IOOC Route to Substituted Chiral Pyrrolidines. Potential Glycosidase Inhibitors

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Branched-chain five-membered ring aza-sugar analogues, synthesized from amino acids by an intramolecular oxime−olefin cycloaddition reaction, the IOOC route, were found to be selective glycosidase inhibitors. The derivative 2,4(*S*)-di(hydroxymethyl)-3(*S*)-aminopyrrolidine, obtained from D-serine, was about 1 order of potency more active than its enantiomer obtained from L-serine.

Introduction

Alkaloids[1] and synthetic aza-sugars that structurally resemble monosaccharides, where the ring O is replaced by N, and display glycosidase inhibitory properties are of significant importance not only for the potential treatment of diabetes but also for chemotherapy of cancer and AIDS.[2] Recently reported syntheses of aza-sugars are based primarily on manipulations of natural sugars and their derivatives,[2,3] non-sugar-based syntheses,[4] enzyme-based synthetic methodologies,[5] and a few approaches using amino acids as starting materials.[6] Although hydroxylated aza-sugars have been studied intensively, amino-hydroxy aza-sugars, especially branched-chain aza-sugars, remain virtually unexplored.

We report here new approaches to substituted chiral pyrrolidines based on an intramolecular oxime−olefin cycloaddition (IOOC) route,[7] starting from naturally occurring amino acids and their enantiomers. These reactions have been shown to be convenient stereoselective routes to isoxazolidine derivatives and hence to amino alcohols. A preliminary communication describing this system has appeared.[8]

Results and Discussion

Two general paths, A and B, were explored for the synthesis of pyrrolidines **I** (Scheme 1). The planned synthetic approach to compounds **I** involved reduction of the N−O bond and deprotection of the respective bicyclic (**IIa**) or tricyclic (**IIb**) intermediates that contain a pyrrolidine skeleton fused to an isoxazolidine ring. These intermediates might be available via a key IOOC reaction from the unsaturated oximes **IIIa** or **IIIb**, accessible from the corresponding N,O-diprotected-α-amino esters, obtained from **IV**. In this retrosynthetic analysis, the five-membered ring aza-sugar derivatives **I** were selected, because it has been observed[9,5a−c] that pyrrolidine-type aza-sugars are frequently better glycosidase inhibitors than the corresponding piperidine-type analogues. Furthermore, this route enabled us to stereoselectively introduce an amino function into the pyrrolidine ring and to introduce either OH or SH groups into one of the side chains. Although many polyhydroxylated pyrrolidines have been studied and found to exhibit glyscosidase inhibition, little is known about the effect of substituting an NH_2 group for an OH on the pyrrolidine ring.

According to the retrosynthetic analysis (Scheme 1), derivatives **I** can be approached via noncyclic (path A) or cyclic (path B) intermediates. Compounds **2** were

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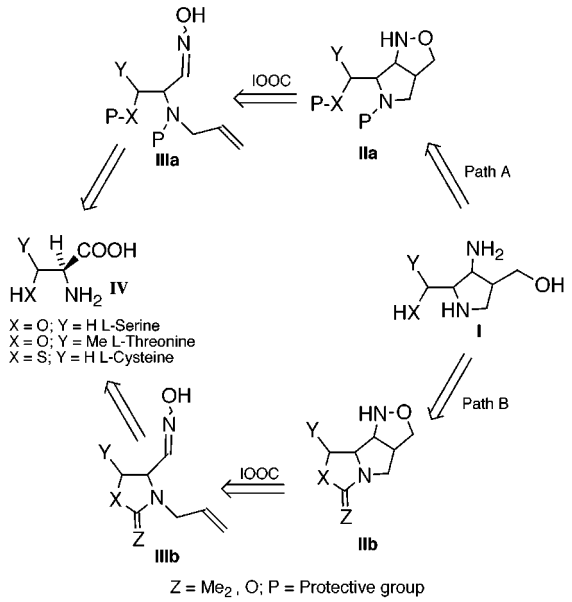
Scheme 1. IOOC-Based Retrosynthetic Analysis



prepared following path A by individual protection of the O and N groups. Attempted N-allylation of **2** by the method of Cheung and Benoiton[10] was unsuccessful, as even at 5 °C **2a** underwent β-elimination concomitant with N-allylation to give **3**. A second L-serine derivative, *N*-Boc-*O*-Bn-Ser[11] **2b** (Scheme 2), expected to be less susceptible to β-elimination when treated with allyl iodide under the same conditions, led to the desired intermediate **4**, accompanied by minor amounts of the corresponding β-elimination byproduct **3**. Esterification of **4** to give **5**, followed by reduction, led to the diprotected α-amino aldehyde **6**. Although **6** contains an allylic group and an aldehyde (as a precursor for an oxime), necessary for the key IOOC step, the many steps involved and the low yields obtained led us to set aside path A in favor of path B (Scheme 1). First, L-serine was converted to oxazolidine **7a**;[12] however, even under mild conditions (Me_3SiCl/NaI[13]) Boc removal caused total deprotection of **7a** to give **8**. Next, *N*-Cbz-oxazolidine **7b** was prepared, but hydrogenolysis of the Cbz group proceeded with concomitant N-deprotection and ring reduction to the *N*-isopropyl derivative **13**. The NMR spectra of **7a** and **7b** showed that these compounds were present as pairs of amide rotamers. Different catalysts and reaction conditions for Cbz removal were explored and $Rh/Al_2O_3/Et_2O$ was found to be the best chemoselective catalyst for Cbz reduction. With **9** in hand, it was expected that N-allylation followed by reduction would provide the desired α-amino aldehyde **11**. Although reaction of **9** with allyl bromide afforded **10**, subsequent treatment with DIBAL-H unfortunately again caused reductive ring opening to give **14**.[14]

In view of the difficulties encountered with protection of L-serine as oxazolidines **7**, the protection was switched to the more stable oxazolidin-2-ones **L-15a,b** derived from L-serine and L-threonine, respectively. Analogously, L-cysteine was converted to thiazolidin-2-one **L-15c** by treatment of **1** with triphosgene.[15] Subsequent N-allylation, DIBAL-H reduction, and oximation of oxazolidinones **L-15a,b** and thiazolidinone **L-15c** afforded the desired key intermediate ene-oximes **L-17a**−**c**. Reaction of **L-17a**−**c** under IOOC conditions (heating at 165 °C) gave the tricyclic **L-18a**−**c** as single diastereomers as indicated by chromatographic behavior and ^{1}H and ^{13}C NMR (Scheme 4). The structural and stereochemical assignments for the tricyclic **L-18** and the bicyclic amino alcohols **L-19**, as well as for the final pyrrolidines **L-21**, are based on ^{1}H and ^{13}C NMR and NOE data shown for **L-18a** and **L-19b** and NOESY of **L-21a** (Scheme 4). IOOC ring closure of **L-17a**−**c** to **L-18a**−**c** produced solely an *anti-syn* fused ring system consistent with the stereoselectivity of previous IOOC ring closures.[7] Even the threonine-derived product **L-18b** was formed stereospecifically. The isoxazolidine ring of **L-18a,b** underwent N−O bond reduction with Raney Ni to produce **L-19a,b**, but thiazolidin-2-one **L-18c** also underwent desulfurization to give pyrrolidine **20**. However, the alternative reduction of **L-18c** with Zn gave amino alcohol **L-19c**. Oxazolidin-2-ones **L-19a,b** and thiazolidin-2-one **L-19c** were rather stable toward subsequent aqueous hydrolytic conditions. O,N-deprotection to **L-21a**−**c** required overnight reflux in the presence of catalytic amounts of Cs_2CO_3[16] for **L-19a**,**b** and KOH[17] for **L-19c** (Scheme 3). The stereochemical 2*H*,3*H*-trans relationship in compounds **L-21** was unambiguously established on the basis of NMR data (Scheme 4).[18] Moreover, reaction of **L-21a** with phenylisothiocyanate gave the corresponding thiourea derivative **L-22**. The NMR spectrum of **L-22** showed very broad ^{1}H and ^{13}C NMR lines at room temperature due to the dynamics of the thiourea group, which could be sharpened by heating the sample to 320 K. Inspection of the spectrum of **L-22** by resolution enhancement revealed a very small (1 Hz) coupling for $J_{2,3}$, indicating the trans stereochemistry between these two H's,[19] which was further confirmed by NOE (Scheme 4). By analogy with **L-21a**, the stereochemistry of **L-21b,c** was assigned as shown.

In a preliminary communication,[8] we reported on the presence of a stereoisomer of **L-21a**. Further examination indicated that this species is a covalently bound adduct of **L-21a** and CO_2 (e.g., a carbamic acid derivative). The presence of analogous adducts was detected in **L-21b** and **D-21a** (see below) but was absent in the case of thiol derivative **L-21c**. The relative amount of this material could be reduced to virtually zero by heating the D_2O solution of **L-21a** used for NMR determination to 90 °C for about 1 h. Conversely, the concentration of this adduct could be increased considerably by exposing solid **L-21a** to a CO_2 atmosphere.

