Synthesis of L-Vancosamine Derivatives from Methyl α-D-Mannopyranoside

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Abstract: Concise synthesis of L-vancosamine, the amino sugar constituent of vancomycin and other antibiotics, has been achieved. The key steps include (1) stereoselective addition of methylcerium reagent to oximino ether, and (2) stereoselective hydrogenation of 5,6-unsaturated glycoside with C(5) inversion to give L-vancosamine derivative. C-Glycosidation of vancosaminyl acetate with iodoresorcinol proceeded in the presence of $Sc(OTf)_3$ in high yield.

Key words: vancosamine, oximino ether, organocerium reagent, stereoselectivity, branched amino sugar, aryl *C*-glycoside

L-Vancosamine (**1**) and *N*,*N*-dimethyl-L-vancosamine (**2**) are the sugar constituents of antibiotics of diverse structural types. For example, L-vancosamine[1] is installed in the glycopeptide antibiotic vancomycin, which is an important drug used for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA),[2] while *N*,*N*-dimethyl analogue **2** occurs as an *O*-glycoside in the nocardicyclin antibiotics[3] and as a *C*-glycoside in the pluramycin antibiotics **3** (Figure 1).[4]

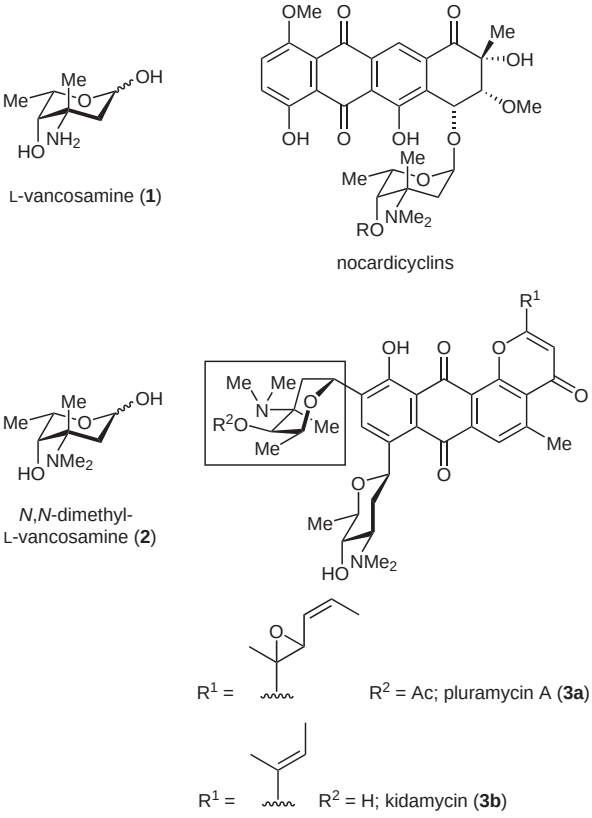

Figure 1

We have been interested in the synthesis of aryl *C*-glycoside antibiotics[5] involving the pluramycins **3**, in which we required a reliable synthetic route to such L-vancosamine derivatives. Among numerous preceding syntheses of vancosamine derivatives starting either from carbohydrates[6] or non-carbohydrate materials,[7] several are elegantly achieved, but less practical due to the use of toxic reagents or expensive starting materials, and few are applicable to a high-yielding, large-scale preparation.

Herein, we describe a steady, stereoselective route to L-vancosamine derivatives. A preliminary study on the aryl C-glycosidation will be also described.

The synthesis started with the known conversion of methyl α-D-mannopyranoside (**4**) into ketone **6** (Scheme 1).[8] For introduction of the C(3) methyl-branched amino group, we took the strategy of adding a methyl anion to the oximino ether.[9] Treatment of ketone **6** with *O*-methylhydroxylamine hydrochloride and NaOAc (MeOH, r.t., 12 h) afforded the oximino ether **7** in 83% yield, which was treated with methylcerium chloride[10] at –78 °C. During gradual warming to 0 °C and further stirring at this temperature for three hours, the addition occurred smoothly to give the isomer **8** as a single product. Greven et al. reported that five equivalents of methylcerium chloride was needed for completion of the reaction of the corresponding benzyl imino ether.[11] However, we found that the cerium reagent could be reduced to two equivalents, if the reaction was carried out at 0 °C or warmed to 15 °C for three hours. The stereostructure of **8** was assigned by ^{1}H NMR nuclear Overhauser enhancement difference (NOED) experiment (Figure 2). Highly stereoselective addition of the methyl anion to the oximino ether could be ascribed to the steric effect of the anomeric methoxy group, retarding attack of the bulky cerium reagent from the α-face.

