Efficient Synthetic Route to Ravidosamine Derivatives

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Abstracts: Concise synthesis of ravidosamine, the amino sugar constituent of ravidomycin and other antibiotics, has been achieved. The key steps include (1) regioselective reduction of benzylidene acetal with DIBAL, and (2) stereoselective reduction of oxime to the corresponding amine by using samarium diiodide in the presence of methanol.

Key words: ravidosamine, regioselectivity, boron trifluoride etherate, stereoselectivity, samarium diiodide, amino sugar

Amino sugars are involved as an important partial structure of many antibiotics or cytotoxic natural products, and play essential roles in their biological activities.[1] Therefore, considerable attention has been focused on development of their efficient and highly stereoselective synthetic methods.[2]

Ravidomycin (**1**), an amino sugar antibiotics, exhibits strong inhibitory effect on Gram positive microorganisms and potent antitumor activity.[3] We previously accomplished the total synthesis of **1**, albeit long synthetic sequence remained to be improved.[4] Recently, we found a viable protocol for the *C*-glycoside formation of a 3-azido-3-deoxy sugar as the amino sugar surrogate,[5] which will enable the improved synthesis of **1**. Herein, we wish to describe an efficient entry to the constituent amino sugar, ravidosamine (**2**), and the corresponding azido derivative. This amino sugar is included also in deacetylravidomycin M[6] and komodoquinone A[7] (Figure 1).

Although the natural ravidosamine is a D-series sugar, exploratory studies were carried out by using its L-enantiomer, just because we sought for a synthesis starting from fucose, in which the L-antipode is much cheaper than D-counterpart. Once an optimized synthetic pathway was established, it should be applied to the D-series sequence as well.

Methyl α-L-fucoside (**3**)[8] was converted to alcohol **4** in 80% overall yield by the reported method (Scheme 1).[9] The C(3) hydroxyl group in **4** was temporarily protected as an ethoxyethyl ether, and the acetate and benzoate protecting groups were removed by barium oxide in methanol. After the resulting hydroxyl groups in **5** were protected as benzyl ethers, the ethoxyethyl ether was

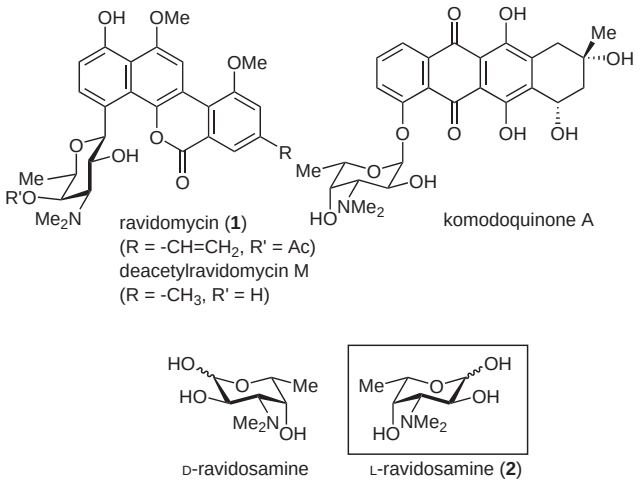
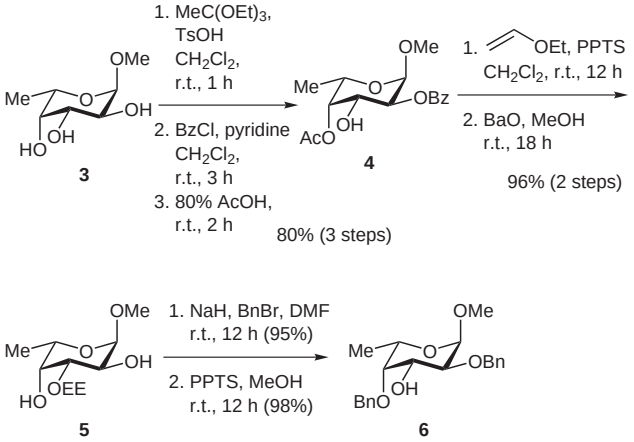


Figure 1

cleaved under mild acidic conditions to give alcohol **6** in 98% isolated yield.

