ORGANIC LETTERS

2005
Vol. 7, No. 9
1785−1788

Regioselectivity of Rhodium Nitrene Insertion. Syntheses of Protected Glycals of L-Daunosamine, D-Saccharosamine, and L-Ristosamine

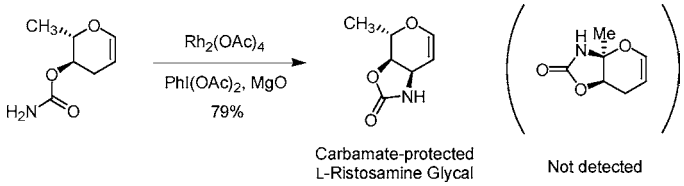
Kathlyn A. Parker* and Wonsuk Chang

Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794-3400

kparker@notes.cc.sunysb.edu

Received February 18, 2005

ABSTRACT



The carbamate-protected glycals of naturally occurring 3,4-*cis*-3-amino-2,3,6-trideoxyhexoses (L-daunosamine, D-saccharosamine, and L-ristosamine) were prepared from noncarbohydrate starting materials. The short, high-yield syntheses are based on the chemoselective insertion of a rhodium nitrene in an allylic C–H bond rather than in a C–H bond that is α to an oxygen substituent.

Protected 3-amino glycals are versatile synthetic intermediates that may serve as precursors for amino glycal reagents,[1] for 2-deoxy sugars[2] and 2-oxygenated sugars,[3] and for glycosylated antibiotics[4] and peptides.[5] Historically, the preparation of 3-amino glycal synthons has relied on the modification of simple glycosides.[6,7]

In a break with this tradition, we have explored a strategy in which a 3-deoxy glycal available from the cycloisomerization of a chiral homopropargyl alcohol undergoes an intramolecular nitrogen insertion at C3, completing the functionalization pattern of the 3-amino glycal. This approach is inherently a convergent one that enables the development of efficient asymmetric syntheses from noncarbohydrate precursors. Proof of principle for this approach was demonstrated in the vancosamine system (Scheme 1).[1a]

In the synthesis of the protected L-vancosamine derivative **2**, the site and stereochemistry of nitrogen insertion were predicted with confidence. In the vancosamine precursor **3**, both the C3−H and the C5−H bonds are activated, the former because it is tertiary and allylic (vinylogously α to the pyranoside oxygen) and the latter because it is tertiary

(1) (a) Parker, K. A.; Chang, W. *Org. Lett.* **2003**, *5*, 3891. (b) Florent, J. C.; Ughetto-Monfrin, J.; Monneret, C. *Carbohydr. Res.* **1998**, *181*, 253. (c) Horton, D.; Priebe, W.; Sznaidman, M. *Carbohydr. Res.* **1989**, *187*, 145. (d) Hall, R. H.; Jordaan, A.; Lourens, G. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 38.

(2) (a) Cutchins, W. W.; McDonald, F. E. *Org. Lett.* **2002**, *4*, 749. (b) Dulin, M. L.; Noecker, L. A.; Kassel, W. S.; Giuliano, R. M. *Carbohydr. Res.* **2003**, *338*, 1121. (c) Abbaci, B.; Florent, J. C.; Monneret, C. *Bull. Soc. Chim. Fr.* **1989**, 667.

(3) (a) Link, J. T.; Raghavan, S.; Gallant, M.; Danishefsky, S. J.; Chou, T. C.; Ballas, L. M. *J. Am. Chem. Soc.* **1996**, *118*, 2825. (b) Link, J. T.; Danishefsky, S. J.; Schulte, G. *Tetrahedron Lett.* **1994**, *35*, 9131. (c) Knapp, S.; Lal, G. S.; Sahai, D. *J. Org. Chem.* **1986**, *51*, 380.

