All Eight Stereoisomeric D-Glyconic-δ-lactams: Synthesis, Conformational Analysis, and Evaluation as Glycosidase Inhibitors

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An efficient and general synthetic route to all eight stereoisomeric D-glycono-δ-lactams has been developed. The strategy involves, as a key step, a stereodivergent δ-lactam formation with configurational retention or inversion at C-4 of a starting γ-lactone to lead to two epimers of δ-lactam from one parent γ-lactone. Conformations of eight glycono-δ-lactams were examined by X-ray crystallographic analysis and molecular modeling. Analyses of conformation and glycosidase-inhibition provide useful information for the design of new glycosidase inhibitors.

Introduction

The intense interest in the chemistry, biochemistry and pharmacology of glycosidase inhibitors has grown during the past decade due to both unraveling of the mechanism of action of glycosidases[1] and their chemotherapeutic potential in the prevention and treatment of a variety of diseases,[2] including cancer,[3] diabetes,[4] AIDS,[5] and influenza infection.[6] Glycosidase inhibitors have general structural homology with natural glycosides, and are traditionally polyhydroxylated six- and five-membered heterocyclic rings—often azacyclic rings.[1−7] Various types of inhibitors have also been designed based on a positive-charged, flattened half-chair oxocarbenium ion in a transition state of the reaction catalyzed by glycosidase[8] (Figure 1). Typical inhibitors are illustrated in Figure 2. Excellent pioneering studies on a relationship between structure and inhibitory activity in glycosidase inhibitors by the Ganem group,[9] Wong group[7c] and Vasella group[10] have shown that good glycosidase inhibitors should have

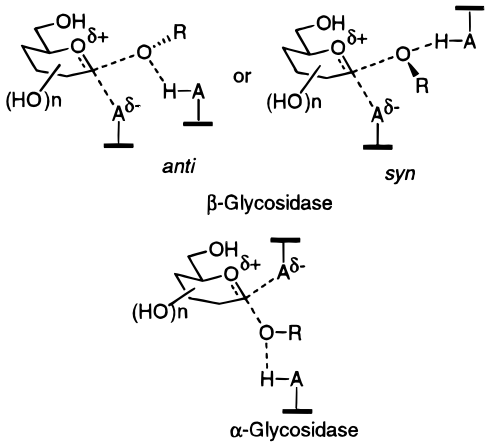

Figure 1. Presumed oxocarbenium ions in a transition state of hydrolysis by α- and β-glycosidases.[7c,10b]

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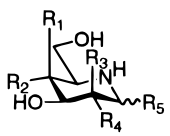
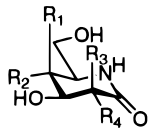
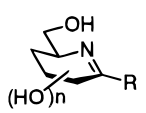


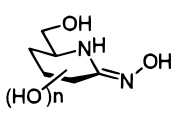
Nojirimycin (**1**): R_1=R_3=H, R_2=R_4=R_5=OH
Deoxynojirimycin (**2**): R_1=R_3=R_5=H, R_2=R_4=OH
Mannojirimycin (**3**): R_1=R_4=H, R_2=R_3=R_5=OH
Deoxymannojirimycin (**4**): R_1=R_4=R_5=H, R_2=R_3=OH
Galactostatin (**5**): R_1=R_4=R_5=OH, R_2=R_3=H
Deoxygalactostatin (**6**): R_1=R_4=OH, R_2=R_3=R_5=H



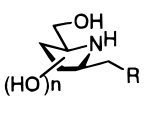
Glucono-δ-lactam (**7**): R_1=R_3=H, R_2=R_4=OH
Mannono-δ-lactam (**8**): R_1=R_4=H, R_2=R_3=OH
Galactono-δ-lactam (**9**): R_1=R_4=OH, R_2=R_3=H



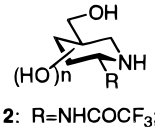
10a: R=NH_2; NH-NH_2



10b



11: R=OH; NHAc



12: R=NHCOCF_3; H

Figure 2. Representative glycosidase inhibitors.

a flattened half-chair conformation with a positive charge character around the anomeric carbon and ring heteroatom, and with the correct configuration at C-2, -3, -4, and -5 (half-chair conformation and electrostatic factors). In the course of our study on glycosidase inhibitors,[11] we have become interested in the influence of the conformation of glycono-*δ*-lactams on glycosidase inhibitory activities. The known glyconolactams, D-glucono-, D-mannono- and D-galactono-*δ*-lactams (**7**, **8**, and **9**) show significant competitive inhibition against the corresponding glycosidases.[12−14] Mannonolactam **8** is also known to be a better glucosidase inhibitor than gluconolactam **7**.[13,15] These glycono-*δ*-lactams were obtained by transformation of natural azasugars **1**, **3**, and **5**, respectively, and also by total synthesis.[12,13,16−19] Furthermore, **7** and **8** have also been isolated from a fermentation broth of marine actinomycete.[15] Asymmetric synthesis (82% ee) of D-idono-*δ*-lactam (**29**) was also reported.[20] However, to our knowledge, little is known about systematic study on synthesis of all eight stereoisomeric glycono-*δ*-lactams (glucono-, mannono-, galactono-, talono-, altrono-, idono-, gulono- and allono-*δ*-lactam), their conformational analysis, and the relationship between their conformations and inhibitory activities. Here we report logical synthesis, rigorous conformational analysis and evaluation of inhibitory activity of D-glucono- (**7**), D-mannono- (**8**), D-galactono- (**9**), D-gulono- (**25**), D-allono- (**26**), D-talono- (**27**), D-altrono- (**28**), and D-idono-*δ*-lactam (**29**) as a fundamental probe of the half-chair conformation-inhibitory activity profile.

Results and Discussion

Synthesis. Our synthetic strategy, as a key step, involves stereodivergent *δ*-lactam formation with configurational retention or inversion at C-4 of a starting *γ*-lactone to afford two epimers of *δ*-lactam from one parent *γ*-lactone (Scheme 1). The former *δ*-lactam formation has readily been achieved from 5-azido-*γ*-lactone **13** by well-known methods[21] of usual catalytic reduction (route a in Scheme 2). On the other hand, the latter *δ*-lactam formation proved troublesome until we uncovered that treatment of 5-azido-*γ*-lactone **13** with triphenylphosphine gave the desired product **19** (route b in Scheme 2). The latter *δ*-lactam formation likely proceeded via intramolecular phosphonium-salt like the Mitsunobu reaction:[22] initial attack by triphenylphosphine on the azide group to form the iminophosphorane **15**,[23] then subsequent formation of an intramolecular aminophosphonium-salt **16** and then an alkoxyphosphonium salt **17**, and epimerization (S_N2 type displacement of the resulting species **17**) would form the epimeric *γ*-lactone **18** then leading to the desired *δ*-lactam **19** (route b in Scheme 2). Thus, this methodology has made it possible to prepare efficiently all eight stereoisomeric glycono-*δ*-lactams from four starting *γ*-lactones.

Synthesis of D-gulono- and allono-*δ*-lactams (**25** and **26**) from L-mannonic acid *γ*-lactone (**21**) was performed as outlined in Scheme 3. The synthesis began with 2,3;5,6-

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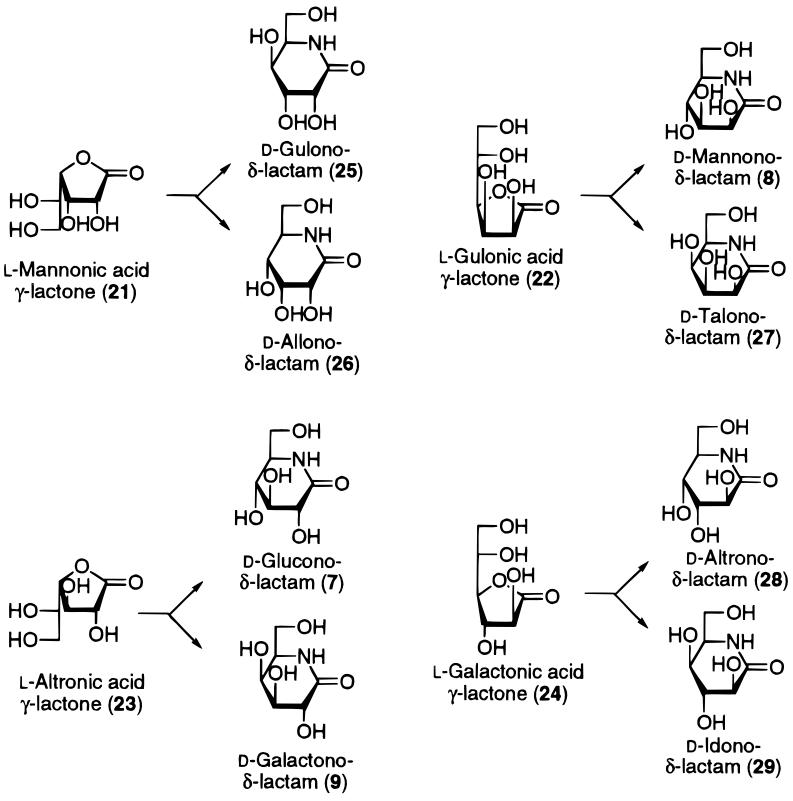
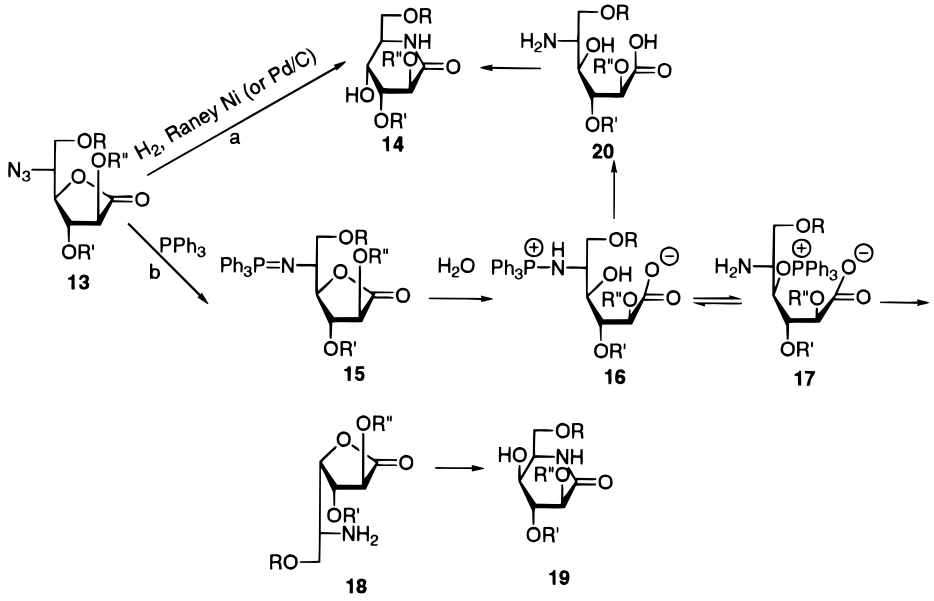
Scheme 1