A shorter route from methyl α-L-fucoside (**3**) to the intermediate **6** was also opened by adopting the method originated by Guo et al.[10] Protection of 3,4-diol with benzylidene acetal[11] produced a diastereomeric mixture **7** in 76% yield, and subsequent masking of the remaining hydroxyl group as benzyl ether gave the isomeric acetals **8** (50%) and **9** (48%), which were easily separable by silica gel chromatography (Scheme 2). The structures of **8** and **9** were assigned by ^{1}H NMR nuclear Overhauser enhancement difference (NOED) experiments (Figure 2).



Scheme 1

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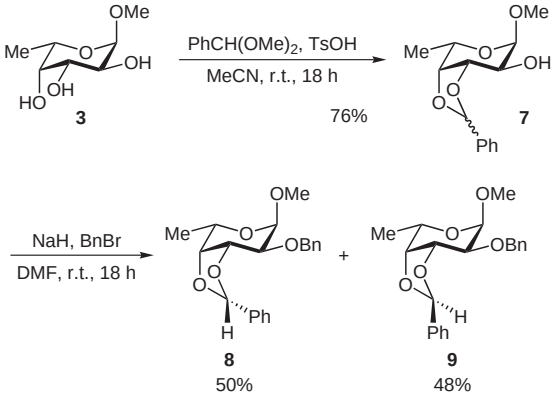


Scheme 2

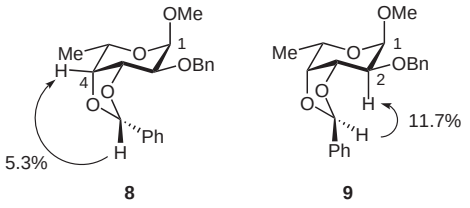
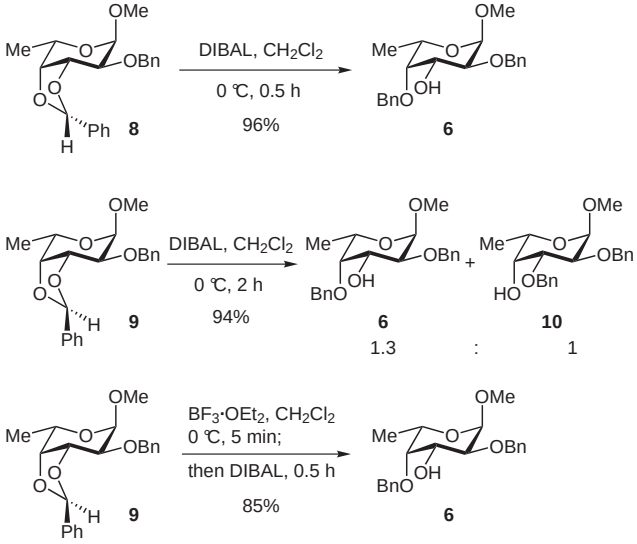


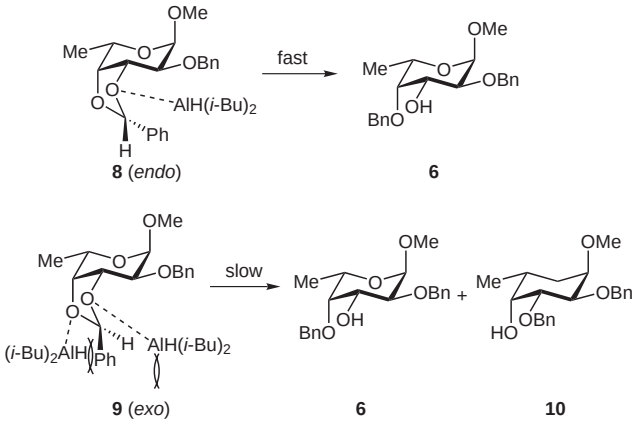
Figure 2 ^{1}H NMR studies of NOE (%) for **8** and **9**