(4) (a) Kolar, C.; Dehmel, K.; Kraemer, H. P. *Carbohydr. Res.* **1990**, *201*, 249. (b) Tu, C. J.; Lednicer, D. *J. Org. Chem.* **1987**, *52*, 5624. (c) Thang, T. T.; Imbach, J. L.; Fizames, C.; Lavelle, F.; Ponsinet, G.; Olesker, A.; Lukacs, G. *Carbohydr. Res.* **1985**, *135*, 241. (d) Pearlman, B. A.; McNamara, J. M.; Hasan, I.; Hatakeyama, S.; Sekizaki, H.; Kishi, Y. *J. Am. Chem. Soc.* **1981**, *103*, 4248. (e) Arcamone, F.; Bargiotti, A.; Cassinelli, G.; Redaelli, S.; Hanessian, S.; Di Marco, A.; Casazza, A. M.; Dasdia, T.; Necco, A.; Reggiani, P.; Supino, R. *J. Med. Chem.* **1976**, *19*, 733.

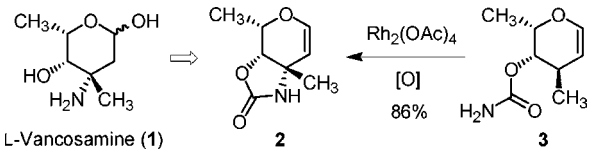
(5) (a) Mouton, C.; Tillequin, F.; Seguin, E.; Monneret, C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2055. (b) Kessler, H.; Michael, K.; Kottenhahn, M. *Liebigs Ann. Chem.* **1994**, 811.

(6) (a) Pelyás, I. F.; Monneret, C.; Herczegh, P. *Synthetic Aspects of Aminodeoxy Sugars of Antibiotics*; Springer-Verlag: Berlin, 1988; see also references therein. (b) Dushin, R. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 3471.

(7) For an exception and recent contribution, see ref 2a.

10.1021/ol050356l CCC: $30.25 © 2005 American Chemical Society
Published on Web 03/22/2005

Scheme 1



and α to the pyranoside oxygen. However, only the C3−H bond is sterically accessible to the reactive species. The clean conversion of substrate **3** to the protected amino glycal **2** under the catalytic conditions of Du Bois was a gratifying but not unexpected result.

In this communication, we disclose the extension of the cycloisomerization/nitrene insertion approach to derivatives of the unbranched amino sugar daunosamine. Furthermore, we report that the Du Bois intramolecular rhodium carbamate nitrene insertion[8] is selective for allylic C−H bonds over C−H bonds that are α to ether substituents. This selectivity endows our approach to 3,4-*cis*-3-amino-3-deoxy glycals with broad scope, permitting its application in the preparation of protected glycals of ristosamine and saccharosamine as well as to daunosamine.Of the 2,3,6-trideoxy-3-amino sugars,

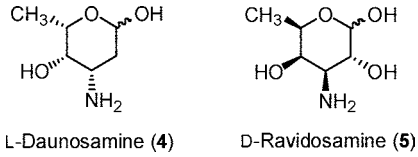


Figure 1.

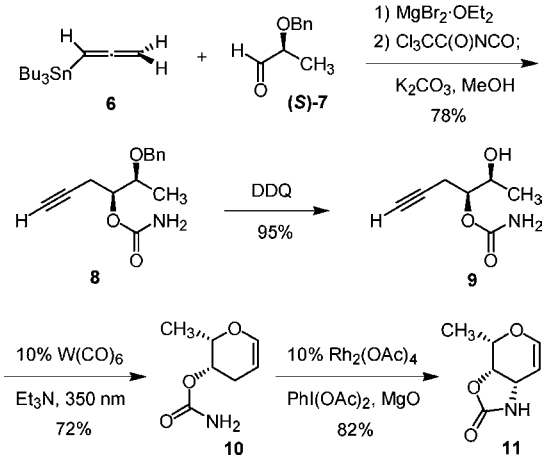
branched and unbranched, daunosamine has received the most attention from medicinal and synthetic chemists. L-Daunosamine (**4**) is the glycosidic constituent of the important anthracycline antitumor antibiotics daunorubicin and doxorubicin.[9]

A protected daunosamine glycal is a valuable synthon. Functionalized L-daunosamine glycals have been used to glycosylate anthracyclinones in the synthesis of anthracyclines and their analogues.[4] Furthermore, protected D-daunosamine glycals are potentially useful[3] for the preparation of derivatives of D-ravidosamine (**5**), the sugar component of ravidomycin.[10]

