Practical Synthesis of α-Amino Acid *N*-Carboxy Anhydrides of Polyhydroxylated α-Amino Acids from *β*-Lactam Frameworks. Model Studies toward the Synthesis of Directly Linked Peptidyl Nucleoside Antibiotics

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A straightforward method for the synthesis of polyhydroxylated α-amino acid *N*-carboxy anhydrides (NCAs) is described as the means by which short peptide segments comprised of a polyhydroxylated chain are easily affordable. The entire sequence lies in the preparation of nonracemic 3-hydroxy *β*-lactams through the highly diastereoselective Staudinger reaction of hydroxyketene equivalents with chiral α-oxyaldehyde-derived imines, followed by TEMPO radical assisted cycloexpansion to the corresponding NCA and subsequent peptide coupling with α-amino acid esters. The method has been applied to the synthesis of short peptide segments derived from carbamoylpolyoxamic acid, some glycoglycines, as well as C_2 symmetric hydroxy amino acids.

Introduction

In recent years, polyhydroxylic α-amino acids have been the focus of major interest, in part due to their utility as precursors of alkaloidal sugar mimics with a nitrogen in the ring (azasugars), including both monocyclic and bicyclic derivatives[1] and, in part, because of their occurrence in complex nucleoside antibiotics that exhibit a variety of biological activities.[2] One example of the latter, Figure 1, is the family of polyoxins **1**, which has as a common structural feature a dipeptide comprised of an unusual hydroxylated α-amino acid **3**, linked to one of the related nucleoside α-amino acids.[3] The free form **2** of **3** is commonly called polyoxamic acid. As a consequence of the potent antifungal activity associated with this type of peptidyl nucleosides, many methods for the preparation of both **2** and **3** have been proposed over the past few years.[4] Since most of these methods involve a relatively large number of steps, a practical short route to this amino acid still remains of interest. In addition, a strategy that allows the combination of the synthesis of the polyhydroxylated α-amino acid with a peptide coupling step would represent a conceptually new approach to peptidyl nucleoside antibiotics.[4,5] We have recently reported the first synthesis of a derivative of polyoxamic acid **2** that fulfills this criterion.[6] The strategy, Figure 2, is based on the use of glycolic acid that derivatizes imines in the primary step in such a way that a four membered ring is formed. Then the oxidation of the alcohol and subsequent Baeyer−Villiger rearrangement of the resulting intermediate α-keto *β*-lactam

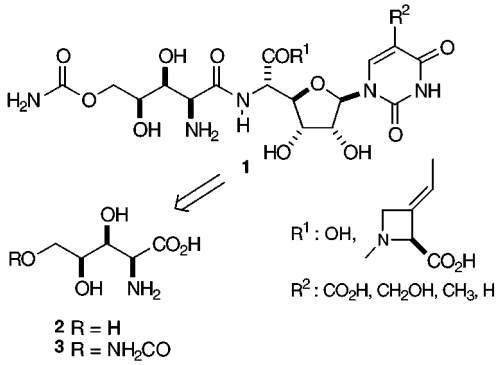

Figure 1.

provides, in an one-pot procedure, an α-amino acid *N*-carboxy anhydride (NCA) ready for peptide couplings.[7,8] Thus, the access to NCAs, which has traditionally relied on dehydration procedures of α-amino acids,[9] can now be achieved from non-α-amino acid precursors in a very concise and practical fashion. We now report the implementation of this strategy to the synthesis of

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(1) For recent reviews, see: Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P. *Chem. Rev.* **1995**, *95*, 1677.

(2) (a) Isono, K. *J. Antibiot.* **1988**, *41*, 1711. (b) Isono, K. *Pharmac. Ther.* **1991**, *52*, 269. (c) Knapp, S. *Chem. Rev.* **1995**, *95*, 1859.

(3) Garner, P. In *Studies in Natural Product Chemistry, Vol 1, Stereoselective Synthesis*; Rahman, A.-U., Ed.; Elsevier: Amsterdam, 1988; Part A, p 397.

(4) (a) Saksena, A. K.; Lovey, R. G.; Girigavallabhan, V. M.; Ganguly, A. K. *J. Org. Chem.*. **1986**, *51*, 5024. (b) Savage, I.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1989**, 717. (c) Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabuga, F. *Tetrahedron* **1990**, *46*, 265. (d) Dondoni, A.; Franco, S.; Merchán, F. L.; Merino, P.; Tejero, T. *Tetrahedron Lett.* **1993**, *34*, 5479. (e) Jackson, R. F. W.; Palmer, N. J.; Wythes, M. J.; Clegg, W.; Elsegood, M. R. J. *J. Org. Chem.* **1995**, *60*, 6431. (f) Kang, S. H.; Choi, H.-w. *Chem. Commun.* **1996**, 1521. (g) Dondoni, A.; Franco, S.; Junquera, F.; Merchán, F. L.; Merino, P.; Tejero, T. *J. Org. Chem.* **1997**, *62*, 5497. (h) Garner, P.; Park, J. M. *J. Org. Chem.* **1988**, *53*, 2979. (i) Dureault, A.; Carreaux, F.; Depezay, J. C. *Synthesis* **1991**, 150. (j) Irama, M.; Hioki, H.; Ito, S. *Tetrahedron Lett.* **1988**, *29*, 3125. (k) Banik, B. K.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1993**, *58*, 307. (l) Paz, M. M.; Sardina, F. J. *J. Org. Chem.* **1993**, *58*, 6990. (m) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1994**, *35*, 733. (n) Trost, B. M.; Krueger, A. C.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc.* **1996**, *118*, 6520. (o) Marshall, J. A.; Seletsky, B. M.; Coan, P. S. *J. Org. Chem.* **1994**, *59*, 5139. (p) Bandini, E.; Martelli, G.; Spunta, G.; Bongini, A.; Panunzio, M.; Piersanti, G. *Tetrahedron: Asymmetry* **1997**, *8*, 3717. (q) Veeresa, G.; Datta, A. *Tetrahedron Lett.* **1998**, *39*, 119.

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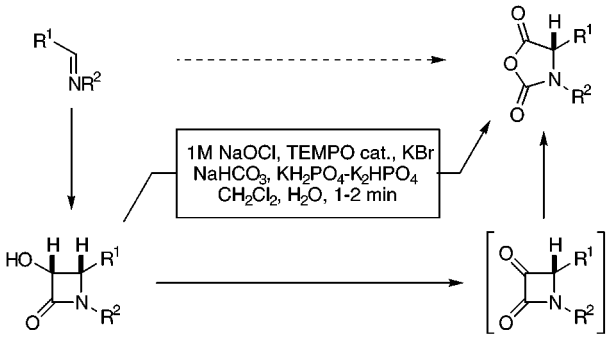


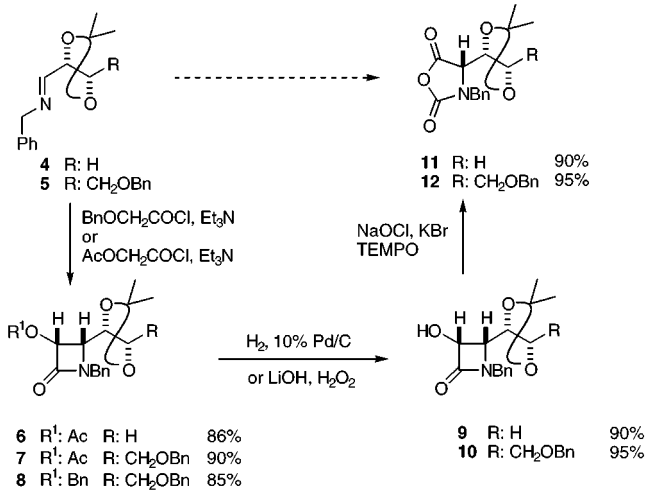
Figure 2. General strategy for the asymmetric carboxylation of imines with concomitant carboxyl group activation.

NCAs formally derived from polyhydroxylated α-amino acids, such as the carbamoyl polyoxamic acid **3** and some glycoglycines,[10] and demonstrate the benefit of the entire process for the synthesis of directly linked peptidyl nucleoside antibiotics.

Results and Discussion

Approach to Carbamoylpolyoxamic Acid-Derived NCAs. The approach to the NCA formally derived from the carbamoylpolyoxamic acid **3** takes advantage of the highly stereocontrolled cycloaddition reaction of hydroxyketene equivalents with α-oxy aldehyde-derived imines,[11] independently pionered by Hubschwerlen[12] and Bose.[13] By this means, the required starting α-hydroxy

Scheme 1



β-lactams, Scheme 1, are obtained essentially as single diastereomers. For example, the cycloaddition reaction of acetoxyketene, generated from (acetoxy)acetyl chloride and triethylamine, with imines **4**[13] and **5**,[14] afforded **6** and **7** in yields of 86% and 90%, respectively. Mild deprotection of these compounds with lithium hydroperoxide led to the α-hydroxy β-lactam **9** and **10** in 90% and 95% yield. Likewise, the cycloaddition reaction of benzyloxyketene, generated from (benzyloxy)acetyl chloride and triethylamine, to the imine **5** furnished **8** in 85% yield. In each case, a single diastereomer was produced whose relative cis configuration was established on the basis of the value of the proton NMR coupling constant ($J_{3,4}$ = 5 Hz). When both **9** and **10** were subjected to treatment with a solution of commercial bleach and a catalytic amount of TEMPO within about 1−2 min, the corresponding NCAs **11** and **12**, the latter formally derived from polyoxamic acid **2**, were produced in 90% and 95% yield, respectively.