Scheme 2



di-*O*-isopropylidene-L-mannonic acid γ-lactone (**30**)[24] readily prepared from **21**. Selective removal of the 5,6-*O*-isopropylidene group of **30** with acetic acid gave 2,3-*O*-isopropylidene derivative **31** which was transformed into 6-*O*-trityl-2,3-*O*-isopropylidene-L-mannonic acid γ-lactone (**33**) *via in situ* formation of the cyclic stannoxane **32** by treatment with dibutyltin oxide[25] and a subsequent tritylation in good yield. Trifluoromethanesulfonylation of **33** followed by displacement of the resultant sulfonate with NaN_3 gave the pivotal intermediate, the azide **34**. Catalytic reduction of **34** with Raney Ni straightforwardly afforded the protected D-gulono-δ-lactam **35**. Removal of protecting groups of **35** by treatment with hydrogen chloride in dioxane resulted in the crystalline D-gulono-δ-lactam (**25**) in good yield. On the other hand, treatment of **34** with triphenylphosphine in CH_3CN and a successive hydrolysis gave the desired D-allono-δ-lactam derivative **36** in 92% yield. Then, removal of protecting

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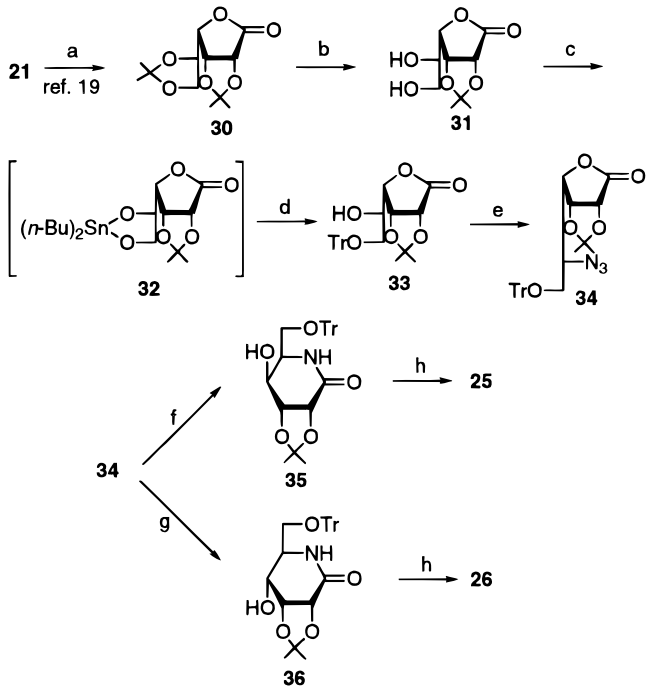
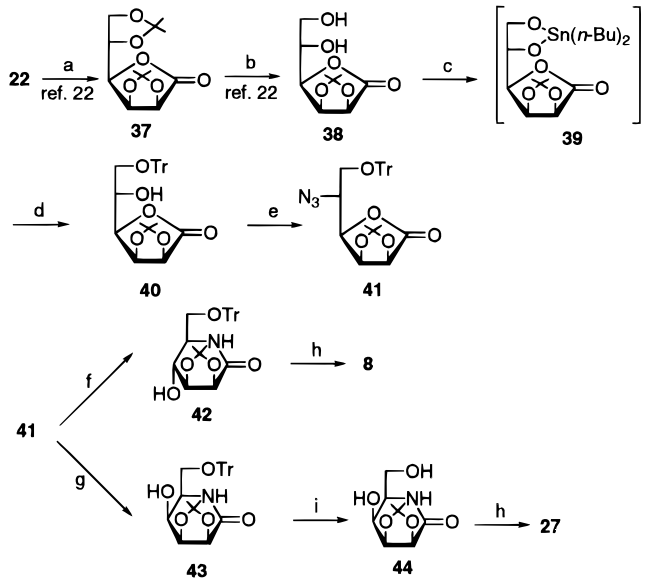
Scheme 3[a]



[a] Reagents and conditions: (a) $(MeO)_2CMe_2$, CH_3COCH_3, *p*-TsOH, rt; (b) 80% AcOH, 30 °C; (c) $(n\text{-}Bu)_2SnO$, PhH, MS4A, 80 °C; (d) Ph_3CCl, $(i\text{-}Pr)_2NEt_2$, DMF, rt; (e) (i) $(CF_3SO_2)_2O$, Py, CH_2Cl_2, −40 °C, (ii) NaN_3, DMF, rt; (f) H_2, Raney Ni, MeOH, rt; (g) PPh_3, CH_3CN, rt; H_2O, rt; (h) 4 M HCl/dioxane.

Scheme 4[a]

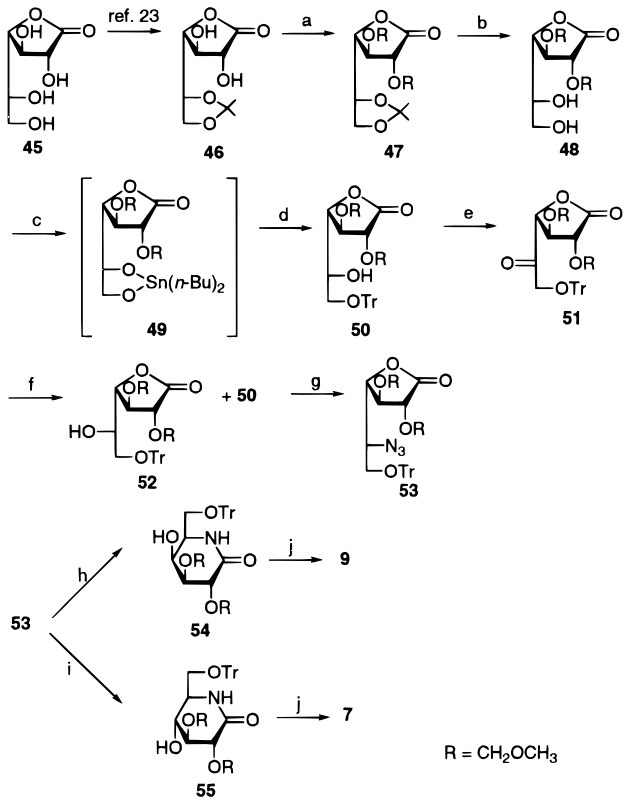


[a] Reagents and conditions: (a) $(MeO)_2CMe_2$, CH_3COCH_3, *p*-TsOH, rt; (b) 80% AcOH, rt; (c) $(n\text{-}Bu)_2SnO$, PhH, MS4A, 85 °C; (d) Ph_3CCl, $(i\text{-}Pr)_2NEt$, DMF, rt; (e) (i) $(CF_3SO_2)_2O$, Py, CH_2Cl_2, −40 °C, (ii) NaN_3, DMF, rt; (f) Raney Ni, H_2, MeOH/AcOEt; (g) PPh_3, CH_3CN, rt; H_2O, rt; (h) 4 M HCl/dioxane (i) H_2/Pd-C, EtOH.

groups with acid hydrolysis yielded the crystalline D-allono-*δ*-lactam (**26**) in good yield.

Synthesis of D-mannono- and D-talono-*δ*-lactams (**8** and **27**) from L-gulonic acid *γ*-lactone (**22**) was outlined in Scheme 4. The key intermediate, azide **41** was prepared from the known starting 2,3-*O*-isopropylidene-L-gulonic acid *γ*-lactone (**38**)[19] by sequences of reactions similar to those mentioned above. Catalytic reduction of **41** with

Scheme 5[a]



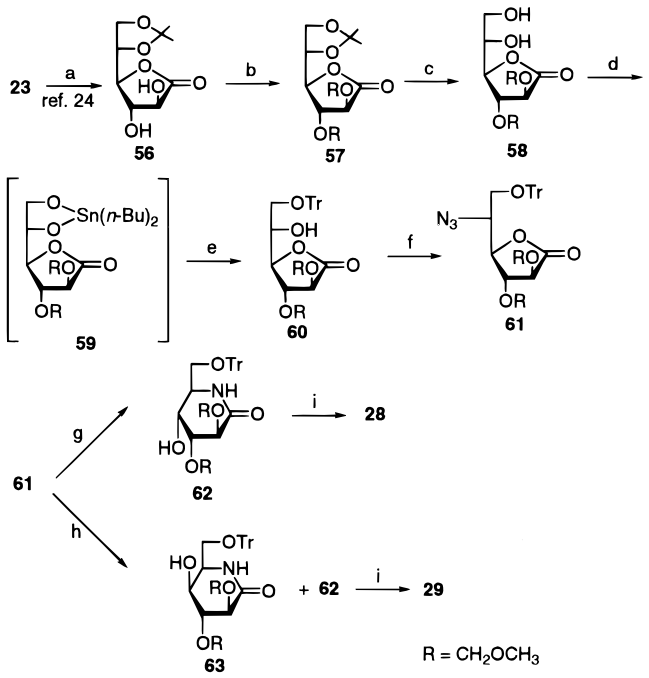
[a] Reagents and conditions: (a) MOMCl, $(n\text{-}Bu)_4NI$, $(i\text{-}Pr)_2NEt$, 70 °C; (b) 80% AcOH, 40 °C; (c) $(n\text{-}Bu)_2SnO$, PhH, MS4A, 80 °C; (d) Ph_3CCl, $(i\text{-}Pr)_2NEt$, DMF, rt; (e) Dess−Martin periodinane, CH_2Cl_2; (f) $NaBH_4$, MeOH/CH_2Cl_2; (g) (i) $(CF_3SO_2)_2O$, Py, CH_2Cl_2, −40 °C, (ii) NaN_3, DMF, rt; (h) H_2, Raney Ni, MeOH; (i) PPh_3, CH_3CN, rt; H_2O, rt; (j) 4 M HCl/dioxane.

Raney Ni gave the protected D-mannono-*δ*-lactam **42**, while treatment with PPh_3 in CH_3CN followed by hydrolysis resulted in D-talono-*δ*-lactam derivative **43** as a sole product. Acid hydrolysis of **42** straightforwardly resulted in the crystalline D-mannono-*δ*-lactam (**8**).[13,18,19] On the other hand, simultaneous removal of trityl and isopropylidene groups in **43** by acid hydrolysis with hydrogen chloride in dioxane proceeded unfavorably to give many decomposed products. Removal of protecting groups of **43** was best achieved by the two step sequences of deprotection of trityl group by hydrogenolysis with palladium on carbon and acid hydrolysis of the isopropylidene group to afford the crystalline D-talono-*δ*-lactam (**27**).

D-Glucono- and D-galactono-*δ*-lactams (**7** and **9**) were synthesized as outlined in Scheme 5. The starting L-altronic acid *γ*-lactone (**23**) was not commercially available, and therefore the desired precursor, 2,3-di-*O*-(methoxymethyl)-6-*O*-trityl-L-altronic acid *γ*-lactone (**52**) was prepared from D-galactonic acid *γ*-lactone (**45**). Inversion of the stereochemistry at carbon-5 of **45** is required for the desired **52**. The readily available 5,6-*O*-isopropylidene-D-galactonic acid *γ*-lactone (**46**)[26] was converted to 2,3-di-*O*-(methoxymethyl)-6-*O*-trityl-D-galactonic acid *γ*-lactone (**50**) by protection of the 2,3-diol and 6-*O*-tritylation *via in situ* formation of the 5,6-cyclic stannoxane. The last epimerization at carbon-5 of **50** was best achieved by two step sequences of oxidation with

(26) Fleet, G. W. J.; Son, J. C. *Tetrahedron* **1988**, *44*, 2637.

Scheme 6[a]



[a] Reagents and conditions: (a) $(MeO)_2CMe_2$, CH_3COCH_3, *p*-TsOH, rt; (b) MOMCl, $(n\text{-}Bu)_4NI$, $(i\text{-}Pr)_2NEt$, 70 °C; (c) 80% AcOH, 40 °C; (d) $(n\text{-}Bu)_2SnO$, PhH, MS4A, 80 °C; (e) Ph_3CCl, $(i\text{-}Pr)_2NEt$, DMF, rt; (f) (i) $(CF_3SO_2)_2O$, Py, CH_2Cl_2, −40 °C, (ii) NaN_3, DMF, rt; (g) H_2, Raney Ni, MeOH (h) PPh_3, CH_3CN, rt; H_2O, rt; (i) 4 M HCl/dioxane.

