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A Synthesis of L-Vancosamine Derivatives from Non-Carbohydrate Precursors by a Short Sequence Based on the Marshall, McDonald, and Du Bois Reactions

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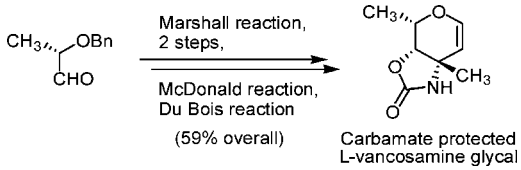
ABSTRACT



The carbamate-protected L-vancosamine glycal, viewed as a universal precursor for vancosamine derivatives, was prepared by a short scheme based on diastereoselective addition of an allenyl stannane to a lactaldehyde ether, the tungsten-catalyzed alkynol cycloisomerization, and the rhodium-catalyzed C–H insertion of a carbamate nitrogen. This sequence is a prototype for a new and efficient strategy for the synthesis of 3-amino sugar derivatives. The key intermediate was elaborated to the silyl ether of *N*,*N*-dimethyl vancosamine glycal.

L-Vancosamine (**1**) and *N*,*N*-dimethylvancosamine (**2**) are constituents of complex antibiotics of diverse structural types. L-Vancosamine is a functional component of vancomycin,[1] the glycopeptide that has attained the status of antibiotic of last resort against resistant Gram-positive bacteria.[2,3] *N*,*N*-Dimethylvancosamine appears as an O-glycoside in the norcardicyclin (anthracycline) antibiotics[4] and as a C-glycoside in the pluramycin (kidamycin) antibiotics.[5]

For the synthesis of aryl C-glycoside antibiotics, we wish to establish the key aryl C-glycoside connections by a "reverse polarity strategy" based on the addition of lithiated glycals to quinonoid substrates.[6] If we are to implement this approach for members of the pluramycin group of antitumor antibiotics, we need access to a protected *N*,*N*-dimethyl-L-vancosamine glycal, particularly the silyl ether **3**. Although it would be reasonable to prepare this type of intermediate from L-vancosamine (which is available from synthesis[7] and from degradation[8] of vancomycin), we have been interested in devising a direct preparation of this and related reagents.

In fact, the racemic vancosamine glycal derivative **4** has been prepared by McDonald in an 8-step sequence[7s] based on a Staudinger cycloaddition and the author's own alkynol

(1) (a) Grdadolnik, S. G.; Pristovsek, P.; Mierke, D. F. *J. Med. Chem.* **1998**, *41*, 2090. (b) Williams, D. H.; Waltho, J. P. *Biochem. Pharmacol.* **1988**, *37*, 133.

(2) (a) Williams, D. H.; Bardsley, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1172. (b) Malabarba, A.; Nicas, T. I.; Thompson, R. C. *Med. Res. Rev.* **1997**, *17*, 69.

(3) Even vancomycin has encountered resistant organisms. New analogues with a mode of action different from that of vancomycin have been shown to be effective against resistant strains. See: (a) Walsh, C. *Science* **1999**, *284*, 442. (b) Ge, M.; Chen, Z.; Onishi, H. R.; Kohler, J.; Silver, L. L.; Kerns, R.; Fukuzawa, S.; Thompson, C.; Kahne, D. *Science* **1999**, *284*, 507. (c) Ritter, T. K.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2001**, *40*, 3508.

(4) An earlier designation for these compounds was as 0624-A and -B; see: (a) Tanaka, Y.; Mikami, Y.; Yazawa, K. U.S. Patent 5,965,407, 1999. (b) Tanaka, Y.; Gräefe, U.; Yazawa, K.; Mikami, Y. *J. Antibiot.* **1998**, *51*, 589. (c) Tanaka, Y.; Gräfe, U.; Yazawa, K.; Mikami, Y.; Ritzau, M. *J. Antibiot.* **1997**, *50*, 822.

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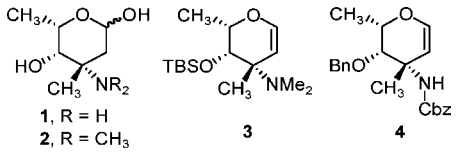


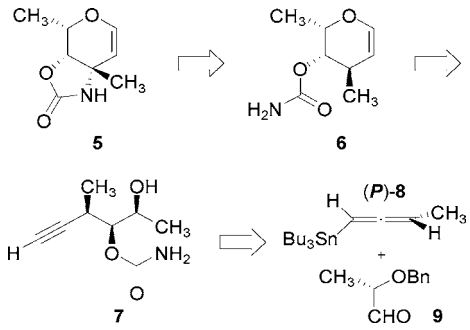
Figure 1. L-Vancosamine (**1**), *N*,*N*-dimethyl-L-vancosamine (**2**), silyl-protected *N*,*N*-dimethyl-L-vancosamine glycal **3**, and protected L-vancosamine glycal **4**.

cycloisomerization reaction.[9] Although both efficient and stereoselective, this synthesis did not appear to us to be readily adaptable to the preparation of chiral glycal derivatives.

