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Concise and divergent approach to 3-*O*-acyl-L-noviose derivatives and their 3-amino bioisosteres: 3-*O*-benzoyl-L-noviose and *N*-benzoyl-3-amino-L-noviose

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ABSTRACT

Generally applicable concise approaches to 3-*O*-acyl-L-noviose derivatives and their 3-amino bioisosteres, represented by **5** and **6**, were described. Chiral aldehyde **7** was thus prepared from dimethyl L-tartrate in five steps, and converted into **5** and **6** by employing substrate induced asymmetric aldehyde or *N*-sulfinyl aldimine allylation and dihydropyrane epoxidation as key steps, respectively.

Novobiocin **1**, clorobiocin **2,** and coumermycin A1 **3** (Fig. 1) are members of aminocoumarin antibiotics produced by different *streptomysis* species.[1] Being recognized as potent DNA gyrase B inhibitors and effective antibacterial agents for more than a half century, these coumarin-derived molecules are conceived as valuable templates in searching for novel antimicrobial drugs.[2] L-noviose (**4**, Fig. 1) is a rare pyranose subunit shared by all these natural products and has received intensive synthetic studies.[3] However, the abundance of available approaches to **4** did not result in significant advance in the chemical synthesis of aminocoumarin antibiotics. So far, no total synthesis has been documented, and a possible reason is that regioselective modification of **4**, that is, installation of the 3′-*O*-carbamyl or pyrrolylcarbonyl branch in the molecules of **1** or **2** and **3**, is not as easy as it seems.[3i]

A skillful semi-synthesis of **3** reported by Olson[4] suggested that L-noviose derivatives bearing preexisting 3-*O*-acyl groups might be more useful building blocks for this class of molecules. Moreover, bioisosteric replacement is a widely adapted strategy in drug discovery for acquiring new molecules with retained biological activities but improved metabolic and physical properties.[5] Accordingly, aminocoumarin bioisosteres with 3′-*O* replaced by a 3′-*N*, and thereby the corresponding pyranose building blocks are of considerable interest. Based upon these ideas, we recently developed a generally applicable concise approach to 3-*O*-acyl-L-noviose derivatives and their 3-amino bioisosteres represented by **5** and **6** (Fig. 1), both bearing benzoyl as model acyl group.

As depicted in Scheme 1, chiral aldehyde **7** and the corresponding *N*-*tert*-butanesulfinyl aldimide **8** were designed as initial chiral building blocks for compound **5** and **6**, respectively. Substrate induced asymmetric addition of properly sourced allyl anion to **7** and **8** were then expected to give *syn* adduct **9** and **10**, which would be subsequently converted into **11** and **12**. After proper transformation of **11** and **12** into dihydropyrane derivative **13** and **14**, the 2-β-OH was to be introduced by stereo-selective epoxidation and the following in situ hydrolysis. A significant feature of this plan is that protective group utilization was minimized and selective acylation of the 3-OH (or 3-NH_2) eased by making the 2-OH introduction the last step. However, feasibility of this plan is largely dependent on the stereochemistry outcomes of the allylation and the epoxidation steps.

The synthesis of previously unknown aldehyde **7** started with dimethyl L-tartrate (Scheme 2). Monosilyl ether **15** was previously prepared from the starting material using TBS triflate and 2,6-lutidine.[6] However, less expensive TBSCl and pyridine[7] are used instead in our hand, and the product was isolated in 69% yield from the reaction in DMF. On treatment of **15** with dimethyl sulfate under phase transfer condition, compound **16** was obtained in good yield and then subjected to Grignard reaction with large excess of methyl magnesium chloride to afford diol **17**. After removal of the TBS group in the molecule of **17**, the resulting triol **18** was oxidized with $NaIO_4$ to deliver aldehyde **7** in excellent yield.[8]

Stereoselective allylation of **7** is of central importance in our synthetic plan (Table 1). Although reagents capable of aldehyde allylations are abundant, our choices were limited to those tolerating free hydroxyl containment in the substrate. Therefore, we first examined the possibility of using allyl Grignard reagent to realize the stereoselective transformation of **7** into **9**. Results from the first set of experiments (Table 1, entries 1–4) indicated that nonpolar solvents strongly favored the formation of desired *syn* adduct **9**,