As previously noted by Guo, the isomers, **8** and **9** showed significant difference in the reactivity for reductive acetal cleavage (Scheme 3).[10] *Endo*-isomer **8** rapidly reacted with diisobutylaluminum hydride (DIBAL, 3 equiv) in dichloromethane within 30 minutes, affording the desired product **6** as single product in 96% yield. On the other hand, the corresponding reaction of *exo*-isomer **9** reacted much slower under the same conditions, and two hours was needed for the complete consumption of **9**, giving a mixture of regioisomers **6** and **10** (1.3:1). We reasoned that the lower reactivity of **9** was due to the presence of the *exo*-phenyl group, retarding the coordination of DIBAL to the acetal oxygen(s) (Scheme 4).[12] This issue was nicely solved by using DIBAL in combination with $BF_3{\cdot}OEt_2$. Upon exposure of *exo*-acetal **9** with $BF_3{\cdot}OEt_2$ (2 equiv) for 5 minutes (0 °C, CH_2Cl_2), followed by the addition of DIBAL (3 equiv), the reaction was complete within 0.5 hours to furnish the desired product **6** as a single isomer in 85% yield.

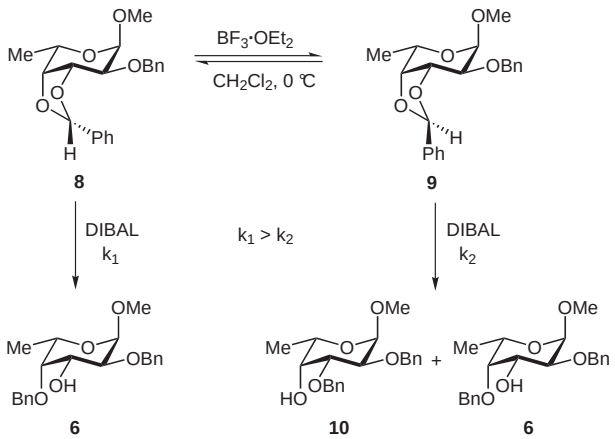
Concerning this highly favorable result, a typical Curtin–Hammett system was relevant (Scheme 5). Upon treatment with $BF_3{\cdot}OEt_2$, the isomers **8** and **9** became quickly equilibrated, although the ratio was only 2:1.[13] However, as a consequence of the rapid equilibrium and also the fact that **8** reacts with DIBAL much faster than **9** (vide supra), the entity that undergoes reduction is **8**, only giving the product **6**. The *exo*-isomer **9** could serve as an in situ source of the reactive isomer **8**. Indeed, we can also use a mixture of **8** and **9** by prior treatment with $BF_3{\cdot}OEt_2$ followed by exposure to DIBAL under the same conditions to afford product **6**, although the yield was less than expected (Scheme 6).