In this letter we present a novel strategy for the synthesis of oxazolidinone **5**, which we view as a universal precursor to vancosamine derivatives. Furthermore, we describe the conversion of this key compound to the protected *N*,*N*-dimethyl-L-vancosamine glycal **3**, intended for use in our approach to the synthesis of pluramycin antibiotics.

In our retrosynthetic analysis (Scheme 1), we envisaged oxazolidinone **5** to be available from the stereospecific C−H

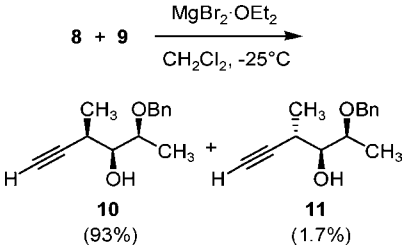
Scheme 1. Oxazolidinone **5**, and Its Retrosynthetic Analysis



bond insertion reaction (Du Bois reaction)[10] of the 3-methyl 3-deoxy glycal **6**, which would be accessed through the cycloisomerization (McDonald reaction) of alkynol **7**. The preparation of the selectively functionalized **7** would be based on the diastereoselective addition (Marshall reaction)[11,12] of a (*P*)-allenyl stannane to an (*S*)-lactic aldehyde.

The resulting scheme involves the sequential application of three recently developed reactions, each of which accomplishes a previously difficult or impossible transformation. Implementation of the plan was remarkably facile.

Scheme 2. Stereoselectivity of the Marshall Reaction



Alkynol **10** was obtained by the addition of (*P*)-allenyl stannane **8**[13] to (*S*)-lactic aldehyde benzyl ether **9**[14] according to the method of Marshall.[11] Purification by filtration through KF-loaded Celite, a procedure described by Roush et al.,[15] followed by flash column chromatography provided the major product, alkynol **10**, and a small amount of the diastereomeric alkynol **11**.[16] Protecting group modification was required prior to the cycloisomerization reaction. Therefore, alkynol **10** was functionalized as the carbamate **12** by treatment with trichloroacetyl isocyanate followed by methanolysis.[17] Then the benzyl group was removed with DDQ to afford alkynol **7**, the substrate for the McDonald reaction. Irradiation of a solution of alkynol **7** at 350 nm was carried out in the presence of 10 mol % of $W(CO)_6$ and excess triethylamine. After low-temperature workup (see Supporting Information), crystalline glycal **6** was obtained in 87% yield.

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(10) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598.

(11) (a) Marshall, J. A.; Wang. X. J. *J. Org. Chem.* **1991**, *56*, 3211. (b) Marshall, J. A.; Wang. X. J. *J. Org. Chem.* **1992**, *57*, 1242.

(12) For a review of this and related stereoselective addition reactions, see: Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31.

(13) Prepared from commercially available (*R*)-(+)-3-butyn-2-ol in two steps by the reported procedure: (a) Marshall, J. A.; Lu, Z.-H.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 817. (b) Marshall, J. A.; Grant, C. M. *J. Org. Chem.* **1999**, *64*, 8214.

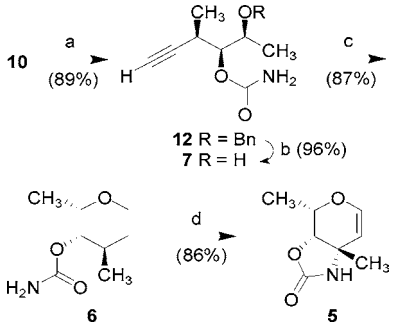
(14) Prepared in two steps from ethyl (*S*)-(−)-lactate. *O*-Benzylation according to Vaelis and Johnson[14a] gave ethyl (*S*)-2-(benzyloxy)propionate ($[\alpha]^{22}_D$ −87.0 in $CHCl_3$, *c* 2.54) with enantiomeric purity >99%, determined by ^1H NMR study with chiral shift reagent, Eu(hfc)$_3$. DIBAL reduction by the procedure of Solladié-Cavallo and Bonne[14b] provided aldehyde **9** ($[\alpha]^{22}_D$ −61.2 in $CHCl_3$, *c* 6.68): (a) Varelis, P.; Johnson, B. L. *Aust. J. Chem.* **1995**, *48*, 1775. (b) Solladié-Cavallo, A.; Bonne, F. *Tetrahedron*: *Asymmetry* **1996**, *7*, 171.