Dess−Martin periodinane and reduction with $NaBH_4$ to give **52** and **50** in a ratio of 2 to 1. Compound **52** was transformed into the key intermediate, azide **53**, by a method similar to that mentioned above. Catalytic reduction of **53** afforded the protected D-galactono-δ-lactam **54**, and the analogous treatment of **53** with PPh_3 gave D-glucono-δ-lactam derivative **55** as the sole product. Acid hydrolysis of **54** and **55** with hydrogen chloride in dioxane resulted in crystalline D-galactono-δ-lactam (**9**)[16,18] and D-glucono-δ-lactam (**7**),[12,17,18] respectively.

D-Altrono- and D-idono-δ-lactams (**28** and **29**) were synthesized by the similar strategy from the known 5,6-*O*-isopropylidene-L-galactonic acid γ-lactone (**56**)[27] as outlined in Scheme 6. However, in this case different from in other cases, the δ-lactam formation using triphenylphosphine afforded both the inversion isomer **63** and the retention isomer **62** in a ratio of 3:5. It is likely that the aminophosphonium salt **16** is more stable than the alkoxyphosphonium salt **17** in this case (Scheme 2).

Conformational Analysis. Conformational analysis was carried out by X-ray crystallographic studies. The structures of **9** and **25**−**29** were solved by direct methods (SHELX86), and the non-hydrogen atoms were anisotropically refined. On the other hand, the X-ray crystallographic analyses of **7** and **8** were already achieved by Niwa *et al.*[12] and Ogura et al.,[28] respectively, and their data were also used in this study. The ORTEP drowings of **7**−**9** and **25**−**29** are shown in Figure 3. As shown in Figure 3, conformations of eight glycono-δ-lactams (**7**−**9** and **25**−**29**) can be classified into three types of conformers: boat, half-chair, and skew-boat. D-Glucono-, D-galactono-, D-gulono-, and D-allono-δ-lactams (**7**, **9**, **25**, and **26**) adopt half-chair conformers, while D-mannono-, D-talono-, and D-idono-δ-lactams (**8**, **27**, and **29**) adopt $B_{5,2}$-boat conformers. D-Altrono-δ-lactam **28** has an exceptional skew-boat conformer. The structures of all eight glycono-δ-lactams (**7**−**9** and **25**−**29**) were also optimized with PM3 in MOPAC[29] using the atomic coordinates obtained by X-ray crystallographic analysis. The optimized structures with PM3/MOPAC were superimposed well on the structures obtained by X-ray crystallographic analysis except for **8**, **27**, and **29** (Figure 4). Molecules of D-glycono-δ-lactams in the crystal structure commonly form networks of intermolecular hydrogen bonds as well as intramolecular hydrogen bonds[28] (see Supporting Information), and consequently, X-ray crystallographic analysis gives the conformation of a molecule as a result of overall inter- and intramolecular interactions. On the other hand, the optimization of the structure with PM3/MOPAC analyzes the conformation of one molecule without intermolecular interactions. Therefore, the conformation obtained by the molecular modeling sometimes turns out to be different from the conformation determined by the X-ray crystallographic analysis. Especially, in the case of D-talono-δ-lactam (**27**), there is a large difference of structure between the X-ray crystallographic analysis and the molecular modeling. Intermolecular hydrogen bonds between O(2)−H and O(5) (2.802 Å), O(5)−H and O(2) (2.762 Å) and N−H and O(4) (2.986 Å) as well as an intramolecular hydrogen bond between O(1) and O(2)−H (2.689 Å) are observed in the X-ray crystallographic analysis, resulting a $B_{5,2}$-boat conformation. On the other hand, a distinguishing intramolecular hydrogen bond between O(2) and O(4)−H (1.841 Å) appears in the molecular modeling with PM3/MOPAC, resulting in a half-chair conformation of flap-up type. These results of X-ray crystallographic analysis and molecular modeling indicate that the absolute configuration at C-2 position may play an important role in fixing the conformation in glycono-δ-lactams. The glycono-δ-lactams with *R*-configuration at C-2 position (**7**, **9**, **25**, and **26**) are in a half-chair conformation. On the other hand, the glycono-δ-lactams with *S*-configuration at C-2 position (**8**, **27**, **28**, and **29**) are in a boat conformation. Molecular modeling was next undertaken to verify the contribution of the configurational energy at C-2 on the overall conformational energy of glycono-δ-lactams between half-chair conformers with *R*-configuration and boat conformers with *S*-configuration. The optimized structures of D-glucono-, D-galactono-, D-gulono-, and D-allono-δ-lactams (**7**, **9**, **25**, and **26**) with PM3 in MOPAC which have the half-chair conformers with *R*-configuration were then optimized altering only configuration at C-2 position. The structures obtained corresponding to D-mannono-, D-talono-, D-idono-, and D-altrono-δ-lactams (**8**, **27**, **29**, and **28**), respectively, were identical to those shown in Figure 4.

As shown in Figure 4, when the *R*-configurations at C-2 in **7**, **25**, and **26** were converted to the *S*-configurations in optimization with PM3 in MOPAC, these structures were deformed simultaneously from the half-chair conformer to the skew-boat conformer. These results explain well why the structures with *R*-configuration and *S*-configuration at C-2 position are the half-chair conformer and the boat conformer, respectively. It is clearly

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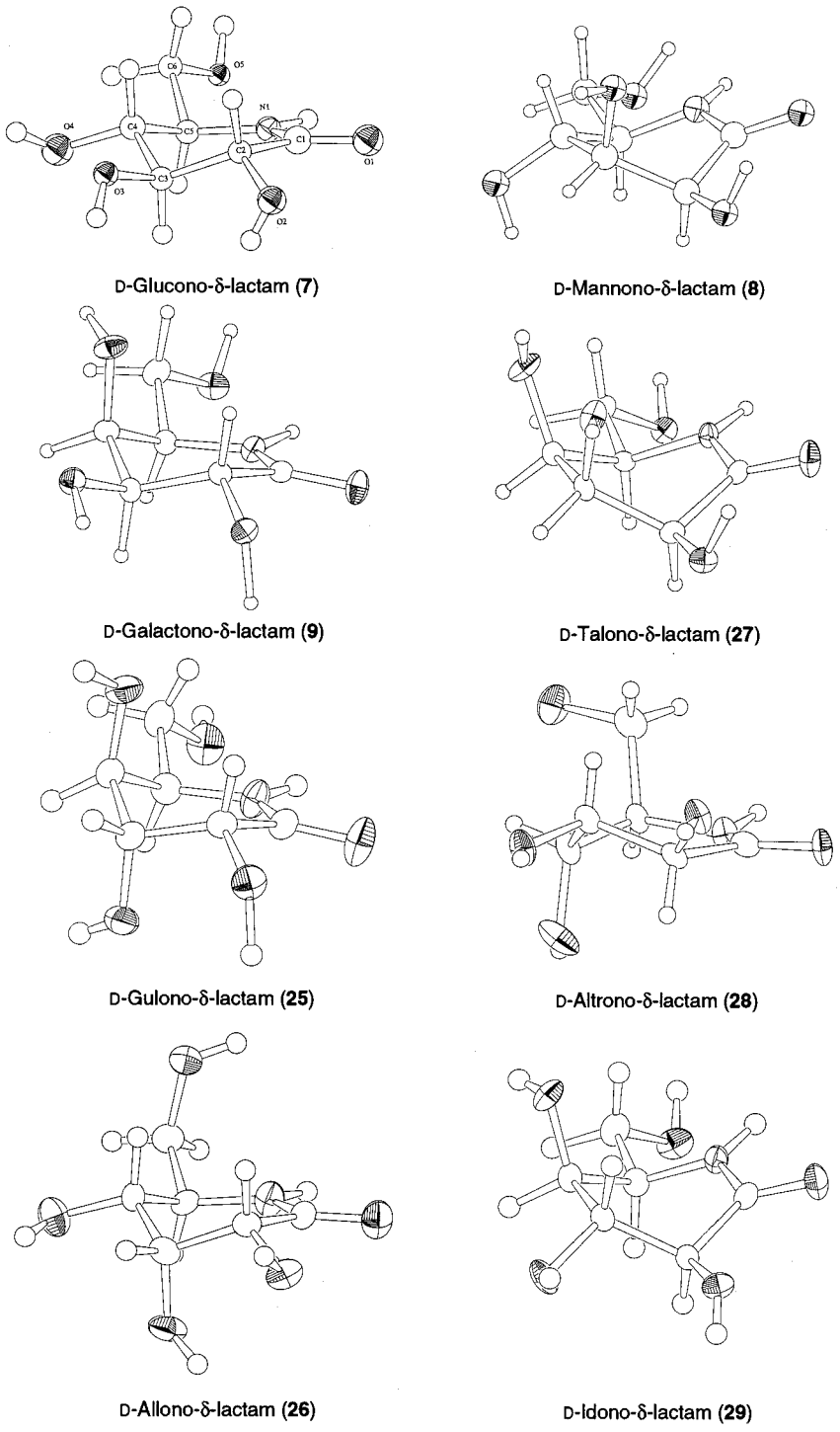

Figure 3. X-ray crystal structures of eight glycono-*δ*-lactams.

indicated that the absolute configuration at C-2 is a chief determining factor to fix the conformation of glycono-*δ*-lactams. It is also likely that the hydrogen bond between the lactam carbonyl and the adjacent hydroxy group at C-2 position may make a large contribution to the overall conformational energy: the five-membered rings of the α-hydroxy ketones are generally effective in strong intramolecular hydrogen bonding.[30] However, when the *R*-configuration at C-2 of **9** was converted to the *S*-configuration in optimization with PM3/MOPAC, the structure corresponding D-talono-*δ*-lactam (**27**) showed a similar half-chair conformer to the original **9** and was different from the structure obtained by X-ray crystallographic analysis. As discussed above, this result suggests that the intramolecular hydrogen bond between *S*-configurational 2-OH and *S*-configurational 4-OH groups make a large contribution to the overall structure in PM3/MOPAC calculation.