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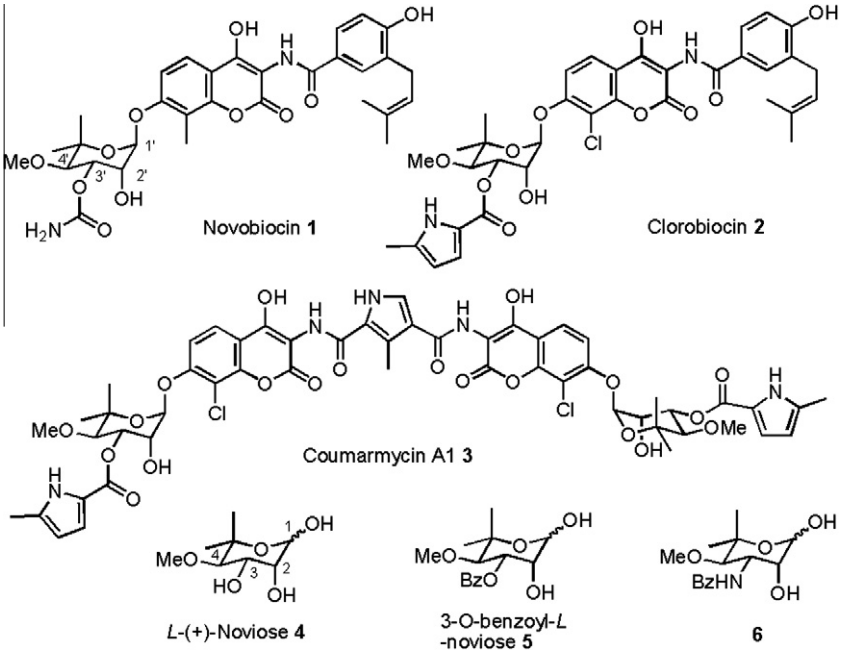
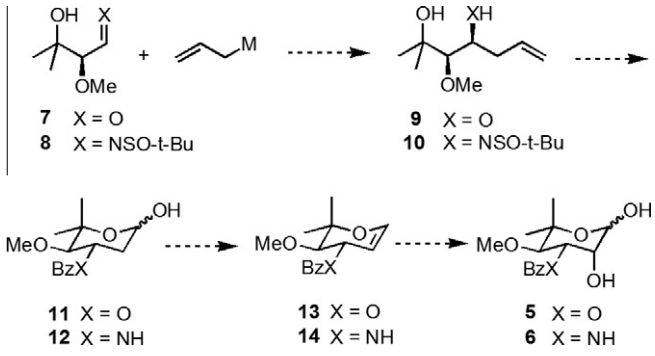
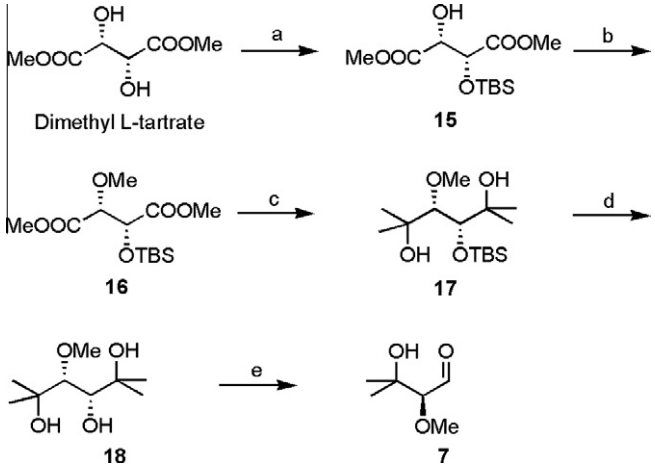


Figure 1. Aminocoumarin antibiotics and L-noviose derivatives.



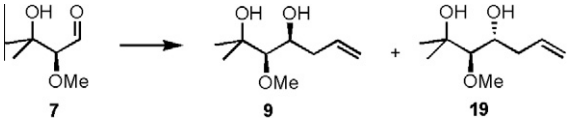
Scheme 1. Synthetic plan for **5** and **6**.