Because the substrates of glycosidases are the natural sugars that possess the D configuration, it may be expected that aza-sugar analogues that also possess this

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(18) Before a NOESY experiment was carried out, **L-21a** had been erroneously assigned in our preliminary communication[8] as the 2,3-*cis* isomer. The uncertainty in stereochemical assignment in five-membered rings and the utility of NOE in such systems has been pointed out.[19]
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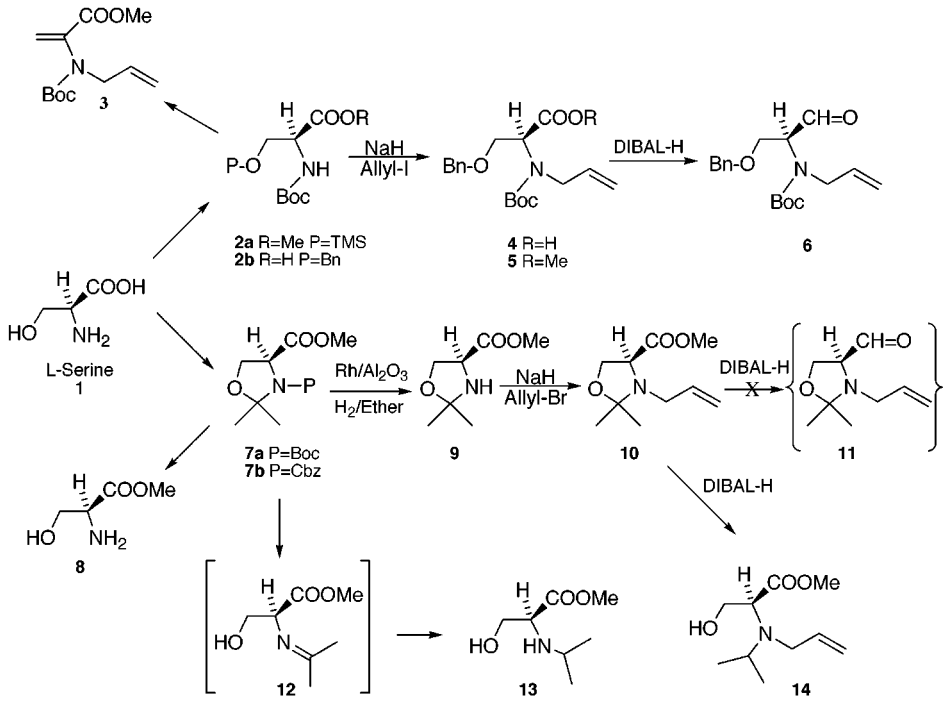
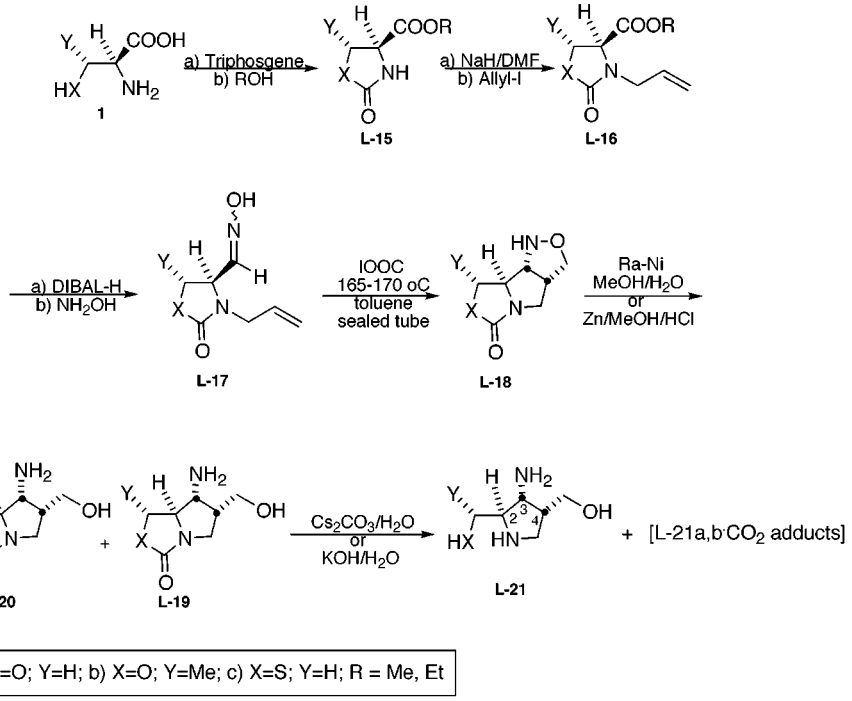
Scheme 2



Scheme 3



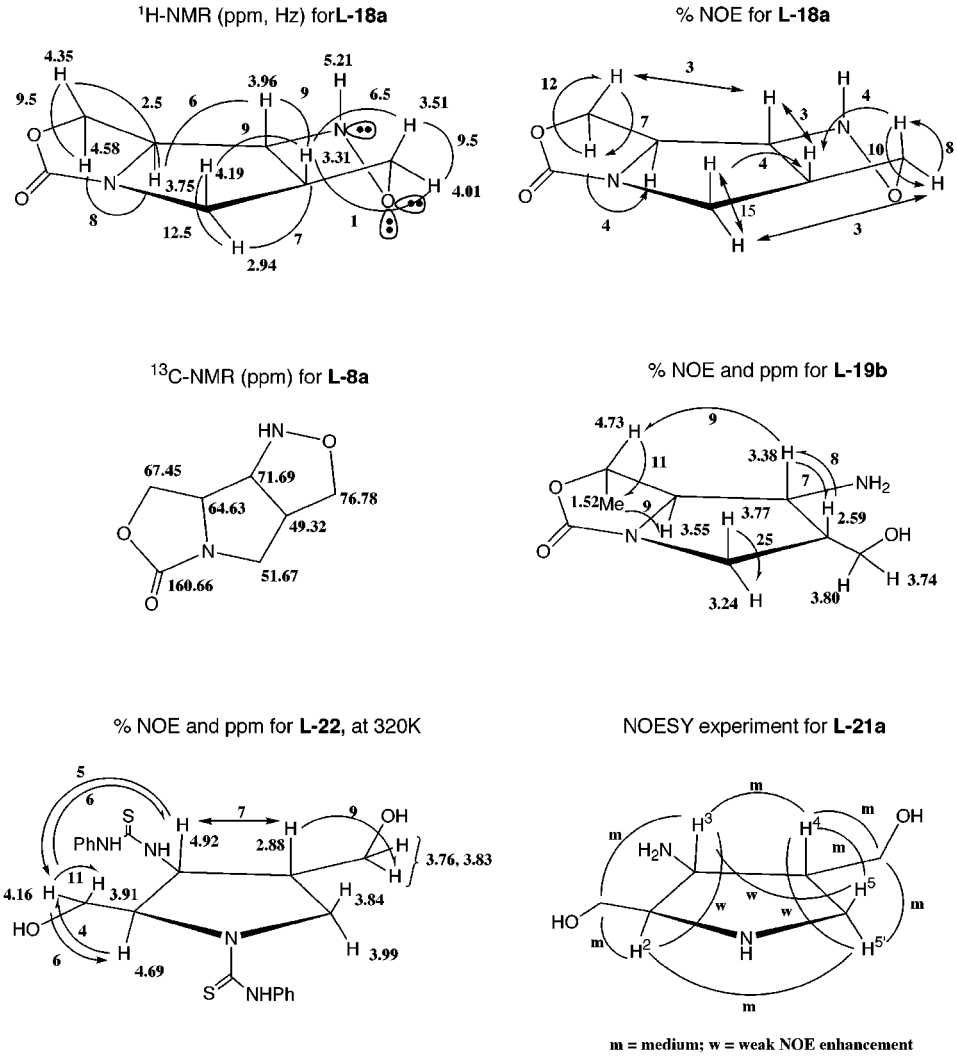
a) X=O; Y=H; b) X=O; Y=Me; c) X=S; Y=H; R = Me, Et

D configuration may be better inhibitors than their enantiomers. The stereochemistry of the aza-sugar analogues described above is L, because they were prepared from the corresponding L-amino acids. To be able to compare the biological activity of the enantiomers, we chose to prepare also the D enantiomer of compound **L-21a**; the latter was found to be the most active of this family of branch-chained aza-sugar analogues (vide infra). Because the overall yield of **L-21a** prepared as described in Scheme 3 was quite low, we considered examining a slightly altered approach to the synthesis of its D enantiomer. The synthetic steps up to **D-18** were as shown in Scheme 3. At this point, the sequence of deprotection steps was switched so that initially the carbamate group was hydrolyzed to give the bicyclic isoxazolidine **D-23**, followed by subsequent reduction of the N−O bond to give the desired enantiomer **D-21a** (Scheme 5). Although a very clean reduction of **D-23** to **D-21a** was obtained, the hydrolysis of **D-18** to **D-23** was found to be more difficult than that of **L-19a** to **L-21a**, so that the overall yield of **D-21a** was similar to that of its enantiomer.

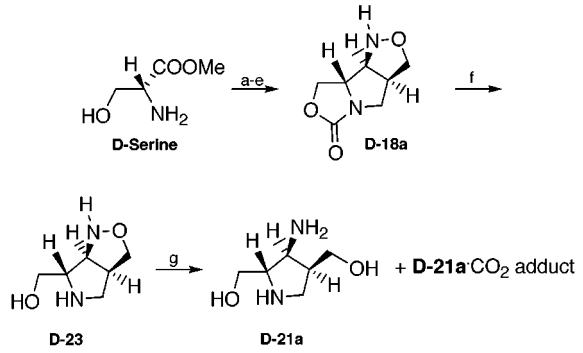
Biological Activity

In many recent examples, aza-sugars and their analogues have shown glycosidase inhibition.[1,2] It was pointed

