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Selective hydroxyl protection of (+)-noviose via improved synthesis

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ABSTRACT

Coumarin antibiotics are biologically important molecules embedded with (+)-noviose as signature moiety. A challenging problem concerning the synthesis of these molecules and their analogues is the difficulty in selective protection of the two non-anomeric OHs of (+)-noviose. In order to provide a useful solution to this problem, we report here a new strategy of (+)-noviose synthesis, modified from Musicki's previous study. Dihydrofuranone **8** was thus prepared from L-arabinose and was employed as key intermediate to provide previously unknown 3-*O*-BOM-Noviose **9** in seven steps (40% overall yield). Compound **9** was then efficiently converted into noviose 1,2-acetonide **6** (66%, two steps), which was otherwise only available from controlled degradation of naturally occurring novobiocin **1**.

Coumarin antibiotics, such as novobiocin, chlorobiocin, and coumarmycin A1 (**1**–**3**, Fig. 1), are potent bacterial DNA gyrase B inhibitors.[1] Evidence also accumulated that these natural products, as well as their simplified analogues, also represented a unique class of Heat Shock Protein 90 (Hsp90) inhibitors.[2] Therefore, practical synthesis of these compounds and their analogues is of great importance in searching for novel anti-infectious and anticancer drugs.

Whereas the molecules of coumarin antibiotics are featured with the presence of 3-O-acylated (+)-noviose moiety, most of the known noviose synthetic studies merely target the unmodified sugar.[3–13] Unfortunately, direct modification to noviose usually lacks regio-selectivity, and examples of 2- and 3-OH differently functionalized (or protected) noviose derivatives are rarely reported, except that Musicki[6] obtained 3-O-acylated noviose **5** by chromatographic separation and Olson[14] prepared noviose 1,2-acetonide **6** by controlled degradation of novobiocin **1**. These facts indicated that more efficient solutions to the problem of noviose regio-selective modification are still in need. In this Letter, we report a new strategy of noviose synthesis, so that the two non-anomeric OHs were selectively protected without ambiguity.

Our synthetic design was largely inspired by Musicki's earlier study, in which lactone **7** was prepared from L-arabinose and finally converted into noviose **4** (Scheme 1).[6] Instead of keeping the *cis*-diol protecting acetonide group through the whole synthetic procedure, we assume that acidic hydrolysis of this intermediate would first release the two protected hydroxyls and then trigger an intramolecular rearrangement to give thermodynamically more stable furanone **8**. By forming five-membered lactone ring, the carbonyl group could then be envisioned not only as a latent site to introduce the noviose C-5 *gem*-dimethyl group, but also a selective 2-OH protecting group. Meanwhile, by taking advantage of their difference in steric hindrance, the primary and secondary alcohol functions presenting in this molecule would provide a wide open window for further protecting group manipulation and finally result in selective hydroxyl protection in the noviose molecule (Scheme 2).

In order to illustrate the effectiveness of this assumption, we set forth to the synthesis of previously unknown 3-O-BOM-noviose **9** and its subsequent conversion into noviose 1,2-acetonide **6**, to which no de novo approach is available so far. Thus, lactone **7** was prepared from L-arabinose by repeating Musicki's procedure[6] and was heated with catalytic amount of concentrated hydrochloric acid in methanol. As it was expected, lactone **8** was isolated in 87% yield as single product. Selective primary hydroxyl protection of **8** was then carried out with TBSCl/immidazole at 0 °C to give TBS ether **10** in 92% yield. By subsequent BOM protection of the secondary hydroxyl group utilizing DIPEA as base and tetrabuytlammonium iodide as catalyst, compound **11** was isolated in 85% yield. On treatment of **11** with excessive methyl magnesium chloride, *gem*-dimethyl group at C-5 was introduced to provide diol **12** in 80% yield. The newly released C-2 secondary OH was then protected as benzoate in 95% yield to form **13**, and on exposure of this precursor to iodine in methanol, diol **14** was prepared in good yield. After **14** was subjected to PCC oxidation and the following DIBAL-H reduction of resulted **15**, 3-O-BOM-Noviose **9** was obtained as 7/1 mixture of anomers based on ^{1}H NMR (Scheme 3).