In light of the accessibility of the vancosamine synthon **2** by the nitrogen insertion approach, we initiated the synthesis of the protected L-daunosamine glycal **11** by a similar strategy. The Du Bois substrate **10** was prepared by a six-step sequence from ethyl (*S*)-lactate in which the key step was the diastereoselective addition of allenyl stannane **6**[11] to aldehyde (*S*)-**7**.[1a] The crude reaction product was washed with aqueous sodium bisulfite and subjected to Roush's KF/Celite protocol[12] for removing residual tin. The resulting semipurified material was subjected to carbamoylation[13] to afford the diastereomerically pure carbamate **8** in 78% yield after recrystallization (two steps). Oxidative cleavage of the benzyl ether protecting group gave hexynol **9** in 95% yield. The tungsten-catalyzed cycloisomerization was slow relative to the previously studied branched system;[1a] however, glycal **10**[14] was obtained in 72% yield after 6 h. Rhodium nitrene insertion completed the synthesis, providing protected L-daunosamine glycal **11** in five steps and 44% yield overall from the lactic acid derivative (*S*)-**7**.

Similar schemes directed toward other 3,4-*cis*-3-amino glycals would be successful only if the key functionalization steps were regioselective, leading to insertion at the C3−H bond. As there were no examples of the competition between two activated but functionally different C−H bonds in carbamate nitrogen insertion reactions,[15] we examined the regiochemistry in systems that would be informative and suited to practical applications.

Scheme 2



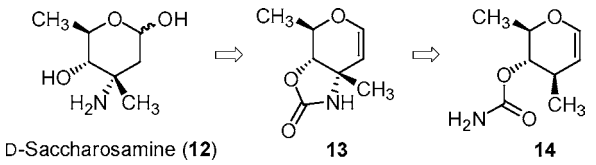
D-Saccharosamine (**12**) is an element of the recently isolated saccharomicin, an oligosaccharide antibiotic active against multiply resistant strains of *Staphylococcus aureus* and vancomycin-resistant enterococci.[16] A synthesis of its

(8) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598.
(9) Monneret, C. *Eur. J. Med. Chem.* **2001**, *36*, 483.
(10) Futagami, S.; Ohashi, Y.; Imura, K.; Hosoya, T.; Ohmori, K.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 1063.

(11) Prepared from commercially available propargyl bromide by the reported procedure: Tanaka, H.; Abdul Hai, A. K. M.; Ogawa, H.; Torii, S. *Synlett* **1993**, *11*, 835.
(12) See the Supporting Information for: 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.
(13) Kocovsky, P. *Tetrahedron Lett.* **1986**, *27*, 5521.
(14) McDonald et al. have applied the cycloisomerization reaction to the preparation of related 3-unsubstituted glycal derivatives. See: McDonald, F. E.; Zhu, H. Y. H. *J. Am. Chem. Soc.* **1998**, *120*, 4246.
(15) $Rh_2(OAc)_4$-catalyzed sulfamate nitrogen insertion exhibits no preference for ether C^{α}−H, tertiary C−H, or benzylic C−H. However, the $Rh_2(O_2CCPh_3)_4$-catalyzed transformation favors insertion in the ether C^{α}−H. See: Fiori, K. W.; Fleming, J. J.; Du Bois, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 4349.
(16) (a) Kong, F.; Zhao, N.; Siegel, M. M.; Janota, K.; Ashcroft, J. S.; Koehn, F. E.; Borders, D. B.; Carter, G. T. *J. Am. Chem. Soc.* **1998**, *120*, 13301. (b) Singh, M. P.; Petersen, P. J.; Weiss, W. J.; Kong, F.; Greenstein, M. *Antimicrob. Agents Chemother.* **2000**, *44*, 2154.

