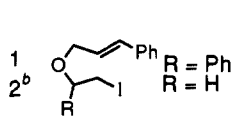
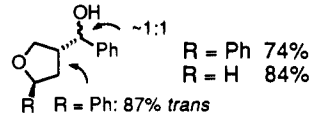
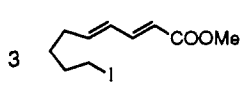
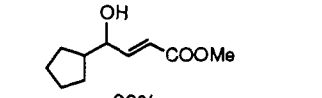
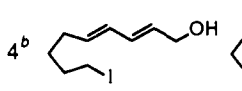
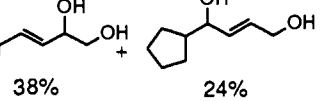
Table II. Oxygenative Radical Cyclization[a]

entry	halide	product (%)
1		
2[b]		
3		
4[b]		

[a] Dry air was bubbled for 5-24 h into a mixture of an iodide and Bu_3SnH in 0.2 M toluene at 0 °C (12 °C in entries 2 and 4). [b] Under ultrasound irradiation.

of the alcohol formation is low (entries 3 and 7), steric hindrance at the carbon bearing the halide atom poses little problem. For instance, conversion of a tertiary halide to a tertiary alcohol can be achieved in excellent yield (cf. entry 6). (2) While the regiochemistry of the hydroxylation is yet to be solved,[13] the olefin geometry of the allylic halide is maintained (>99%, cf. entries 1, 2, and 4). This is an advantage of the low-temperature conditions: the oxygenation of the 100% *Z*-allylic halide in entry 2 at 95 °C proceeded with loss of the stereochemistry (61% *E*-allylic alcohol).[14] (3) The present reaction tolerates a wide range of functional groups. Figure 1 illustrates the examples of the conversion of an iodo lactone and a Boc-protected β-iodo amine to the corresponding alcohols without affecting the neighboring functional groups.

The aerobic conversion of halides to alcohols provides an especially powerful synthetic strategy for intramolecular radical cyclization (Scheme II). Thus, bubbling air into a mixture of Bu_3SnH (2.1-2.5 equiv) and an olefinic iodide (**A**) at 0-12 °C gave the cyclization product **B** in good yield (Table II). Despite the presence of several competitive reaction pathways, the reaction gave the cyclization product as a single predominant product, together with small amounts (5-20%) of the uncyclized product **C** and/or reduced product **D**. Unlike the conventional *reductive* cyclization (**A** → **D**),[15] which generates one ring at the expense at two functional groups (halogen and olefin), the present *oxygenative* cyclization (**A** → **B**) generates a ring *and* a hydroxy group.[16,17] In light of this functional group economy, good chemoselectivity (cf. Figure 1), and procedural simplicity, the present reaction will add to the versatility of radical-based ring formation strategies.

Acknowledgment. We thank Y. Imanishi for some experiments and gratefully acknowledge the Yamanouchi Award in Synthetic Organic Chemistry, Japan, and the Sound Technology Promotion Foundation for financial support.

Supplementary Material Available: A detailed version of Table I, experimental details, and characterization of the compounds in the tables (12 pages). Ordering information is given on any current masthead page.

(13) Regioisomers such as **4** and **5** arise either from oxygen trapping at two allylic termini or from rearrangement of the peroxy radical **2**; cf.: Porter, N. A.; Kaplan, J. K.; Dussault, P. H. *J. Am. Chem. Soc.* **1990**, *112*, 1266.

(14) The activation energy of allyl radical isomerization is only 15.7 kcal/mol: Korth, H.-G.; Trill, H.; Sustmann, R. *J. Am. Chem. Soc.* **1981**, *103*, 4483. We thank Prof. T. Cohen for drawing our attention to this reference. See also: Feller, D.; Davidson, E. R.; Borden, W. T. *J. Am. Chem. Soc.* **1984**, *106*, 2513.