Scheme 2. Reagents and conditions: (a) TBSCl, Pyridine, DMF, 69%; (b) Me_2SO_4, NaOH, *n*-Bu_4NHSO_4, CH_2Cl_2/H_2O, 85%; (c) MeMgCl (5 equiv), THF; (d) TBAF, THF, 92% in two steps; (e) $NaIO_4$, $MeOH/H_2O$, 98%.

but the combined yields of **9** and **19** were unacceptably low.[9] The reason for this is that, when allyl magnesium bromide was added

Table 1
Diastereoselective allylation of **7**

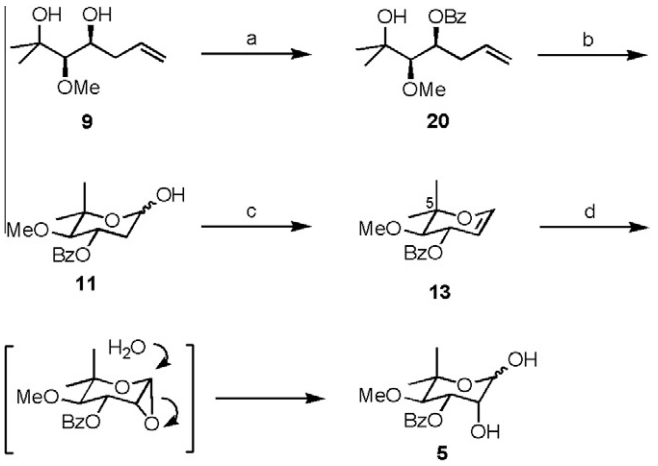


Entry	Reagent	Solvent	*T* (°C)	Yield[c] (**9**/**19**)[d]
1[a]	C_3H_5MgBr	Et_2O	−10	27% (1.1/1)
2[a]	C_3H_5MgBr	Et_2O	−20	39% (1.5/1)
3[a]	C_3H_5MgBr	CH_2Cl_2	−20	37% (4.4/1)
4[a]	C_3H_5MgBr	Toluene	−20	43% (5.5/1)
5[b]	C_3H_5MgBr	Toluene	−20	73% (4.7/1)
6[b]	C_3H_5MgBr, $CeCl_3$	Toluene	−20	78% (5.2/1)
7	C_3H_5Br, In	H_2O	+20	93% (4.0/1)

[a] Addition of Grignard reagent into solution of **7**.
[b] Addition of **7** into solution of Grignard reagent.
[c] Combined yield of **9** and **19**.
[d] Based on isolated products.

to a solution of **7**, the instantly formed basic magnesium alkoxide species might decompose unreacted **7**. Accordingly, the same reaction in toluene with reversed order of addition was carried out and resulted in substantially improved yield and comparably good d.r. (Table 1, entry 5). Also, by using anhydrous $CeCl_3$ as co-reagent,[10] slightly elevated yield and d.r. were observed (Table 1, entry 6). In addition to the optimized results from the Grignard reactions, we also examined the indium induced reductive coupling of allyl bromide with aldehyde **7** in aqueous media.[11] To our delight, the reaction proceeding with 1.3 equiv of indium and 3 equiv of allyl bromide at room temperature afforded **9** and **19** in a combined yield up to 93% (Table 1, entry 7). In spite of the slightly lower d.r., this procedure was preferred in our practical preparation of **9** for good isolated yield (74%) and convenience of operation.

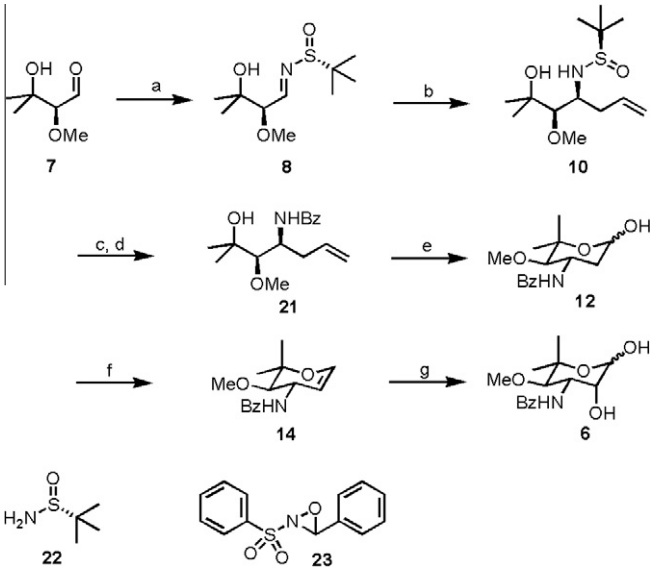
With feasible approach to **9** established, this key intermediate was converted into benzoate **20**, and then subjected to OsO_4 catalyzed double bond cleavage using $NaIO_4$ as real oxidant to provide 2-dehydroxyl L-noviose derivative **11**. After dehydration of **11** with methane-sulfonyl chloride and triethylamine,[12] the resulting