(15) Scheidt, K. A.; Bannister, T. D.; Tasaka, A.; Wendt, M. D.; Savall, B. M.; Fegley, G. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 6981.

(16) Alkynol **11** was identified by its ^1H NMR spectrum: Marshall, J. A.; Chobanian, H. R. *J. Org. Chem.* **2000**, *65*, 8357. The reported enantiomeric excess of commercially available (*R*)-(+)-3-butyn-2-ol (Aldrich Chemical Company) was greater than 95%; therefore, a small amount of the (*M*)-isomer of the allenyl stannane was presumably involved in the reaction.

(17) Kocovsky, P. *Tetrahedron Lett.* **1986**, *27*, 5521.

Scheme 3. Completion of the Synthesis of Oxazolidinone **5**[a]



[a] Reagents and conditions: (a) $CCl_3C(O)NCO$, CH_2Cl_2; K_2CO_3/MeOH. (b) DDQ, CH_2Cl_2, pH 7 buffer. (c) 10 mol % of $W(CO)_6$, Et_3N, THF, *hν*, 57 °C. (d) 10 mol % of $Rh_2(OAc)_4$, $PhI(OAc)_2$, MgO, CH_2Cl_2, 40 °C.

The synthesis of the potentially versatile intermediate, protected L-vancosamine glycal **5**, was completed by the regio- and stereoselective C−H insertion of the urethane nitrogen, presumably via the rhodium nitrene[18] derived from urethane **6**. A modification of the optimal conditions of Du Bois et al.[10] (10 mol % of $Rh_2(OAc)_4$) afforded crystalline oxazolidinone **5** in high yield. As shown in Figure 2, an

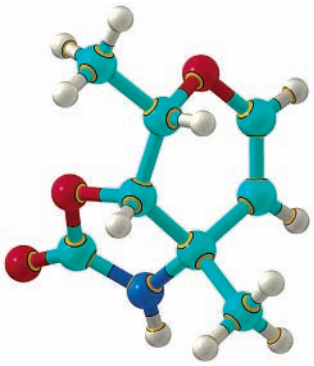
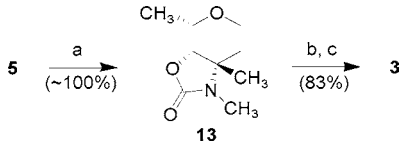


Figure 2. The X-ray crystal structure of oxazolidinone **5**.

X-ray crystal structure confirmed the relative stereochemistry of the three chiral centers in **5** and corroborated the structure of alkynol **10** as well. Thus, the useful L-vancosamine glycal equivalent **5** is available in 44% overall yield based on ethyl (*S*)-(−)-lactate in seven steps.

Our interests directed us to pursue the preparation of protected *N*,*N*-dimethyl-L-vancosamine glycal **3** as our next target. Reaction of protected glycal **5** with NaH and Me_2SO_4 provided *N*-methyl oxazolidinone **13** in quantitative yield. Reduction with lithium aluminum hydride provided crude *N*,*N*-dimethyl vancosamine glycal, which was directly subjected to silylation. Thus, the desired **3** was obtained in 83% yield from the key vancosamine synthon **5**. Short

Scheme 4. Preparation of Protected *N*,*N*-Dimethyl-L-vancosamine Glycal[a]



[a] Reagents and conditions: (a) NaH, Me_2SO_4, CH_2Cl_2. (b) LAH, ether. (c) TBSOTf, 2,6-lutidine, CH_2Cl_2.

sequences based on the principle demonstrated in this letter should provide improved and practical preparations of 3-amino glycals, branched and unbranched, in both chiral series.[19,20] As glycals are generally useful precursors to both O-[21] and C-glycosides,[6,22] our strategy should find broad application in the synthesis of a variety of antibiotics that contain amino sugars. The use of aminoglycal reagents, including the protected *N*,*N*-dimethylvancosamine glycal **3**, in further synthetic transformations will be reported in due course.

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Supporting Information Available: Experimental details and full characterization for all new compounds; X-ray crystallographic data of **5** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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