(15) (a) Reviews: Curran, D. P. *Synthesis* **1988**, 417, 489. Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. Thebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron* **1990**, *46*, 1385. Giese, B., Ed. *Selectivity and Synthetic Applications of Radical Reactions*; *Tetrahedron Symposia-in-Print, number 22* **1985**, *41*, 3887. (b) Stork, G. In *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon Press: Oxford, England, 1983. Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564.

(16) An equivalent two-step sequence based on conventional radical cyclizations: Jolly, R. S.; Livinghouse, T. *J. Am. Chem. Soc.* **1988**, *110*, 7536. Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 4796.

(17) (a) Porter, N. A.; Funk, M. O. *J. Org. Chem.* **1975**, *40*, 3614. Corey, E. J.; Shih, C.; Shih, N. Y.; Shimoji, K. *Tetrahedron Lett.* **1984**, *25*, 5013. (b) Radical oxygenation of organomercurials: Hill, C. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 870.

Asymmetric Synthesis of Lactones with High Enantioselectivity by Intramolecular Carbon-Hydrogen Insertion Reactions of Alkyl Diazoacetates Catalyzed by Chiral Rhodium(II) Carboxamides

Michael P. Doyle,* Arjan van Oeveren, Larry J. Westrum, Marina N. Protopopova,[‡] and Thomas W. Clayton, Jr.

Department of Chemistry, Trinity University
San Antonio, Texas 78212

Received August 5, 1991

The catalytic uses of rhodium(II) carboxylates and rhodium(II) carboxamides for intramolecular carbon-hydrogen insertion reactions of diazo esters and diazo ketones has made possible the synthesis of γ-lactones and cyclopentanones with high regio- and diastereoselectivity and in moderate to high yield.[1-3] With few exceptions,[4,5] these reactions exhibit an overwhelming preference for five-membered-ring formation and, where insertion can occur at more than one C-H bond, conformational preferences as well as electronic influences appear to govern regioselection.[6] In contrast, copper catalysts have not shown similar suitability for carbon-hydrogen insertion reactions,[7] and dirhodium(II) compounds are now recognized to be the catalysts of choice for these transformations.

We have recently reported that chiral dirhodium(II) carboxamides are remarkably effective catalysts for asymmetric intramolecular cyclopropanation reactions of allyl diazoacetates.[8] The design of these catalysts, in particular dirhodium(II) tetrakis-[methyl 2-pyrrolidone-5(*S*)-carboxylate], $Rh_2(5S\text{-MEPY})_4$, and its enantiomeric form, $Rh_2(5R\text{-MEPY})_4$, with their cis orientation for the two nitrogen donor atoms on each rhodium,[9] is particularly suitable for highly enantioselective intramolecular transformations. For comparison, chiral dirhodium(II) carboxylates, whose architecture places the chiral center perpendicular to the rhodium-carbene bond axis, have recently been reported to catalyze in-

[‡] Visiting research associate: N. D. Zelinsky Institute of Organic Chemistry, Moscow, USSR.

(1) (a) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919. (b) Maas, G. *Top. Curr. Chem.* **1987**, *137*, 75. (c) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765.

(2) (a) Wenkert, E.; Davis, L. L.; Mylari, B. L.; Solomon, M. F.; da Silva, R. R.; Shulman, S.; Warnet, R. J.; Ceccherelli, P.; Curini, M.; Pellicciari, R. *J. Org. Chem.* **1982**, *47*, 3242. (b) Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686. (c) Monteiro, J. J. *Tetrahedron Lett.* **1987**, *28*, 3459. (d) Corbel, B.; Hernot, D.; Haelters, J.-P.; Sturtz, G. *Tetrahedron Lett.* **1987**, *28*, 6605. (e) Sonawane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kulkarni, D. G. *J. Org. Chem.* **1991**, *56*, 1434.