Scheme 4



Scheme 5



a) Triphosgene; b) NaH/DMF/AllylI; c) DIBAL-H; d) NH_2OH; e) IOOC 165-170°C/toluene/sealed tube; f) Cs_2CO_3/H_2O; g) Ra-Ni/MeOH/H_2O

out that, because pyrrolidine sugar analogues[5a−c,9,20a] and piperidine sugar analogues[20b,c] are very good mimics of the transition state for glycoside hydrolysis with respect to both the flattened half-chair conformation and the charge distribution, they should bind tightly to the enzyme and thus make good inhibitors. Furthermore, it was suggested[20b] that these factors provide the major contribution to binding of some inhibitors, and the position of the hydroxyl substituents is less important. Pyrrolidine sugar analogues **21** contain a hydroxymethylene substituent at C-4 instead of a hydroxyl group and thus could be considered "branched-chain aza-sugar" analogues with potential inhibitory activity. In addition, an amino group was introduced in place of one of the hydroxy substituents, which is isosteric and is expected to maintain hydrogen bonding. One of these sugar analogues, **L-21c**, was further modified by replacing another hydroxy group by a thiol. The three sugar analogues **L-21a**−**c** were derived from the natural L−α-amino acids, thus bearing *R* absolute configurations at their C-2 and C-4 positions. The fourth analogue, **D-21a**, is the mirror image of **L-21a**, as it was synthesized from *(R)*-serine. Thus, whereas the former three compounds are analogous to L sugars, the latter resembles the natural D sugar stereochemistry. In light of the suggested limited importance of the hydroxy substitution pattern, we hoped that these modifications would not significantly affect binding. Thus, the four branched-chain sugar analogues **L-21a**−**c** and **D-21a** were tested as potential reversible inhibitors of four different glycosidases. Compound **L-21a** was tested as an inhibitor for both α- and

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Table 1. Inhibitory Activity of Aza-Sugar Analogues

	inhibitors			
enzyme	**D-21a**	**L-21a**	**L-21b**	**L-21c**
α-glucosidase	$K_i = 0.018$ mM	$K_i = 0.15$ mM	$K_i = 0.24$ mM	ni[a]
β-glucosidase	nd[d]	ni[b]	$IC_{50} = 1.22$ mM[e]	$IC_{50} = 1.12$ mM[f]
α-galactosidase	nd	ni[c]	nd	ni[a]
β-galactosidase	nd	ni[c]	nd	ni[a]

[a] ni; no inhibition observed: up to [I] = 1.12 mM. [b] Up to [I] = 4.0 mM. [c] Up to [I] = 1.4 mM. [d] nd; not determined. [e] At [S] = 1.1 mM. [f] At [S] = 0.54 mM.

β-glucosidases. It did not inhibit β-glucosidase to any extent with inhibitor concentrations of up to 4 mM. On the other hand, **L-21a** inhibited α-glucosidase with an apparent $K_i = 0.15$ mM. Compound **L-21b**, derived from L-threonine and bearing an additional methyl substituent at the C-2 side chain, exhibited moderate inhibition of both α- and β-glucosidases. Compound **L-21c**, the thio analogue derived from L-cysteine, exhibited a different selectivity by inhibiting β-glucosidase while having no effect on α-glucosidase. Compounds **L-21a** and **L-21c** failed to inhibit α- and β-galactosidases. Because compounds **L-21a**−**c** are L sugar analogues, we compared the inhibitory activity of **D-21a**, the analogue derived from *(R)*-serine, toward α-glucosidase with that of its enantiomer **L-21a**. (It should be noted that as enantiomers all three chiral centers are of opposite configuration, not only the one corresponding to the sugar C-4 position). As might be expected, **D-21a** inhibited α-glucosidase an order of magnitude better than **L-21a** ($K_i = 0.018$ mM). These results are summarized in Table 1.

The results described above support the importance of the flattened ring conformation and the positive charge in the differential stabilization of the transition state of the glycosidase catalytic activity. Although comparison of K_i values of these inhibitors with K_m [21] values of glucosidase substrates suggests that the extensive modifications in these compounds led to inferior interactions with the enzyme, possibly due to a lack of similarity in their substitution patterns or to steric hindrance, the present results do indicate that the newly synthesized branched-chain aza-sugar analogues **21** act as selective glucosidase inhibitors.

Experimental Section

^{1}H and ^{13}C NMR spectra were obtained at 200 or 300 MHz and 50 or 75 MHz, respectively. NOE and NOESY experiments were carried out at 600 MHz. For chloroform solutions, chemical shifts are expressed in ppm downfield from Me_4Si as internal standard; for D_2O solutions, the HOD peak was taken as δ 4.80 (^{1}H spectra), or the peak of a small amount of added MeOH was taken as δ 49.50 (^{13}C). Multiplicities in the ^{13}C NMR spectra were determined by off-resonance decoupling. Mass spectra were obtained in CI (chemical ionization), DCI (desorption chemical ionization), EI (electron impact) or HRMS, (high-resolution) modes. The progress of the reactions was monitored by TLC on silica gel or alumina. Flash chromatography was carried out on silica gel (32−63 μm).

2(*S*)-*tert*-Butoxycarbonylamino-3-trimethylsilanyloxypropionic Acid Methyl Ester (2a). *N*-Boc serine methyl ester (1.5 g, 6.8 mmol), Et_3N (1.14 mL, 8.2 mmol), DMAP (0.28 g, 2.25 mmol), and Me_3SiCl (1 mL, 7.5 mmol) were stirred in CH_2Cl_2 (10 mL) under N_2 at room temperature. After 3 days, the reaction mixture was poured into water (10 mL), the organic phase was separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated to give **2a** as a yellow oil (1.23 g, 62%): ^{1}H NMR ($CDCl_3$) δ 0.70 (s, 9H), 1.45 (s, 9H), 3.78 (s, 3H), 3.80 (dd, 1H, *J* = 8, 3 Hz), 4.00 (dd, 1H, *J* = 8, 3 Hz), 4.38 (m, 1H), 5.40 (bd, 1H); ^{13}C NMR ($CDCl_3$) δ −0.7 (s), 28.4 (s), 52.2 (q), 55.6 (d), 63.1 (t), 80.3 (s), 155.7 (s), 171.2 (s); MS (CI) (NH_3) *m/z* 292 (MH^+, 5), 236, 192.

***N*-Boc-*O*-benzyl-L-serine (2b).** This compound was prepared as described[11] but was isolated as the free acid (22%): ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 3.73 (dd, 1H, *J* = 9, 3 Hz), 3.91 (dd, 1H, *J* = 9, 2 Hz), 4.43 (m, 1H), 4.47 (s, 2H), 5.50 (d, 1H), 7.20−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.3 (s), 54.2 (d), 70.2 (t), 73.3 (t), 79.8 (s), 127.6, 127.7, 128.3, 133.2 (*Ph*), 155.6 (s), 173.9 (s); MS (CI) (isobutane) *m/z* 296 (MH^+, 95), 240.

***N*-Boc-*N*-allyl-Δ-alanine Methyl Ester (3)**. To a stirred solution of **2a** (0.51 g, 1.75 mmol) in dry THF (5 mL) was added NaH (60%, 0.13 g, 3.3 mmol) at 0 °C. After the evolution of H_2 ceased, allyl iodide (1.2 mL, 13 mmol) in THF (5 mL) was added. The reaction mixture was stirred at 25 °C for 24 h or at 5 °C for 72 h and then filtered. The filtrate was diluted with EtOAc (10 mL) and washed with aqueous $Na_2S_2O_3$ (20 mL), and the organic layer separated, dried ($MgSO_4$), and evaporated to give **3** as a yellow oil (0.2 g, 45%): ^{1}H NMR ($CDCl_3$) δ 1.42 (bs, 9H), 3.78 (s, 3H), 4.10 (dt, 2H, *J* = 6, 1 Hz), 5.15 (dq, 1H, *J* = 10, 1 Hz), 5.18 (dq, 1H, *J* = 18, 1 Hz), 5.40 (s, 1H), 5.83 (s, 1H), 5.85 (ddd, 1H, *J* = 18, 10, 6 Hz); ^{13}C NMR ($CDCl_3$) δ 28.2 (s), 46.0 (t), 52.3 (q), 81.2 (s), 116.6 (t), 116.8 (d), 133.9 (s), 135.4 (d), 153.6 (s), 169.8 (s); MS (CI) (NH_3) *m/z* 242 (MH^+, 63), 259.

***N*-Boc-*N*-allyl-*O*-benzyl-L-serine (4).** To a stirred solution of **2b** (1 g, 3.39 mmol) in dry THF (11 mL) was added NaH (60%, 0.41 g, 10 mmol) at 0 °C. After the evolution of H_2 ceased, allyl iodide (2.5 mL, 27 mmol) was added. The reaction mixture was stirred at 5 °C for 72 h, and then the solvent was removed to give a white residue which was dissolved in water and acidified to pH 3 (3 N HCl). The yellow oil obtained was separated from the solution and was extracted with EtOAc (2 × 10 mL); the organic phase washed with aqueous $Na_2S_2O_3$ (10 mL), dried ($MgSO_4$), and evaporated to give an oil (0.85 g, 75%): ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 3.80−4.00 (m, 2H), 4.05 (dt, 1H, *J* = 15, 0.5 Hz), 4.10 (dt, 1H, *J* = 15, 1 Hz), 4.58 (s, 2H), 4.60 (bm, 1H), 5.10−5.20 (m, 2H), 5.80−6.00 (m, 1H), 7.20−7.40 (m, 5H); MS (CI) (isobutane) *m/z* 336 (MH^+, 12).

***N*-Boc-*N*-allyl-*O*-benzyl-L-serine Methyl Ester (5).** To a stirred solution of **4** (0.70 g, 2 mmol) in DMF (5 mL) was added K_2CO_3 (0.31 g, 2.24 mmol) at 0 °C. After 10 min of stirring, MeI (0.25 mL, 4 mmol) was added; stirring continued for 30 min at 0 °C and for an additional hour at room temperature. The reaction mixture was filtered, the filtrate was partitioned between EtOAc (20 mL) and water (10 mL), and the organic phase was washed with brine (10 mL), separated, dried ($MgSO_4$), and evaporated to give a yellow oil (0.3 g, 43%): ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 3.80 (s, 3H), 3.80−4.00 (m, 2H), 4.05 (dt, 1H, *J* = 15, 0.5 Hz), 4.10 (dt, 1H, *J* = 15, 1 Hz), 4.56 (s, 2H), 4.60 (bs, 1H), 5.10−5.20 (m, 2H), 5.80−6.00 (m, 1H), 7.20−7.40 (m, 5H).