Analysis of Glycosidase Inhibition. The inhibitory activities of these glycono-*δ*-lactams against α-glucosidase (baker's yeast), *β*-glucosidase (almonds), α-mannosidase (jack beans), *β*-mannosidase (snail), α-galactosidase

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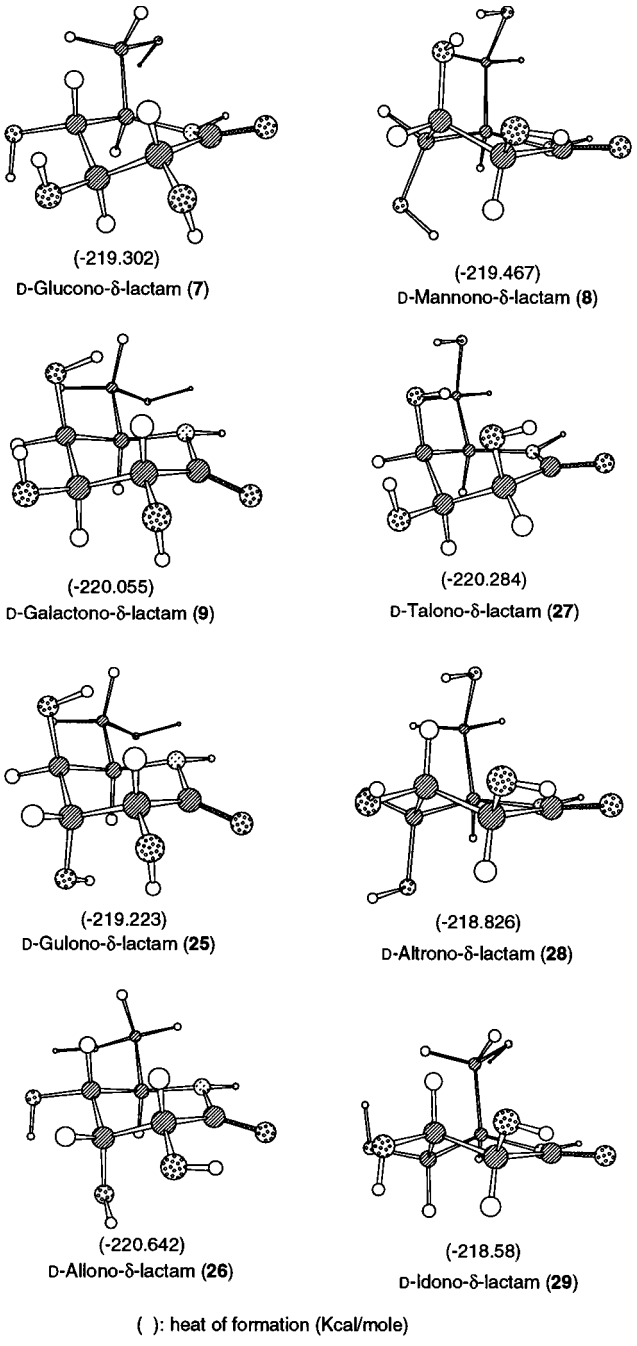

Figure 4. Optimized structures of eight glycono-δ-lactams by PM3 in MOPAC.

(*Aspergillus niger*), and β-galactosidase (*A. niger*) were evaluated, and the IC_{50} values and the inhibition constants (K_i) are summarized in Tables 1 and 2. All D-glycono-δ-lactams were proved to be competitive inhibitors by Lineweaver−Burk plot, and the K_i values were elucidated by Dixon plot. β-Glucosidase was inhibited by D-glucono, D-mannono, D-galactono, D-talono, and D-idono-δ-lactams (**7**, **8**, **9**, **27**, and **29**). β-Galactosidase was also inhibited by D-galactono and D-talono-δ-lactams (**9** and **27**). On the other hand, α- and β-mannosidases were inhibited only by D-mannono-δ-lactam (**8**). D-Gulono, D-allono and D-altrono-δ-lactams (**25**, **26**, and **28**) showed no inhibition of the glycosidases evaluated. These results indicate that all D-glycono-δ-lactams (**8**, **27** and **29**) having the boat conformation in the X-ray crystallographic analysis (Figure 3) showed inhibition against β-glucosidase. There exists a better correlation between the inhibitory activity against β-glucosidase and the X-ray crystallographic structures (Figure 3) rather than the molecular modeling structures (Figure 4). Furthermore, D-mannono-δ-lactam (**8**) having a boat conformation was a better inhibitor for β-glucosidase than D-glucono-δ-lactam (**7**) having a half-chair conformation. Then, molecular modeling of a glucopyranosyl cation in β-glucosidase hydrolysis (Figure 1) was undertaken to understand the structure−activity relation of the above inhibitors. The structure of the glucopyranosyl cation (**64**) was first optimized with PM3 in MOPAC. Three candidates, the boat conformers ($B_{5,2}$ (**64a**) and $B^{5,2}$ (**64b**)) and the half-chair conformer of flap-up type (**64c**) were calculated for the structure of the glucopyranosyl cation (Figure 5 and Table 3). Unexpectedly, the highest energy conformer **64a** among these three structures more resembles D-manno-δ-lactam (**8**) which shows better inhibition for β-glucosidase than D-glucono-δ-lactam (**7**). The discrepancy between the calculations and the inhibitor conformations may come from the neglect of the influence of interactions such as hydrogen bonds between the molecule and the active site of the enzyme in the calculation of molecular modeling with PM3/MOPAC. D-Galactono, D-talono and D-idono-δ-lactams (**9**, **27**, and **29**) having a *S*-configurational at C-4 inhibited almond β-glucosidase similarly to D-glucono and D-mannono-δ-lactams (**7** and **8**) having an *R*-configuration at C-4, indicating that the 4-OH group is probably not so important for binding in almond β-glucosidase as 1-*N*-iminosugars (**65**−**67**) with a *S*-configuration at C-4 are good inhibitors of β-glucosidase.[31,32] Many glycosidases are known to be nonspecific with respect to the C-4 configuration of the sugar moiety.[33] Especially, β-glucosidases classified in family 1 have been proved to show low *gluco*/*galacto* selectivity.[10b,34] The low *gluco*/*galacto* selectivity has also been shown in inhibition of almond β-glucosidase by the above glycono-δ-lactams, although there are no information whether almond β-glucosidase is classified in family 1 or not. However, the stereochemistry of C_3-C_4 (*S* and *S*) is important for binding in β-galactosidase as only D-galactono and D-talono-δ-lactams (**9** and **28**) among eight glycono-δ-lactams were effective against β-galactosidase. On the other hand, interestingly, mannosidases were inhibited only by **8** among the glycono-δ-lactams with the $B_{5,2}$-conformation (Figure 3). These results suggest that all stereochemistries of $C_2-C_3-C_4-C_5$ are important for boat-form recognition in the catalytic mechanism of β-mannosidase hydrolysis. A galactosyl cation **69** and a mannopyranosyl cation **70** were also calculated to be half-chair and skew-boat conformers, respectively, by optimization with PM3/MOPAC (Figure 7, Table 3). The whole results of the structure−activity relations seem to indicate that boat conformers as well as half-chair ones may reflect similarly the structures of glycopyranosyl cations in the active pockets of glycosidases. On the other hand, we do not clearly understand at this stage the reason these glycono-δ-lactams little

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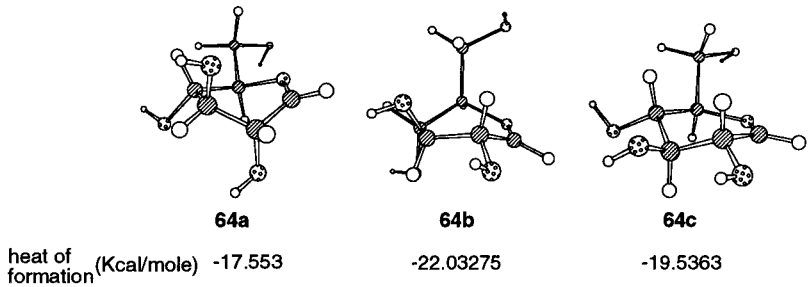


Figure 5. Optimized structures of glucopyranosyl cation by PM3 in MOPAC.

Table 1. Inhibitory Activities (IC_{50} M) of 7−9 and 25−29 against Glycosidases

enzyme	7	8	9	25	26	27	28	29
α-glucosidase[a]	NI	NI	NI	NI[g]	NI	NI	NI	NI
β-glucosidase[b]	6.2×10^{-5}	7.9×10^{-7}	1.6×10^{-4}	NI	NI	1.8×10^{-4}	NI	7×10^{-5}
α-mannosidase[c]	NI	1.0×10^{-4}	NI	NI	NI	NI	NI	NI
β-mannosidase[d]	NI	1.1×10^{-5}	NI	NI	NI	NI	NI	NI
α-galactosidase[e]	NI	NI	NI	NI	NI	NI	NI	NI
β-galactosidase[f]	NI	NI	1.7×10^{-5}	NI	NI	6.2×10^{-5}	NI	NI

[a] Baker's yeast. [b] Almonds. [c] Jack beans. [d] Snail. [e] *Aspergillus nier*. [f] *Aspergillus niger*. [g] NI: no inhibition at 5.6×10^{-2} M.

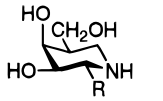
Table 2. Glycosidase Inhibition Constants of 7−9, 27, and 29

compd	enzyme	K_i (M)
7	β-glucosidase (almond)	5.1×10^{-5}
8	β-glucosidase (almond)	5.1×10^{-7}
	α-mannosidase (jack bean)	6.8×10^{-5}
	β-mannosidase (snail)	9.0×10^{-6}
9	β-glucosidase (almond)	8.5×10^{-5}
	β-galactosidase (*Aspergillus niger*)	4.5×10^{-6}
27	β-glucosidase (almond)	1.2×10^{-4}
	β-galactosidase (*Aspergillus niger*)	1.5×10^{-5}
29	β-glucosidase (almond)	4.6×10^{-5}

Table 3. Calculated Partial Charge Distribution of Glycopyranosyl Cations

atom	glucopyranosyl cation (**64a**)	galactopyranosyl cation (**69**)	mannopyranosyl cation (**70**)
C_1	0.3782	0.3962	0.3384
C_2	0.0001	−0.0240	0.0082
C_3	0.0468	0.0457	0.0270
C_4	0.0170	0.0220	0.0235
C_5	−0.0297	0.0037	−0.0017
O	−0.0055	−0.0339	−0.0057

affect α-glycosidases. However, it is likely that the carbonyl groups of these glycono-δ-lactam inhibitors may be topographically equivalent to the glycosidic oxygen atom of the high energy transition state in β-glycosidase rather than α-glycosidase as shown in Figure 1 and Figure 3. Heightman and Vasella[10b] have elegantly interpreted the selectivity of neutral lactone-type inhibitors in the inhibition of β- over α-glycosidases by the directionality of the hydrogen bond between the catalytic acid and the glycosidic heteroatom of the inhibitors: in α-glycosidases these groups are unfavorably oriented for a strong hydrogen bond. On the whole, the inhibitory activities of these glycono-δ-lactams having a neutral character against glycosidases are also weaker than those of the representative glycosidase inhibitors (**1**−**6** and **10**−**12**) with a basic character (Figure 2). This indicate that the positive charge of the inhibitors (protonation by the glycosidases[10b]) plays an important role for strong binding and recognition of glycosidases.[7c,9] Thus, although the information from three-dimensional structures of glycosidase-ligand and/or inhibitor complexes in a study of the inhibitors of influenza virus neuraminidase[5,35] were



65: R=NHCOCH$_3$

66: R=NHCOCF$_3$

67: R=H

Figure 6. 1-*N*-Iminosugar inhibitors with a *S*-configurational 4-OH group of β-glucosidase.

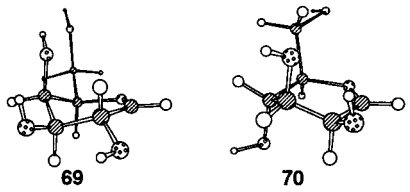


Figure 7. Optimized structures of galactosyl and mannosyl cations (**69** and **70**, respectively) by PM3 in MOPAC.

useful for the rational design of glycosidase inhibitors, the conformational analysis of inhibitors by a combination of X-ray crystallographic study and molecular modeling also provide useful information for the design of new glycosidase inhibitors based on a transition state with glycosyl ion character in the reaction catalyzed by glycosidases.