(3) Doyle, M. P.; Bagheri, V.; Pearson, M. M.; Edwards, J. D. *Tetrahedron Lett.* **1989**, *30*, 7001.

(4) (a) Cane, D. E.; Thomas, P. J. *J. Am. Chem. Soc.* **1984**, *106*, 5295. (b) Lee, E.; Jung, K. W.; Kim, Y. S. *Tetrahedron Lett.* **1990**, *31*, 1023.

(5) (a) Brown, P.; Southgate, R. *Tetrahedron Lett.* **1986**, *27*, 247. (b) Doyle, M. P.; Taunton, J.; Pho, H. Q. *Tetrahedron Lett.* **1989**, *30*, 5397.

(6) (a) Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J. Org. Chem.* **1991**, *56*, 820. (b) Adams, J.; Poupart, M.-A.; Grenier, L. *Tetrahedron Lett.* **1989**, *30*, 1753. (c) Adams, J.; Poupart, M.-A.; Grenier, L.; Schaller, C.; Quimet, N.; Frenette, R. *Tetrahedron Lett.* **1989**, *30*, 1749.

(7) (a) Burke, S. D.; Greico, P. A. *Org. React. (N.Y.)* **1979**, *26*, 361. (b) Taber, D. F.; Saleh, S. A.; Korsmeyer, R. W. *J. Org. Chem.* **1980**, *45*, 4699.

(8) Doyle, M. P.; Pieters, R. J.; Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Müller, P. *J. Am. Chem. Soc.* **1991**, *113*, 1423.

(9) Doyle, M. P.; Brandes, B. D.; Kazala, A. P.; Pieters, R. J.; Jarstfer, M. B.; Watkins, L. M.; Eagle, C. T. *Tetrahedron Lett.* **1990**, *31*, 6613.

0002-7863/91/1513-8982$02.50/0

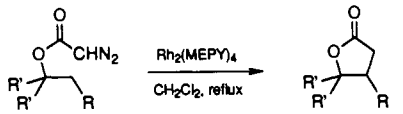
Table I. Enantioselectivities of $Rh_2(MEPY)_4$-Catalyzed Carbon–Hydrogen Insertion Reactions

lactone	R	R′	catalyst	yield,[a] %	$[\alpha]^{23}_D$, deg	ee,[b] %	confign
2a	CH_3O	H	$Rh_2(5S\text{-MEPY})_4$	62 (40)	−58.6	91	*S*
			$Rh_2(5R\text{-MEPY})_4$	73 (56)	+58.7	91	*R*
2b	CH_3CH_2O	H	$Rh_2(5S\text{-MEPY})_4$	64 (49)	−59.1	89	*S*
			$Rh_2(5R\text{-MEPY})_4$	63 (42)	+58.7	89	*R*
2c	$PhCH_2O$	H	$Rh_2(5S\text{-MEPY})_4$	64 (49)	−47.2	87	*S*
			$Rh_2(5R\text{-MEPY})_4$	69 (45)[c]	+46.8	87	*R*
2d[d]	CH_3O	CH_3	$Rh_2(5S\text{-MEPY})_4$	68 (38)	+27.4	56	*S*
			$Rh_2(5R\text{-MEPY})_4$	70 (53)	−28.3	57	*R*
2e	$PhCH_2O$	CH_3	$Rh_2(5S\text{-MEPY})_4$	85 (45)	+34.6	51	*S*
2f	Ph	H	$Rh_2(5S\text{-MEPY})_4$	42 (24)	−23.0	46	*R*
			$Rh_2(5R\text{-MEPY})_4$	34 (24)	+22.5	45	*S*