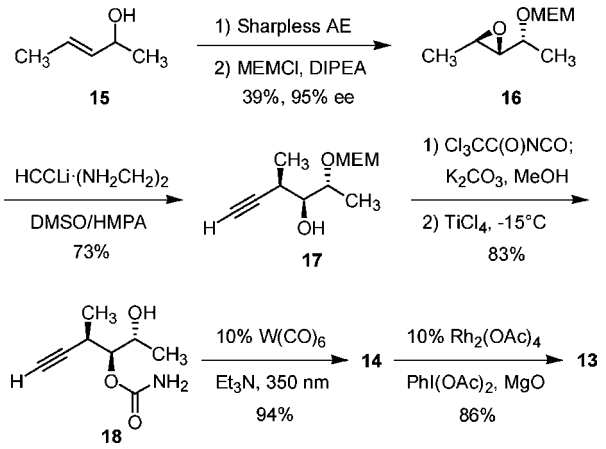
glycal by application of the Du Bois reaction to the 3-deoxy glycal provides an opportunity to test the preference of the rhodium nitrene for insertion at a tertiary allylic position (vinylogously α to an oxygen) versus a position α to an oxygen (Scheme 3).

Scheme 3



The preparation of substrate **18** (Scheme 4) began with the kinetic resolution[17] of racemic pentenol **15**. The resulting

Scheme 4

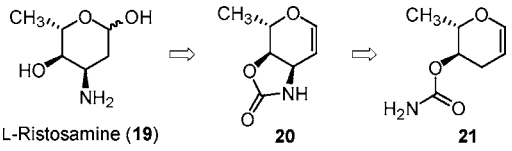


epoxy alcohol underwent MEM protection,[18] providing epoxide **16**.[19] Treatment with lithium acetylide·ethylenediamine complex gave hexynol **17**, characterized as its Mosher ester (95% ee). Urethane functionalization[13] followed by Lewis acid-promoted deprotection with $TiCl_4$[18] provided carbamate **18**.

Cycloisomerization of substrate **18** with a workup modified to minimize decomposition gave glycal **14** in 94% yield. Protected D-saccharosamine glycal **13** was obtained from the rhodium nitrene insertion reaction of urethane **14** in 79% yield. No *N*,*O*-acetal product (C5−H inserted) could be detected in the 600 MHz ^{1}H NMR spectrum of the crude reaction product mixture.

L-Ristosamine (**19**), the carbohydrate constituent of the glycopeptides ristocetin A[20] and the avoparcins[21] (members of the vancomycin antibiotic group), provides a more stringent test of the chemoselectivity of the nitrene insertion reaction. If the appropriate substrate **21** is to give the target **20** (Scheme 5), the active species must select the C−H bond

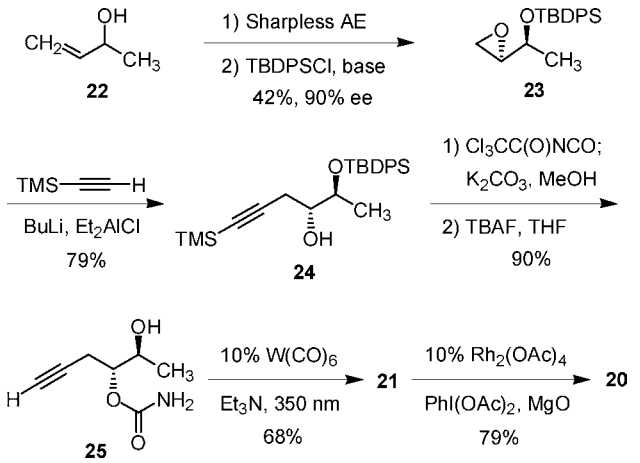
Scheme 5



that is secondary and vinylogously α to an oxygen over the one that is tertiary and α to an oxygen.

The functionalized dihydropyran **21** was prepared in six steps from racemic 3-buten-2-ol (Scheme 6). Sharpless

Scheme 6



kinetic resolution accompanied by silyl protection gave a mixture that was separated by column chromatography to give epoxide **23**.[22] Treatment with 2 equiv of alkynylalane reagent[23] gave 2,3-*anti*-hexynol **24**. Then, carbamate functionalization[13] and silyl deprotection with TBAF afforded the desired **25**. Again, the cycloisomerization of this C3-unbranched system was slow but not inconveniently so, and glycal **21**[14] was obtained in 68% yield.

