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Stereoselective Synthesis of Vancosamine and Saccharosamine Glycals via Tungsten-Catalyzed Alkynol Cycloisomerization

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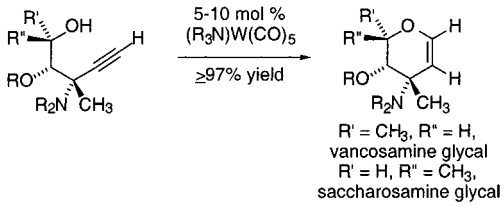
ABSTRACT



A stereoselective synthesis of the C-3 branched amino glycals of vancosamine and saccharosamine is described that features a tungsten carbonyl catalyzed cycloisomerization of the corresponding alkynyl alcohol.

Partially deoxygenated carbon branched amino sugars are important components of several classes of medicinally useful compounds with demonstrated antibiotic and anticancer activity. In particular, the 3-amino-3-methyl-2,3,6-trideoxy *lyxo*-hexose L-vancosamine **1** (Figure 1) is an essential constituent of vancomycin, an antibiotic generally considered to be the last line of defense for many severe bacterial infections.[1] A diastereomer of vancosamine, D-saccharosamine **2**, has more recently been isolated as a component of saccharomicin,[2] an oligosaccharide antibiotic that is active against bacteria resistant to vancomycin.

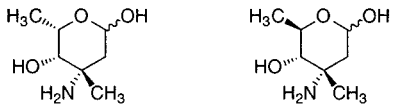


Figure 1. Representative 3-amino-2,3,6-trideoxyhexoses.

The synthesis of these carbon-branched sugars and their derivatives present challenges primarily in the construction of the amine-bearing C-3 quaternary center. Several syntheses of vancosamine have appeared in the literature.[3] Although no specific syntheses of saccharosamine **2** have been reported, its nitro analogue, D-decilonitrose, has been known for some time, and several syntheses that pass through a saccharosamine intermediate have appeared.[4] We wished to

(1) Ritter, T. K.; Wong, C. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 3508.

(2) Kong, F.; Zhao, N.; Siegal, M. M.; Janota, K.; Ashcroft, J. S.; Koehn, F. E.; Borders, D. B.; Carter, G. T. *J. Am. Chem. Soc.* **1998**, *120*, 13301.

(3) (a) Dyong, I.; Friege, H. *Chem. Ber.* **1979**, *112*, 3273. (b) Ahmad, H. I.; Brimacombe, J. S.; Mengech, A. S.; Tucker, L. C. N. *Carbohydr. Res.* **1981**, *93*, 288. (c) Giovanni, F.; Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G. *Tetrahedron Lett.* **1981**, *22*, 5073. (d) Brimacombe, J. S.; Mengech, A. S.; Rahman, K. M. M.; Tucker, L. C. N. *Carbohydr. Res.* **1982**, *110*, 207. (e) Hamada, Y.; Kawai, A.; Shioiri, T. *Tetrahedron Lett.* **1984**, *25*, 5413. (f) Hauser, F. M.; Ellenberger, S. R.; Glusker, J. P.; Smart, C. J.; Carrell, H. L. *J. Org. Chem.* **1986**, *51*, 50. (g) Klemer, A.; Wilbers, H. *Liebigs Ann. Chem.* **1987**, *10*, 815. (h) Greven, R.; Juetten, P.; Scharf, H. D. *Carbohydr. Res.* **1995**, *275*, 83. (i) 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. (k) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Vega, J. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2525.

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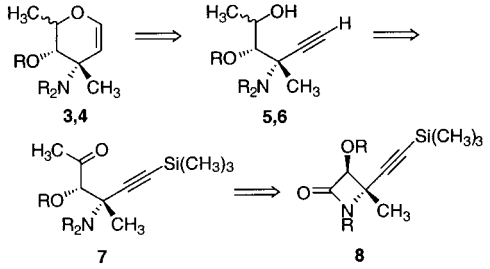
Scheme 1. Retrosynthetic Analysis