[a] Yield of product following chromatographic separation of catalyst and, in parentheses, product yield after distillation (≥95% homogeneous). Reactions were performed on a 1–2-mmol scale, and yields have not been optimized. [b] Reported values were determined through enantiomer separations on a Chiraldex γ-cyclodextrin trifluoroacetate column (**2a-d** and **2f**). Specific rotations for **2a**, **2c**, and **2f**[14] confirmed chromatographic determinations; **2c** was hydrogenolyzed to **3** ($[\alpha]^{23}_D = -67.9°$ (*c* = 1.44, EtOH) relative to enantiomerically pure **3**, $[\alpha]^{21}_D = 88.9°$ (*c* = 1.36, EtOH)[12]), and **3** was converted to **2a** ($[\alpha]^{23}_D = -56.0°$ (*c* = 1.55, EtOH) for 87% ee). Hydrogenolysis of **2e** yielded **3**, $[\alpha]^{24}_D = -5.66°$ (*c* = 1.52, $CHCl_3$) relative to enantiomerically pure **3**, $[\alpha]^{23}_D = -11°$ (*c* = 1.5, $CHCl_3$).[13b] For **2d**, chiral NMR shift reagent $Eu(tfc)_3$ gave base-line separation of α-methylene protons. [c] Recrystallization from ethanol gave **2c** with 95% ee. [d] The product mixture prior to purification contained 4% of the product from C–H insertion into the methyl group R′.

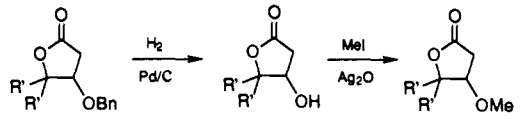
tramolecular C–H insertion reactions of α-diazo β-keto esters[10] and an α-diazo β-keto sulfone[11] to form 3-substituted cyclopentanone derivatives with enantiomeric excesses ranging from 10 to 46%. We now report the significant enhancement in enantioselection that can be achieved with chiral dirhodium(II) carboxamides.

The suitability of $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(5R\text{-MEPY})_4$ for enantioselective intramolecular C–H insertions is exemplified in the results (Table I) from preliminary experiments with a series of 2-alkoxyethyl diazoacetates **1a–e** and 2-phenethyl diazoacetate (**1f**). Slow addition (5–6 h) of **1a–f** to a solution of the chiral $Rh_2(MEPY)_4$ catalyst (0.5–1.0 mol %) in refluxing anhydrous CH_2Cl_2 provided the corresponding 3-substituted γ-butyrolactones (eq 1) in moderate to high yields and with consistently high enantioselectivities. The exceptional correspondence in enantioselection between enantiomeric dirhodium(II) catalysts defines their versatility.



(1)

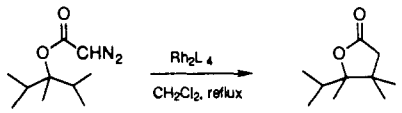
The absolute configurations of **2a** and **2c** were assigned on the basis of the sign of rotation of the known hydroxy lactone **3** (R′ = H),[12] which was formed from **2c** by hydrogenolysis and converted to **2a** by etherification (eq 2, R′ = H), and that of **2b** is inferred. Lactone **2d** was formed from the known hydroxy lactone



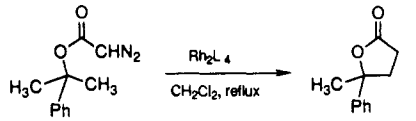
(2)

3 (R′ = Me)[13] by a similar procedure, and the absolute configuration of **2f** has been previously established.[14] The major competing reactions to C–H insertion were the formation of carbene dimers and azine, and these processes were less pronounced with the $Rh_2(MEPY)_4$ catalysts than with $Rh_2(OAc)_4$. With dirhodium(II) tetrakis[neopentyl 2-pyrrolidone-5(*S*)-carboxylate], $Rh_2(5S\text{-NEPY})_4$, whose bulkier ester group might be expected to facilitate a higher degree of enantiocontrol, **1d** formed (*S*)-**2d** with 66% ee (84% yield), but the formation of (*S*)-**2a**, (*S*)-**2b**, and (*S*)-**2c** occurred with lower enantioselectivities than with the $Rh_2(5S\text{-MEPY})_4$ catalyst: 82% ee (92% yield), 83% ee (72% yield), and 78% ee (55% yield), respectively. It is noteworthy that **2f** has the configuration opposite to that of **2a–e** when formed from either $Rh_2(5S\text{-MEPY})_4$ or $Rh_2(5R\text{-MEPY})_4$.

