoselectivity for various reducing agents

Reducing agent	Yield (%)	3*S*	3*R*
$LiAlH_4$, THF, 0°C	>95	1	2
DIBAL-H, toluene, rt	>95	>99	<1
L-Selectride®, toluene, −78°C	>95	4	1
K-Selectride®, toluene, 0°C to rt	72	<1	>99

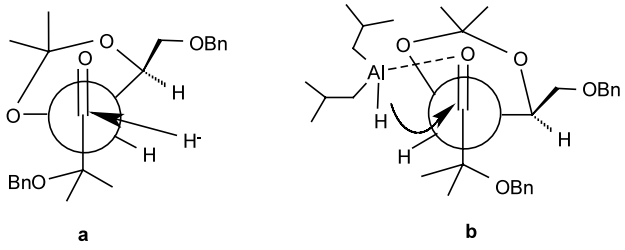


Figure 2. (a) Felkin–Ahn model; (b) Houk's model with DIBAL-H.

Table 2. Selected ^1H NMR data[a] for lactones **9** and **15**

Compound	H-2	H-3	H-4
9	4.63 (d *J* 8.7)	4.78 (dd *J* 3.9, 8.7)	3.41 (d *J* 3.9)
15	4.05 (d *J* 10.8)	3.95 (dd *J* 9.3, 10.8)	3.57 (d *J* 9.3)

[a] Recorded at 300 MHz in $CDCl_3$.

Methylation and debenzylation of the reduced product **13** afforded the diol **14** in excellent yield (80% over two steps).

In this series, TPAP oxidation using NMO as co-oxidant[18] proved to be the method of choice to furnish the lactone, **15**, in 91% yield, which upon reduction with DIBAL-H yielded a mixture of α- and β-lactols, **16**, as well as the acyclic aldehyde in 89% yield. Deprotection of the acetonide, under standard conditions, afforded the cyclic noviose **17** as a mixture of anomers in 92% yield. Table 2 summarises the ^1H NMR data for lactones **9** and **15** and shows the differences in the conformation of the chair forms with **9** being $^4C_1$ and **15** being $^1C_4$.

In conclusion, an efficient, high-yielding and stereoselective synthesis of noviose and its C-(4) epimer has been developed from a relatively inexpensive and readily available starting material. Easy access to both C-(4) epimers now sets the scene for SAR studies related to coumarin antibiotics.

Acknowledgements

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16. Compound **10**: colourless crystals, mp 91–93°C (from EtOAc/hexane); $[\alpha]_D$ +1.6° (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.31–1.54 (12H, 4×s, 4×CH_3), 3.32 (1H, d, *J* 4.1, 4-H), 3.40 (1H, d, *J* 6.0, OH), 3.50 (3H, s, OCH_3), 3.97 (1H, t, *J* 6.0, 2-H), 4.63 (1H, dd, *J* 4.1, 6.0, 3-H), 5.02 (1H, t, *J* 6.0, 1-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.3, 25.3, 27.3, 29.5, 58.7, 72.1, 75.4, 77.7, 80.8, 92.2, 110.5; HRMS *m*/*e* 232.1304 (M^+, 0.02%), calcd for $C_{11}H_{20}O_5$, 232.1311; found: C, 56.93; H, 8.64. $C_{11}H_{20}O_5$, requires C, 56.88; H, 8.68.
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