Next, the synthesis of the carbamoylpolyoxamic acid-derived NCA **16** was addressed as shown in Scheme 2. In this regard, the introduction of the carbamoyl group at the terminal position of the β-lactam C_4-side chain could be accomplished by chemoselective deprotection of the primary hydroxy group in **8**. This was cleanly performed by exposure of **8** to H_2 over Pd on charcoal at room temperature for 5−7 h to give **13** in 95% isolated yield, provided the reaction progress is carefully monitored by TLC in order to avoid overexposure to H_2. Further carbamoylation[15] of the free hydroxy group in **13** provided **14** in 90% isolated yield, which on prolonged exposure to the above hydrogenolytic conditions led to the 5-*O*-carbamoylpolyoxamic NCA precursor **15** in 91% isolated yield. Thus, treatment of **15** with a solution of commercial bleach and a catalytic amount of TEMPO

(5) For some additional examples on the synthesis of hydroxylated α-amino acids, see: (a) Shioiri, T.; Hamada, Y. *Heterocycles* **1988**, *27*, 1035. (b) Ariza, J.; Font, J.; Ortuño, R. M. In *Trends Org. Chem.* **1992**, *3*, 53. (c) Varela, O. *Pure Appl. Chem.* **1997**, *69*, 621. (d) Dondoni, A.; Perrone, D. *Aldrichim. Acta* **1997**, *30*, 35. (e) Rassu, G.; Zanardi, F.; Corria, M.; Casiragi, G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2431. (f) Kirihata, M.; Nakao, Y.; Mori, M.; Ichimoto, I. *Heterocycles* **1995**, *41*, 2271. (g) Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A.; García, J. I. *Tetrahedron* **1996**, *52*, 9563. (h) Ojea, V.; Ruiz, M.; Quintela, J. M. *Synlett* **1997**, 83. (i) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1997**, *8*, 3489. (j) Kimura, T.; Vassilev, V. P.; Shen, G.-J.; Wong, C.-H. *J. Am. Chem. Soc.* **1997**, *119*, 11734. For general reviews on α-amino acid synthesis, including hydroxylated α-amino acids, see: (k) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1988. (l) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. For α-amino acids from sugars, see: (m) Cintas, P. *Tetrahedron* **1991**, *47*, 6079. For α-amino acids from α-cation equivalents, see: (n) Bailey, P. D.; Clayson, J.; Boa, A. N. *Contemp. Org. Synth.* **1995**, *2*, 173. For a recent review on coupling methods for the incorporation of noncoded amino acids into peptides, see: (o) Humphrey, J. M.; Chamberlain, A. R. *Chem. Rev.* **1997**, *97*, 2243.

(6) Palomo, C.; Oiarbide, M.; Esnal, A. *Chem. Commun.* **1997**, 691.

(7) For a conceptually different β-lactam route to the nonnatural enantiomer of polyoxamic acid, see ref 4k. For a recent review on the use of β-lactams as buildig-blocks of β-amino acid derivatives, see: Palomo, C.; Aizpurua, J. M.; Ganboa, I. In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley VCH: New York, 1997; p 279.

(8) (a) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Carreaux, F.; Cuevas, C.; Maneiro, E.; Ontoria, J. M. *J. Org. Chem.* **1994**, *59*, 3123. (b) Palomo, C.; Aizpurua, J. M.; Cuevas, C.; Urchegui, R.; Linden, A. *J. Org. Chem.* **1996**, *61*, 4400.

(9) To date, the synthesis of NCA's invariably requires the prior construction of the desired α-amino acid followed by dehydration. For a detailed discussion on this topic, see: (a) Kricheldorf, H. R. *α-Amino Acid N-Carboxy-Anhydride and Related Heterocycles*; Springer-Verlag: Berlin, 1987. (b) Reference 8a.

(10) We adopted the term of glycoglycines instead of *C*-glycosylglycines according to the recent observation made by Dondoni, who indicated that the usual name of *C*-glycosyl α-amino acids appears appropriate only for compounds wherein the amino acid moiety is linked to the sugar anomeric carbon. See: Dondoni, A.; Junquera, F.; Merchán, F. L.; Merino, P.; Ascherrmann, M.-C.; Tejero, T. *J. Org. Chem.* **1997**, *62*, 5484.

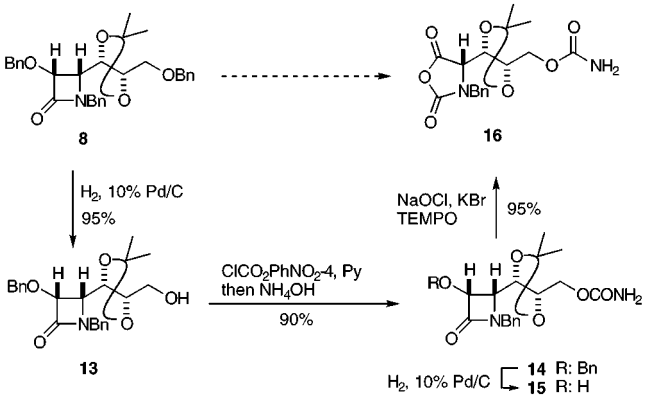
(11) For a review on ketene−imine cycloadditions, see: Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1992; p 295. For a review on the construction of chiral molecules using α-hydroxy acids or aldehydes, see: Coppola, G. M.; Schuster, H. F. *α-Hydroxy Acids in Enantioselective Syntheses*; VCH: Weinheim, 1997.

(12) Hubschwerlen, C.; Schmid, G. *Helv. Chim. Acta* **1983**, *66*, 2206.

(13) (a) Wagle, D. R.; Garai, G.; Chiang, J.; Monteleone, M. G.; Kurys, B. E.; Strohmeyer, T. W.; Hedge, V. R.; Mahnas, M. S.; Bose, A. K. *J. Org. Chem.* **1988**, *53*, 4227. (b) Banik, B. K.; Manhas, M. S.; Kaluza, Z.; Barakat, J. K.; Bose, A. K. *Tetrahedron Lett.* **1992**, *33*, 3603.

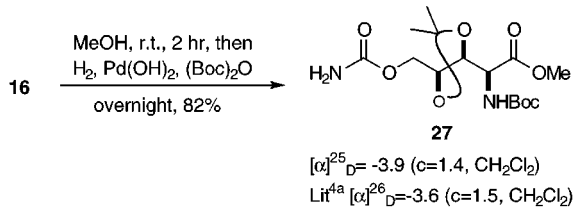
(14) For the use of this imine in the synthesis of 3-amino β-lactams, via the cycloaddition approach, see: Saito, S.; Ishikawa, T.; Morinake, T. *Synlett* **1993**, 139.

Scheme 2



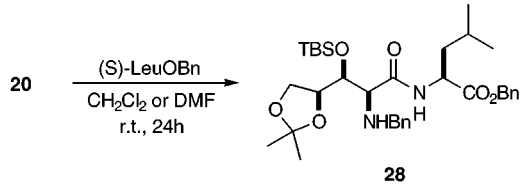
furnished the NCA **16** in 90% isolated yield.[16] For reasons that will be outlined later, the NCA **20**, Scheme 3, was also prepared following the same sequence of reactions as above. Namely, the cycloaddition reaction of benzyloxyketene with the imine **17**, prepared from the corresponding aldehyde and benzylamine,[17] gave the *β*-lactam **18** in 87% yield essentially as the sole diastereomer. Subsequent O-debenzylation with H_2 over Pd on charcoal carried out in ethyl acetate as solvent led to the 3-hydroxy *β*-lactam **19**, which was converted into **20** by following the protocol used for compounds **11**, **12**, and **16** in 90% yield for the entire sequence. It should also be mentioned that when the O-debenzylation of **18** was carried out in methanol as solvent, a simultaneous opening of the dioxolane ring took place, affording triol **21** as the major isolated product.