Applications with diazo esters that undergo insertion into a C–H bond vicinal to the incipient chiral center demonstrated further advantages of this catalytic methodology for asymmetric synthesis. 2,3,4-Trimethyl-3-pentyl diazoacetate (**4**) formed lactone **5**[3] exclusively (eq 3) in 60% ee (77% isolated yield) with $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(5R\text{-MEPY})_4$ and in 70% ee with $Rh_2(5S\text{-NEPY})_4$ (82% isolated yield).[15] Cumyl diazoacetate (**6**) underwent insertion into the normally disfavored primary C–H bond to yield lactone **7**[16] in 76% ee (30% isolated yield) with $Rh_2(5S\text{-MEPY})_4$ (predominantly (*R*)-**7**) and $Rh_2(5R\text{-MEPY})_4$ (predominantly (*S*)-**7**) and in 79% ee (39% isolated yield) with $Rh_2(5S\text{-NEPY})_4$ (predominantly (*R*)-**7**).[17]



(3)



(4)

The high degree of enantiocontrol in C–H insertion reactions with such a diversity of diazoacetates suggests unique advantages for chiral dirhodium(II) catalysts derived from pyrrolidone-5-carboxylates. Both lactone enantiomers are accessible from a single diazo ester, and the absence of byproducts of similar composition allows convenient product isolation. Efforts are underway to determine the utility of these catalysts for the broader classification of insertion reactions.

(10) Hashimoto, S.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1990**, *31*, 5173.
(11) Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Roos, G. H. P. *J. Chem. Soc., Chem. Commun.* **1990**, 361.
(12) Tanaka, A.; Yamashita, K. *Synthesis* **1987**, 570.
(13) (a) Sterling, J.; Slovin, E.; Barasch, D. *Tetrahedron Lett.* **1987**, *28*, 1685. (b) Lemmich, J.; Nielsen, B. E. *Tetrahedron Lett.* **1969**, 3.
(14) Lawston, I. W.; Inch, T. D. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2629.
(15) Enantioselectivities were determined with the use of $Eu(tfc)_3$ chiral NMR shift reagent and by GC on a Chiraldex γ-cyclodextrin trifluoroacetate column.
(16) Musierowicz, S.; Wroblewski, A. E. *Tetrahedron* **1978**, *34*, 461.
(17) Aromatic cycloaddition is competitive with carbon–hydrogen insertion, but the product yields of the resulting bicyclic compound are only half those of **7**; carbene dimers and azine constitute the remainder of the product distribution.

Acknowledgment. Financial support for this investigation from the National Science Foundation and the National Institutes of Health (GM-42160) is gratefully acknowledged. We thank the Johnson Matthey Company for their loan of rhodium(III) chloride and NATO for their travel grant. Fellowship support for T.W.C. was received from the Pew Midstates Science and Mathematics Consortium. Jeffrey K. Lavender performed analytical chromatographic determinations of enantioselectivities, and Matthew Pearson obtained preliminary results with **2f**.

Supplementary Material Available: Experimental details for the preparation of diazo esters, their catalytic reactions, and product characterization (5 pages). Ordering information is given on any current masthead page.

Mimicking the Glucosidase Transition State: Shape/Charge Considerations

Bruce Ganem* and George Papandreou

Department of Chemistry, Baker Laboratory
Cornell University, Ithaca, New York 14853-1301
Received July 2, 1991

The enzyme-catalyzed hydrolysis of glucosidic bonds, a pivotal reaction in carbohydrate metabolism,[1] is thought to involve a transient, point-charge-stabilized oxocarbonium ion **1** (Scheme I) whose subsequent processing results in overall retention or inversion of glucoside stereochemistry. Analogues of this glucosyl cation have long represented an attractive synthetic target for the design of potent glucosidase inhibitors.