***N*-Boc-*N*-allyl-*O*-benzyl-L-serinal (6).** To a solution of **5** (0.3 g, 0.85 mmol) in dry toluene (5 mL), cooled to −78 °C under N_2, was added dropwise DIBAL-H in toluene (1.5 M, 2 mL, 3 mmol), while the temperature was maintained below −75 °C. After 2 h, MeOH (1 mL) was added followed by Et_2O (10 mL) and saturated aqueous sodium potassium tartrate (10 mL). Vigorous stirring was continued for ca. 2 h until all the

(21) Fleet, G. W. J.; Nicholas, S. J.; Smith, P. W.; Evans, S. V.; Fellows, L. E.; Nash, R. J. *Tetrahedron Lett.* **1985**, *26*, 3127.

solids dissolved. The organic layer was separated, dried ($MgSO_4$), and evaporated to give **6a** as a yellow oil (0.1 g, 37%): ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 3.80−4.00 (m, 2H), 4.10 (dt, 2H, J = 15, 1 Hz), 4.40 (m, 1H), 4.50 (s, 2H), 5.00−5.20 (m, 2H), 5.80−6.00 (m, 1H), 7.15−7.40 (m, 5H), 9.52 (bd, 1H).

N-Boc-4(*S*)-carbomethoxy-2,2-dimethyloxazolidine (7a) and N-Cbz-4(*S*)-carbomethoxy-2,2-dimethyloxazolidine (7b). Boc-serine, Cbz-serine, and their methyl esters were prepared by standard procedures.[12,22] Esterification of Cbz-L-serine with MeI was carried out in 75% yield with K_2CO_3 instead of $NaHCO_3$, without the need of chromatography. **7a** was obtained as a pale yellow oil (50%): bp 70 °C/0.5 Torr; ^{1}H NMR ($CDCl_3$) for the major rotamer δ 1.42 (s, 9H), 1.54 (s, 3H), 1.67 (s, 3H), 3.76 (s, 3H), 4.04 (dd, 1H, J = 9, 3 Hz), 4.16 (dd, 1H, J = 9, 7 Hz), 4.39 (dd, 1H, J = 7, 3 Hz); for the minor rotamer 1.50 (s, 9H), 1.50 (s, 3H), 1.64 (s, 3H), 3.76 (s, 3H), 4.06 (dd, 1H, J = 9, 2 Hz), 4.14 (dd, 1H, J = 9, 7 Hz), 4.49 (dd, 1H, J = 7, 2 Hz); ^{13}C NMR ($CDCl_3$) for major rotamer δ 24.4 (q), 25.0 (q), 28.3 (s), 52.2 (q), 59.3 (d), 66.3 (t), 80.3 (s), 95.1 (s), 151.2 (s), 171.6 (s, 3H); for minor rotamer δ 25.24 (q), 26.04 (q), 28.3 (s), 52.4 (q), 59.3 (d), 66.0 (t), 80.9 (s), 94.4 (s), 152.1 (s), 171.2 (s); MS (CI) (NH_3) m/z 277 (MNH_4^+, 48), 260; The *N*-Cbz derivative **7b** was obtained as a yellow oil in 86% yield after distillation: bp 128−130 °C/0.02 Torr; $[\alpha]^{20}_D$ −40.86° (c = 0.046, $CHCl_3$); ^{1}H NMR ($CDCl_3$) for the major rotamer δ 1.56 (s, 3H), 1.71 (s, 3H), 3.64 (s, 3H), 4.09 (dd, 1H, J = 9, 3 Hz), 4.17 (dd, 1H, J = 9, 7 Hz), 4.48 (dd, 1H, J = 7, 3 Hz), 5.04 (d, 1H, J = 12 Hz), 5.17 (d, 1H, J = 12 Hz), 7.30−7.40 (m, 5H); for the minor rotamer δ 1.49 (s, 3H), 1.65 (s, 3H), 3.77 (s, 3H), 4.17 (dd, 1H, J = 9, 6.5), 4.19 (dd, 1H, J = 9, 2.5 Hz), 4.56 (dd, 1H, J = 6.5, 2.5 Hz), 5.17 (d, 1H, J = 12 Hz), 5.21 (d, 1H, J = 12 Hz), 7.30−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ for the major rotamer 24.1 (q), 24.9 (q), 52.3 (q), 58.8 (d), 66.5 (t), 66.7 (t), 95.4 (s), 127.7, 127.9, 128.3, 136.3 (*Ph*), 151.7 (s), 171.1 (s); for the minor rotamer δ 25.2 (q), 26.0 (q), 52.4 (q), 59.5 (d), 66.1 (t), 67.5 (t), 94.8 (s), 127.9, 128.1, 128.6, 136.0 (*Ph*), 152.8 (s), 170.9 (s); MS (CI) (NH_3) m/z 311 (MNH_4^+, 95), 294. HRMS (DCI) calcd for $C_{15}H_{19}NO_5$ + H 294.1341, found 294.1331.

4(*S*)-Carbomethoxy-2,2-dimethyloxazolidine (9). A solution of **7b** (2 g, 6.8 mmol) in dry Et_2O (100 mL) was hydrogenated at 1 atm over 5% Rh/Al_2O_3 for 18 h. The catalyst was filtered, and the filtrate was evaporated under reduced pressure to give **9** as a colorless liquid (0.91 g, 84%): bp 40 °C/1 Torr; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.48 (s, 3H), 2.50 (bs, 1H, NH), 3.77 (t, 1H, J = 8 Hz), 3.78 (s, 3H), 4.05 (dd, 1H, J = 14, 8 Hz), 4.11 (dd, 1H, J = 14, 8 Hz); ^{13}C NMR ($CDCl_3$) δ 26.0 (q), 26.7 (q), 52.4 (q), 59.7 (d), 67.7 (t), 96.2 (s), 172.9 (s); MS (CI) (NH_3) m/z 160 (MH^+, 100), 144.

***N*-Allyl-4(*S*)-carbomethoxy-2,2-dimethyloxazolidine (10).** A heterogeneous mixture of **9** (0.98 g, 6.2 mmol), allyl bromide (0.6 mL, 6.9 mmol), diisopropylethylamine (1 mL, 5.7 mmol), K_2CO_3 (0.95 g, 6.9 mmol), and NaI (7 mg) in dry MeCN was refluxed for 4 h. The mixture was filtered, and the filtrate was evaporated to give a dark oil that was washed with Et_2O (15 mL). The organic layer was decanted, the solvent was evaporated, and the residue was distilled to give **10** as a colorless liquid (0.69 g, 56%): bp 85 °C/20 Torr; ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 3H), 1.38 (s, 3H), 3.19 (ddt, J = 14, 7, 1 Hz, 1H), 3.45 (ddt, J = 14, 8, 1 Hz, 1H), 3.65 (dd, 1H, J = 8, 5 Hz), 3.70 (s, 3H), 3.94 (dd, 1H, J = 8, 5 Hz), 4.11 (t, 1H, J = 8 Hz), 5.07 (dq, 1H, J = 10, 1 Hz), 5.18 (dq, 1H, J = 17, 1 Hz), 5.85 (dddd, 1H, J = 17, 10, 8, 7 Hz); MS (CI) (NH_3) m/z 200 (MH^+, 65), 160.

***N*-Isopropyl-L-serine Methyl Ester (13).** A solution of **7b** (0.5 g, 1.7 mmol) in MeOH (45 mL) was hydrogenated at 1 atm over 5% Pd/C for 4 h. The catalyst was filtered, and the filtrate was evaporated under reduced pressure to give **3** as a yellow oil (0.174 g, 63%): ^{1}H NMR ($CDCl_3$) δ 1.05 (d, 3H, J = 6 Hz), 1.10 (d, 3H, J = 6 Hz), 2.40 (bs), 2.83 (septet, 1H, J = 6 Hz), 3.48 (dd, 1H, J = 6.5, 4 Hz), 3.54 (dd, 1H, J = 10.5, 6.5 Hz), 3.75 (s, 3H), 3.76 (dd, 1H, J = 10.5, 4 Hz);^{13}C NMR ($CDCl_3$) δ 22.0 (q), 23.2 (q), 47.4 (d), 51.9 (q), 60.2 (d), 62.8 (t), 173.8 (s); MS (EI) m/z 162 (M^+, 1), 130, 102.

***N*-Allyl-*N*-isopropyl-L-serine Methyl Ester (14).** Compound **10** was reduced as described for **6** to give **14** as a yellow oil (60%): bp 62 °C/0.02 Torr; ^{1}H NMR ($CDCl_3$) δ 1.00 (d, 3H, J = 6 Hz), 1.11 (d, 3H, J = 6 Hz), 3.20 (septet, 1H, J = 6 Hz), 3.00−3.20 (m, 1H), 3.35−3.45 (m, 1H), 3.38 (dd, 1H, J = 6.5, 4 Hz), 3.60 (dd, 1H, J = 10.5, 6.5), 3.65 (dd, 1H, J = 10.5, 4 Hz), 3.70 (s, 3H), 5.07 (dq, 1H, J = 10, 1 Hz), 5.20 (dq, 1H, J = 17, 1 Hz), 5.78 (dddd, 1H, J = 17, 10, 8, 7 Hz); MS (CI) (isobutane) m/z 202 (MH^+, 100).