From the above approach, two key elements are especially noteworthy. First, the creation of the α stereogenic center of the polyoxamic acid or its carbamoyl derivative is virtually diastereoselectively complete, which contrasts with the mixtures obtained by reported procedures employing Mukaiyama's aldehyde as the starting material.[4a−g] Second, the generation of an activated derivative of the carbamoylpolyoxamic acid **3** ready for further coupling reactions has been achieved for the first time. On pursuing this latter aspect we found, however, that the coupling reaction of the above NCAs **11**, **12**, and **16** with α-amino acid esters, Scheme 4, proceeded to give the expected coupling products **22**, **23**, and **24** along with the corresponding epimerized products *epi*-**22**, *epi*-**23**, and *epi*-**24**, respectively, depending upon the nature of the solvent employed. For example, the coupling reaction of the NCA **11** with (*S*)-LeuOBn carried out in methylene chloride gave **22a** as the only diastereomeric product, but when the reaction was performed in DMF as solvent, a mixture of **22a**/*epi*-**22a** was formed in a 75:25 ratio. In a similar way, the coupling reaction of the NCA **12** with (*S*)-LeuOBn in DMF furnished an equimolar mixture of **23a**/*epi*-**23a**, whereas in either diethyl ether or methylene chloride, only **23a** was obtained. Likewise, the coupling in methylene chloride of the NCA **16** with (*S*)-LeuOBn afforded **24a** in 87% yield as the sole diastereomeric product. As Scheme 4 illustrates, both **24a** and **24b** were then converted under usual conditions into **25a** and **25b**, respectively. Then **25a** was N-debenzylated to give the corresponding free carbamoylpolyoxamic dipeptide **26** in 98% over the two steps. Finally, to corroborate the configuration of the carbamoyl polyoxamic acid and hence the otherwise stated products, the NCA **16** was transformed into the known methyl ester **27**, as shown in eq 1.



(1)

The results obtained in these coupling reactions upon the use of different solvents are summarized in Table 1, which also includes some solvent physical constants. From these data, a good agreement between the magnitude of the dipolar moment of the solvent μ and the degree of isomerization is observed. With two exceptions, a plausible correlation could also be established between the value of the dielectric constant of the solvent used, ϵ, and the degree of isomerization. However, it appears that there is not any obvious relationship between the polarity of the solvent, as E_T, and the isomerization degree. Although at this point of the study we did not have a well-evidenced explanation for the observed epimerization nor for the influence of the solvent on it, we speculated on the role played by the rigid dioxolane ring. Hence, Dreiding stereomodel structures for **11**, **12**, and **16** suggest an unfavorable disposition of the C═O(oxazolidin-2,3-dione ring)/C−O(dioxolane ring) dipoles that could in part be circumvented in the epimeric structures. This circumstance could actually be the driving force that induces the epimerization process to take place. In fact, we prepared the NCA **20**, vide supra, which possesses a higher conformational freedom allowing a better C═O/C−O relative orientation, and subjected it to treatment with (*S*)-LeuOBn. Regardless of the reaction solvent employed, compound **28** was the only dipeptide product formed (eq 2).



(2)

To further demonstrate the scope of this method for coupling NCAs under racemization free conditions, we have prepared the C_2-symmetric bis-NCA **31** according to the reactions depicted in Scheme 5. The cycloaddition of the bis-imine **29**[18] with benzyloxyacetyl chloride and triethylamine provided **30** after usual O-deprotection of the resulting intermediate adduct. Exposure of this

(15) Tabusa, F.; Yamada, T.; Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1984**, 405. See also ref 4c.

(16) NCA **11** and **16** rapidly became white solids and could be stored under nitrogen in a cool room for several days without appreciable decomposition. All other NCAs so far described in this article did not solidify easily and were used within a few hours of isolation.

(17) The imine was prepared from the commercially available methyl 3,4-*O*-isopropylidene-L-threonate by standard *tert*-butyldimethylsilylation of the secondary hydroxy group and subsequent reduction of the methyl ester by treatment with DIBAL at −78 °C in toluene. The resulting aldehyde was treated with equimolar amounts of benzylamine in methylene chloride in the presence of magnesium sulfate at 0 °C for 1 h. After usual workup, the crude imine was used as such.

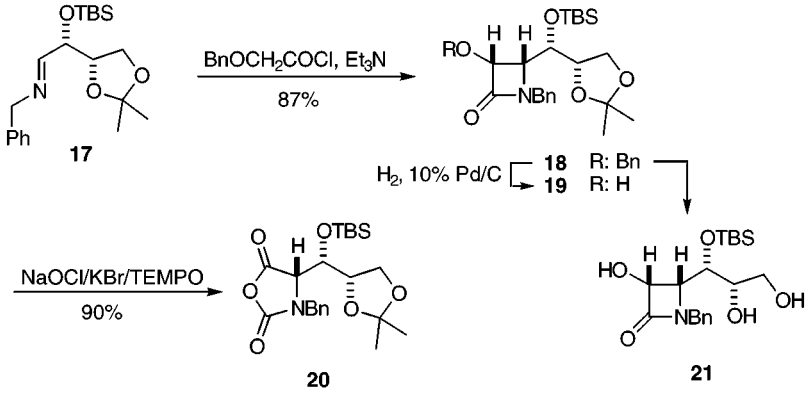
(18) Jayaraman, M.; Deshmukh, A. R. A. S.; Bhawal, B. M. *J. Org. Chem.* **1994**, *59*, 932.

Table 1. Diastereomeric Ratios of the Reaction Products Obtained in Different Solvents by the Coupling of (*S*)-LeuOBn with NCA 11, 12, 16, and 20, Respectively[a]

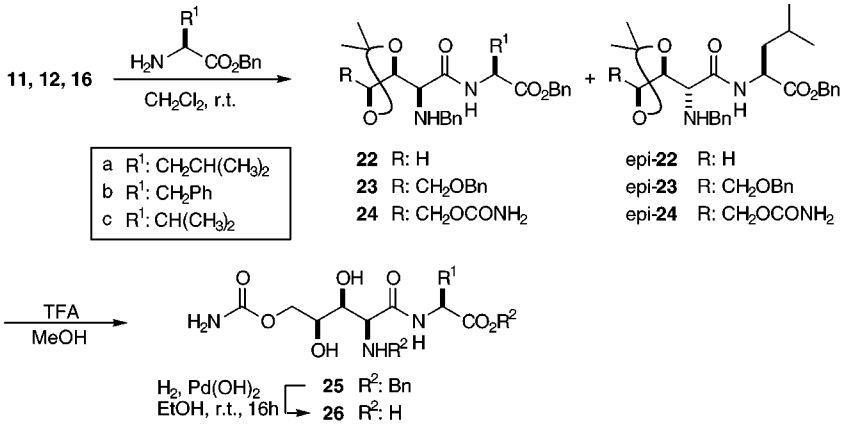
solvent	μ[b]	ϵ	E_T	**22a**:*epi*-**22a**[c]	**23a**:*epi*-**23a**[c]	**24a**:*epi*-**24a**[c]	**28**:*epi*-**28**[c]
Et_2O	3.8	4.2	0.117		100:0[d]		100:0
CH_2Cl_2	5.2	8.93	0.309	100:0[d]	100:0[d]	100:0	100:0
$MeNO_2$	11.9	35.94	0.481		92:8		
MeCN	11.8	35.94	0.460		85:15		
DMSO	13.5	46.45	0.444		51:49		
DMF	10.8/12.88[e]	36.71	0.404	75:25[d]	50:50	64:36[d]	100:0
HMPA	18.5	29.6	0.315		28:72		mixture

[a] Reactions conducted on a 0.25 mmol scale at room temperature in the corresponding solvent (2.5 mL); NCA/(*S*)-LeuOBn 1:2. [b] From Reichardt, C. In *Solvent Effects in Organic Chemistry*; Ebel, H. F., Ed.; Verlag Chemie GmbH: Weinheim, 1990; p 407 [μ (10^{-30} Cm) at 20−30 °C; ϵ, relative permitivity at 25 °C; E_T^N at 25 °C]. [c] Determined by ^{1}H NMR analysis of the crude products. [d] Corroborated by HPLC analysis. [e] From the same book as in (b), 1978 ed.