The transition state leading to **1** involves substantial positive charge buildup and significant flattening of the substrate's pyranose ring; however, the relative impact of these electrostatic and conformational changes on enzyme binding remains controversial. Here we report detailed kinetic studies on several new glucose derivatives which suggest that the shape, not the charge, of reactive intermediate **1** is a much more important determinant for binding to β-glucosidase.

Most known inhibitors until now have been imperfect structural mimics of **1**. For example, protonated 1-deoxynojirimycin **2** may simulate the charge of **1** but does not possess the same shape.[2] Alternatively D-gluconolactone **3**,[3] its oxime **4**,[4] and the corresponding 5-amino-5-deoxylactam **5**[5] adopt distorted half-chair conformations which flatten the anomeric region somewhat[6] but can only achieve the requisite charge and endocyclic π-electron density of **1** in minor, dipolar resonance structures. Nevertheless significant competitive inhibition is observed with **2–5**, suggesting that both conformational and electrostatic factors may be important in active site binding.

Recently we reported the synthesis of glucose analogue **6**, a highly basic amidine (pK_a 10.6) whose structure, shape, and charge in aqueous solution closely resembled that of cation **1**.[7] Unlike **2–5**, amidine **6** proved to be a potent, broad-spectrum competitive inhibitor of gluco-, manno-, and galactosidases, an observation which led us to hypothesize that many glycosidases experience strong H-bonding, electrostatic and/or other noncovalent interactions with this glycosyl cation mimic.[7] We now report the synthesis of amidrazone **7** and amidoxime **8**, two novel relatives of amidine **6** which exhibit enhanced stability at elevated pH. Both **7** and **8** are potent, broad-spectrum glycosidase inhibitors, thus

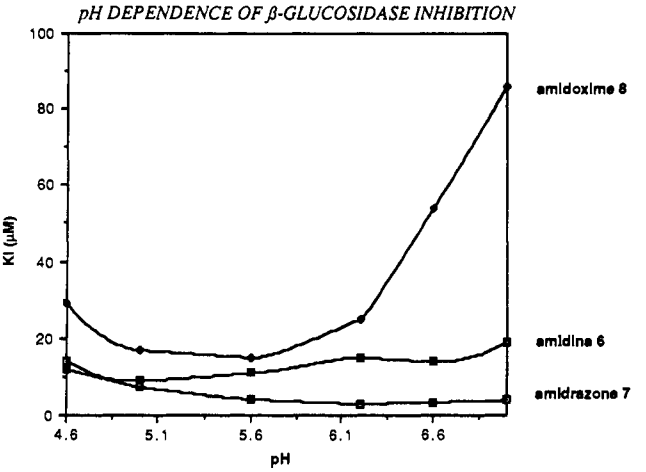
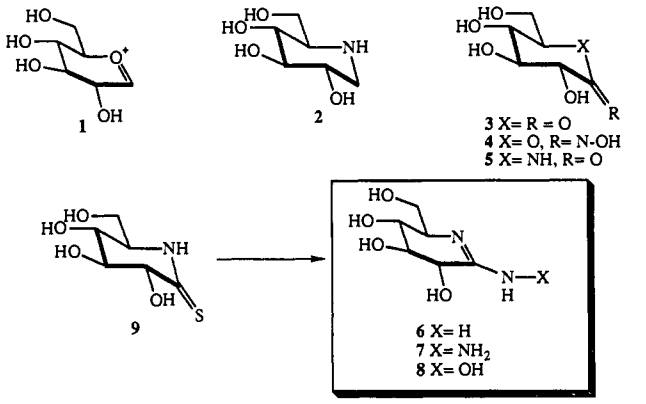


Figure 1.