General Procedure for the Synthesis of Oxazolidin-2-ones L-15 from L-1 Amino Acids or their Respective Esters. Procedure A: Compounds **L-15** were obtained from the amino acids **1** as described.[15] **Procedure B:** To a solution of a methyl or ethyl ester of **1** (64 mmol) and K_2CO_3 (13.8 g, 0.1 mol) in water (65 mL) at room temperature was added triphosgene (7.6 g, 25.6 mmol) in toluene (65 mL), and the mixture was stirred for 3 h. The solvents were concentrated to dryness, and the solid residue was triturated with warm EtOAc (2 × 40 mL). The solution was filtered and evaporated, and the residue was distilled to give **15**.

4(*S*)-Carbomethoxy-oxazolidine-2-ones (L-15a).[15] This compound was obtained in 47% by Procedure A and in 62% from L-serine methyl ester by Procedure B.

4(*R*)-Carbomethoxy-oxazolidine-2-ones (D-15a). An ice-cold solution of D-serine methyl ester (6.66 g, 42.8 mmol), Et_3N (18 mL, 3 equiv) and triphosgene (6.35 g, 0.5 equiv) in dry CH_2Cl_2 (260 mL) was stirred for 2 h, followed by additional stirring at room temperature for 48 h. The mixture was then filtered through a silica gel column, and the filtrate was evaporated to give **D-15a** in ca. quantitative yield. $[\alpha]^{20}_D$ +14.18° (c = 0.013 CH_2Cl_2). The ^{1}H and ^{13}C NMR spectra were identical to those of its L-enantiomer.

4(*S*)-Carbomethoxy-5(*R*)-methyl-oxazolidine-2-one (L-15b).[15] Obtained (56%) by Procedure A.

4(*S*)-Carbomethoxythiazolidine-2-one (L-15c).[15] Obtained (66%) by Procedure A.

4(*S*)-Carboethoxythiazolidine-2-one (L-15c′). This compound was obtained as a clear yellow oil in 68% by Procedure B from L-cysteine ethyl ester hydrochloride: bp 150−152 °C/0.3 Torr; $[\alpha]^{20}_D$ −16.48° (c = 0.018, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3H, J = 7 Hz), 3.62 (dd, 1H, J = 11, 5 Hz), 3.71 (dd, 1H, J = 11, 8 Hz), 4.28 (q, 2H, J = 7 Hz), 4.44 (ddd, 1H, J = 8, 5, 1 Hz), 6.61(bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 31.8 (t), 56.1 (d), 62.4 (t), 170.0 (s), 174.6 (s); MS (CI) (NH_3) m/z 193 (MNH_4^+, 100), 176; HRMS (CI CH_4) calcd for $C_6H_9NO_3S$ + H 176.0381, found 176.0284.

***N*-Allylation of Oxazolidine-2-ones 15 to 16. General Procedure.** To a stirred solution of **15** (40 mmol) in dry DMF (60 mL) at 0 °C was added NaH (60%, 1.86 g, 46.5 mmol). After the evolution of H_2 ceased, allyl iodide (40 mmol) was added. The reaction mixture was stirred at room temperature for 24 h and was then partitioned between EtOAc (200 mL) and aqueous $Na_2S_2O_3$ (150 mL). The organic layer was separated, and the aqueous phase was extracted again with EtOAc (200 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, and the residue was chromatographed (hexanes−EtOAc) to give **16**.

***N*-Allyl-4-carbomethoxy-oxazolidine-2-ones L-16a and D-16a.** The respective enantiomers **16a** were obtained from **15a** (chromatography, hexane−EtOAc 1:1) as a pale yellow oil (50%): bp 110−112 °C/0.2 Torr; **L-16a** $[\alpha]^{20}_D$ −14.38° (c = 0.014, $CHCl_3$) and **D-16a** $[\alpha]^{20}_D$ +10.51° (c = 0.075, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.74 (ddt, 1H, J = 15, 8, 0.5 Hz), 3.81 (s, 3H), 4.25 (ddt, 1H, J = 15, 5, 1 Hz), 4.34 (dd, 1H, J = 11, 4 Hz), 4.36 (dd, 1H, J = 10, 4 Hz), 4.49 (dd, 1H, J = 11, 10 Hz), 5.24 (dq, 1H, J = 17, 1 Hz), 5.26 (dq, 1H, J = 8, 1 Hz), 5.77 (dtd, 1H, J = 17, 8, 5 Hz); ^{13}C NMR ($CDCl_3$) δ 46.1 (t), 52.7 (q), 56.3 (d), 64.3 (t), 119.4 (t), 131.4 (d), 157.5 (s), 170.0 (s); MS (CI) (NH_3) m/z 203 (MNH_4^+, 100), 186 (MH^+, 50); HRMS (CI CH_4) calcd for $C_8H_{11}NO_4$ + H 186.0766, found 186.0810.

***N*-Allyl-4(*S*)-carbomethoxy-5(*R*)-methyloxazolidine-2-one (L-16b).** Obtained from **L-15b** (chromatography, hexane−

(22) Hwang, D.-R.; Helquist, P.; Shekhani, M. S. *J. Org. Chem.* **1985**, *50*, 1264.

EtOAc 2:1, then hexane−EtOAc 1:1) as a yellow oil (75%): bp 100−102 °C/0.1 Torr; $[\alpha]^{20}_D$ +31.57° (*c* = 0.019, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.51 (d, 3H, *J* = 6 Hz), 3.72 (ddt, 1H, *J* = 15, 8, 0.5 Hz), 3.80 (s, 3H), 3.90 (d, 1H, *J* = 5 Hz), 4.26 (ddt, 1H, *J* = 15, 5, 2 Hz), 4.57 (dq, 1H, *J* = 6, 5 Hz), 5.23 (dq, 1H, *J* = 18, 1 Hz), 5.25 (dq, 1H, 10, 1 Hz), 5.76 (dddd, 1H, *J* = 17, 10, 8, 5 Hz); ^{13}C NMR ($CDCl_3$) δ 21.0 (q), 45.9 (t), 52.8 (bq), 63.0 (d), 73.0 (v), 119.5 (q), 131.5 (d), 156.8 (s), 169.8 (q); MS (CI) (NH_3) *m*/*z* 217 (MNH_4^+, 100), 200; HRMS (CI CH_4) calcd for $C_9H_{13}NO_4$ + H 200.0922, found 200.0908.

N-Allyl-4(*S*)-carbethoxy-thiazolidine-2-one (L-16c′). Obtained from **L-15c′** (chromatography, hexane−EtOAc 1:1) as a yellow oil (68%): $[\alpha]^{20}_D$ −47.00° (*c* = 0.023, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3H, *J* = 7 Hz), 3.39 (dd, 1H, *J* = 11, 2.5 Hz), 3.58 (ddt, 1H, *J* = 16, 7.5, 1 Hz), 3.61 (dd, 1H, *J* = 11, 8 Hz), 4.28 (q, 2H, *J* = 7 Hz), 4.36 (dd, 1H, *J* = 8, 2.5 Hz), 4.49 (*d*dt, 1H, *J* = 16, 4.5, 1.5 Hz), 5.20 (dq, 1H, *J* = 17, 1 Hz), 5.24 (dq, 1H, *J* = 10, 1 Hz), 5.77 (dddd, 1H, *J* = 17, 10, 7.5, 4.5 Hz); ^{13}C NMR (CDCl3) δ 14.2 (q), 29.1 (t), 46.7 (t), 59.6 (d), 62.2 (t), 119.0 (t), 132.0 (d), 169.9 (s), 171.3 (s); MS (CI) (NH_3) *m*/*z* 233 (MNH_4^+, 100), 216; HRMS (CI CH_4) calcd for $C_9H_{13}NO_3S$ + H 216.0694, found 216.0670.

General Procedure for Reduction and Oximation of 16 to Aldoximes 17. To a solution of **16** (0.43 mmol) in dry CH_2Cl_2 (13 mL) under N_2 was added DIBALH in hexane (1 M, 9.1 mL, 9.1 mmol) dropwise over 30−60 min, while the temperature was maintained below −75 °C. After 2 h, MeOH (1 mL) was added. The reaction mixture was then partitioned between EtOAc (25 mL) and saturated aqueous sodium potassium tartrate (15 mL), NH_2OH·HCl (0.64 g, 9.2 mmol), and NaOH (0.4 g, 10 mmol) at pH = 11−12. Vigorous stirring was continued at room temperature for 12 h until all the solids dissolved. The organic layer was separated, and the aqueous phase was again extracted with EtOAc (2 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel to give **17**.

N-Allyl-4-oxazolidine-2-one-4-carboxaldehyde Oximes L-17a and D-17a. The respective oximes **17a** were obtained from **16a** as colorless needles when chromatographed (hexane−EtOAc 1:4) followed by crystallization from toluene (60%): mp 113−115 °C; **L-17a** $[\alpha]^{20}_D$ +30.0° (*c* = 0.01, $CHCl_3$); **D-17a** $[\alpha]^{20}_D$ −20.63° (*c* = 0.016, $CHCl_3$); ^{1}H NMR ($CDCl_3$) for the major *syn*-isomer δ 3.64 (ddt, 1H, *J* = 15.5, 7, 1 Hz), 4.10 (ddt, 1H, *J* = 15.5, 5, 1.5 Hz), 4.19 (dd, 1H, *J* = 8, 5 Hz), 4.45 (ddd, 1H, *J* = 9, 7, 5 Hz), 4.50 (t, 1H, *J* = 8.5 Hz), 5.24 (ddt, 1H, *J* = 17, 1.5, 1 Hz), 5.26 (ddt, 1H, *J* = 10, 1.5, 1 Hz), 5.76 (dddd, 1H, *J* = 17, 10, 7, 5 Hz), 7.35 (d, 1H, *J* = 7 Hz), 7.85 (bs, 1H). ^{1}H NMR ($CDCl_3$) for the minor *anti*-isomer δ 3.69 (ddt, 1H, *J* = 15.5, 7, 1 Hz), 4.11 (dd, 1H, *J* = 9, 6 Hz), 4.12 (ddt, 1H, *J* = 15.5, 5, 1.5 Hz), 4.60 (t, 1H, *J* = 9 Hz), 5.01 (ddd, 1H, *J* = 9, 6, 5.5 Hz), 5.27 (ddt, 1H, *J* = 17, 1.5, 1 Hz), 5.28 (ddt, 1H, *J* = 10, 1.5, 1 Hz), 5.80 (dddd, 1H, *J* = 17, 10, 7, 5 Hz), 6.90 (d, 1H, *J* = 5.5 Hz), 8.12 (bs, 1H); ^{13}C NMR ($CDCl_3$) for the major isomer δ 45.2 (t), 54.8 (d), 65.0 (t), 119.5 (t), 131.2 (d), 147.5 (d), 157.8 (s); for the minor isomer δ 45.9 (t), 50.6 (d), 65.8 (t), 119.6 (t), 131.2 (d), 149.0 (d), 158.2 (s); MS (CI) (isobutane) *m*/*z* 171 (MH^+, 100); HRMS (CI, CH_4) calcd for $C_7H_{10}N_2O_3$ + H 171.0769, found 171.0746.