Scheme 3



Scheme 4



compound to commercial bleach and a catalytic amount of TEMPO cleanly led to the expected bis-NCA **31** in almost quantitative yield. The coupling of this bis-NCA **31** with 2 equiv of (*S*)-PheOMe, carried out in methylene chloride as solvent, furnished the peptide product **32**, which contains a C_2-symmetric diaminodiol unit. Inspection of the ^{1}H NMR of the crude reaction mixture revealed the absence of epimerization, which was further confirmed by HPLC analysis. Again, after carrying out the coupling reaction in DMF as solvent, an intractable mixture of compounds was formed. On the other hand, given the prominence of C_2-symmetric diaminodiols in biologically important peptide sequences relevant to antiviral chemotherapy,[19] the method reported herein could be beneficial for the creation of small peptide libraries containing the 3,4-dihydroxylated 2,5-diaminoadipic acid as part of the backbone.[20]

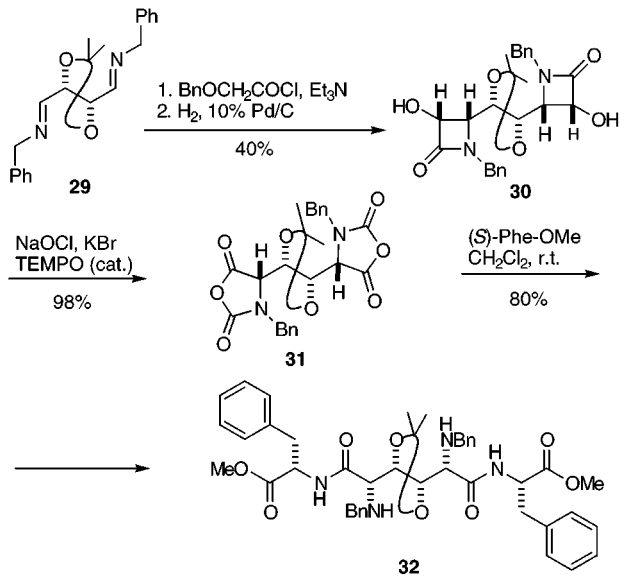
Approach to Glycoglycine−NCAs. The potential utility of this method for the synthesis of densely functionalized NCAs was also explored. In particular, the synthesis of some illustrative carbon-linked glycoglycines, such as α-aminofuranuronic acid derivatives,[21] was undertaken. To this end, we chose to use the β-lactam **34**,

(19) For some representative reviews, see: (a) Erickson, J. W. *Perspect. Drug Discovery Des.* **1993**, *1*, 109. (b) Abdel-meguid, S. S. *Med. Res. Rev.* **1993**, *6*, 731. (c) March, D. R.; Fairlie, D. P. In *Designing New Antiviral Drugs for AIDS: HIV-1 Protease and Its Inhibitors*; Wise, R., Ed.; R. G. Landes Publishers: Austin, TX, 1996; p 1. (d) Dorsch, D.; Raddatz, P.; Schmitges, C.-d.; von der Helm, K.; Rippmann, F. *Kontackte* **1993**, 48.

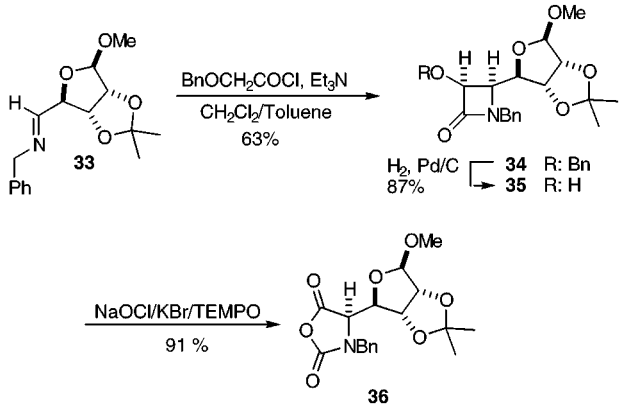
(20) Recently, a homologated amino acid, the 4,5-dihydroxy-3,6-diamino-1,6-hexanedicarboxylic acid, has been employed for the construction of a pseudo-C_2-symmetric cyclic urea as intermediate in the synthesis of HIV-protease inhibitors; see: Schreiner, E. P.; Pruckner, A. *J. Org. Chem.* **1997**, *62*, 5380.

(21) For the syntheses of α-aminofuranuronic acids, see: (a) ref 4g, 10, and references therein. (b) Bouifraden, S.; Lavergne, J.-P.; Martínez, J.; Viallefont, P.; Riche, C. *Tetrahedron: Asymmetry* **1997**, *8*, 949. (c) Bouifraden, S.; Lavergne, J.-P.; Martinez, J.; Viallefont, P. *Synth. Commun.* **1997**, *27*, 3909. (d) Gethin, D. M.; Simpkins, N. S. *Tetrahedron* **1997**, *53*, 14417.

Scheme 5

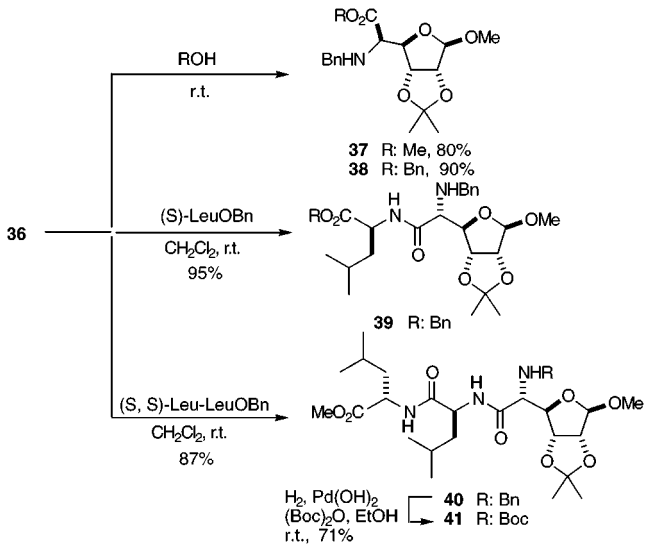


Scheme 6

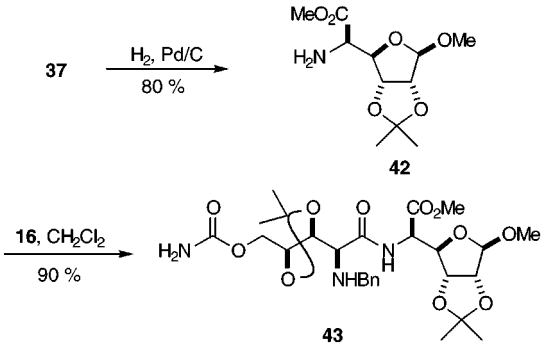


Scheme 6, prepared in 45% yield by addition of benzyloxyacetyl chloride to the imine **33** and triethylamine, according to the method of Bose.[22] A better yield was obtained, however, when a solution of the imine in toluene was added to the preformed ketene in methylene chloride. In this way, **34** was isolated in 63% yield and then O-debenzylated to give **35** in 87% yield. As expected, the cycloexpansion of **35** promoted by TEMPO proceeded cleanly to afford the NCA **36** in 91% yield, ready for subsequent couplings. These coupling reactions were successfully carried out with both O- and N-nucleophiles, Scheme 7. Thus, the exposure of **36** to a large excess of methanol smoothly produced the methyl ester **37** in 80% yield after 2 h at room temperature. Likewise, treatment of **36** with a slight excess of benzyl alcohol in methylene chloride as solvent for 16 h provided the benzyl ester **38** in 90% isolated yield. In both cases, no epimerization at the sensitive stereocenters occurred during ring opening as judged by ^{13}C NMR and HPLC analyses of the corresponding reaction crudes. Next, the coupling of the α-aminofuranuronic-NCA **36** with some representative α-amino acid esters was examined. For example, the coupling reaction of **36** with (*S*)-LeuOBn, carried out in methylene chloride at room temperature, furnished the dipeptide product **39** in 95% yield. Likewise, the coupling of **36** with the dipeptide (*S*,*S*)-Leu-LeuOBn afforded the tripeptide **40** in 87% isolated yield, which was then converted into the *N*-Boc derivative **41**. Finally, the glycoglycine methyl ester **42**, prepared from **37**, Scheme 8, was coupled with the NCA **16** to give the unnatural carbamoylpolyoxamic derivative **43**. Although the configuration of the carbon atom at the α-position of the amino group of the sugar moiety in compound **43** is opposite to that found in natural polyoxins, the above example illustrates the potential of the approach to the synthesis of directly linked peptidyl nucleoside antibiotics.[23]

Scheme 7



Scheme 8

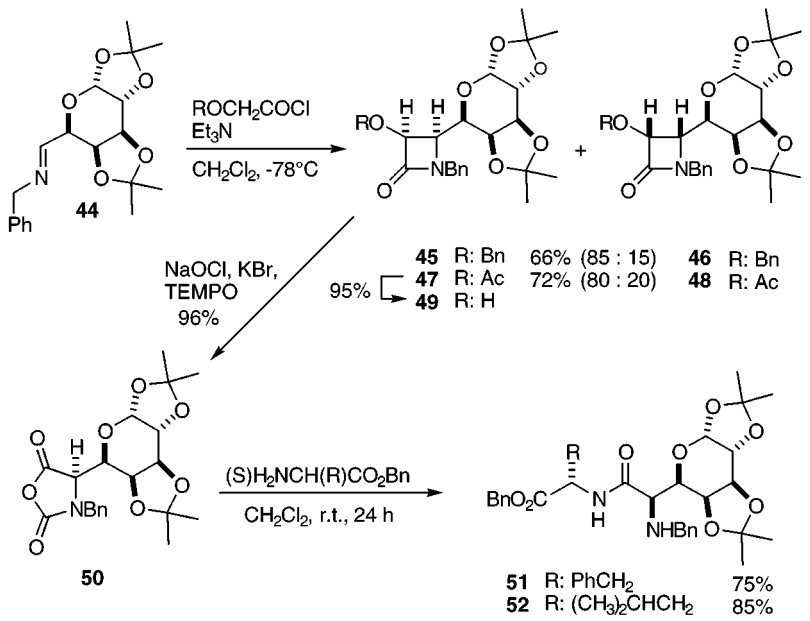


Next, the synthesis of pyranose type glycoglycine NCAs and derived peptides was investigated. In these instances, an unexpected lowering in the stereoselectivity of the ketene-α-oxyimine cycloaddition reaction was observed. In general, the ketene−imine cycloaddition reaction affords only one of the two possible cis diastereomers, and the absolute configuration of the α carbon to the *β*-lactam nitrogen atom is that predicted by the α stereogenic center of the starting α-oxy aldehyde-derived imine.[24] However, as Scheme 9 illustrates, the cycloaddition reaction of benzyloxyketene to the imine **44** furnished an inseparable mixture of **45** and its cis diastereomer **46** in a 85:15 ratio. Likewise, the reaction

(22) Wayle, D. R.; Garai, C.; Monteleone, M. G.; Bose, A. K. *Tetrahedron Lett.* **1988**, *29*, 1649.