In summary, an efficient and general synthetic route to all eight stereoisomeric D-glycono-δ-lactams has been developed. The strategy involves, as a key step, a novel

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methodology based on stereodivergent δ-lactam formation by configurational retention or inversion at C-4 of a starting γ-lactone to provide two epimers of δ-lactam from one parent γ-lactone. Conformations of eight glycono-δ-lactams were analyzed by X-ray crystallographic studies, and these structures were also in fair agreement with those obtained by optimization with PM3 in MOPAC except for D-manno, D-talono and D-idono-δ-lactams. These conformations can be classified into three types of conformers: boat ($B_{5,2}$), half-chair of flap-up type, and skew-boat. It is likely that the X-ray crystallographic structure explains well the relationship between the structure and the inhibitory activity against glycosidases. X-ray crystallographic analysis and molecular modeling in this study indicate that the major factor for recognition of inhibitor in transition state by glycosidase should be the conformation of inhibitors for β-glucosidase and the stereochemistry of inhibitors for β-mannosidase and β-galactosidase as well as a positive charge character.

Experimental Section

General Procedures for Enzyme Inhibition Assay. The enzymes α-glucosidase (baker's yeast), β-glucosidase (almond), α-mannosidase (jack beans), β-mannosidase (snail), β-galactosidase (*Aspergillus niger*), and α-galactosidase (*Aspergillus niger*) were purchased from Sigma Chemical Co. α- and β-glucosidases were assayed using *p*-nitrophenyl α-D-glucopyranoside (1.5×10^{-3}M) and β-D-glucopyranoside (2×10^{-3}M) as substrates at pH 6.3 (0.025 M citrate-phosphate buffer) and 5.0 (0.025 M acetate buffer), respectively. α- and β-Mannosidases were assayed using *p*-nitrophenyl α-D-mannopyranoside (2×10^{-3}M) and β-D-mannopyranoside (2×10^{-3}M) as substrates at pH 4.5 (0.05 M acetate buffer) and 4.0 (0.05 M acetate buffer), respectively. α- and β-Galactosidases were assayed using *p*-nitrophenyl α- and β-D-galactopyranoside (2×10^{-3}M) at pH 4.0 (0.025 M citrate-phosphate buffer). The reaction mixture contained 0.5 mL of buffer, 0.1 mL of substrate solution and water or aqueous solution containing the test compound. The mixture was incubated at 37 °C for 3 min, and 0.01 mL of enzyme was added. After 30 min of reaction, 1.0 mL and 0.3 M glycine-sodium hydroxide buffer (pH 10.5) was added and the absorbance of the liberated nitrophenol or phenolphthalein measured at 400 or 525 nm, respectively. The percent inhibition was calculated by the formula $(A - B)/A \times 100$, where A is the nitrophenol liberated by the enzyme without an inhibitor and B is that with an inhibitor. The IC_{50} value is the concentration of inhibitor at 50% of enzyme activity. *Ki* values were determined using six substrate (0.25−10 mM of *p*-nitrophenyl β-D-glucopyranoside; 0.5−8.0 mM of *p*-nitrophenyl α-D-mannopyranoside; 0.25−4.0 mM of *p*-nitrophenyl β-D-mannopyranoside; 0.1−1.0 mM of *p*-nitrophenyl β-D-galactopyranoside) and four inhibitor (usually 0−140 μM) concentrations. K_i values were also elucidated by Dixon plot.

2,3-*O*-Isopropylidene-L-mannono-γ-lactone (31). A solution of **30**[24] (17.0 g, 65.8 mmol) in 80% aqueous acetic acid (500 mL) was stirred at room-temperature overnight. Evaporation of the solvent gave an oil, which was subjected to column chromatography on silica gel. Elution with a mixture of chloroform-methanol (5:1) gave **31** (8.4 g, 59%) as a colorless solid. The solid was crystallized from a mixture of ethyl acetate−diethyl ether to give colorless crystals: mp 100−102 °C; $[\alpha]_D$ −69.3 °C (*c* 0.51, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 and 1.50 (3H each, s), 2.00 (1H, br t, *J* = 5.2 Hz), 2.69 (1H, d, *J* = 5.4 Hz), 3.80 (1H, dt, *J* = 5.2 and 11.7 Hz), 3.95 (1H, ddd, *J* = 2.9, 5.2 and 11.7 Hz), 4.06 (1H, m), 4.51 (1H, dd, *J* = 3.8 and 9.0 Hz), 4.86 (1H, d, *J* = 5.7 Hz), 4.97 (1H, dd, *J* = 3.8 and 5.7 Hz). Anal. Calcd for $C_9H_{14}O_6$: C, 49.53; H, 6.46. Found: C, 49.49; H, 6.49.

2,3-*O*-Isopropylidene-6-*O*-triphenylmethyl-L-mannono-γ-lactone (33). To a solution of **31** (5.0 g, 22.9 mmol) in dry benzene (170 mL) were added dibutyltin oxide (8.29 g, 33.3 mmol) and molecular sieve 4A, and the reaction mixture was refluxed with stirring overnight. After evaporation of the solvent, the resulting residue was dissolved in dry DMF (170 mL). To the mixture were added triphenylmethyl chloride (12.4 g, 44.4 mmol) and *N*,*N*-diisopropylethylamine (15.5 mL, 88.8 mmol), and the mixture was stirred at room temperature for 3 h. Filtration and evaporation of the filtrate gave an oil, which was dissolved in chloroform. The solution was washed with water, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave an oil, which was subjected to column chromatography on silica gel. Elution with a mixture of toluene−acetone (10:1) gave **33** (9.13 g, 87%) as a colorless solid: $[\alpha]^{23}_D$ −38.4° (*c* 0.43, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 and 1.46 (3H each, s), 2.66 (1H, d, *J* = 6.4 Hz), 3.40 (1H, dd, *J* = 5.1 and 10.2 Hz), 3.51 (1H, dd, *J* = 3.4 and 10.2 Hz), 4.08 (1H, m), 4.47 (1H, dd, *J* = 3.6 and 8.3 Hz), 4.81 (1H, d, *J* = 5.3 Hz), 4.91 (1H, dd, *J* = 3.6 and 5.3 Hz), 7.22∼7.35 (9H, m), 7.41∼7.47 (6H, m). Anal. Calcd for $C_{28}H_{28}O_6$: C, 73.02; H, 6.12. Found: C, 72.74; H, 5.93.

5-Azide-5-deoxy-2,3-*O*-isopropylidene-6-*O*-triphenylmethyl-D-gulono-γ-lactone (34). To a solution of **33** (5.0 g, 11.9 mmol) in dry CH_2Cl_2 (100 mL) were added dry pyridine (3.51 mL, 43.4 mmol) and trifluoromethanesulfonic anhydride (3.65 mL, 21.7 mmol) at −40 °C, and the reaction mixture was stirred at −40 °C for 2 h. After dilution with chloroform, the solution was washed with water, dried over $MgSO_4$ and filtered. Evaporation of the filtrate gave an oil, which was dissolved in dry DMF (100 mL). To the solution was added sodium azide (7.05 g, 108 mmol), and the mixture was stirred at room-temperature overnight. Evaporation of the solvent gave an oil, which was dissolved in ethyl acetate. The solution was washed with water, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave an oil, which was subjected to column chromatography on silica gel. Elution with a mixture of toluene−acetone (20:1) gave **34** (2.70 g, 51%) as a colorless foam: $[\alpha]^{24}_D$ −22.4° (*c* 0.55, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 and 1.36 (3H each, s), 3.27 (1H, dd, *J* = 3.2 and 10.0 Hz), 3.63 (1H, dd, *J* = 3.2 and 10.0 Hz), 3.80 (1H, dt, *J* = 3.2 and 8.8 Hz), 4.21 (1H, dd, *J* = 3.2 and 5.1 Hz), 4.68∼4.73 (2H, m), 7.23∼7.36 (9H, m), 7.42∼7.50 (6H, m); HRMS (FAB) calcd for $C_{28}H_{27}O_5N_3Na$ (MNa^+) 508.1848, found 508.1819.

2,3-*O*-Isopropylidene-6-*O*-triphenylmethyl-D-gulono-δ-lactam (35). A solution of **34** (51.6 mg, 0.106 mmol) in methanol (2.0 mL) was stirred with RaneyNi under hydrogen atmosphere at room temperature for 4 h. After filtration, evaporation of the filtrate gave an oil. The oil was subjected to preparative thin-layer chromatography (PTLC) on silica gel developed with toluene-acetone (2:1) to give **35** (38.6 mg, 79%) as a colorless foam: $[\alpha]^{23}_D$ +13.1° (*c* 0.89, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 and 1.43 (3H each, s), 3.29 (1H, d, *J* = 3.9 Hz), 3.48 (2H, dd, *J* = 5.4 and 10.3 Hz), 3.70 (1H, m), 4.00 (1H, m), 4.40 (1H, dd, *J* = 3.7 and 7.0 Hz), 4.49 (1H, d, *J* = 7.0 Hz), 7.22−7.34 (9H, m), 7.37−7.43 (6H, m). Anal. Calcd for $C_{28}H_{29}NO_5$: C, 73.18; H, 6.36; N, 3.04. Found: C, 73.49; H, 6.56; N, 2.75.

2,3-*O*-Isopropylidene-6-*O*-triphenylmethyl-D-allono-δ-lactam (36). To a solution of **34** (1.19 g, 2.45 mmol) in acetonitrile (47.6 mL) was added triphenylphosphine (964 mg, 3.67 mmol), and the reaction mixture was stirred at room-temperature overnight. After addition of water (2.4 mL), the mixture was stirred at room-temperature overnight. Evaporation of the solvent gave an oil, which was dissolved in chloroform. The solution was washed with water, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave an oil. The oil was subjected to PTLC on silica gel developed with toluene-acetone (2:1) to give **36** (1.04 g, 92%) as a colorless foam.

36: $[\alpha]^{24}_D$ +33.0° (*c* 0.71, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 and 1.50 (3H each, s), 2.33 (1H, d, *J* = 8.0 Hz), 3.22 (1H, dd, *J* = 7.8 and 9.8 Hz), 3.56 (1H, dd, *J* = 3.9 and 9.8 Hz), 3.61 (1H, dt, *J* = 3.9 and 7.8 Hz), 3.72 (1H, dt, *J* = 3.9 and 7.8 Hz), 4.44 (1H, d, *J* = 6.6 Hz), 4.52 (1H, dd, *J* = 3.9 and 6.6 Hz), 5.97 (1H, s), 7.20−7.35 (9H, m), 7.38−7.45 (6H,

m). Anal. Calcd for $C_{28}H_{29}NO_5$: C, 73.18; H, 6.36; N, 3.04. Found: C, 73.37; H, 6.49; N, 2.94.

D-Gulono-*δ*-lactam (25). Compound **35** (90.0 mg, 0.196 mmol) was dissolved in 4M hydrogen chloride in dioxane, and the reaction mixture was stirred at room temperature for 6 h. After addition of ether, the resulting precipitates were collected and washed with ether. The solid was dissolved in water, and the mixture was neutralized with Dowex WGR. After filtration, evaporation of the filtrate gave an oil, which was subjected to PTLC on silica gel developed with chloroform-methanol-30% NH_4OH (1:2:0.5 *v*/*v*) to give **25** (25.1 mg, 88%) as an oil. The oil was crystallized from a mixture of methanol−ethanol−H_2O to give colorless crystals: mp 163∼164 °C; $[\alpha]^{24}_D$ +60.5° (*c* 0.31, H_2O) [lit[18,36] −27.0° (*c* 0.50, H_2O) and −20.6° (*c* 0.65, H_2O) for L-gulono-*δ*-lactam: a large discrepancy of the optical rotation value between this **25** (D-gulono-*δ*-lactam) and L-gulono-*δ*-lactams reported by Pandit group[18] and Fleet group[36] is incomprehensible, although the structure of **25** and its purity are confirmed by X-ray crystallographic analysis and combustion elemental analysis, respectively]; ^{1}H NMR (400 MHz, D_2O) *δ* 3.55 (1H, m), 3.62∼3.70 (2H, m), 4.07 (1H, dd, *J* = 2.7 and 4.1 Hz), 4.11 (1H, t, *J* = 4.1 Hz), 4.26 (1H, d, *J* = 4.1 Hz). Anal. Calcd for $C_6H_{11}NO_5$: C, 40.67; H, 6.25; N, 7.90. Found: C, 40.60; H, 6.29; N, 7.75.