With **9** in hand, 1,2-acetonide formation was carried out in acetone and 2,2-dimethoxypropane in the presence of catalytic

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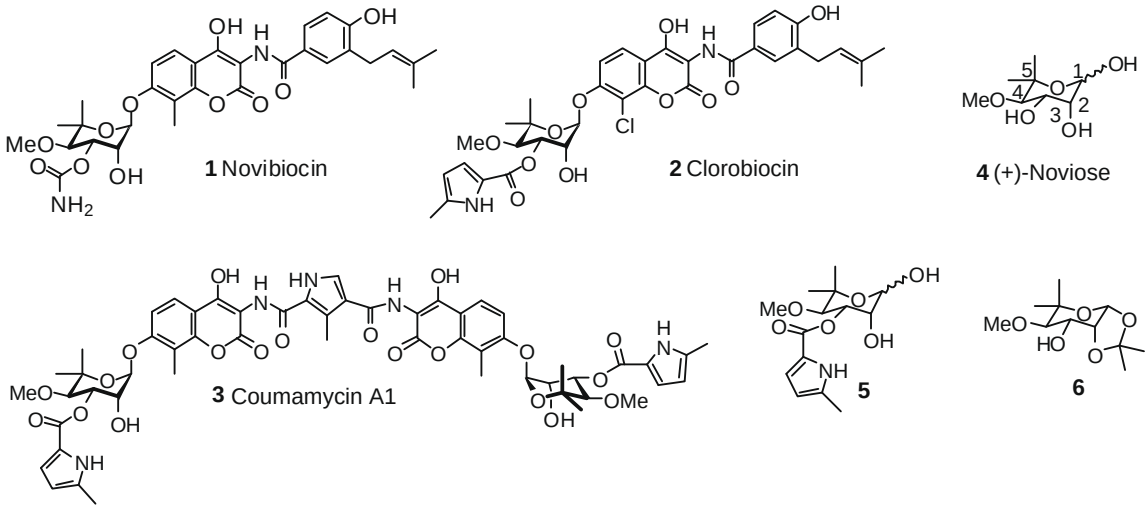
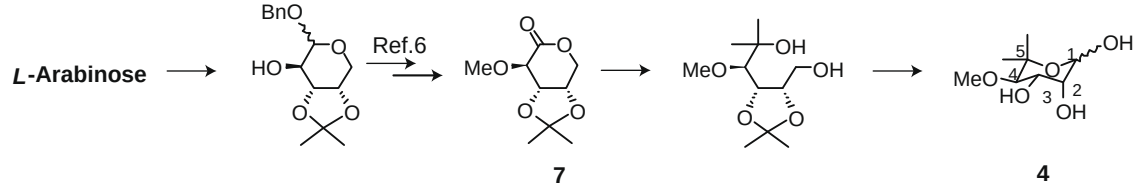
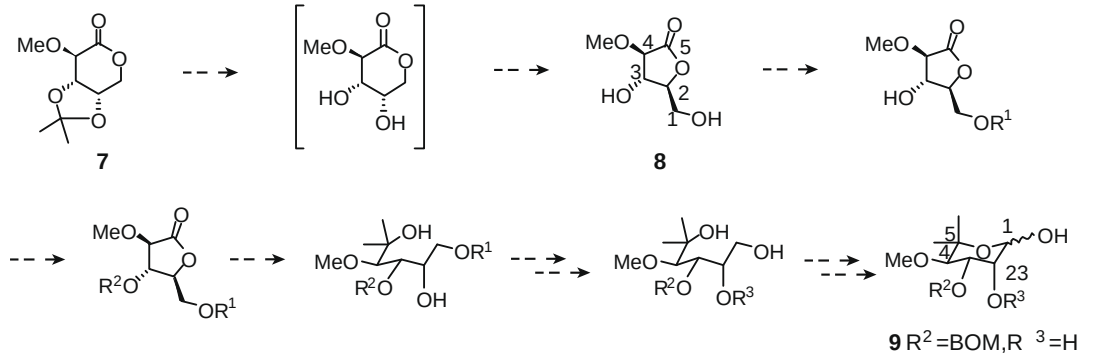


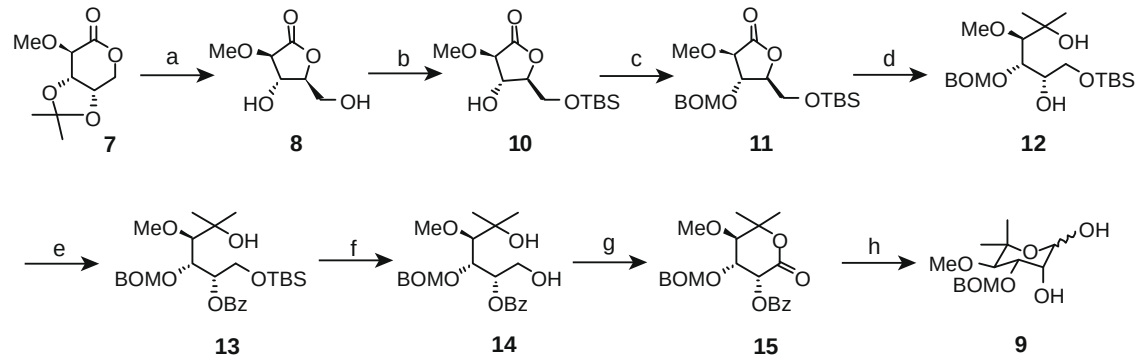
Figure 1. Coumarin antibiotics and known (+)-noviose derivatives.