The next stage was the amidation and the reductive cleavage of the N–O bond. Although the cleavage of N–O bond by catalytic hydrogenolysis is one of the most useful method, we reasoned that not only the N–O bond, but also the benzylidene acetal would undergo hydrogenolysis. Thus, we centered our attention to samarium diiodide, which was known to cleave N–O bonds.[12] Thus, after

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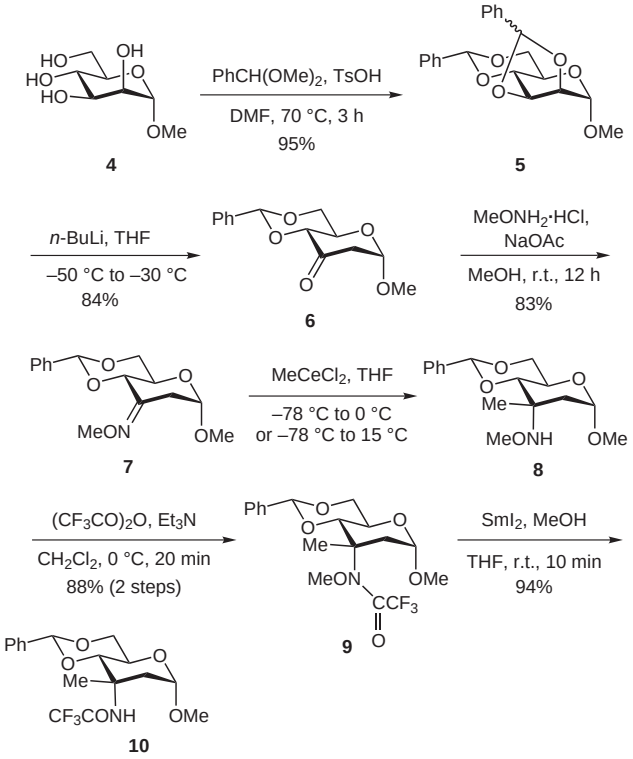


Scheme 1

hydroxyamino sugar **8** was protected as a trifluoroacetamide **9**, which was treated with samarium diiodide, where the cleavage of the N–O bond completed in 10 minutes, giving amide **10** in 94% yield.

Opening of the benzylidene acetal in **10** was attempted by treatment with *N*-bromosuccinimide (NBS) and $BaCO_3$ in refluxing CCl_4.[13] This process, however, turned to be capricious, and the yield fluctuated in the range of 22–71% (Scheme 2). Careful drying of the reaction flask, reagents and the solvent, or control experiments with/without room light illumination, were all incapable of solving the poor reproducibility. However, the situation was solved by adding one equivalent of pyridine,[14] instead of $BaCO_3$, in refluxing CCl_4 under normal room light illumination to produce bromide **11** in 73% yield.[9] Dehydrobromination was effected by using DBU in hot DMF (90 °C, 4 h).[15] Finally, catalytic hydrogenation of the resulting enol ether furnished the L-vancosamine derivative **13**.[16]

For the glycoside formation, we needed a better leaving group at the C(1) position rather than a methoxy group.[17] Thus, methyl glycoside **13** was hydrolyzed in 20% aqueous AcOH (100 °C, 12 h),[18] and acetylation of the

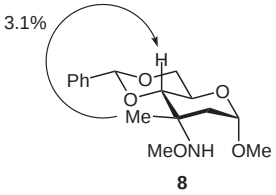
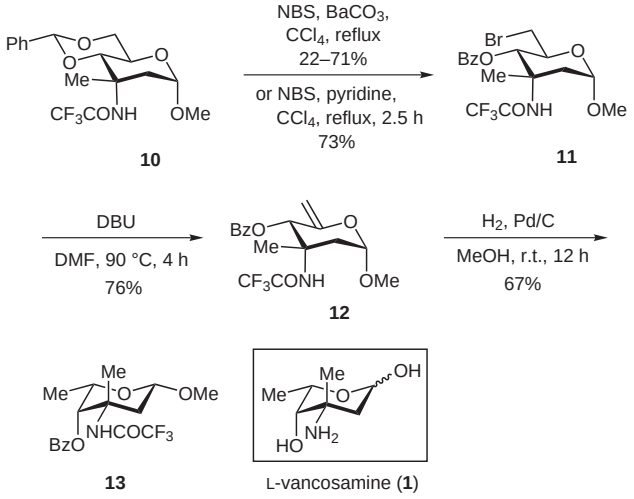
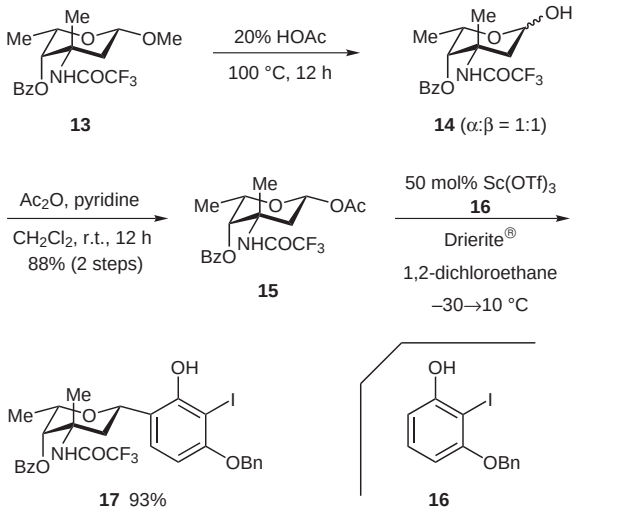


Figure 2 ^{1}H NMR study of NOE for **8**.