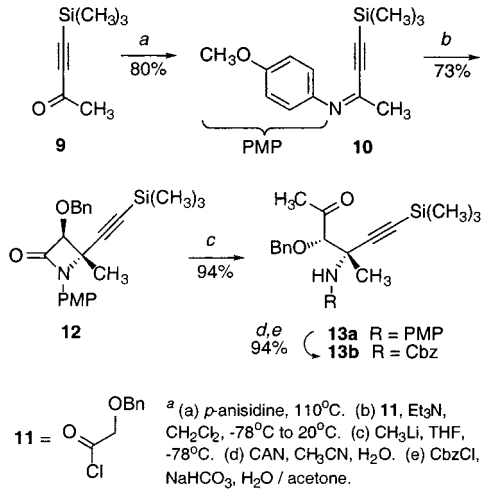


explore our tungsten-catalyzed alkynol cycloisomerization methodology[5] for the synthesis of vancosamine **1** and stereoisomeric sugars including saccharosamine **2** in order to evaluate the compatibility of our methodology with nitrogen-containing substrates. With glycals **3** and **4** in hand, we would then seek to construct naturally occurring oligosaccharides containing those amino sugars.

Our retrosynthetic analysis is presented in Scheme 1. Deconstructing each of the amino sugar glycals using our *endo*-cyclization methodology gave alkynyl alcohols **5** and **6**. We hypothesized that either alcohol diastereomer could be prepared by action of a judiciously selected reducing agent on ketone **7**, which would arise from nucleophilic opening of β-lactam **8**. We planned to employ a Staudinger cycloaddition[6] between the appropriate ketene and imine to rapidly build the β-lactam framework.

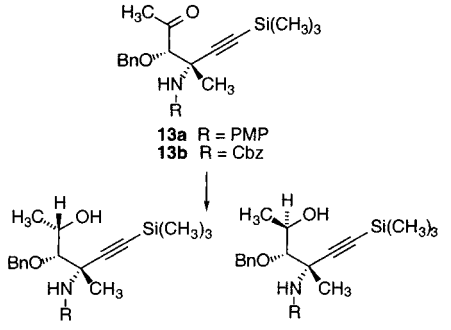
Our synthesis began with the condensation of *p*-anisidine and 4-trimethylsilyl-3-butyn-2-one to give imine **10** in 80% yield as a single diastereomer (Scheme 2). The stereochemistry is tentatively assigned as *Z* on the basis of the absence of any NOE enhancement between the methyl and aromatic hydrogens. Combination of **10** with the ketene derived from benzyloxyacetyl chloride **11** gave β-lactam **12** as a single diastereomer.[7] The relative stereochemistry was again tentatively assigned as shown due to the absence of any NOE enhancement between the methyl and methine protons directly attached to the β-lactam. Analysis of subsequent compounds eventually proved our assignment to be correct (vide infra). The stereochemistry of the lactam is also consistent with nucleophilic addition of the *Z* imine nitrogen atom to the ketene *sp*-hybridized carbon followed by conrotatory ring closure.[8]

Scheme 2. Diastereoselective Synthesis of β-Lactam **12** and Conversion to **13**



[a] (a) *p*-anisidine, 110°C. (b) **11**, Et_3N, CH_2Cl_2, -78°C to 20°C. (c) CH_3Li, THF, -78°C. (d) CAN, CH_3CN, H_2O. (e) CbzCl, $NaHCO_3$, H_2O / acetone.

Scheme 3. Stereoselective Reductions of Ketones **13a,b**



	R	conditions[a]	isolated yield, % **14** : **15**
1	PMP	$NaBH_4$ / $CeCl_3$, CH_3OH, CH_2Cl_2	84 : 4
2	PMP	DIBAL-H, CH_2Cl_2	(4 : 1)[b]
3	PMP	$LiAlH_4$, THF	(6 : 1)[b]
4	Cbz	DIBAL-H, CH_2Cl_2	73 : 14
5	Cbz	$Zn(BH_4)_2$, Et_2O	6 : 39[c]
6	Cbz	$Zn(BH_4)_2$, CH_2Cl_2	3 : 71

[a] All reactions run at −78 °C. [b] Ratios determined by 400 MHz ^{1}H NMR, conversion >80%. [c] 31% recovered **13b**.