(23) Attempts to epimerize the amino acid ester at the α-position through the benzaldimine intermediate were unsuccessful, and the starting material was recovered without change. For this epimerization process, see: (a) Clark, J. C.; Phillipps, G. H.; Steer, M. R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 475. (b) Honnoraty, A.-M.; Mion, L.; Collet, H.; Teissedre, R.; Commeyras, A. *Bull. Soc. Chim. Fr.* **1995**, *132*, 709.

Scheme 9



of **44** with acetoxyacetyl chloride and triethylamine gave **47** along with its cis diastereoisomer **48** in a ratio of 80:20. Again, the relative cis configuration of the ring substituents was established on the basis of the ^{1}H NMR coupling constants at the C_3 and C_4 positions of the β-lactam ring ($J_{3,4} = 4.8-5.0$ Hz). Despite this relatively low diastereoselectivity,[25] compound **47**, which serves to illustrate the utility of the approach to NCAs derived from α-aminopyranuronic acids,[26] could easily be isolated by column chromatography and subjected to saponification affording the α-hydroxy β-lactam **49** in 95% yield. Accordingly, exposure of **49** to a solution of commercial bleach and a catalytic amount of TEMPO gave within about 1−2 min the NCA **50**, which on coupling with (*S*)-PheOBn and (*S*)-LeuOBn in methylene chloride led to the sugar dipeptides **51** and **52** in good overall yields over the last two steps. Finally, single-crystal X-ray analysis of **34**, **39**, and **48** confirmed the assigned configuration for the products.[27]

In summary, the results reported here set the basis for the development of a pratical and short access to simultaneously amino-protected and carboxy-activated forms of polyhydroxylated α-amino acids without the necessity to have previously prepared each individual α-amino acid.

Experimental Section

Melting points were determined with capillary apparatus and are uncorrected. Proton nuclear magnetic resonance (300 MHz) spectra and ^{13}C spectra (75 MHz) were recorded at room temperature for $CDCl_3$ solutions, unless otherwise stated. All chemical shifts are reported as δ values (ppm) relative to residual $CHCl_3$ δ_H (7.26 ppm) and $CDCl_3$ δ_C (77.0 ppm) as internal standards, respectively. Mass spectra were obtained on a mass spectrometer (70 eV) using GC−MS coupling (column: fused silica gel, 15 m, 0.25 mm, 0.25 mn phase SPB-5). Optical rotations were measured at 25 ± 0.2 °C in methylene chloride unless otherwise stated. HPLC analyses were performed on analytical columns (25 cm, phase Lichrosorb-Si60 and 25 cm, phase Chiralcel OD) with flow rates of 1 and 0.5 mL/min respectively, using a DAD detector. Flash chromatography was executed with Merck Kiesegel 60 (230−400 Mesh) using mixtures of ethyl acetate and hexane as eluants. Et_2O and THF were distilled over sodium. Methylene chloride was shaken with concentrated sulfuric acid, dried over potassium carbonate, and distilled. DMF was purified by distillation on barium oxide. CH_3CN was dried by refluxing over calcium hydride and distilled. DMSO was distilled from potassium hydroxide. MeOH was dried over magnessium metal and iodine.

General Procedure for the Preparation of 3-Benzyloxy and 3-Acetoxy β-Lactams. Method A. A mixture of the corresponding aldehyde (25 mmol), 4A MS, and benzylamine (2.14 g, 20 mmol) in methylene chloride (100 mL) was stirred at 0 °C under a nitrogen atmosphere for 1 h. The solution was filtered, the solvent evaporated, and the residue analyzed by ^{1}H NMR to ensure complete comsuption of the amine. The crude thus obtained was dissolved in dry methylene chloride and cooled to −78 or 0 °C under a nitrogen atmosphere, and to the resulting solution were succesively

(24) For a mechanistic discussion on this subject, see: (a) Palomo, C.; Cossío, F. P, Cuevas, C.; Lecea, B.; Mielgo, A.; Román, P.; Luque, A.; Martínez-Ripoll, M. *J. Am. Chem. Soc.* **1992**, *114*, 9360. (b) Cossío, F. P., Arrieta, A.; Lecea, B.; Ugalde, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 2085. For further experimental evidence on the stereochemical outcome of cycloaddition reactions involving α-oxy aldehyde-derived imines, see: (c) Palomo, C.; Cossío, F. P.; Ontoria, J. M.; Odriozola, J. M. *Tetrahedron Lett.* **1991**, *32*, 3105. (d) Brown, A. D.; Colvin, E. W. *Tetrahedron Lett.* **1991**, *32*, 5187. (e) Kobayashi, Y.; Takemoto, Y.; Kamijo, T.; Harada, H.; Ito, Y.; Terashima, S. *Tetrahedron* **1992**, *48*, 1853. (f) Palomo, C.; Aizpurua, J. M.; Urchegui, R.; García, J. M. *J. Org. Chem.* **1993**, *58*, 1646. (g) Alcaide, B.; Miranda, M.; Pérez-Castells, J.; Polanco, C.; Sierra, M. A. *J. Org. Chem.* **1994**, *59*, 8003. (h) Kramer, B.; Franz, T.; Picasso, S.; Pruschek, P.; Jager, V. *Synlett* **1997**, 295.

(25) These results contrast with those previously reported by Bose and his colleagues who achieved a complete diastereoselectivity in the reactions of alkoxyketenes with the imine **44**. For pertinent information, see: (a) Bose, A. K.; Mathur, C.; Wagle, D. R.; Nagui, R.; Manhas, M. S. *Heterocycles* **1994**, *39*, 491. (b) Kaluza, Z.; Manhas, M. S.; Barakat, K. J.; Bose, A. K. *Biorg. Med. Chem. Lett.* **1993**, *3*, 2357.

(26) For the synthesis of α-aminopyranuronic acids, see: (a) ref 10 and references therein. (b) Czerniecki, S.; Horns, S.; Valery, J.-M. *J. Org. Chem.* **1995**, *60*, 650. (c) Czerniecki, S.; Franco, S.; Horns, S.; Valery, J.-M. *Tetrahedron Lett.* **1996**, *37*, 4003. (d) Czerniecki, S.; Franco, S.; Valery, J.-M. *J. Org. Chem.* **1997**, *62*, 4845.

(27) The X-ray crystal structure analyses have been performed by one of us (A.L.) at the Organisch-chemisches Institut der Universität Zürich. Atomic coordinates, bond lengths and angles, and thermal parameters for compounds **34**, **39**, and **48** have been deposited at the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2, 1EZ, UK. E-mail: deposit@ccdc.cam.ac.uk.

added triethylamine (10 mL, 70 mmol) and dropwise a solution of either (benzyloxy)acetyl chloride or (acetoxy)acetyl chloride (30 mmol) in dry methylene chloride (35 mL). The resulting mixture was stirred overnight at room temperature and then was washed with water (3 × 50 mL), 0.1 N HCl (3 × 50 mL), and a saturated solution of $NaHCO_3$ (50 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure to give the corresponding crude β-lactam, which was further purified by column chromatography. **Method B.** A solution of the imine, prepared as before, in toluene was dropwise added to a cooled solution of the acid chloride and triethylamine in methylene chloride. After the mixture was stirred at room temperature overnight, the workup procedure described in method A was followed.

(3*R*,4*S*)-1-Benzyl-4-[(1*S*)-3,3-dimethyl-2,4-dioxacyclopentane-1-yl]-3-acetoxyazetidin-2-one (6). Method A was followed starting from D-glyceraldehyde dimethylacetonide: yield 4.43 g (70%); mp 97−98 °C; $[\alpha]^{25}_D = -54.1$ (c = 0.51, CH_2Cl_2); IR (KBr) 1759 (CO), 1744 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.36−7.27 (m, 5H), 5.76 (d, 1H, J = 14.6 Hz), 4.85 (d, 1H, J = 14.6 Hz), 4.28 (d, 1H, J = 14.7 Hz), 4.82−4.25 (m, 1H), 3.92 (dd, 1H J = 6.7 Hz, J' = 8.7 Hz), 3.63 (dd, 1H, J = 4.9 Hz, J' = 8.9 Hz), 3.50 (dd, 1H, J = 6.0 Hz, J' = 8.7 Hz), 2.12 (s, 3H), 1.35 and 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 169.2, 164.2, 135.1, 128.8, 128.6, 127.8, 109.9, 76.3, 74.0, 66.2, 59.1, 45.4, 26.5, 25.0, 20.4. Anal. Calcd for $C_{17}H_{21}NO_5$ (397.47): C, 63.94; H, 6.63; N, 4.38. Found: C, 63.63; H, 6.57; N, 4.33.