Scheme 2

resulting hydroxy group gave glycosyl acetate **15** (β:α = >20:1),[19] ready for the C-glycosidation (Scheme 3). Indeed, upon treatment of glycosyl acetate **15** with phenol **16** in the presence of 50 mol% amount of $Sc(OTf)_3$ and powdered Drierite® in 1,2-dichloroethane at –30 °C followed by gradual warming to 10 °C, the *C*-glycoside **17** was obtained in 93% yield.[20] The stereostructures of **15** and **17** were assigned by ^{1}H NMR NOE experiments (Figure 3).



Scheme 3

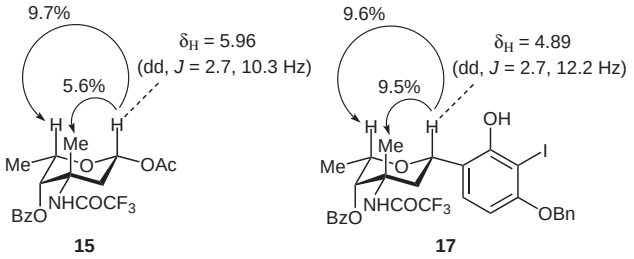


Figure 3 Selected data of ^{1}H NMR and NOE for **15** and **17**.

In summary, we have developed an efficient and preparative synthetic route of L-vancosamine derivatives, which was accomplished in 9 steps from methyl α-D-mannopyranoside (**4**) with an overall yield of 20%. In addition, no chromatographic purification procedures are required from the intermediate **5** to **8**. Total synthesis of the pluramycins and the related natural products is now in progress, and the results will be reported in due course.

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(19) Compound **15**: mp 168–169 °C (CH_2Cl_2–hexane); $[\alpha]_D^{28}$ +10 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.16–8.13 (m, 2 H), 7.67–7.48 (m, 3 H), 6.99 (br s, 1 H), 5.96 (dd, *J* = 2.7, 10.3 Hz, 1 H), 5.07 (br s, 1 H), 4.17 (dq, *J* = 1.0, 6.6 Hz, 1 H), 2.61 (dd, *J* = 2.7, 12.6 Hz, 1 H), 2.15 (s, 3 H), 2.10 (dd, *J* = 10.3, 12.6 Hz, 1 H), 1.77 (s, 3 H), 1.29 (d, *J* = 6.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1 (C), 167.7 (C), 156.3 (q, *J* = 37 Hz, C), 134.1 (CH), 130.0 (CH), 128.7 (CH), 128.3 (C), 115.2 (q, *J* = 290 Hz, C), 90.6 (CH), 73.4 (CH), 69.1 (CH), 57.2 (C), 35.3 (CH_2), 21.2 (CH_3), 21.0 (CH_3), 17.2 (CH_3). IR (neat): 3334, 3076, 2989, 1728, 1556, 1452, 1273, 1161, 1049, 908, 758, 715 cm^{-1}. Anal. Calcd: C, 53.60; H, 5.00; N, 3.47. Found: C, 53.39; H, 5.25; N, 3.37.

(20) Compound **17**: mp 89–90 °C (Et_2O–hexane); $[\alpha]_D^{29}$ –0.3 (*c* 0.98, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.38 (s, 1 H), 8.19–8.16 (m, 2 H), 7.68–7.28 (m, 8 H), 7.01 (d, *J* = 8.5 Hz, 1 H), 6.88 (br s, 1 H), 6.42 (d, *J* = 8.5 Hz, 1 H), 5.22 (br s, 1 H), 5.16 (s, 2 H), 4.89 (dd, *J* = 2.7, 12.2 Hz, 1 H), 4.20 (q, *J* = 6.6 Hz, 1 H), 2.49 (dd, *J* = 2.7, 12.4 Hz, 1 H), 2.28 (dd, *J* = 12.2, 12.4 Hz, 1 H), 1.84 (s, 3 H), 1.31 (d, *J* = 6.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6 (C), 158.3 (C), 156.3 (q, *J* = 37 Hz, C), 155.3 (C), 136.5 (C), 134.1 (CH), 130.1 (CH), 128.9 (CH), 128.5 (CH), 128.2 (C), 127.8 (CH), 127.5 (CH), 126.9 (CH), 118.6 (C), 115.2 (q, *J* = 290 Hz, C), 104.2 (CH), 79.0 (C), 75.5 (CH), 73.7 (CH), 71.0 (CH), 70.9 (CH_2), 56.7 (C), 37.1 (CH_2), 20.4 (CH_3), 17.8 (CH_3). IR (neat): 3340, 3064, 2985, 1728, 1614, 1452, 1269, 1063, 908, 735, 714 cm^{-1}. Anal. Calcd: C, 52.03; H, 4.07; N, 2.09. Found: C, 52.18; H, 4.33; N, 2.14.