D-Allono-*δ*-lactam (26). Compound **26** was synthesized similarly from **36** as in the preparation of **25** from **35**; the yield was 57%. The amorphous solid was crystallized from a mixture of methanol, ethanol and water to give colorless crystals: mp >265 °C dec; $[\alpha]^{24}_D$ +68.3° (*c* 0.31, H_2O); ^{1}H NMR (400 MHz, D_2O) *δ* 3.40 (1H, ddd, *J* = 2.7, 4.4 and 9.4 Hz), 3.60 (1H, dd, *J* = 4.4 and 12.1 Hz), 3.68 (1H, dd, *J* = 2.7 and 12.1 Hz), 3.88 (1H, dd, *J* = 2.5 and 9.4 Hz), 4.11 (1H, d, *J* = 2.5 Hz), 4.13 (1H, t, *J* = 2.5 Hz). Anal. Calcd for $C_6H_{11}NO_5$: C, 40.67; H, 6.25; N, 7.90. Found: C, 40.62; H, 6.30; N, 7.77.

2,3-*O*-Isopropylidene-6-*O*-triphenylmethyl-L-gulono-*γ*-lactone (40). Compound **40** was synthesized similarly from **38**[19] as in the preparation of **33** from **31**; the yield was 97%. The colorless solid was crystallized from a mixture of chloroform, ether and hexane to give colorless crystals: mp 160∼162 °C; $[\alpha]^{24}_D$ +18.8° (*c* 0.31, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 1.23 and 1.39 (3H each, s), 2.60 (1H, d, *J* = 4.4 Hz), 3.30 (1H, dd, *J* = 3.9 and 10.0 Hz), 3.54 (1H, dd, *J* = 4.4 and 10.0 Hz), 4.13 (1H, m), 4.44 (1H, dd, *J* = 3.4 and 5.4 Hz), 4.67 (1H, dd, *J* = 3.4 and 7.3 Hz), 4.76 (1H, d, *J* = 5.4 Hz), 7.22−7.35 (9H, m), 7.43−7.48 (6H, m). Anal. Calcd for $C_{28}H_{28}O_6$: C, 73.02; H, 6.12. Found: C, 72.90; H, 6.19.

5-Azido-5-deoxy-2,3-*O*-isopropylidene-6-*O*-triphenylmethyl-D-mannono-*γ*-lactone (41). Compound **41** was synthesized similarly from **40** as in the preparation of **34** from **33**; the yield was 80%. The colorless solid was crystallized from a mixture of dichloromethane and diethyl ether to give colorless crystals: mp 90∼92 °C; $[\alpha]^{23}_D$ +11.3° (*c* 0.40, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 1.42 and 1.44 (3H each, s), 3.40 (1H, dd, *J* = 6.3 and 10.3 Hz), 3.59 (1H, dd, *J* = 2.4 and 10.3 Hz), 3.79 (1H, ddd, *J* = 2.4, 6.3 and 9.9 Hz), 4.36 (1H, dd, *J* = 3.4 and 9.9 Hz), 4.78 (1H, d, *J* = 5.2 Hz), 4.85 (1H, dd, *J* = 3.4 and 5.2 Hz), 7.22−7.35 (9H, m), 7.44−7.49 (6H, m). Anal. Calcd for $C_{28}H_{27}N_3O_5$: C, 69.26; H, 5.60; N, 8.65. Found: C, 69.52; H, 5.57; N, 8.79.

2,3-*O*-Isopropylidene-6-*O*-triphenylmethyl-D-mannono-*δ*-lactam (42). Compound **42** was synthesized similarly from **41** as in the preparation of **35** from **34**; the yield was 65%: $[\alpha]^{23}_D$ +13.7° (*c* 0.67, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 1.36 and 1.43 (3H each, s), 2.61 (1H, br s), 3.11 (1H, dd, *J* = 8.3 and 9.8 Hz), 3.45 (1H, dt, *J* = 3.4 and 8.3 Hz), 3.53 (1H, ddd, *J* = 3.4, 7.8 and 8.3 Hz), 3.65 (1H, dd, *J* = 3.4 and 9.8 Hz), 4.23 (1H, t, *J* = 7.8 Hz), 4.59 (1H, d, *J* = 7.8 Hz), 6.14 (1H, s), 7.23−7.35 (9H, m), 7.37−7.43 (6H, m); HRMS (FAB) calcd for $C_{28}H_{30}O_5N$ (MH^+) 460.2124, found 460.2128.

2,3-*O*-Isopropylidene-6-*O*-triphenylmethyl-D-talono-*δ*-lactam (43). Compound **43** was synthesized similarly from **41** as in the preparation of **36** from **34**; the yield was 77%: $[\alpha]^{24}_D$ +3.6° (*c* 0.69, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 1.40 and 1.51 (3H each, s), 2.33 (1H, s), 3.41−3.52 (3H, m), 3.92 (1H, br d, *J* = 3.4 Hz), 4.40 (1H, dd, *J* = 3.4 and 8.4 Hz), 4.55 (1H, d, *J* = 8.4 Hz), 5.83 (1H, s), 7.22−7.35 (9H, m), 7.37∼7.43 (6H, m). Anal. Calcd for $C_{28}H_{29}NO_5$: C, 73.18; H, 6.36; N, 3.04. Found: C, 73.12; H, 6.49; N, 2.90.

2,3-*O*-Isopropylidene-D-talono-*δ*-lactam (44). A solution of **43** (330 mg, 0.727 mmol) in ethanol (6.6 mL) was stirred with 10% Pd−C (330 mg) under hydrogen atmosphere at room-temperature overnight. After filtration, evaporation of the filtrate gave **44** (94 mg, 60%) as a colorless solid. The solid was crystallized from ethanol to give colorless needles: mp 200−201 °C; $[\alpha]^{25}_D$ −12.3° (*c* 0.64, MeOH); ^{1}H NMR (400 MHz, CD_3OD) *δ* 1.38 and 1.49 (3H each, s), 3.44 (1H, ddd, *J* = 2.0, 6.2 and 7.5 Hz), 3.75 (1H, dd, *J* = 7.5 and 11.0 Hz), 3.79 (1H, dd, *J* = 6.2 and 11.0 Hz), 4.07 (1H, dd, *J* = 2.0 and 3.7 Hz), 4.46 (1H, dd, *J* = 3.7 and 8.3 Hz), 4.55 (1H, d, *J* = 8.3 Hz). Anal. Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.44. Found: C, 50.01; H, 7.12; N, 6.31.

D-Mannono-*δ*-lactam (8). Compound **8** was synthesized similarly from **42** as in the preparation of **25** from **35**; the yield was 68%. The amorphous solid was crystallized from a mixture of ethanol and water to give colorless crystals: mp 169−171 °C (lit.[13] mp 169−170 °C; 165−169 °C; 170−172 °C); $[\alpha]^{22}_D$ +1.0° (*c* 1.0, H_2O) (lit.[13] +1.6° (H_2O); +0.9° (H_2O); +2.0° (H_2O)); ^{1}H NMR (400 MHz, D_2O) *δ* 3.20 (1H, dt, *J* = 3.9 and 6.3 Hz), 3.53 (1H, dd, *J* = 6.3 and 11.7 Hz), 3.65 (1H, dd, *J* = 3.9 and 11.7 Hz), 3.69 (1H, t, *J* = 6.3 Hz), 3.86 (1H, dd, *J* = 3.9 and 6.3 Hz), 4.17 (1H, d, *J* = 3.9 Hz).

D-Talono-*δ*-lactam (27). Compound **27** was synthesized similarly from **44** as in the preparation of **25** from **35**; the yield was 34%. The amorphous solid was crystallized from a mixture of methanol, ethanol and water to give colorless crystals: mp 151−153 °C; $[\alpha]^{24}_D$ +27.1° (*c* 0.27, H_2O); ^{1}H NMR (400 MHz, D_2O) *δ* 3.56 (1H, dt, *J* = 4.9 and 5.6 Hz), 3.65 (1H, dd, *J* = 4.9 and ∼12 Hz), 3.65 (1H, dd, *J* = 5.6 and ∼12 Hz), 4.02 (1H, dd, *J* = 2.9 and 4.4 Hz), 4.10 (1H, d, *J* = 4.4 Hz), 4.18 (1H, dd, *J* = 2.9 and 5.6 Hz). Anal. Calcd for $C_6H_{11}NO_5$: C, 40.67; H, 6.25; N, 7.90. Found: C, 40.28; H, 6.37; N, 7.66.

2,3-Di-*O*-methoxymethyl-5,6,-*O*-isopropylidene-D-galactono-*γ*-lactone (47). To a solution of **46**[26] (14.8 g, 67.8 mmol) in DMF (148 mL) were added *N*,*N*-diisopropylethylamine (94.5 mL, 54.2 mmol), chloromethylmethyl ether (30.9 mL, 40.7 mmol) and *tetra*-*n*-butylammonium iodide (57.6 g, 15.6 mmol) at room temperature, and the reaction mixture was stirred at 50 °C overnight. After dilution with chloroform, the solution was washed with water, dried over $MgSO_4$ and filtered. Evaporation of the filtrate gave an oil, which was subjected to column chromatography on silica gel. Elution with a mixture of toluene and acetone (2:1) gave **47** (13 g, 68%) as a colorless foam: $[\alpha]^{26}_D$ −11.8° (*c* 0.61, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 1.37 and 1.41 (3H each, s), 3.41 and 3.46 (3H each, s), 3.99 (1H, dd, *J* = 6.8 and 8.8 Hz), 4.11 (1H, dd, *J* = 6.8 and 8.8 Hz), 4.20 (1H, dd, *J* = 2.9 and 7.0 Hz), 4.38 (1H, dt, *J* = 2.9 and 6.8 Hz), 4.46 (1H, t, *J* = 7.0 Hz), 4.53 (1H, d, *J* = 7.0 Hz), 4.73 and 4.84 (2H, ABq, *J* = 6.8 Hz), 4.78 and 5.06 (2H, ABq, *J* = 6.8 Hz). Anal. Calcd for $C_{13}H_{22}O_8$: C, 50.97; H, 7.23. Found: C, 51.17; H, 7.23.

2,3-Di-*O*-methoxymethyl-D-galactono-*γ*-lactone (48). Compound **48** was synthesized similarly from **47** as in the preparation of **31** from **30**; the yield was 93%. The solid was crystallized from a mixture of chloroform and diethyl ether to give colorless crystals: mp 70−71 °C; $[\alpha]^{26}_D$ −24.3° (*c* 0.44, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 2.59 (1H, br s), 3.11 (1H, br d, *J* = 5.9 Hz), 3.41 and 3.46 (3H each, s), 3.70−3.85 (2H, m), 3.96 (1H, m), 4.28 (1H, m), 4.52−4.58 (2H, m), 4.72 and 4.85 (2H, ABq, *J* = 6.8 Hz), 4.78 and 5.04 (2H, ABq, *J* = 6.8 Hz). Anal. Calcd for $C_{10}H_{18}O_8$: C, 45.11; H, 6.81. Found: C, 45.41; H, 6.90.