(3*R*,4*S*)-1-Benzyl-4-[(1*S*,5*S*)-5-benzyloxymethyl-3,3-dimethyl-2,4-dioxacyclopentane-1-yl]-3-benzyloxyazetidin-2-one (7). Method A was followed starting from Mukaiyama's aldehyde: yield 8.29 g (85%); mp 74−76 °C; $[\alpha]^{25}_D = -1.6$ (c = 1.0, MeOH); IR (KBr) 1738 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.36−7.17 (m, 15H), 4.85 (d, 1H, J = 14.5 Hz), 4.84 (d, 1H, J = 11.4 Hz), 4.57 (d, 1H, J = 11.4 Hz), 4.57 (d, 1H, J = 4.8 Hz), 4.36 (s, 2H), 4.20 (dd, 1H, J = 6.6 Hz, J' = 8.9 Hz), 4.18 (d, 1H, J = 14.5 Hz), 3.97 (td, 1H, J = 2.4 Hz, J' = 6.6 Hz), 3.64 (dd, 1H, J = 2.4 Hz, J' = 10.4 Hz), 3.58 (dd, 1H, J = 4.8 Hz, J' = 8.9 Hz), 3.42 (dd, 1H, J = 6.6 Hz, J' = 10.4 Hz), 1.85 and 1.45 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 167.3, 138.1, 136.6, 135.7, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 127.6, 127.5, 110.5, 80.4, 79.3, 78.4, 73.2, 72.8, 70.7, 59.0, 45.0, 27.6, 27.4; MS m/z (M^+) 488. Anal. Calcd for $C_{30}H_{33}NO_5$ (487.6): C, 73.89; H, 6.82; N, 2.87. Found: C, 73.76; H, 7.14; N, 2.92.

(3*R*,4*S*)-3-Acetoxy-1-benzyl-4-[(1*S*,5*S*)-5-benzyloxymethyl-3,3-dimethyl-2,4-dioxacyclopentane-1-yl]azetidin-2-one (8). Method A was followed starting from the corresponding aldehyde: yield 7.91 g (90%); mp 82−84 °C; $[\alpha]^{25}_D = -15.8$ (c = 1.0, CH_2Cl_2); IR (KBr) 1759 (CO), 1744 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.40−7.22 (m, 10H), 5.82 (d, 1H, J = 5 Hz), 4.91 (d, 1H, J = 15.0 Hz), 4.53 (s, 2H), 4.21 (d, 1H, J = 15.0 Hz), 4.17 (dd, 1H, J = 6.2 Hz, J' = 7.7 Hz), 3.93 (dt, 1H, J = 5.7 Hz, J' = 6.2 Hz), 3.79 (dd, 1H, J = 5 Hz, J' = 7.7 Hz), 3.45 (d, 2H, J = 5.7 Hz), 1.90, 1.40 and 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 169.3, 164.8, 137.5, 135.1, 128.7, 128.4, 128.3, 127.8, 127.6, 110.5, 78.2, 77.9, 74.0, 73.3, 70.0, 58.0, 45.5, 27.8, 27.5, 20.2; MS m/z (M^+) 440. Anal. Calcd for $C_{25}H_{29}NO_6$ (439.50): C, 68.32; H, 6.65; N, 3.19. Found: C, 67.92; H, 7.05; N, 3.28.

(3*R*,4*R*)-1-Benzyl-4-[(*S*)-1-*tert*-butyldimethylsilyloxy-[(1*S*)-3,3-dimethyl-2,4-dioxacyclopentane-1-yl]methyl]-3-benzyloxyazetidin-2-one (18). Method A was followed starting from the corresponding imine **17**:[17] yield 8.9 g (87%); mp 66−68 °C; $[\alpha]^{25}_D = -6.1$ (c = 1.0, CH_2Cl_2); IR (KBr) 1735 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.40−7.20 (m, 10H), 4.95 (d, 1H, J = 15 Hz), 4.84 (d, 1H, J = 11.9 Hz), 4.73 (d, 1H, J = 11.9 Hz), 4.54 (d, 1H, J = 5.0 Hz), 4.13 (dd, 1H, J = 4.2 Hz, J' = 6.2 Hz), 4.03 (d, 1H, J = 15 Hz), 4.02 (ddd, 1H, J = 6.2 Hz, J' = 6.2 Hz, J'' = 7.3 Hz), 3.69 (dd, 1H, J = 6.2 Hz, J' = 8.2 Hz), 3.50 (dd, J = 7.3 Hz, J' = 8.2 Hz), 3.47 (dd, 1H, J = 4.2 Hz, J' = 5.0 Hz), 1.83 and 1.30 (s, 3H), 0.94 (s, 9H), 0.12 and 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 168.2, 137.1, 135.6, 128.9, 128.6, 128.4, 128.2, 128.0, 109.4, 81.2, 78.1, 73.2, 69.8, 65.4, 56.6, 45.8, 26.6, 26.2, 25.2, 18.4, −4.4, −4.6; EIMS m/z (M^+) 511. Anal. Calcd for $C_{29}H_{41}NO_5Si$ (511.73): C, 68.07; H, 8.07; N, 2.74. Found: C, 67.90; H, 8.06; N, 2.79.

(2*R*,3*R*,4*R*,5*R*)-5-((3′*S*,4′*R*)-1-Benzyl-3-benzyloxyazetidin-2-one-4-yl)-3,4-dihydroxy-3,4-di-*O*-isopropylidene-2-methoxytetrahydrofuran (34). Method B was followed, starting from the corresponding sugar aldehyde: yield 5.53 g (63%); mp 140−142 °C; $[\alpha]^{25}_D = -62.6$ (c = 1.0, CH_2Cl_2); IR (KBr) 1737 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.40−7.13 (m, 10H), 4.97 (d, 1H, J = 12.3 Hz), 4.88 (s, 1H), 4.82 (d, 1H, J = 15.7 Hz), 4.71 (d, 1H, J = 12.3 Hz), 4.67 (d, 1H, J = 5.0 Hz), 4.61 (dd, 1H, J = 1.1 Hz, J' = 6.0 Hz), 4.51 (dd, 1H, J = 1.1 Hz, J' = 10.1 Hz), 4.42 (d, 1H, J = 6.0 Hz), 4.30 (d, 1H, J = 15.8 Hz), 3.75 (dd, 1H, J = 5.0 Hz, J' = 10.1 Hz), 2.90 (s, 3H), 1.45 and 1.28 (s, 3H). ^{13}C NMR ($CDCl_3$, δ) 168.1, 137.1, 136.0, 128.6, 128.3, 127.8, 127.6, 127.4, 127.2, 112.3, 110.1, 88.8, 84.5, 81.8, 80.5, 72.6, 59.1, 55.1, 44.4, 26.5, 24.9; EIMS m/z 440 (M + 1). Anal. Calcd for $C_{25}H_{29}NO_6$ (439.3): C, 68.35; H, 6.65; N, 3.19. Found: C, 67.97; H, 6.73; N, 3.26.

(2*R*,3*R*,4*S*,5*S*,6*R*)-6-((3′*S*,4′*R*)-3-Acetoxy-1-benzylazetidin-2-one-4-yl)-2,3,4,5-tetrahydroxy-2,3:4,5-bis(di-*O*-isopropylidene)tetrahydropyran (47). Method B was followed starting from the corresponding sugar aldehyde: yield 5.15 g (58%); oil; $[\alpha]^{25}_D = -54.4$ (c = 1.0, CH_2Cl_2); IR (film) 1770 (CO), 1754 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.29−7.26 (m, 5H), 5.84 (d, 1H, J = 4.8 Hz), 5.59 (d, 1H, J = 5.0 Hz), 4.83 (d, 1H, J = 14.4 Hz), 4.57 (dd, 1H, J = 2.4 Hz, J' = 7.7 Hz), 4.34 (dd, 1H, J = 2.4 Hz, J' = 5.0 Hz), 4.26 (d, 1H, J = 14.4 Hz), 4.05−3.95 (m, 3H), 2.11 (s, 3H), 1.53 (s, 3H), 1.33 (s, 6H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 168.9, 164.5, 135.3, 128.7, 128.4, 127.5, 109.7, 108.8, 96.1, 74.2, 70.6, 70.0, 68.6, 55.0, 45.6, 25.8, 25.7, 24.8, 24.5, 20.5; MS m/z 448 (M + 1).