The Du Bois conditions effected the conversion of substrate **21** to the protected ristosamine glycal **20**. As in the case of the saccharosamine glycal synthesis, no trace of an *N*,*O*-acetal could be detected in the NMR spectrum of the crude reaction mixture. After chromatography, the clean product **20** was obtained in 79% yield.

(17) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(18) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, *17*, 809.

(19) Racemic epoxide **16** and its conversion to racemic hexynol **17** have been reported previously: Inanaga, J.; Kawanami, Y.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1521.

(20) Sztaricskai, F.; Harris, C. M.; Neszmelyi, A.; Harris, T. M. *J. Am. Chem. Soc.* **1980**, *102*, 7093.

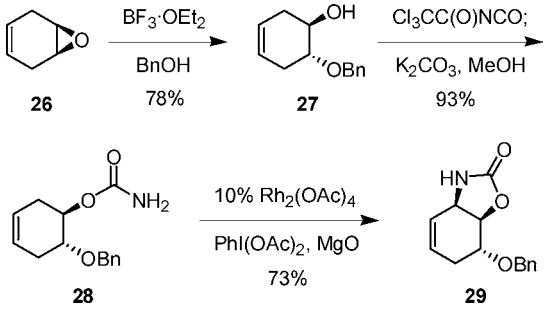
(21) (a) McGahren, W. J.; Martin, J. H.; Morton, G. O.; Hargreaves, R. T.; Leese, R. A.; Lovell, F. M.; Ellestad, G. A.; O'Brien, E.; Holker, J. S. E. *J. Am. Chem. Soc.* **1980**, *102*, 1671. (b) Ellestad, G. A.; Leese, R. A.; Morton, G. O.; Barbatschi, F.; Gore, F.; McGahren, W. J.; Armitage, I. M. *J. Am. Chem. Soc.* **1981**, *103*, 6522.

(22) Enantiomer of epoxide **23** has been reported previously: Bijoy, P.; Avery, M. A. *Tetrahedron Lett.* **1998**, *39*, 209.

(23) Lin, N.-H.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9062.

In our protected amino glycal syntheses, the chemoselectivity of the rhodium nitrene insertion event involved competition between a C−H bond that was α to an oxygen and one that was vinylogously α to an oxygen. We wanted to determine the selectivity in a system in which the competition was between a C−H bond α to an oxygen and one that was simply allylic. Thus, we prepared substrate **28** from 1,4-cyclohexadiene (Scheme 7) and subjected it to the

Scheme 7



Du Bois conditions. In this system, as in the glycal systems described above, the nitrogen insertion was chemospecific for the allylic position, affording oxazolidinone **29** as a single product.

In conclusion, we have developed an efficient synthetic pathway to prepare the carbamate-protected glycals of L-daunosamine, D-saccharosamine, and L-ristosamine, each in seven steps from noncarbohydrate starting materials. The overall yields were 36%, 19% (38% if corrected for the kinetic resolution), and 16% (32% if corrected for the kinetic resolution), respectively. As a glycal is a valuable synthetic precursor for both *O*-[24] and *C*-glycosides,[25] we believe that our approach should find broad application in the synthesis of a variety of antibiotics and natural products that contain amino sugars.

Along our synthetic journey we discovered that the rhodium-coordinated carbamate nitrene chooses insertion in an allylic C−H over insertion in a C−H α to an oxygen. This chemoselective functionalization may find general application in the preparation of a variety of structures.

Acknowledgment. This work was supported by the National Cancer Institute (Grant CA-87503).

Supporting Information Available: Experimental details and full characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050356L

(24) 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.

(25) For example, see: (a) Lehmann, U.; Awasthi, S.; Minehan, T. *Org. Lett.* **2003**, *5*, 2405. (b) Tius, M. A.; Gomez-Galeno, J.; Gu, X. Q.; Zaidi, J. H. *J. Am. Chem. Soc.* **1991**, *113*, 5775. (c) Friesen, R. W.; Sturino, C. F. *J. Org. Chem.* **1990**, *55*, 2572. (d) Lesimple, P.; Beau, J.-M.; Jaurand, G.; Sinaÿ, P. *Tetrahedron Lett.* **1986**, *27*, 6201.