

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

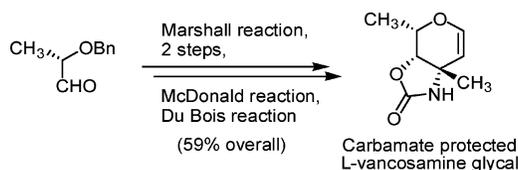
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ABSTRACT



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 nor-cardicyclin (anthracycline) antibiotics⁴ 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 synthesis⁷ and from degradation⁸ 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.

(5) (a) Furukawa M.; Itai, A.; Iitaka, Y. *Tetrahedron Lett.* **1973**, *13*, 1065. (b) Nadig, H.; Séquin, U. *Helv. Chim. Acta* **1987**, *70*, 1217.

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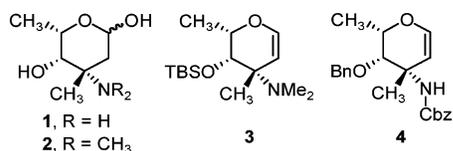


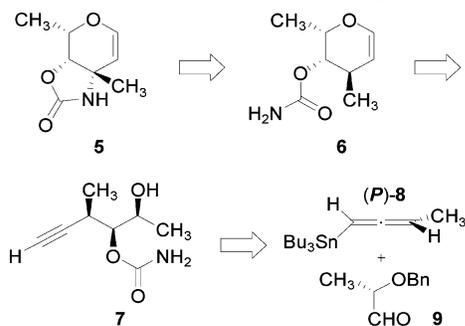
Figure 1. L-Vancosamine (**1**), *N,N*-dimethyl-L-vancosamine (**2**), silyl-protected *N,N*-dimethyl-L-vancosamine glycal **3**, and protected L-vancosamine glycal **4**.

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



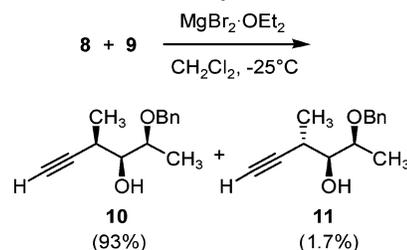
bond insertion reaction (Du Bois reaction)¹⁰ of the 3-methyl 3-deoxy glycal **6**, which would be accessed through the

(7) Synthesis of vancosamine or its derivatives: (a) Thang, T. T.; Winternitz, F.; Olesker, A.; Lagrange, A.; Lukacs, G. *J. Chem. Soc., Chem. Commun.* **1979**, 153. (b) Dyong, I.; Friege, H. *Chem. Ber.* **1979**, *112*, 3273. (c) Thang, T. T.; Winternitz, F.; Olesker, A.; Lagrange, A.; Lukacs, G. *Tetrahedron Lett.* **1980**, *21*, 4495. (d) Ahmad, H. I.; Brimacombe, J. S.; Mengech, A. S.; Tucker, L. C. *N. Carbohydr. Res.* **1981**, *93*, 288. (e) Dyong, I.; Friege, H.; Luftmann, H.; Merten, H. *Chem. Ber.* **1981**, *114*, 2669. (f) Fronza, G.; Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G. *Tetrahedron Lett.* **1981**, *22*, 5073. (g) Brimacombe, J. S.; Mengech, A. S.; Rahman, K. M. M.; Tucker, L. C. *N. Carbohydr. Res.* **1982**, *110*, 207. (h) Fronza, G.; Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G. *J. Carbohydr. Chem.* **1983**, *2*, 225. (i) Hamada, Y.; Kawai, A.; Shioiri, T. *Tetrahedron Lett.* **1984**, *25*, 5413. (j) Hauser, F. M.; Ellenberger, S. R. *J. Org. Chem.* **1986**, *51*, 50. (k) Dyong, I.; Weigand, J.; Thiem, J. *Liebigs Ann. Chem.* **1986**, 577. (l) Klemmer, A.; Wilbers, H. *Liebigs Ann. Chem.* **1987**, 815. (m) Hamada, Y.; Kawai, A.; Matsui, T.; Hara, O.; Shioiri, T. *Tetrahedron* **1990**, *46*, 4823. (n) Greven, R.; Jütten, P.; Scharf, H.-D. *Carbohydr. Res.* **1995**, *275*, 83. (o) Nicolaou, K. C.; Mitchell, H. J.; van Delft, F. L.; Rübsam, F.; Rodriguez, R. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1871. (p) Nicolaou, K. C.; Mitchell, J. J.; Jain, N. F.; Bando, T.; Hughes, R.; Winssinger, N.; Natarajan, S.; Koumbis, A. E. *Chem. Eur. J.* **1999**, *5*, 2648. (q) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Vega, J. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2525. (r) Smith, G. R.; Giuliano, R. M. *Carbohydr. Res.* **2000**, *323*, 208. (s) Cutchins, W. W.; McDonald, F. E. *Org. Lett.* **2002**, *4*, 749.

cycloisomerization (McDonald reaction) of alkyne **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



Alkyne **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, alkyne **10**, and a small amount of the diastereomeric alkyne **11**.¹⁶ Protecting group modification was required prior to the cycloisomerization reaction. Therefore, alkyne **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 alkyne **7**, the substrate for the McDonald reaction. Irradiation of a solution of alkyne **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.