Scheme I



adding further support to the above-mentioned hypothesis.[8] Moreover their effect on sweet almond β-glucosidase (β-Glu) casts a revealing light on the relative importance of electrostatic effects and conformational changes in the glucosidase transition state.

Following the method for **6**, enantiomerically pure **7** and **8** were synthesized by reacting thionolactam **9** with anhydrous hydrazine (CH_3OH, 5 °C, 2 h) or hydroxylamine[9] (CH_3OH, room temperature, 14 h), respectively. Compared to **1**, amidrazone **7** (73% yield, pK_a = 8.7) was remarkably stable at basic pH ($t_{1/2}$ = 8 h at pH 11), while amidoxime **8** (75% yield; pK_a = 5.6)[10] was unchanged after several weeks in aqueous base at pH 11.

Glucoamidrazone **7**, when assayed against a wide variety of enzymes, proved in all respects similar to amidine **6**. Under steady-state conditions, **7** competitively inhibited β-glu with a K_I of 8.4 ± 0.9 μM (*p*-nitrophenyl-β-D-glucopyranoside as substrate; 37 °C; K_M = 2.1–3.5 mM). Like **6** (K_I = 10 ± 2 μM), inhibition of β-glu by **7** was pH-independent between 4.6 and 7.0 (Figure 1), suggesting that the protonated amidrazone interacted with the more dissociated of the two active site carboxyl residues (pK_a values for β-glu: 4.4, 6.7).[11] Glucoamidoxime **8** also exhibited broad-spectrum inhibition but with pH-dependent behavior (for

(1) Review: Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319.
(2) Saul, R.; Molyneux, R. J.; Elbein, A. D. *Arch. Biochem. Biophys.* **1984**, *230*, 668.
(3) Conchie, J.; Hay, A. J.; Strachan, I.; Levvy, G. A. *Biochem. J.* **1967**, *102*, 929.
(4) Beer, D.; Vasella, A. *Helv. Chim. Acta* **1986**, *69*, 267.
(5) Inouye, S.; Tsuruoka, T.; Ito, T.; Niida, T. *Tetrahedron* **1968**, *23*, 2125.
(6) While **3–5** incorporate an sp^2 carbon at C-1 (corresponding to the anomeric center of **1**), their conformations are distinctly different from **1**, as methylenecyclohexane is from cyclohexene.
(7) Tong, M. K.; Papandreou, G.; Ganem, B. *J. Am. Chem. Soc.* **1990**, *112*, 6137.
(8) The corresponding D-mannoamidrazone and D-mannoamidoxime, synthesized in analogous fashion, also exhibit the same pattern of indiscriminate (i.e., broad-spectrum) inhibition. Besides inhibiting jackbean α-mannosidase (K_I = 166 ± 13 nM), mung bean α-mannosidase (IC_{50} = 400 nM), fungal β-mannosidase (IC_{50} = 150 nM), and bovine β-galactosidase (K_I = 57 ± 3 μM), the mannoamidrazone also inhibits Golgi α-mannosidase I (IC_{50} = 4 μM), α-mannosidase II (IC_{50} = 90–100 nM), and endoplasmic reticulum α-mannosidase (IC_{50} = 1 μM): Pan, Y. T.; Kaushal, G. P.; Papandreou, G.; Ganem, B.; Elbein, A. D. *J. Biol. Chem.*, submitted for publication.
(9) Watt, G. W.; McBride, W. R. *J. Am. Chem. Soc.* **1955**, *77*, 2088.
(10) Satisfactory 300-MHz ^1H and ^{13}C NMR, IR, and mass spectral data (FAB, exact mass) were obtained for this and all other new substances.
(11) Dale. M. P.; Ensley, H. E.; Kern, K.; Sastry, K. A. R.; Byers, L. D. *Biochemistry* **1985**, *24*, 3530.

0002-7863/91/1513-8984$02.50/0