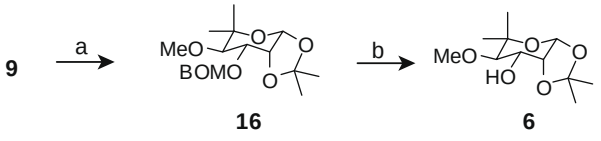
Scheme 1. Musicki's synthesis of (+)-noviose from L-arabinose.



Scheme 2. Proposed noviose synthesis resulting in selective hydroxyl protection.



Scheme 3. Reagents and conditions: (a) HCl (1 M), MeOH, reflux, 87%; (b) TBSCl, imidazole,THF, 0 °C ~ rt, 92%; (c) BOMOCl, DIPEA, $Bu_4N^+I^-$, THF, 0 °C ~ rt, 85%; (d) CH_3MgCl, THF, 0 °C, 80%; (e) BzCl, Et_3N, DMAP, CH_2Cl_2, 0 °C ~ rt, 95%; (f) I_2, MeOH, rt, 90%; (g) PCC, CH_2Cl_2, rt, 84%; (h) DIBAL-H, CH_2Cl_2, −78 °C, 88%.



Scheme 4. Reagents and conditions: (a) 2,2-Dimethoxy-propane, PTS, acetone, rt, 86%; (b) 1 atm H_2, 10% Pd–C, THF, rt, 77% (95% based on recovered **16**).

amount of PTS to give **16**. After removal of the BOM group by hydrogenolysis, target molecule **6** was isolated as colorless oil (Scheme 4). Although Olson et al. did not provide any structural data for **6** in their published paper, ^{1}H NMR data gained from our sample of **6** fit well to the required relative stereochemistry, and the use of L-arabinose as source of all chiral centers in the molecule of **6** leaves little doubt to the absolute configuration.[15]

In conclusion, we proposed that furanone **8**, resulted from acidic hydrolysis of known compound **7**, is a practically useful intermediate leading to 2- or 3-OH selectively protected noviose derivatives, and therefore provides an effective solution to the problem of regio-selective functional modification toward noviose. The effectiveness of this proposal was well illustrated by the preparation of previously unknown 3-O-BOM-Noviose **9** (40% yield, seven steps from **8**). By efficient conversion of **9** into noviose 1,2-acetonide **6** (66%, two steps; 81% based on recovered intermediate), we were also able to accomplish the first de novo synthesis of this synthetically versatile noviose derivative.

Acknowledgments

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Supplementary data

Experimental details for the synthesis and characterization data for key intermediates are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.194.

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15. A small sample of (+)-noviose was isolated as by-product from the reaction of the hydrogenolysis step. Optical rotation of this sample is identical with that of (+)-noviose prepared by repeating Laurin's whole procedure in our laboratory, and fits well to the previously reported data: $[\alpha]_D^{20}$ +32.2 (*c* 1.0, EtOH/H_2O 1:1); {lit.[13] $[\alpha]_D^{20}$ +33.6/+27.4 (*c* 0.2, EtOH/H_2O 1:1)}; NMR data were consistent with those previous reported[13]: ^{1}H NMR (CD_3OD, 600 MHz), mixture of anomers 8:5, δ4.94 (d, *J* = 3.6 Hz, 1H, minor, H-1), 4.80 (d, *J* = 1.2 Hz, 1H, major, H-1), 3.93 (dd, *J* = 8.4 Hz, 3.6 Hz, 1H, minor, H-3), 3.71 (dd, *J* = 3.6 Hz, 1.2 Hz, 1H, major, H-2), 3.64 (app.t, *J* = 3.6 Hz, 1H, minor, H-2), 3.60 (dd, *J* = 9.9 Hz, 3.6 Hz, 1H, major, H-3), 3.50 (s, 3H, major, OMe), 3.47 (s, 3H, minor, OMe), 3.15 (d, *J* = 8.4 Hz, 1H, minor, H-4), 3.11 (d, *J* = 9.9 Hz, 1H, major, H-4), 1.25 (s, 3H, minor, Me), 1.22 (s, 3H, major, Me), 1.21 (s, 3H, minor, Me), 1.08 (s, 3H, major, Me); ^{13}C NMR (CD_3OD, 125 MHz) δ95.6, 90.9, 85.8, 85.2, 78.1, 75.7, 73.8, 73.3, 72.5, 69.7, 62.1, 61.5, 29.0, 28.5, 25.1, 18.6; HRMS (ESI^+) $C_8H_{16}O_5$ calcd for $[M+Na]^+$ 215.0895, found 215.0895.