N-Allyl-5(*R*)-methyloxazolidine-2-one-4(*S*)-carboxaldehyde Oxime (L-17b). Obtained from **L-16b** as colorless needles when chromatographed (hexane−EtOAc 1:4) followed by crystallization (60%): mp 140−142 °C; $[\alpha]^{20}_D$ +58.33° (*c* = 0.012, $CHCl_3$); ^{1}H NMR ($CDCl_3$) for the major *syn*-isomer δ 1.47 (d, 3H, *J* = 6 Hz), 3.63 (ddt, 1H, *J* = 15, 6, 1 Hz), 3.97 (dd, 1H, *J* = 6, 8 Hz), 4.07 (ddt, 1H, *J* = 15, 5, 1.5 Hz), 4.44 (*a*pentet, 1H, *J* = 6 Hz), 5.23 (dq, 1H, *J* = 16, 1 Hz), 5.27 (dq, 1H, *J* = 10, 1 Hz), 5.75 (dddd, 1H, *J* = 16, 10, 6, 5 Hz), 7.31 (d, 1H, *J* = 8 Hz), 7.85 (bs, 1H); ^{1}H NMR ($CDCl_3$) for the minor *anti*-isomer δ 1.52 (d, 3H, *J* = 6 Hz), 3.65 (ddt, 1H, *J* = 15, 6, 1 Hz), 4.12 (ddt, 1H, *J* = 15, 5, 1.5 Hz), 4.42 (*a*pentet, 1H, *J* = 6 Hz), 4.64 (t, 1H, *J* = 6 Hz), 5.26 (dq, 1H, *J* = 16, 1 Hz), 5.27 (dq, 1H, *J* = 10, 1 Hz), 5.77 (dddd, 1H, *J* = 16, 10, 6, 5 Hz), 6.82 (d, 1H, *J* = 6 Hz), 8.11 (bs, 1H); ^{13}C NMR ($CDCl_3$) for the major isomer δ 19.3 (q), 45.3 (t), 61.8 (d), 73.4 (d), 119.4 (t), 131.3 (d), 147.7 (d), 157.1 (s); for the minor isomer δ 20.4 (q), 45.8 (t), 56.6 (d), 74.4 (d), 119.5 (t), 131.3 (d), 149.5 (d), 157.3 (s); MS (CI) (NH_3) *m*/*z* 202 (MNH_4^+, 100), 185; HRMS (CI CH_4) calcd for $C_8H_{12}N_2O_3$ + H 185.0926, found 185.0970.

N-Allyl-thiazolidine-2-one-4(*S*)-carboxaldehyde Oxime (L-17c). Obtained from **L-16c′** as a white solid when chromatographed (hexane−EtOAc 1:1) (50%): mp 95−97 °C; $[\alpha]^{20}_D$ +18.18° (*c* = 0.011, $CHCl_3$); ^{1}H NMR ($CDCl_3$) for the major *syn*-isomer δ 3.17 (dd, 1H, *J* = 11, 4.5 Hz), 3.56 (dd, 1H, *J* = 11, 8 Hz), 3.57 (ddt, 1H, *J* = 15, 8, 0.5 Hz), 4.28 (ddt, 1H, *J* = 15, 5, 0.5 Hz), 4.45 (dt, 1H, *J* = 8, 4.5 Hz), 5.18−5.30 (m, 2H), 5.73 (dddd, 1H, *J* = 17, 10, 7, 5 Hz), 7.45 (d, 1H, *J* = 8 Hz), 7.95 (bs, 1H). ^{1}H NMR ($CDCl_3$) for the minor *anti*-isomer δ 5.14 (ddd, 1H, *J* = 8, 6, 4 Hz), 6.93 (d, 1H, *J* = 6 Hz), 8.34 (bs, 1H); ^{13}C NMR ($CDCl_3$) for the major isomer δ 29.5 (t), 45.9 (t), 57.8 (d), 119.0 (t), 131.6 (d), 147.9 (d); for the minor isomer δ 29.3 (t), 46.5 (t), 52.8 (d), 119.1 (t), 131.5 (d), 149.9 (d); MS (CI) (NH_3) *m*/*z* 204 (MNH_4^+, 100), 187; HRMS (DCI CH_4) calcd for $C_7H_{10}N_2O_2S$ + H 187.0541, found 187.0567.

General Procedure for IOOC of 17 to Isoxazolidines 18. A mixture of **17** (0.59 mmol) in dry toluene (30 mL) was heated at 165−170 °C for 16 h in a sealed tube, under Ar. The tube was opened (TLC indicated complete consumption of starting material), and the solvent was evaporated to give **18**.

[3a-(3aα,8a*β*,8bα)]-Hexahydro-3*H*,6*H*-oxazolo[3′4′:1,2]-pyrrolo[3,4-c]isoxazol-6-one (L-18a and D-18a). Obtained from **17a** as white solids upon chromatography (EtOH−EtOAc 1:4) (80%): mp 114−115 °C; **L-18a** $[\alpha]^{20}_D$ −68.86° (*c* = 0.033, $CHCl_3$); **D-18a** $[\alpha]^{20}_D$ +38.20° (*c* = 0.009, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.95 (dd, 1H, *J* = 12.5, 7 Hz), 3.30 (ddddd, 1H, *J* = 9, 9, 7, 6, 0.5 Hz), 3.52 (dd, 1H, *J* = 9.5, 6 Hz), 3.76 (ddd, 1H, *J* = 7.5, 6.5, 2.5 Hz), 3.96 (dd, 1H, *J* = 9, 6.5 Hz), 4.02 (d, 1H, *J* = 9.5 Hz), 4.20 (dd, 1H, *J* = 12.5, 9 Hz), 4.35 (dd, 1H, *J* = 9.5, 2.5 Hz), 4.59 (dd, 1H, *J* = 9.5, 7.5 Hz), 5.21 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 49.3 (d), 51.7 (t), 64.63 (d), 67.5 (t), 71.7 (d), 76.8 (t), 160.7 (s); MS (DCI) (NH_3) *m*/*z* 188 (MNH_4^+, 100), 171; HRMS (DCI) calcd for $C_7H_{10}N_2O_3$ + H 171.0769, found 171.0747.

[3a*R*-(3aα,8aα,8a*β*,8bα)]-Hexahydro-3*H*,6*H*-8-methyl-oxazolo[3′4′:1,2]pyrrolo[3,4-c]isoxazol-6-one (L-18b). Obtained from **L-17b** as a white solid when chromatographed (EtOH−EtOAc 1:4) (55%): $[\alpha]^{20}_D$ −34.00° (*c* = 0.010, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.53 (d, 3H, *J* = 6 Hz), 2.92 (dd, 1H, *J* = 12.5, 7 Hz), 3.31 (ddddd, 1H, *J* = 9, 9, 7, 6, 0.5 Hz), 3.38 (dd, 1H, *J* = 6, 2.5 Hz), 3.50 (dd, 1H, *J* = 9.5, 6 Hz), 3.95 (dd, 1H, *J* = 9, 6 Hz), 4.00 (d, 1H, *J* = 9.5 Hz), 4.18 (dd, 1H, *J* = 12.5, 9 Hz), 4.60 (dq, 1H, *J* = 6, 2.5, Hz), 5.20 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 21.4 (q), 49.2 (d), 51.2 (t), 70.9 (d), 71.4 (d), 76.4 (d), 76.6 (t), 156.0 (s); MS (CI) (NH_3) *m*/*z* 202 (MNH_4^+, 100), 185; HRMS (CI CH_4) calcd for $C_8H_{12}N_2O_3$ + H 185.0926, found 185.0930.

[3a*R*-(3aα,8a*β*,8bα)]-Hexahydro-3*H*,6*H*-thiazolo[3′4′:1,2]-pyrrolo[3,4-c]isoxazol-6-one (L-18c). Obtained from **L-17c** as a white solid when chromatographed (EtOH−EtOAc 1:4) (75%): mp > 170 °C (dec); $[\alpha]^{20}_D$ −81.81° (*c* = 0.022, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.87 (dd, 1H, *J* = 12.5, 7 Hz), 3.30 (dd, 1H, *J* = 11.5, 8 Hz), 3.36 (ddddd, 1H, *J* = 9.5, 8.5, 7, 6.5, 1 Hz), 3.53 (dd, 1H, *J* = 9.5, 6.5 Hz), 3.62 (dd, 1H, *J* = 11.5, 4.5 Hz), 3.90 (ddd, 1H, *J* = 8, 7, 4.5 Hz), 3.96 (dd, 1H, *J* = 8.5, 7 Hz), 4.01 (dd, 1H, *J* = 9.5, 1 Hz), 4.24 (dd, 1H, *J* = 12.5, 9.5 Hz), 5.25 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 30.0 (t), 49.3 (d), 49.7 (t), 66.4 (d), 70.1 (d), 76.9 (t), 172.5 (s); MS (CI) (NH_3) *m*/*z* 204 (MNH_4^+, 100), 187; HRMS (DCI CH_4) calcd for $C_7H_{10}N_2O_2S$ + H 187.0541, found 187.0470.