(2*R*,3*R*,4*S*,5*S*,6*R*)-6-((3′*R*,4′*S*)-3-Acetoxy-1-benzylazetidin-2-one-4-yl)-2,3,4,5-tetrahydroxy-2,3:4,5-bis(di-*O*-isopropylidene)pyran (48): yield 1.29 g (14%); mp 132−134 °C; $[\alpha]^{25}_D = -78.5$ (c = 1.0, CH_2Cl_2); IR (film) 1770 (CO), 1758 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.30−7.25 (m, 5H), 5.93 (d, 1H, J = 4.8 Hz), 5.40 (d, 1H, J = 5.1 Hz), 4.66 (d, 1H, J = 15 Hz), 4.56 (dd, 1H, J = 2.5 Hz, J' = 7.9 Hz), 4.28 (dd, 1H, J = 2.5 Hz, J' = 5.1 Hz), 4.22 (d, 1H, J = 15 Hz), 4.01 (dd, 1H, J = 2.1 Hz, J' = 7.9 Hz), 3.94 (dd, 1H, J = 4.8 Hz, J' = 9.2 Hz), 3.79 (dd, 1H, J = 2.1 Hz, J' = 9.2 Hz), 2.15 (s, 3H), 1.54 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 169.4, 166.8, 136.1, 128.5, 128.2, 127.7, 109.5, 108.6, 95.9, 73.6, 70.8, 70.5, 69.7, 66.4, 56.7, 45.9, 25.8, 25.8, 24.8, 24.5, 20.7; MS m/z 448 (M + 1).

Monodebenzylation of 7. To a solution of **7** (12.7 g, 26 mmol) in methanol (200 mL) was added 10% palladium on charcoal (1.5 g), and the mixture was kept under hydrogen (1 atm). The reaction mixture was stirred at room temperature until the dissappearance of the starting material as monitored by TLC (5−7 h). Then, the suspension was filtered through a pad of Celite and evaporated to yield **13**, which was purified by column chromatography and further crystallization from Et_2O/hexane: yield 9.82 g (95%); mp 76−78 °C; $[\alpha]^{25}_D = +22.4$ (c = 1.0, CH_2Cl_2); IR (KBr) 3433 (OH), 1738 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$, δ) 7.42−7.26 (m, 10H), 5.01 (d, 1H, J = 11.4 Hz), 4.86 (d, 1H, J = 14.5 Hz), 4.72 (d, 1H, J = 14.5 Hz), 4.64 (d, 1H, J = 5.0 Hz), 4.22 (dd, 1H, J = 6.9 Hz, J' = 8.9 Hz), 4.20 (d, 1H, J = 11.4 Hz), 3.80 (dt, 1H, J = 4.9 Hz, J' = 6.9 Hz), 3.66 (dd, 2H, J = 4.9 Hz, J' = 5.9 Hz), 3.59 (dd, 1H, J = 5.0 Hz, J' = 8.9 Hz), 1.39 (s, 3H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 166.8, 136.0, 135.6, 128.8, 128.7, 128.6, 128.5, 128.3, 127.7, 109.7, 80.2, 80.0, 78.7, 73.0, 62.7, 58.5, 45.1, 27.3; MS m/z (M^+) 398. Anal. Calcd for $C_{23}H_{27}NO_5$ (397.47): C, 69.50; H, 6.85; N, 3.52. Found: C, 69.87; H, 7.24; N, 3.62.

Carbamoylation of 13. To a solution of *p*-nitrophenyl chloroformate (31.12 g, 87.77 mmol) and pyridine (73.14 mL, 0.9 mol) in dry methylene chloride (250 mL) at 0 °C was added a solution of **13** (9.82 g, 24.7 mmol) in methylene chloride (250 mL) dropwise. The resulting mixture was stirred at room temperature for 45 min, the solution was washed with 0.5 M H_2SO_4 (3 × 300 mL), saturated solution of $NaHCO_3$ (3 × 300 mL), and brine (3 × 300 mL), dried over $MgSO_4$, and filtered, and the solvent was evaporated under reduced pressure. The resulting residue was redissolved in THF (200 mL), cooled to 0 °C, and treated with a 25% aqueous solution of NH_3 (55 mL). After the mixture was stirred for 30 min at room temperature,

it was washed with a saturated solution of $NaHCO_3$ (3 × 200 mL), the organic layer was then dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. The crude product thus obtained was subjected to column chromatography (eluent EtOAc/hexane 1:3) to afford compound **14** as a white solid: yield 9.95 g (92%); mp 190−193 °C; $[\alpha]^{25}_D$ = +13.7 (c = 1.0, CH_2Cl_2); IR (KBr) 3433 (NH_2), 1748 (CO), 1691 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.38−7.22 (m, 10H), 4.93 (d, 1H, J = 11.5 Hz), 4.85 (d, 1H, J = 14.7 Hz), 4.72 (d, 1H, J = 11.5 Hz), 4.61 (d, 1H, J = 5.1 Hz), 4.48 (d, 1H, J = 10.0 Hz), 4.22 (dd, 1H, J = 6.7 Hz, J' = 9.0 Hz), 4.17 (d, 1H, J = 14.7 Hz), 4.00 (m, 1H), 3.96 (m, 1H), 3.58 (dd, J = 5.1 Hz, J' = 9.0 Hz), 1.40 and 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 167.3, 156.3, 135.6, 128.6, 128.5, 128.2, 127.6, 110.6, 79.9, 78.2, 77.9, 72.8, 65.1, 58.6, 45.0, 27.5, 27.3; EIMS m/z 382 (M − 58). Anal. Calcd for $C_{24}H_{28}N_2O_6$ (440.27): C, 65.47; H, 6.41; N, 6.36. Found: C, 65.77; H, 6.49; N, 6.11.

General Procedure for the Preparation of 3-Hydroxy *β*-Lactams. Method A. To a solution of the corresponding 3-(benzyloxy)azetidin-2-one (7 mmol) in methanol (40 mL) was added 10% palladium on charcoal (10% w/w), and the mixture was kept under hydrogen (1 atm). The reaction mixture was stirred at room temperature for 16 h. Then, the suspension was filtered through a pad of Celite and evaporated to yield the corresponding 3-hydroxyazetidin-2-one, which was purified by column chromatography and further crystallization. **Method B**. To a solution of the corresponding 3-acetoxyazetidin-2-one (17.5 mmol) in a mixture of THF (175 mL) and water (60 mL) at 0 °C were added LiOH (0.84 g, 35 mmol) and a 30% solution of H_2O_2 (10.82 mL, 105 mmol). The resulting solution was stirred at the same temperature for 3 h, and then a solution of $Na_2S_2O_3$ (1.5 M, 140 mL, 93.3 mmol) was added. Most of the THF was removed under vacuum from the mixture, the resulting residue was dissolved in methylene chloride (250 mL), the solution washed with a saturated solution of $NaHCO_3$ (2 × 250 mL) and dried over $MgSO_4$, and the solvent was finally removed under reduced pressure. The crude product thus obtained was purified by crystallization.

(3*R*,4*S*)-1-Benzyl-4-[(1*S*)-3,3-dimethyl-2,4-dioxolan-1-yl]-3-hydroxyazetidin-2-one (9). Method B was followed starting from **6**: yield 4.46 g (92%); mp 159−160 °C; $[\alpha]^{25}_D$ = −42.7 (c = 1.0, CH_2Cl_2); IR (KBr) 3270 (OH), 1722 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.34−7.22 (m, 5H), 4.81 (d, 1H, J = 14.8 Hz), 4.80 (m, 1H), 4.54−4.52 (m, 1H), 4.38−4.32 (m, 1H), 4.14 (d, 1H, J = 14.9 Hz), 4.15 (dd, 1H, J = 6.44, J' = 8.4 Hz), 3.71 (dd, 1H, J = 5.1 Hz, J' = 9.0 Hz), 3.53 (dd, 1H, J = 4.9 Hz, J' = 6.8 Hz), 1.39 and 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 170.7, 135.9, 129.2, 128.3, 110.2, 77.1, 75.8, 67.2, 61.2, 45.7, 27.2, 25.6. Anal. Calcd for $C_{15}H_{19}NO_4$ (277.31): C, 64.96; H, 6.91; N, 5.05. Found: C, 65.91; H, 6.59; N, 5.07.