(8) Dushin, R. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 3471.

(9) McDonald, F. E.; Reddy, K. S.; Diaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4304.

(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.

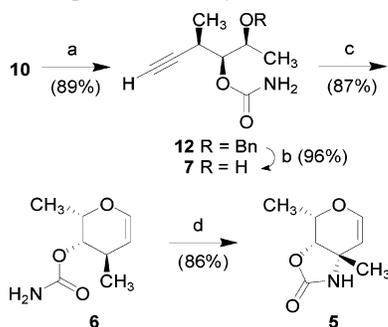
(13) Prepared from commercially available (*R*)-(+)-3-butyn-2-ol in two steps by the reported procedure: (a) Marshall, J. A.; Lu, Z.-H.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 817. (b) Marshall, J. A.; Grant, C. M. *J. Org. Chem.* **1999**, *64*, 8214.

(14) Prepared in two steps from ethyl (*S*)-(–)-lactate. *O*-Benzoylation according to Vaelis and Johnson^{14a} gave ethyl (*S*)-2-(benzyloxy)propionate ([α]_D²² –87.0 in CHCl₃, *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** ([α]_D²² –61.2 in CHCl₃, *c* 6.68): (a) Vaelis, 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) Alkyne **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) $\text{CCl}_3\text{C(O)NCO}$, CH_2Cl_2 ; $\text{K}_2\text{CO}_3/\text{MeOH}$. (b) DDQ, CH_2Cl_2 , pH 7 buffer. (c) 10 mol % of W(CO)_6 , Et_3N , THF, $h\nu$, 57 °C. (d) 10 mol % of $\text{Rh}_2(\text{OAc})_4$, $\text{PhI}(\text{OAc})_2$, 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 nitrene¹⁸ derived from urethane **6**. A modification of the optimal conditions of Du Bois et al.¹⁰ (10 mol % of $\text{Rh}_2(\text{OAc})_4$) afforded crystalline oxazolidinone **5** in high yield. As shown in Figure 2, an

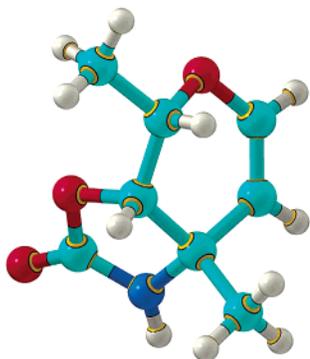


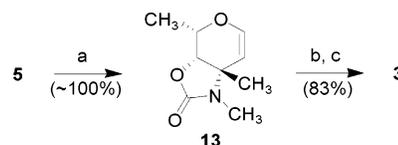
Figure 2. The X-ray crystal structure of oxazolidinone **5**.

X-ray crystal structure confirmed the relative stereochemistry of the three chiral centers in **5** and corroborated the structure of alkyne **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

(18) (a) Breslow, R.; Gellman, S. H. *J. Am. Chem. Soc.* **1983**, *105*, 6728. (b) Nageli, I.; Baud, C.; Bernardinelli, G.; Jacquier, Y.; Moran, M.; Muller, P. *Helv. Chim. Acta* **1997**, *80*, 1087.

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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(19) For a recent review on the approaches to synthesis of deoxy sugars, see: Kirschning, A.; Jesberger, M.; Schöning, K.-U. *Synthesis* **2001**, 507.

(20) For reviews of the syntheses of 3-amino-2,3,6-trideoxyhexoses, see: (a) Hauser, F. M.; Ellenberger, S. R. *Chem. Rev.* **1986**, *86*, 35. (b) Pelyás, I. F.; Monneret, C.; Herczegh, P. *Synthetic Aspects of Aminodeoxy Sugars of Antibiotics*; Springer-Verlag: Berlin, Germany, 1988.

(21) For recent examples, see: (a) McDonald, F. E.; Wu, M. *Org. Lett.* **2002**, *4*, 3979. (b) Yadav, J. S.; Reddy, B. V. S.; Reddy, K. B.; Satyanarayana, M. *Tetrahedron Lett.* **2002**, *43*, 7009. (c) Pachamuthu, K.; Vankar, Y. D. *J. Org. Chem.* **2001**, *66*, 7511. (d) Toshima, K.; Nagai, H.; Ushiki, Y.; Matsumura, S. *Synlett* **1998**, 1007.

(22) For example, see: (a) Prandi, J.; Beau, J.-M. *Tetrahedron Lett.* **1989**, *30*, 4517. (b) Brown, D. S.; Bruno, M.; Davenport, R. J.; Ley, S. V. *Tetrahedron* **1989**, *45*, 4293. (c) Lesimple, P.; Beau, J.-M.; Sinay, P. *Carbohydr. Res.* **1987**, *171*, 289.