General Procedure for Raney Ni Reduction of 18 to Amino Alcohols 19. A solution of **18** (0.43 mmol) in MeOH−water (5:1, 9 mL) was hydrogenated (H_2, 1 atm) over Raney Ni for 24 h. The catalyst was filtered, and the filtrate was evaporated under reduced pressure to give **19**.

[6*R*-(6α,7α,7aα)-]-7-Aminotetrahydro-6-(hydroxymethyl)-1*H*,3*H*-pyrrolo[1,2-c]oxazol-3-one (L-19a). Obtained from **L-18a** as a colorless oil when chromatographed (MeOH−NH_4OH) (76%). $[\alpha]^{20}_D$ −35.00° (*c* = 0.020, H_2O); ^{1}H NMR ($CDCl_3$) δ 2.55 (ddddd, 1H, *J* = 8.5, 8.3, 6.5, 5, 4.5 Hz), 3.22 (dd, 1H, *J* = 12, 4.5 Hz), 3.33 (t, 1H, *J* = 8.3 Hz), 3.72 (dd, 1H, *J* = 11, 6.5 Hz), 3.76 (dd, 1H, *J* = 12, 8.5 Hz), 3.77 (dd, 1H, *J*

= 11, 5 Hz), 3.90 (td, 1H, J = 8.3, 4.5 Hz), 4.37 (dd, 1H, J = 9, 4.5 Hz), 4.64 (dd, 1H, J = 9, 8 Hz); ^{13}C NMR (D_2O) δ 44.1 (d), 48.4 (t), 57.3 (d), 60.5 (t), 64.9 (d), 69.1 (t), 163.9 (s); MS (CI) (NH_3) m/z 190 (MNH_4^+, 100), 173, 160; HRMS (CI CH_4) calcd for $C_7H_{12}N_2O_3$ + H 173.0926, found 173.0950.

[6*R*-(6α,7α,7aα)-1′*R*]-7-Amino-tetrahydro-6-(1′-hydroxyethyl)-1*H*,3*H*-pyrrolo[1,2-c]oxazol-3-one (L-19b). Obtained from **L-18b** as an oil when chromatographed (MeOH−NH_4OH) (82%): $[\alpha]^{20}_D$ −16.47° (c = 0.017, H_2O); ^{1}H NMR (D_2O) δ 1.52 (d, 3H, J = 6.5 Hz), 2.59 (ddddd, 1H, J = 8.2, 8, 6.3, 5.1, 4.7 Hz), 3.24 (dd, 1H, J = 11.8, 4.7 Hz), 3.38 (dd, 1H, J = 8.2, 8 Hz), 3.55 (dd, 1H, J = 8.2, 4.7 Hz), 3.74 (dd, 1H, J = 11.4, 6.3 Hz), 3.77 (dd, 1H, J = 11.8, 8.2 Hz), 3.80 (dd, 1H, J = 11.4, 5.1 Hz), 4.73 (qd, 1H, J = 6.5, 4.7 Hz); ^{13}C NMR (D_2O) δ 21.0 (q), 44.5 (d), 48.0 (t), 57.0 (d), 60.4 (t), 71.6 (d), 79.2 (d), 163.2 (s); MS (CI) (NH_3) m/z 204 (MNH_4^+, 100), 187; HRMS (CI CH_4) calcd for $C_8H_{14}N_2O_3$ + H 187.1082, found 187.1064.

[6*R*-(6α,7α,7aα)]-7-Amino-tetrahydro-6-(hydroxymethyl)-1*H*,3*H*-pyrrolo[1,2-c]thiazol-3-one (L-19c). To a solution of isoxazolidine **L-18c** (51 mg, 0.28 mmol) in MeOH−water (1:1, 4 mL) was added Zn (80 mg) and HCl (32%, 5 drops). The reaction mixture was stirred at room temperature for 12 h, and the solvent was evaporated to give an oil which was chromatographed (MeOH−NH_4OH, 30 mL:7 drops) to give **L-19c** as a colorless oil (22 mg, 42%): $[\alpha]^{20}_D$ −12.40° (c = 0.025, H_2O); ^{1}H NMR (D_2O) δ 2.71 (tddd, 1H, J = 8.1, 6.7, 5, 4.3 Hz), 3.19 (dd, 1H, J = 12.1, 4.3 Hz), 3.40 (t, 1H, J = 8.1 Hz), 3.40 (dd, 1H, J = 11.0, 9.3 Hz), 3.50 (dd, 1H, J = 11.0, 7.7 Hz), 3.72 (dd, 1H, J = 11.5, 6.7 Hz), 3.73 (ddd, 1H, J = 12.1, 8.1, 0.7 Hz), 3.80 (dd, 1H, J = 11.5, 5.0 Hz), 4.20 (dddd, 1H, J = 9.3, 8.1, 7.7, 0.7 Hz); ^{13}C NMR (D_2O) δ 32.9 (t), 45.6 (d), 46.1 (t), 56.9 (d), 60.5 (t), 69.0 (d), 174.7 (s); MS (CI) (NH_3) m/z 206 (MNH_4^+, 45), 189; HRMS (DCI CH_4) calcd for $C_7H_{11}N_2O_2S$ ($M - H$)$^+$ 187.0541, found 187.0540.

3(*S*)-Amino-4(*R*)-hydroxymethyl-2(*S*)-methyl-pyrrolidine 1-Carbaldehyde (L-20). Ra−Ni reduction of **L-18c** (43 mg, 0.23 mmol) and preparative TLC (MeOH−NH_4OH, 10:0.1) gave desulfurization product **L-20** as a colorless oily solid (39%): ^{1}H NMR (D_2O) δ 1.21 (d, 3H, J = 6.5 Hz, minor rotamer *Me*), 1.28 (d, 3H, J = 6.5 Hz, major rotamer *Me*), 2.60−2.75 (m, 4H), 3.20−3.35 (m, 1.5H), 3.40−3.85 (m, 4.5H), 8.11 (s, 1H, minor rotamer C*H*O), 8.14 (s, 1H, major rotamer C*H*O); ^{13}C NMR (D_2O) for the major rotamer δ 20.3 (q), 41.2 (t), 44.8 (d), 57.2 (d), 60.0 (t), 62.8 (d), 164.1 (d); for the minor rotamer δ 17.5 (q), 41.8 (t), 47.5 (d), 57.6 (d), 59.6 (t), 60.6 (d), 164.4 (d); MS (CI) (NH_3) m/z 159 (MH^+, 100).

3a(*S*),6(*R*),6a(*S*)-(Hexahydro-pyrrolo[3,4-c]isoxazol-6-yl)-methanol (D-23). A mixture of **D-18a** (23.4 mg, 0.12 mmol) and Cs_2CO_3 (17 mg, 0.12 mmol, 0.6 equiv) in MeOH−H_2O (1:3, 1.0 mL) was stirred at 83 °C for 14 h and at 103 °C for another 5 h. Chromatography (MeOH−NH_4OH 25%, 9:1) gave **13b** as a light yellow oil (15.1 mg, 0.11 mmol, 75%): $[\alpha]^{20}_D$ +5.26° (c = 0.0038, H_2O); ^{1}H NMR 320 K (D_2O) δ 3.32 (dd, 1H, J = 11.5, 7 Hz), 3.05 (dd, 1H, J = 6.5, 4.5 Hz), 3.32 (dd, 1H, J = 12, 7.5 Hz), 3.48 (dd, 1H, J = 11.5, 8.5 Hz), 3.64 (bdd, 1H), 3.72 (dd, 1H, J = 12, 6.5 Hz), 3.82 (dd, 1H, J = 12, 4.5 Hz), 3.93 (dd, 1H, J = 8.5, 6.5 Hz), 4.00 (d, 1H, J = 7.5 Hz); ^{13}C NMR (D_2O) δ 48.3 (d), 51.3 (t), 61.3 (t), 66.0 (d), 66.7 (d), 76.4 (t); HRMS (CI CH_4) calcd for $C_6H_{13}N_2O_2$ + H 145.0977, found 145.0975.

General Procedure for Hydrolysis of Pyrrolo-Oxazolidinones 19 to Pyrrolidines 21. To an aqueous (5 mL) solution of **19** (0.33 mmol) was added Cs_2CO_3 (20 mg, <0.2 equiv). The reaction mixture was refluxed for 17 h. Evaporation of the solvent followed by chromatography on silica gel (MeOH−NH_4OH) gave **21**.