Reaction with methyllithium gave ketone **13a** as a single product in 94% yield. Whereas literature precedent suggested reaction of carbamate-protected lactams with methyl nucleophiles gave tertiary alcohols,[9] we observed that the PMP-protected β-lactam **13a** was highly resistant to overalkylation by methyllithium, so that even an excess (2 equiv) of methyllithium could be used without generating any tertiary alcohol byproduct.

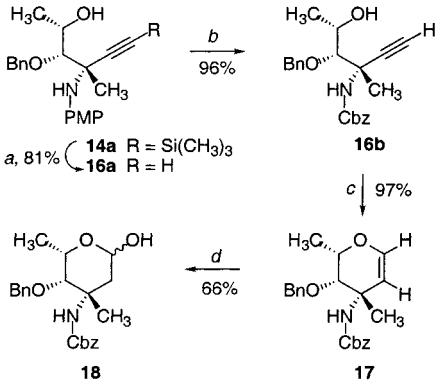
With ketone **13a** in hand, we next explored a variety of reducing agents to selectively prepare both alkynol diastereomers **14** and **15**, leading to vancosamine and saccharosamine, respectively (Scheme 3). We found that Felkin−Anh selectivity could be observed for ketone reductions with both PMP- and Cbz-protected aminoketones **13a,b** favoring formation of the corresponding diastereomer **14a,b**, but the

(4) (a) Noecker, L.; Duarte, F.; Bolton, S. A.; McMahon, W. G.; Diaz, M. T.; Guiliano, R. M. *J. Org. Chem.* **1999**, *64*, 6275. (b) Greven, R.; Juetten, P.; Scharf, H. D. *J. Org. Chem.* **1993**, *58*, 3742. (c) Brimacombe, J. S.; Rahman, K. M. M. *Carbohydr. Res.* **1985**, *140*, 163.

(5) (a) McDonald, F. E.; Reddy, K. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3653. (b) McDonald, F. E.; Reddy, K. S. *J. Organomet. Chem.* **2001**, *617*, 444. (c) McDonald, F. E.; Reddy, K. S.; Díaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4304.

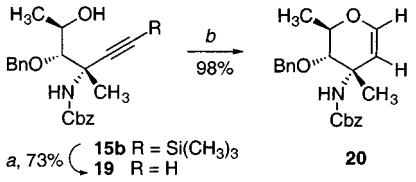
(6) (a) Staudinger, H. *Liebigs Ann. Chem.* **1907**, *356*, 51. (b) Georg, G. I.; Ravinkumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993; pp 256−368. (c) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223.

Scheme 4. Synthesis of Vancosamine Glycal



[a] (a) K_2CO_3, CH_3OH. (b) CAN, CH_3CN, H_2O; CbzCl, K_2CO_3. (c) 5% $W(CO)_6$, THF, Et_3N, hν, 55 °C. (d) CSA, H_2O, THF.

Scheme 5. Synthesis of Saccharosamine Glycal



[a] (a) TBAF, THF. (b) 10% $W(CO)_6$, THF, DABCO, hν, 35 °C.

complementary reduction with chelation control from the adjacent benzyloxy group was achieved only with the Cbz-protected ketone **13b**. Chelate-controlled reduction of **13a** gave reduced selectivity, presumably due to competing chelation with the basic anisidine substituent. We observed that the standard Luche reduction conditions gave the best Felkin−Anh selectivity, providing **14a** from the PMP-protected amino ketone **13a**, whereas $Zn(BH_4)_2$ reduction of the Cbz-protected amino ketone **13b** gave the best selectivity for chelation-controlled reduction to provide the alcohol diastereomer **15b**. Both reactions were highly solvent-dependent. As expected, the Luche reduction did not proceed with any appreciable rate even at room temperature in the absence of methanol but also exhibited poor selectivity if too much methanol was included (see Supporting Information for exact reaction details). Likewise, the zinc borohydride reduction proceeded extremely well in the nonchelating solvent CH_2Cl_2, but with much slower rate and lower diastereoselectivity in ethereal solvents.[10]

As our explorations of the tungsten-catalyzed cycloisomerization of PMP-protected amino-alkynol substrate **16a**[11] were unsatisfactory, we exchanged the PMP in **16a** for the much less basic Cbz-carbamate (Scheme 4) using the same two-step protocol that was employed for the preparation of ketone **13b**. To our delight, substrate **16b** readily underwent cycloisomerization with only 5% $W(CO)_6$ in less than 3 h, to give protected vancosamine glycal **17** in 97% yield.[12] Hydrolysis of the enol ether gave the known vancosamine derivative **18** whose spectral data (^{1}H and ^{13}C NMR and IR) were identical to that reported in the literature.[3i] This correlation also corroborates our stereochemical assignment for formation of β-lactam **12**.