Scheme 3. Reagents and conditions: (a) PhCOCl, TEA, CH_2Cl_2, 91%; (b) OsO_4, $NaIO_4$, dioxane, H_2O, 67%; (c)MsCl, TEA, CH_2Cl_2, 70%; (d) *m*-CPBA, CH_2Cl_2/H_2O, 78.5%.

dihydropyrane **13** was oxidized with *m-CPBA and* in situ hydrolyzed with water to afford target molecule **5** in good yield (Scheme 3). The initially worrying epoxidation of **13**, however, appeared to be highly β-selective, to a large extent owing to the presence of a repelling axial methyl group on α face of the substrate, since no C-2 epimer was found in the reaction mixture.

After straightforward synthesis of **5**, we moved on to embark on preparation of the bioisosteric molecule **6** (Scheme 4). Based on the prediction model provided by Ellman,[13] (*R*)-*tert*-butanesufinamide **22** was condensed with aldehyde **7** using anhydrous copper sulfate as water scavenger to afford *N*-sulfinyl aldimide **8**. As it was expected, the double asymmetrically induced addition of allyl magnesium bromide to **8** in toluene gave the desired *syn* adduct **10** as a single product in 89% yield.[14] Upon removal of the *N*-sulfinyl group of **10** in acidic media and subsequent N-benzoylation, the resulting homoallylic benzamide **21** was subjected to a similar sequence comprising double bond cleavage and dehydration to give the other expected dihydropyrane **14**. Epoxidation of this intermediate with Davis oxidant **23**[15] followed by in situ hydrolysis successfully delivered compound **6**, again without formation of the C-2 epimer.



Scheme 4. Reagents and conditions: (a) **22**, $CuSO_4$, CH_2Cl_2, 94%; (b) allyl magnesium chloride, CH_2Cl_2, 94%; (c) 2 N HCl, 79%; (d) PhCOCl, TEA, CH_2Cl_2, 89%; (e) OsO_4, $NaIO_4$, dioxane, H_2O, 82%; (f) MsCl, TEA, CH_2Cl_2, 68%; (g) **23**, CH_2Cl_2, H_2O, 81%.

In summary, chiral aldehyde **7** was prepared from dimethyl L-tartrate in five easy steps, and subjected to *syn* selective allylation effected by Grignard reaction in nonpolar solvent or indium induced reductive coupling in aqueous media to provide the key intermediate **9**, which was further converted into 3-*O*-benzoyl-L-noviose **5** in four additional steps. All the reactions involved in this synthetic sequence were carried out under mild conditions and the overall yield of the target molecule was up to 17%. By simply diversifying the acylating agent of **9**, this approach is adaptable to the preparation of a variety of 3-*O*-acyl-L-noviose derivatives. In a similar manner, aldehyde **7**, in combination with Ellman's (*R*)-*tert*-butane sulfinamide, provided a useful entrance to 3-amino L-noviose bioisosteres, for example, **6**, in an overall yield up to 13% from dimethyl L-tartrate. With this model study accomplished, we are now tackling the total synthesis of all three known members of aminocoumarin family, and the preparation of their 3′-amino bioisosteres as well.

Acknowledgment

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Supplementary data

Supplementary data (Experimental procedures and analytical data. This material is available free of charge via the Internet at http://www.elsevier.com.) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.02.092.

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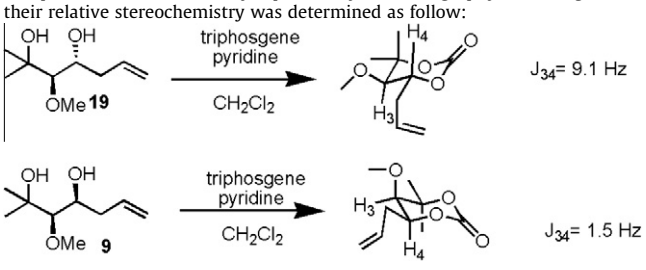
9. Compound **9** and **19** are easily separable by chromatography on silica gel, and their relative stereochemistry was determined as follow:



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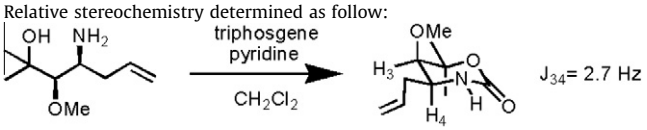

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