2(*R*),4(*R*)-Di(hydroxymethyl)-3(*R*)-aminopyrrolidine (L-21a) and L-21a·CO_2 Adduct. Obtained from **L-19a** as an oil (53%): $[\alpha]^{20}_D$ −14.92° (c = 0.02, H_2O); ^{1}H NMR (D_2O) δ 2.44 (sextet, 1H, J = 7 Hz), 2.96 (dd, 1H, J = 11.5, 7 Hz), 3.15 (td, 1H, J = 6, 5 Hz), 3.25 (dd, 1H, J = 11.5, 7 Hz), 3.39 (dd, 1H, J = 7, 6 Hz), 3.68 (dd, 1H, J = 12, 6 Hz), 3.73 (dd, 1H, J = 11, 7 Hz), 3.79 (dd, 1H, J = 12, 5 Hz), 3.84 (dd, 1H, J = 11, 6.5 Hz); ^{13}C NMR (D_2O) δ 43.7 (d), 47.3 (t), 54.0 (d), 60.0 (t), 61.9 (t), 67.2 (d); MS (CI) (NH_3) m/z 147 (MH^+, 100); HRMS (CI CH_4) calcd for $C_6H_{14}N_2O_2$ + H 147.1133, found 147.1090. A small amount of a minor **L-21a**·CO_2 adduct was also detected: ^{1}H NMR (D_2O) δ 2.60 (m, 1H), 3.24 (dd, 1H, J = 10.5, 9.5 Hz), 3.47 (dd, 1H, J = 10.5, 8 Hz), 3.49 (dd, 1H, J = 5.5, 1.5 Hz), 3.65 (dd, 1H, J = 7.5, 6, 1.5 Hz), 3.72 (dd, 1H, J = 11, 8 Hz), 3.78 (dd, 1H, J = 11.5, 7.5 Hz), 3.80 (dd, 1H, J = 11, 5 Hz), 3.88 (dd, 1H, J = 11.5, 6 Hz); ^{13}C NMR (D_2O) δ 42.7 (d), 47.9 (t), 54.1 (d), 60.1 (t), 63.3 (t), 67.4 (d), 163.8 (s).

2(*S*),4(*S*)-Di(hydroxymethyl)-3(*S*)-aminopyrrolidine (D-21a) and D-21a·CO_2 Adduct. To a solution of **D-23** (27.6 mg, 0.2 mmol) dissolved in 1:5 MeOH−H_2O (4.5 mL) was added an aqueous slurry of Ra−Ni (2 mL), and the mixture was hydrogenated for 28 h. The mixture was filtered, and the filtrate was evaporated. The crude residue was chromatographed (MeOH−NH_4OH 9:1) to give **D-21a**, 16.5 mg (66.5% yield): $[\alpha]^{20}_D$ +12.1° (c = 0.016, H_2O); ^{1}H and ^{13}C NMR spectra were identical to those of **L-21a**. The relative amount of the minor **D-21a**·CO_2 adduct detected in this case was considerably lower than that found in the case of **L-21a**.

3(*R*)-Amino-2(*R*)-[1′(*R*)-hydroxyethyl]-4(*R*)-hydroxymethylpyrrolidine (L-21b). Obtained from **L-19b** as an oil (22 mg, 70%): ^{1}H NMR (D_2O) δ 1.24 (d, 3H, J = 6.5 Hz), 2.37 (sextet, 1H, J = 7 Hz), 2.93 (dd, 1H, J = 11.5, 7 Hz), 2.94 (dd, 1H, J = 6, 5.5 Hz), 3.24 (dd, 1H, J = 11.5, 7 Hz), 3.39 (dd, 1H, J = 7, 6 Hz), 3.64 (dd, 1H, J = 11, 6.5 Hz), 3.76 (dd, 1H, J = 11, 6.5 Hz), 3.93 (qd, 1H, J = 6.5, 5.5 Hz); ^{13}C NMR (D_2O) δ 20.7 (q), 44.5 (d), 47.5 (t), 54.3 (d), 60.0 (t), 67.4 (d), 72.0 (d); MS (CI) (NH_3) m/z 161 (MH^+, 100).

2(*R*)-Mercaptomethyl-4(*R*)-hydroxymethyl-3(*R*)-aminopyrrolidine (L-21c). An aqueous (7 mL) solution of **L-19c** (40 mg, 0.21 mmol) and KOH (0.188 g, 3.35 mmol) under N_2 was refluxed for 24 h. The solvent was evaporated, and the residue was chromatographed on silica gel (MeOH−NH_4OH 4:1) to give **L-21c** as a dark yellow oil (21 mg, 61%): $[\alpha]^{20}_D$ −65.93° (c = 0.018, H_2O); ^{1}H NMR (D_2O) δ 2.56 (*a*sextet, 1H, J = 7 Hz), 2.88 (dd, 1H, J = 14.5, 9 Hz), 3.07 (dd, 1H, J = 12, 7.5 Hz), 3.24 (dd, 1H, J = 14.5, 4 Hz), 3.35 (dd, 1H, J = 12, 7.5 Hz), 3.48 (dd, 1H, J = 7, 6.5 Hz), 3.53 (ddd, 1H, J = 9, 6.5, 4 Hz), 3.76 (dd, 1H, J = 11.5, 6.5 Hz), 3.83 (dd, 1H, J = 11.5, 6.5 Hz); ^{13}C NMR (D_2O) δ 41.4 (t), 44.1 (d), 47.4 (t), 52.2 (d), 60.4 (t), 65.1 (d); MS (CI) (isobutane) m/z 163 (MH^+, 100); HRMS (DCI CH_4) calcd for $C_6H_{14}N_2OS$ + H 163.0905, found 163.0820.

2(*R*),4(*R*)-Bishydroxymethyl-3(*R*)-(3-phenyl-thioureido)-pyrrolidine-1-carbothioic Acid Phenylamide (L-22). Pyrrolidine **L-21a** (12.7 mg, 0.087 mmol) and phenylisothiocyanate (0.1 mL, 0.83 mmol) in EtOAc (2 mL) were mixed at room temperature for 72 h. The solvent was then decanted, and the solution was evaporated to give a solid. The residue was washed with acetone, and the mixture was filtered and evaporated to give additional solid. The solids were combined (22 mg) and chromatographed (EtOAc) to give **22** as a yellow solid (10 mg, 27%): mp 118−120 °C (dec); $[\alpha]^{20}_D$ +19.41° (c = 0.017, acetone); ^{1}H NMR 320 K (acetone-d_6) δ 2.88 (ddddd, 1H, J = 10.5, 8.5, 6, 5.5, 4.5 Hz), 3.76 (dd, 1H, J = 11, 4.5 Hz), 3.83 (dd, 1H, J = 11, 6 Hz), 3.84 (dd, 1H, J = 12, 8.5 Hz), 3.91 (dd, 1H, J = 10.5, 7.5 Hz), 3.99 (dd, 1H, J = 12, 10.5 Hz), 4.16 (dd, 1H, J = 10.5, 4 Hz), 4.69 (ddd, 1H, J = 7.5, 4, 1 Hz), 4.92 (dd, 1H, J = 5.5, 1 Hz), 7.00−7.60 (m, 10 H); ^{1}H NMR 25 °C (acetone-d_6) for a mixture of rotamers δ 2.90 (bs, 1H), 3.75−4.00 (m, 6H), 4.18 (bd, 1H), 4.29 (bs, 1H), 4.72 (bdd, 1H), 4.89 (bt, 1H), 7.00−7.55 (m, 10 H), 7.98 (d, 1H, J = 6 Hz), 9.06 (s, 1H), 9.50 (bs, 1H); ^{13}C NMR 25 °C (acetone-d_6) for a mixture of rotamers δ 42.2 (d), 52.4 (t), 59.7 (d), 60.1 (t), 64.4 (t), 71.4 (d), 124.6, 124.7, 124.9, 125.8, 128.8, 129.7, 141.7 (*Ph*), 181.6 (s), 182.3 (s).

Enzyme Inhibition Assays. α-Glucosidase (EC 3.2.1.20) from baker's yeast, β-glucosidase (EC 3.2.1.21) from almonds, α-galactosidase (EC 3.2.1.22) from green coffee beans, β-galactosidase (EC 3.2.1.23) from Escherichia coli, and the *p*-nitrophenyl α-D-gluco-, β-D-gluco-, α-D-galacto-, and β-D-galactopyranosides were purchased from Sigma Co.

Enzymatic assays were carried out by following the hydrolysis of the appropriate *p*-nitrophenyl glycoside substrates spectrophotometrically at 400 nm (ϵ 11 150 at pH 7.2) at 25

°C. Enzyme concentration was set to obtain a hydrolysis rate of about 10^{-3} OD/sec under substrate saturation. **α-Glucosidase** (at 2 mg/mL) was assayed in 45 mM sodium acetate buffer, pH 7.2. Substrate concentration was 0.25−4.0 mM (K_m 0.2−0.3 mM under our experimental conditions, similar to a published value of 0.3 mM).[21] **β-Glucosidase** (at 2.3 mg/mL) was assayed in 45 mM sodium acetate buffer, pH 7.2. Substrate concentration was 0.54 and 1.08 mM (K_m 2.84 mM under our experimental conditions, similar to a published value of 2.1−3.5 mM).[21] **α-Galactosidase** (at 0.045 units/mL) was assayed in 90 mM potassium phosphate buffer, pH 6.5. Substrate concentration was 0.1−1.1 mM (K_m 0.35 mM under our experimental conditions). **β-Galactosidase** (at 0.4 units/mL) was assayed in 45 mM potassium phosphate buffer, pH 7.0, containing 130 mM NaCl and 0.9 mM $MgCl_2$. Substrate concentration was 0.027−0.2 mM (K_m 0.03 mM under our experimental conditions).

Inhibition studies were carried out by measuring the initial velocity of hydrolysis of an appropriate substrate (in the above-mentioned concentrations) in the presence of varying inhibitor concentrations. Lineweaver−Burk plots ($1/v$ vs $1/[S]$) for the different inhibitor concentrations yielded the K_m app values from the X-axis intercepts (on the basis of the competitive inhibition kinetics equation $v = v_{max}[S]/\{[S] + K_m(1 + [I]/K_i)\}$, where K_m app $= K_m(1 + [I]/K_i)$. Replotting of the K_m app values against inhibitor concentration yielded the kinetic parameter K_i (as K_m/slope). In some of the cases, a single inhibitor concentration was used.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for compounds **2a,b**, **3**−**7a,b**, **8**−**11**, **13**, **14**, **15a**−**c**, **16a**−**c**, **17a**−**c**, **18a**−**c**, **19a**−**c**, **20**, **21a**−**c**, **21a·CO₂** adduct, **22**, and **23** and the spectrum of **L-21a** after the sample was heated to 90 °C (70 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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