Having established the feasibility of the Cbz-protected amine for the cycloisomerization methodology, we next sought to apply this transformation to the synthesis of the saccharosamine glycal (Scheme 5). However, we found that **19** furnished the desired glycal product **20** in only 74% yield using the same conditions employed for the vancosamine glycal. By replacing triethylamine with diaza[2.2.2]bicyclooctane (DABCO), we could increase the yield of glycal **20** to 98%.[5a,b]

The tertiary amine base probably serves two roles: not only does it act as a proton shuttle during the course of the cycloisomerization, but it also stabilizes the catalytically active "$W(CO)_5$" species. DABCO is a better ligand than triethylamine and may stabilize the tungsten species more effectively than triethylamine, preventing it from degrading to catalytically inactive species. Substrates in which cycloisomerization occurs rapidly do not exhibit a pronounced "amine effect" and proceed well regardless of the tertiary amine base used, but sluggish cycloisomerization reactions with lower turnover frequency benefit from DABCO ligation, as the catalytically active "$W(CO)_5$" enjoys a longer lifetime. We note that simply increasing catalyst loading or adding additional tungsten hexacarbonyl during the reaction generally did not improve the product yield, as larger quantities of the spent catalyst proved rather difficult to remove from the glycal products.

In conclusion, a rapid entry to both vancosamine and saccharosamine glycals has been achieved via tungsten-catalyzed cycloisomerizations of acyclic alkynyl alcohols. Studies directed toward the asymmetric synthesis of these

(7) For other examples of stereoselective Staudinger reactions, see: Palomo, C.; Aizpurua, J. M.; García, J. M.; Galarza, R.; Legido, M.; Urchegui, R.; Román, P.; Luque, A.; Server-Carrió, J.; Linden, A. *J. Org. Chem.* **1997**, *62*, 2070.

(8) Although ketene-olefin cycloadditions generally occur by Woodward−Hoffmann allowed [$\pi 2_s - \pi 2_a$] concerted processes (Snider, B. B. *Chem. Rev.* **1988**, *88*, 793), ketene−imine cycloadditions have been demonstrated to proceed by a stepwise mechanism. See: (a) Lynch, J. E.; Riseman, S. M.; Laswell, W. L.; Tschaen, D. M.; Volante, R. P.; Smith, G. B.; Shinkai, I. *J. Org. Chem.* **1989**, *54*, 3792. (b) Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784. (c) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223.

(9) Palomo, C.; Aizpurua, J. M.; García, J. M.; Iturburu, M.; Odriozola, J. M. *J. Org. Chem.* **1994**, *59*, 5184.

(10) For a dramatic example of this phenomena with borohydride reductions, see: Faucher, A. M.; Brochu, C.; Landry, S. R.; Duchesne, S. H.; Hantos, S.; Roy, A.; Myles, A.; Legault, C. *Tetrahedron Lett.* **1998**, *39*, 8425.

(11) Alkynol **16a** was generated by base-promoted removal of the acetylenic silyl group from compound **14a**.

(12) Despite extensive attempts to optimize cycloisomerization reaction conditions for substrate **16a** ($W(CO)_6$, Et_3N or DABCO, THF, $h\nu$ = 350 nm), we could not raise the yield of the reaction above ca. 30%, nor could we separate the glycal from the many other unidentified byproducts. We suspect that the *p*-methoxyphenylamine is poorly compatible with the reaction, either from complexation of the amine with the tungsten catalyst or photolytic degradation of the electron-rich aromatic system.

glycals as well as their application to oligosaccharide synthesis are in progress.

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Supporting Information Available: Experimental details and procedures for compounds **10** and **12**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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