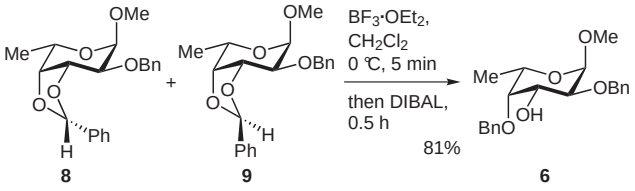
Scheme 3



Scheme 4

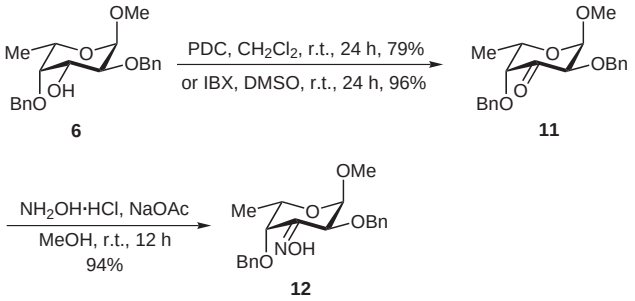


Scheme 5



Scheme 6

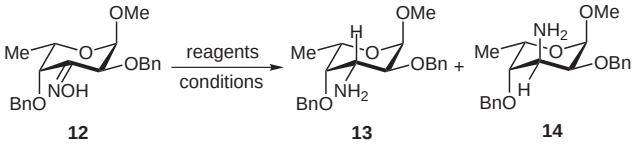
The stage was now set for introduction of the C(3) amino group, for which we took the strategy of the oxime reduction. Oxidation of **6** was achieved by using pyridinium dichromate (PDC) or preferably *o*-iodoxybenzoic acid (IBX),[14] giving a better yield of ketone **11**, which was converted to oxime **12** (Scheme 7).



Scheme 7

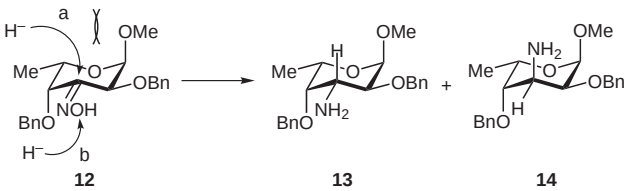
However, initial attempts to reduce oxime **12** with hydride reducing agents gave a poor stereoselectivity, giving the mixture of isomeric amines **13** and **14** (Table 1, entries 1–3). The reduction with $LiAlH_4$ gave the corresponding amines **13** and **14** in moderate selectivity (entry 1). When a bulky hydride reducing agent (e.g. Red-Al) was used, the axial approach became less favorable, presumably due to the hindrance by the C(1) methoxy group (Scheme 8), giving preferentially the undesired amine **14** as a major product.

Table 1 Reduction of Oxime **12** with Hydride Reducing Agents



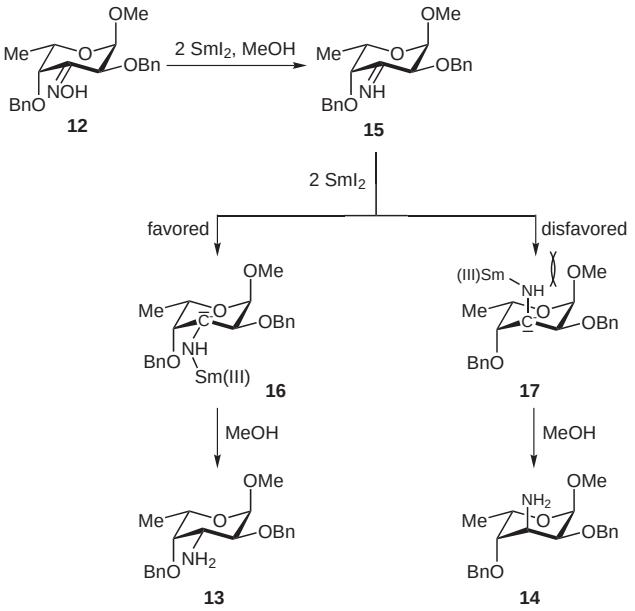
Entry	Reagents	Conditions	Yield (%, ratio)[a]
1	$LiAlH_4$	THF, 0 °C	72 (4:1)
2	Red-Al	THF, 0 °C	57 (1:2)
3	$LiAlH_4$, $AlCl_3$	Et_2O, 0 °C	63 (1:2)
4	Zn, HOAc	r.t. to 100 °C	–[b]
5	SmI_2, MeOH	THF, r.t.	87 (>19:1)

[a] Determined by ^1H NMR.
[b] Recovery of the starting material.