2,3-Di-*O*-methoxymethyl-6-*O*-triphenylmethyl-D-galactono-*γ*-lactone (50). Compound **50** was synthesized similarly from **48** as in the preparation of **33** from **31**; the yield was 47%. The solid was crystallized from a mixture of chlororform and diethyl ether to give colorless crystals: mp 127−128 °C;

(36) Davis, B. G.; Hull, A.; Smith, C.; Nash, R. J.; Watson, A. A.; Winkler, D. A.; Griffiths, R. C.; Fleet, W. J. *Tetrahedron: Asym.* **1998**, *9*, 2947.

$[\alpha]^{25}_D$ −18.3° (*c* 0.57, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.14 (1H, d, *J* = 7.3 Hz), 3.25 (1H, dd, *J* = 6.1 and 9.4 Hz), 3.39 (1H, dd, *J* = 6.8 and 9.4 Hz), 3.38 and 3.44 (3H each, s), 4.00 (1H, m), 4.34 (1H, m), 4.50−4.56 (2H, m), 4.69 and 4.81 (2H, ABq, *J* = 6.8 Hz), 4.76 and 5.03 (2H, ABq, *J* = 6.8 Hz), 7.22−7.34 (9H, m), 7.40∼7.45 (6H, m). Anal. Calcd for $C_{29}H_{32}O_8$: C, 68.48; H, 6.34. Found: C, 68.62; H, 6.32.

5-Keto-2,3-di-*O*-methoxymethyl-6-*O*-triphenylmethyl-L-arabinohexonic acid γ-lactone (51). To a solution of **50** (0.923 g, 1.82 mmol) in dry CH_2Cl_2 (18 mL) was added Dess−Martin periodinane (1.38 g, 3.3 mmol) at room temperature, and the reaction mixture was stirred for 1 h. After addition of ether, the resulting precipitates were removed by filtration. The filtrate was evaporated to give an oil, which was subjected to column chromatography on silica gel. Elution with a mixture of toluene and acetone (10:1) gave **51** (0.744 g, 81%) as colorless oil: $[\alpha]^{23}_D$ +4.6° (*c* 0.93, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.29 and 3.39 (3H each, s), 4.12 and 4.05 (2H, ABq, *J* = 18.1 Hz), 4.43 (1H, d, *J* = 5.4 Hz), 4.47 (1H, t, *J* = 5.4 Hz), 4.66 and 4.89 (2H, ABq, *J* = 6.6 Hz), 4.68 (2H, s), 4.80 (1H, d, *J* = 5.4 Hz), 7.22−7.37 (9H, m), 7.42−7.50 (6H, m); HRMS (FAB) calcd for $C_{29}H_{30}O_8Na$ (MNa^+) 529.1838, found 529.1805.

2,3-Di-*O*-methoxymethyl-6-*O*-triphenylmethyl-L-altrono-γ-lactone (52). To a solution of **51** (6.58, 12.9 mmol) in a mixture of CH_2Cl_2 (77 mL) and methanol (38 mL) was added sodium borohydride (536 mg, 14.1 mmol) at −50 °C, and the reaction mixture was stirred at −50 °C for 1 h. After dilution with chloroform, the solution was washed with saturated NH_4Cl aqueous solution and water. The organic phase was dried over $MgSO_4$ and filtered. The filtrate was evaporated to give an oil. The oil was subjected to PTLC on silica gel developed with toluene-acetone (10:1) to give **52** (2.24 g, 34%) and **50** (1.12 g, 17%) as colorless oil.

52: $[\alpha]^{25}_D$ +27.8° (*c* 0.33, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.62 (1H, d, *J* = 5.8 Hz), 3.33 (1H, dd, *J* = 5.7 and 10.2 Hz), 3.37 (1H, dd, *J* = 4.3 and 10.2 Hz), 3.32 and 3.44 (3H each, s), 3.88 (1H, ddt, *J* = 4.3, 5.7 and 6.3 Hz), 4.38 (1H, dd, *J* = 5.0 and 6.3 Hz), 4.43 (1H, t, *J* = 5.0 Hz), 4.46 (1H, d, *J* = 5.0 Hz), 4.67 and 4.72 (2H, ABq, *J* = 6.4 Hz), 4.74 and 5.00 (2H, ABq, *J* = 6.4 Hz), 7.22−7.35 (9H, m), 7.40∼7.45 (6H, m). Anal. Calcd for $C_{29}H_{32}O_8$: C, 68.48; H, 6.34. Found: C, 68.23; H, 6.30.

5-Azido-5-deoxy-2,3-di-*O*-methoxymethyl-6-*O*-triphenylmethyl-D-galactono-γ-lactone (53). Compound **53** was synthesized similarly from **52** as in the preparation of **34** from **33**; the yield was 55%: $[\alpha]^{24}_D$ −31.1° (*c* 0.46, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.36 and 3.43 (3H each, s), 3.42 (1H, dd, *J* = 5.5 and 9.9 Hz), 3.57 (1H, dd, *J* = 8.0 and 9.9 Hz), 3.76 (1H, ddd, *J* = 2.2, 5.5 and 8.0 Hz), 4.23 (1H, dd, *J* = 2.2 and 7.2 Hz), 4.40 (1H, t, *J* = 7.2 Hz), 4.48 (1H, d, *J* = 7.2 Hz), 4.65 and 4.79 (2H, ABq, *J* = 6.8 Hz), 4.75 and 5.02 (2H, ABq, *J* = 6.8 Hz), 7.22−7.35 (9H, m), 7.41−7.46 (6H, m). Anal. Calcd for $C_{28}H_{28}O_6$: C, 73.02; H, 6.12. Found: C, 72.90; H, 6.19.

2,3-Di-*O*-methoxymethyl-6-*O*-triphenylmethyl-D-gluconо-δ-lactam (54). Compound **54** was synthesized similarly from **53** as in the preparation of **35** from **34**; the yield was 64%: $[\alpha]^{20}_D$ +71.2° (*c* 0.35, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 3.00 (1H, t, *J* = 9.2 Hz), 3.37−3.50 (2H, m), 3.43 and 3.44 (3H each, s), 3.64 (1H, t, *J* = 9.3 Hz), 3.96 (1H, dd, *J* = 2.9 and 9.2 Hz), 4.05 (1H, d, *J* = 9.3 Hz), 4.17 (1H, d, *J* = 1.0 Hz), 4.77 and 4.81 (2H, ABq, *J* = 6.6 Hz), 4.80 and 5.13 (2H, ABq, *J* = 6.8 Hz), 5.94 (1H, s), 7.22−7.35 (9H, m), 7.37−7.43 (6H, m). Anal. Calcd for $C_{29}H_{33}NO_7$: C, 68.62; H, 6.55; N, 2.75. Found: C, 68.24; H, 6.51; N, 2.74.

2,3-Di-*O*-methoxymethyl-6-*O*-triphenylmethyl-D-galactono-δ-lactam (55). Compound **55** was synthesized similarly from **53** as in the preparation of **36** and **34**; the yield was 67%: $[\alpha]^{26}_D$ +77.0° (*c* 0.35, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 2.30 (1H, m), 3.37−3.42 (2H, m), 3.40 and 3.45 (3H each, s), 3.59 (1H, dt, *J* = 2.4 and 6.4 Hz), 3.87 (1H, dd, *J* = 2.4 and 9.8 Hz), 4.11 (1H, m), 4.35 (1H, d, *J* = 9.8 Hz), 4.76 and 4.84 (2H, ABq, *J* = 6.8 Hz), 4.83 and 5.13 (2H, ABq, *J* = 6.4 Hz), 5.83 (1H, s), 7.22−7.35 (9H, m), 7.37−7.43 (6H, m). Anal. Calcd for $C_{29}H_{33}NO_7$: C, 68.62; H, 6.55; N, 2.75. Found: C, 68.45; H, 6.51; N, 2.77.

D-Glucono-δ-lactam (7). Compound **7** was synthesized similarly from **55** as in the preparation of **25** from **35**; the yield was 77%. The amorphous solid was crystallized from a mixture of ethanol and water to give colorless crystals: mp 205−207 °C (lit.[12] mp 202−204 °C; 204−205 °C; 197−199 °C; $[\alpha]^{22}_D$ +59.0° (*c* 0.39, H_2O) (lit.[12] +60° (H_2O); +57° (H_2O); +63° (H_2O)); ^1H NMR (D_2O, 400 MHz) δ 3.20−3.25 (1H, m), 3.55∼3.64 (3H, m), 3.67 (1H, dd, *J* = 2.9 and 12.2 Hz), 3.82−3.90 (1H, m).

D-Galactono-δ-lactam (9). Compound **9** was synthesized similarly from **54** as in the preparation of **25** from **35**; the yield was 69%. The amorphous solid was crystallized from a mixture of ethanol and water to give colorless crystals: mp 202−204 °C (lit.[16] mp 204−206 °C); $[\alpha]^{24}_D$ +120° (*c* 1.0, H_2O) (lit.[16] $[\alpha]^{23}_D$ +122.0° (H_2O)); ^1H NMR (D_2O, 400 MHz) δ 3.45−3.55 (2H, m), 3.57−3.65 (1H, m), 3.77 (1H, dd, *J* = 2.2 and 10.2 Hz), 4.04 (1H, d, *J* = 10.2 Hz), 4.06 (1H, dd, *J* = 2.2 and ∼3 Hz).

5,6-*O*-Isopropylidene-2,3-di-*O*-methoxymethyl-L-galactono-γ-lactone (57). Compound **57** was synthesized similarly from **56**[27] as in the preparation of **47** from **46**; the yield was 81%: $[\alpha]^{23}_D$ +13.7° (*c* 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 and 1.41 (3H each, s), 3.41 and 3.46 (3H each, s), 3.99 (1H, dd, *J* = 6.8 and 8.3 Hz), 4.12 (1H, dd, *J* = 6.8 and 8.3 Hz), 4.20 (1H, dd, *J* = 2.9 and 6.9 Hz), 4.38 (1H, dt, *J* = 2.9 and 6.8 Hz), 4.46 (1H, t, *J* = 6.9 Hz), 4.53 (1H, d, *J* = 6.9 Hz), 4.73 and 4.84 (2H, ABq, *J* = 6.6 Hz), 4.78 and 5.07 (2H, ABq, *J* = 6.8 Hz). Anal. Calcd for $C_{13}H_{22}O_8$: C, 50.97; H, 7.23. Found: C, 51.01; H, 7.23.

2,3-Di-*O*-methoxymethyl-L-galactono-γ-lactone (58). Compound **58** was synthesized similarly from **57** as in the preparation of **31** from **30**; the yield was 80%: $[\alpha]^{21}_D$ +25.3° (*c* 0.40, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.73 (1H, br s), 3.21 (1H, br s), 3.41 and 3.46 (3H each, s), 3.75 (1H, dd, *J* = 4.9 and 11.5 Hz), 3.81 (1H, dd, *J* = 6.4 and 11.5 Hz), 3.95 (1H, m), 4.28 (1H, m), 4.51∼4.58 (2H, m), 4.72 and 4.84 (2H, ABq, *J* = 6.8 Hz), 4.78 and 5.04 (2H, ABq, *J* = 6.8 Hz). Anal. Calcd for $C_{10}H_{18}O_8$: C, 45.11; H, 6.81. Found: C, 45.17; H, 7.11.