Scheme 8

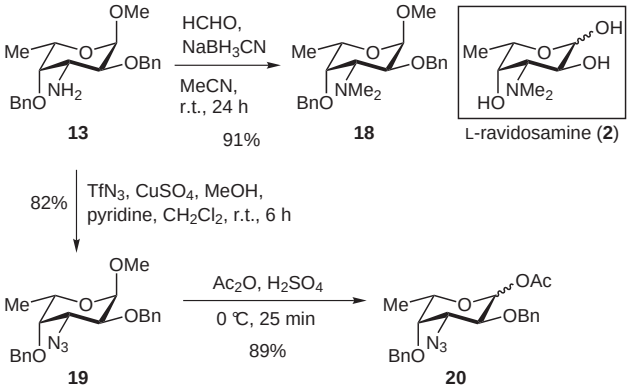
Having limited success with metal hydrides, we turned our attention to the use of an electron transfer reagent. When oxime **12** was treated with zinc powder and glacial acetic acid at room temperature[15] or even at 100 °C, only recovery of the starting material was observed (entry 4). After some experimentation, we were pleased to find that oxime **12** could be reduced in high stereoselectivity (**13**:**14** = 19:1) by using samarium diiodide and methanol[16] in 78% yield (entry 5).



Scheme 9

Scheme 9 shows our rationale for this electron transfer reduction.[17] The oxime is first reduced to imine **15**, and its further reduction generates the isomeric intermediates **16** and **17**. Among these, equatorial disposition of the amino substituent is preferred to avoid the unfavorable 1,3-diaxial interactions, and protonation by the coexisting MeOH gives the desired amine **13** as the major product.

Finally, primary amine **13** was converted to dimethylamino sugar **18** by reductive dimethylation (Scheme 10). This sugar **18** contained the required stereochemistry and functionality of L-ravidosamine (**2**).[18] Azide **20** was also prepared from amine **13**, when treated with triflyl azide and a catalytic amount of cupric sulfate.[19] Acetolysis of **19** gave azide **20**, which is ready for use in the glycoside formation.



Scheme 10

In conclusion, we have developed an efficient synthetic route to ravidosamine derivatives. Total synthesis of ravidomycin and the related natural products is now in progress, and the results will be reported shortly.

Acknowledgment

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(10) Guo and coworkers studied exactly the same system, noting qualitatively the difference in the reactivities of **8** and **9** for DIBAL reduction and also suggested the solution by employing $BF_3{\cdot}OEt_2$. Unfortunately, the exact conclusion could not be drawn from their data, because they used the α/β-anomeric mixture of methyl glycoside. See: Guo, Z.-W.; Deng, S.-T.; Hui, Y.-Z. *J. Carbohydr. Chem.*; **1996**, 15, 965.
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(13) To a stirred solution of **9** (356 mg, 1 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added $BF_3{\cdot}OEt_2$ (0.25 mL, 2 mmol). After stirring for 5 min, the reaction was quenched with sat. aq $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The ^1H NMR indicated that the ratio of **8** and **9** was about 2:1.
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(18) Compound **18**: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.26 (m, 10 H), 4.86 (d, *J* = 11.2 Hz, 1 H), 4.78 (d, *J* = 3.7 Hz, 1 H), 4.64–4.56 (m, 3 H), 4.07 (dd, *J* = 3.7, 11.2 Hz, 1 H), 3.85 (br q, *J* = 6.6 Hz, 1 H), 3.62 (br d, *J* = 2.9 Hz, 1 H), 3.33 (s, 3 H), 3.00 (dd, *J* = 2.9, 11.2 Hz, 1 H), 2.59 (s, 6 H), 1.13 (d, *J* = 6.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2 (C), 138.1 (C), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.5 (CH), 127.4 (CH), 97.2 (CH), 82.9 (CH), 75.2 (CH_2), 75.1 (CH), 71.1 (CH_2), 66.8 (CH), 61.4 (CH), 54.9 (CH_3), 43.5 (CH_3), 16.3 (CH_3). IR (neat): 3030, 2931, 2895, 1454, 1099, 1053, 733, 696 cm^{-1}.
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