2,3-Di-*O*-methoxymethyl-6-*O*-triphenylmethyl-L-galactono-γ-lactone (60). Compound **60** was synthesized similarly from **58** as in the preparation of **33** from **31**; the yield was 85%: $[\alpha]^{26}_D$ +17.4° (*c* 0.28, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.09 (1H, d, *J* = 7.8 Hz), 3.26 (1H, dd, *J* = 6.5 and 9.4 Hz), 3.39 (1H, dd, *J* = 6.5 and 9.4 Hz), 3.39 and 3.45 (3H each, s), 4.01 (1H, dt, *J* = 1.8 and 6.5 Hz), 4.34 (1H, m), 4.50−4.55 (2H, m), 4.69 and 4.81 (2H, ABq, *J* = 6.8 Hz), 4.77 and 5.03 (2H, ABq, *J* = 6.8 Hz), 7.22−7.34 (9H, m), 7.4−7.45 (6H, m). Anal. Calcd for $C_{29}H_{32}O_8$: C, 68.48; H, 6.34. Found: C, 68.86; H, 6.41.

5-Azide-5-deoxy-2,3-di-*O*-methoxymethyl-6-*O*-triphenylmethyl-D-altrono-γ-lactone (61). Compound **61** was synthesized similarly from **60** as in the preparation of **34** from **33**; the yield was 73%: $[\alpha]^{24}_D$ −15.1° (*c* 0.36, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.25 and 3.43 (3H each, s), 3.39 (1H, dd, *J* = 7.3 and 10.0 Hz), 3.41 (1H, dd, *J* = 5.4 and 10.0 Hz), 3.74 (1H, dt, *J* = 5.4 and 7.3 Hz), 4.28 (1H, t, *J* = 5.4 Hz), 4.33 (1H, t, *J* = 5.4 Hz), 4.40 (1H, t, *J* = 5.4 Hz), 4.58 and 4.69 (2H, ABq, *J* = 6.6 Hz), 4.72 and 5.02 (2H, ABq, *J* = 6.8 Hz), 7.22−7.35 (9H, m), 7.42−7.48 (6H, m). Anal. Calcd for $C_{29}H_{31}N_3O_7$: C, 65.27; H, 5.85; N, 7.87. Found: C, 65.29; H, 5.67; N, 7.96.

2,3-Di-*O*-methoxymethyl-6-*O*-triphenylmethyl-D-altrono-δ-lactam (62). Compound **62** was synthesized similarly from **61** as in the preparation of **35** from **34**; the yield was 72%: $[\alpha]^{22}_D$ −23.5° (*c* 0.94, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 3.10 (1H, t, 10.3 Hz), 3.15 (1H, d, *J* = 8.3 Hz), 3.38 and 3.42 (3H each, s), 3.54−3.62 (2H, m), 3.86 (1H, dt, *J* = 2.4 and 8.3 Hz), 3.92 (1H, dd, *J* = 2.4 and 4.4 Hz), 4.15 (1H, d, *J* = 4.4 Hz), 4.68 and 4.96 (2H, ABq, *J* = 6.4 Hz), 4.73 and 4.76 (2H, ABq, *J* = 6.8 Hz), 6.04 (1H, s), 7.20−7.33 (9H, m), 7.37−7.44 (6H, m). Anal. Calcd for $C_{29}H_{33}NO_7$: C, 68.62; H, 6.55; N, 2.75. Found: C, 68.27; H, 6.26; N, 2.66.

2,3-Di-*O*-methoxymethyl-6-*O*-triphenylmethyl-D-idono-δ-lactam (63). Compound **63** was synthesized similarly from **61** as in the preparation of **36** from **34**; the yields were 30% for **63** and 52% for **62**:

63: $[\alpha]^{24}_D$ −18.3° (*c* 0.73, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.38 and 3.42 (3H each, s), 3.37 (1H, dd, *J* = 8.3 and 9.8 Hz), 3.47 (1H, dd, *J* = 3.9 and 9.8 Hz), 3.75 (1H, ddt, *J* = 2.0, 3.9 and 8.3 Hz), 3.89 (1H, dt, *J* = 3.9 and 5.4 Hz), 4.00 (1H, t, *J* = 5.4 Hz), 4.14 (1H, d, *J* = 5.4 Hz), 4.70 and 4.72 (2H, ABq, *J* = 6.8 Hz), 4.74 and 5.04 (2H, ABq, *J* = 6.6 Hz), 5.95 (1H, br s), 7.21−7.34 (9H, m), 7.38−7.45 (6H, m). Anal. Calcd for $C_{29}H_{33}NO_7$: C, 68.62; H, 6.55; N, 2.75. Found: C, 68.22; H, 6.43; N, 2.52.

D-Altrono-δ-lactam (28). Compound **28** was synthesized similarly from **62** as in the preparation of **25** from **35**; the yield was 88%. The solid was crystallized from a mixture of methanol, ethanol and water to give colorless crystals: mp 141−143 °C; $[\alpha]^{26}_D$ −33.7° (*c* 0.30, H_2O); ^{1}H NMR (400 MHz, D_2O) δ 3.41 (1H, dt, *J* = 3.0 and 5.3 Hz), 3.49 (1H, dd, *J* = 5.3 and 11.9 Hz), 3.54 (1H, dd, *J* = 5.3 and 11.9 Hz), 3.87 (1H, dd, *J* = 3.0 and 8.4 Hz), 4.01 (1H, t, *J* = 3.0 Hz), 4.05 (1H, d, *J* = 8.4 Hz). Anal. Calcd for $C_6H_{11}NO_5$: C, 40.67; H, 6.25; N, 7.90. Found: C, 40.25; H, 6.32; N, 7.62.

D-Idono-δ-lactam (29). Compound **29** was synthesized similarly from **63** as in the preparation of **25** from **35**; the yield was 63%. The amorphous solid was crystallized from a mixture of methanol, ethanol and water to give colorless crystals: mp 202∼204 °C; $[\alpha]^{26}_D$ +46.3° (*c* 0.31, H_2O); ^{1}H NMR (400 MHz, D_2O) δ 3.52 (1H, dt, *J* = 3.9 and 5.4 Hz), 3.61 (1H, dd, *J* = 3.9 and 11.7 Hz), 3.65 (1H, dd, *J* = 5.4 and 11.7 Hz), 3.80 (1H t, *J* = 8.1 Hz), 3.88 (1H, d, *J* = 8.1 Hz), 3.91 (1H, dd, *J* = 5.4 and 8.1 Hz). Anal. Calcd for $C_6H_{11}NO_5$: C, 40.67; H, 6.25; N, 7.90. Found: C, 40.29; H, 6.23; N, 7.76.

X-ray Structure Determination. Crystal data for **25**: $C_6H_{11}NO_5$, hexagonal crystal system, space group $P6_1$, a = 6.518(1) Å, c = 30.240(2) Å, Z = 6, μ = 12.12 cm^{-1}, D_{calc} = 1.586 g/cm^3, scan type = ω-2θ. X-ray diffraction experiments were carried out at 294K on a Rigaku AFC7R diffractometer with graphite-monochromated Cu Kα radiation. Data up to $2\theta_{max}$ = 120.2° on a total of 751 reflections were collected, and the 565 with $I > 2.00\ \sigma(I)$ were used in the calculations.

Crystal data for **26**: $C_6H_{11}NO_5$, orthorhombic crystal system, space group $P2_12_12_1$, a = 8.952(2) Å, b = 9.296(1) Å, c = 8.802(2) Å, Z = 4, μ = 12.27 cm^{-1}, D_{calc} = 1.606 g/cm^3, scan type = ω−2θ. X-ray diffraction experiments were carried out at 293K on a Rigaku AFC7R diffractometer with graphite monochromated Cu Kα radiation. Data up to $2\theta_{max}$ = 120.1° on a total of 679 reflections were collected, and the 651 with $I > 2.00\sigma(I)$ were used in the calculations.

Crystal data for **27**: $C_6H_{11}NO_5$, monoclinic crystal system, space group $P2_1$, a = 4.6656(7) Å, b = 10.0524(7) Å, c = 7.7257(5) Å, β = 98.532(7), Z = 2, μ = 12.54 cm^{-1}, D_{calc} = 1.642 g/cm^3, scan type = ω−2θ. X-ray diffraction experiments were carried out at 293K on a Rigaku AFC7R diffractometer with graphite-monochromated Cu Kα radiation. Data up to $2\theta_{max}$ = 120.1° on a total of 657 reflections were collected, and the 487 with $I > 2.00\sigma(I)$ were used in the calculations.

Crystal data for **9**: $C_6H_{11}NO_5$, orthorhombic crystal system, space group $P2_12_12_1$, a = 11.992(1) Å, b = 12.936(2) Å, c = 4.993(1) Å, Z = 4, μ = 11.61 cm^{-1}, D_{calc} = 1.519 g/cm^3, scan type = ω−2θ. X-ray diffraction experiments were carried out at 295K on a Rigaku AFC5S diffractometer with graphite-monochromated Cu Kα radiation. Data up to $2\theta_{max}$ = 126.1° on a total of 623 reflections were collected, and the 577 with $I > 2.00\sigma(I)$ were used in the calculations.

Crystal data for **28**: $C_6H_{11}NO_5$, orthorhombic crystal system, space group $P2_12_12_1$, a = 9.416(1) Å, b = 31.905(2) Å, c = 7.543(1) Å, Z = 12, μ = 11.90 cm^{-1}, D_{calc} = 1.558 g/cm^3, scan type = ω−2θ. X-ray diffraction experiments were carried out at 294K on a Rigaku AFC7R diffractometer with graphite-monochromated Cu Kα radiation. Data up to $2\theta_{max}$ = 120.0° on a total of 2003 reflections were collected, and the 1774 with $I > 2.00\sigma(I)$ were used in the calculations.

Crystal data for **29**: $C_6H_{11}NO_5$, orthorhombic crystal system, space group $P2_12_12_1$, a = 9.097(2) Å, b = 11.426(2) Å, c = 6.981(1) Å, Z = 4, μ = 12.39 cm^{-1}, D_{calc} = 1.622 g/cm^3, scan type = ω−2θ. X-ray diffraction experiments were carried out at 293K on a Rigaku AFC7R diffractometer with graphite-monochromated Cu Kα radiation. Data up to $2\theta_{max}$ = 120.1° on a total of 667 reflections were collected, and the 644 with $I > 2.00\sigma(I)$ were used in the calculations.

The structures were solved by the direct method using a teXan crystallographic software package. Hydrogen atoms were placed on the calculated positions. The refinement with anisotropic thermal parameters converged at R = 0.042 (Rw = 0.058) for **25** and at R = 0.042 (Rw = 0.061) for **26** and R = 0.038 (Rw = 0.050) for **28** and R = 0.050 (Rw = 0.074) for **30** and R = 0.072 (Rw = 0.101) for **31** and R = 0.050 (Rw = 0.068) for **32**. Atom scattering factors and dispersion corrections were taken from the International Tables.

Energy Minimization Calculations. The structures of inhibitors were optimized with PM3 in MOPAC, all equipped in a Tetronix CAChe system operated on a Power Macintosh 8100/80. The same parameter settings, which include keywords BFGS, RHF, and PRECISE, were employed throughout the calculations.

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Supporting Information Available: 400 MHz ^{1}H NMR Spectra of **9** and **25**−**29**) and X-ray structural information for **9** and **25**−**29**. This material is available free of charge via the Internet at http://www.pubs.acs.org.

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