(3*R*,4*S*)-1-Benzyl-4-[(1*S*,5*S*)-5-benzyloxymethyl-3,3-dimethyl-2,4-dioxacyclopentane-1-yl]-3-hydroxyazetidin-2-one (10). Method B was followed starting from **8**: yield 6.61 g (95%); mp 98−102 °C; $[\alpha]^{25}_D$ = −12.9 (c = 1.0, CH_2Cl_2); IR (KBr) 3270 (OH), 1723 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.4−7.2 (m, 10H), 4.82 (d, 1H, J = 14.5 Hz), 4.77 (d, 1H, J = 4.5 Hz), 4.52 (s, 2H), 4.19 (dd, 1H, J = J' = 6.6 Hz), 4.16 (d, 1H, J = 14.5 Hz), 4.13 (s, 1H), 3.98 (dt, 1H, J = 5.6 Hz, J' = 6.6 Hz), 3.64 (d, 2H, J = 5.6 Hz), 3.60 (dd, 1H, J = 4.5 Hz, J' = 6.6 Hz), 1.37 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 168.8, 137.0, 135.4, 128.7, 128.6, 128.5, 128.0, 127.9, 127.8, 110.0, 78.8, 77.7, 76.0, 73.8, 70.4, 59.3, 45.4, 27.1, 27.0; MS m/z 382 (M − 15). Anal. Calcd for $C_{23}H_{27}NO_5$ (397.47): C, 69.50; H, 6.85; N, 3.52. Found: C, 69.15; H, 7.16; N, 3.91.

(3*R*,4*S*)-1-Benzyl-4-[(1*S*,5*S*)-5-carbamoyloxymethyl-3,3-dimethyl-2,4-dioxacyclopentane-1-yl]-3-hydroxyazetidin-2-one (15). Method A was followed starting from **14**: yield 2.79 g (91%); mp 176−178 °C; $[\alpha]^{25}_D$ = −25.4 (c = 1.0, CH_2Cl_2); IR (KBr) 3473 (NH), 3359 (OH), 1714 (CO), 1704 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.36−7.26 (m, 5H), 4.86 (d, 1H, J = 4.8 Hz), 4.72 (d, 1H, J = 14.9 Hz), 4.40 (m, 1H), 4.27 (d, 1H, J = 14.9 Hz), 4.20 (dd, 1H, J = 6.4 Hz, J' = 8.6 Hz), 4.07 (m, 2H), 3.72 (dd, 1H, J = 4.8 Hz, J' = 8.6 Hz), 1.39 and 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 168.1, 156.1, 135.0, 127.5, 126.6, 109.3, 77.7, 76.1, 74.8, 63.8, 59.5, 44.1, 26.6, 26.4; EIMS m/z 440 (M + 1). Anal. Calcd for $C_{17}H_{22}N_2O_6$ (439.3): C, 58.30; H, 6.33; N, 8.00. Found: C, 57.98; H, 6.61; N, 7.86.

(2*R*,3*R*,4*R*,5*R*)-5-((3′*S*,4′*R*)-1-Benzyl-3-hydroxyazetidin-2-one-4-yl)-3,4-dihydroxy-3,4-di-*O*-isopropylidene-2-methoxytetrahydrofuran (35). Method A was followed, starting from **34**: yield 2.37 g (97%); mp 194−196 °C; $[\alpha]^{25}_D$ = −35.3 (c = 1.0, CH_2Cl_2); IR (KBr) 3229 (OH), 1720 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.38−7.20 (m, 5H), 5.0 (s, 1H), 4.96 (d, 1H, J = 4.7 Hz), 4.88 (d, 1H, J = 15.7 Hz), 4.81 (dd, 1H, J = 1.6 Hz, J' = 6.0 Hz), 4.55 (d, 1H, J = 6.0 Hz), 4.51 (dd, 1H, J = 1.6 Hz, J' = 7.2 Hz), 4.18 (d, 1H, J = 15.7 Hz), 3.80 (dd, 1H, J = 4.7 Hz, J' = 7.2 Hz), 3.14 (s, 3H), 1.50 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 169.8, 135.5, 128.7, 127.6, 127.4, 112.6, 110.0, 88.3, 84.7, 81.5, 75.9, 59.9, 55.3, 44.6, 26.4, 24.9; EIMS m/z 350 (M + 1). Anal. Calcd for $C_{18}H_{23}NO_6$ (349.38): C, 61.86; H, 6.63; N, 4.01. Found: C, 61.48; H, 6.92; N, 4.05.

(2*R*,3*R*,4*S*,5*S*,6*R*)-6-((3′*S*,4′*R*)-1-Benzyl-3-hydroxyazetidin-2-one-4-yl)-2,3,4,5-tetrahydroxy-2,3:4,5-bis(di-*O*-isopropylidene)pyrane (49). Method B was followed: yield 6.74 g (95%); oil $[\alpha]^{25}_D$ = −49.7 (c = 1.0, CH_2Cl_2); IR (film) 3330 (OH), 1735 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.29−7.25 (m, 5H), 6.57 (d, 1H, J = 5.1 Hz), 4.83 (d, 1H, J = 4.9 Hz), 4.76 (d, 1H, J = 14.5 Hz), 4.59 (dd, 1H, J = 2.4 Hz, J' = 7.9 Hz), 4.40 (dd, 1H, J = 1.6 Hz, J' = 7.9 Hz), 4.33 (dd, 1H, J = 2.4 Hz, J' = 5.1 Hz), 4.25 (d, 1H, J = 14.5 Hz), 4.12 (dd, 1H, J = 1.6 Hz, J' = 6.6 Hz), 3.80 (dd, 1H, J = 4.9 Hz, J' = 6.6 Hz), 1.54, 1.41, 1.32 and 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 169.8, 135.9, 128.6, 128.5, 127.5, 109.4, 108.9, 96.2, 75.9, 71.0, 70.7, 70.4, 68.0, 57.1, 45.1, 25.9, 24.9, 24.4; EIMS m/z 406 (M + 1).

Synthesis of Bis-*β*-lactam 30. To a solution of (4*R*,5*R*)-(−)-diethyl-2,3-*O*-isopropylidene-L-tartrate (2.44 g, 10 mmol) in dry toluene (30 mL) at −78 °C was added dropwise a 1 M solution of DIBAL (22 mL) in hexane. The resulting solution was stirred for 3 h, and then benzylamine (2.18 mL, 20 mmol) was added in one portion and the reaction mixture allowed to warm to room temperature and stirred for 14 h. The nitrogen balloon was then removed, and the reaction mixture was stirred under air for 8 h. The precipitate formed was filtered off, and the filtrate was concentrated to get the diimine **29**, which was used without further purification. A solution of benzyloxyacetyl chloride (3.94 mL, 25 mmol) in anhydrous methylene chloride (30 mL) was added to a solution of the diimine (18 mmol) and triethylamine (7.48 mL, 54 mmol) in methylene chloride (100 mL) at −20 °C under a nitrogen atmosphere. The resulting mixture was allowed to warm to room temperature and stirred for 14 h. The reaction mixture was washed with water (100 mL), a solution of HCl 1 M (100 mL), and a saturated solution of $NaHCO_3$ (100 mL). The organic layer was dried over $MgSO_4$, the solvent evaporated under vaccum, and the thus obtained crude was purified by column chromatography (silica gel 60, eluent EtOAc/hexane 1:4). The resulting product was dissolved in ethanol (50 mL), and 10% Pd/C (0.6 g) was added. The mixture was stirred under 1 atm H_2 for 15 h and then filtered off using a path of Celite. Evaporation of the solvent afforded compound **30** as a white solid: yield 1.80 g (40%); mp 212−214 °C (EtOAc); $[\alpha]^{25}_D$ = +17.2 (c = 1.0, DMSO); IR (KBr) 3250 (OH), 1748, 1727 cm^{-1} (CO); ^1H NMR (DMSO-d_6, δ) 7.36−7.20 (m, 10H), 6.12 (d, 2H, J = 3.9 Hz), 4.70 (d, 2H, J = 4.4 Hz), 4.56 (d, 2H, J = 14.9 Hz), 4.12 (d, 2H, J = 14.9 Hz), 3.98 (dd, 2H, J = 5.9 Hz, J' = 1.7 Hz), 3.60 (dd, 2H, J = 5.1 Hz, J' = 1.7 Hz), 1.25 (s, 6H); ^{13}C NMR ($CDCl_3$, δ) 168.8, 136.5, 128.5, 127.4, 127.2, 108.5, 78.7, 75.7, 58.6, 44.7, 26.8. Anal. Calcd for $C_{25}H_{28}N_2O_6$ (452.49): C, 66.55; H, 6.23; N, 6.19. Found: C, 66.20; H, 6.56; N, 6.12.

General Procedure for the Preparation of α-Amino Acid *N*-Carboxyanhydrides (NCAs). To a magnetically stirred solution of 3-hydroxyazetidin-2-one (1 mmol) in 5 mL of methylene chloride were added 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) (0.002 g, 0.01 mmol) and a solution of potassium bromide (0.012 g, 0.1 mmol) in water (0.15 mL) at room temperature. The solution was cooled to −5 to 0 °C (ice−salt bath), and aqueous sodium hypochlorite (Aldrich, cat. no. 23,930-5) (10 mL) buffered at pH 7 (0.6 g of sodium hydrogen carbonate for 30 mL of a concentrate buffer solution phosphate,

Aldrich, cat. no. 22,358-1) was added. The resulting reaction mixture was stirred at 0 °C for 0.5−2 min. The organic layer was separated and washed with 20 mL of 10% HCl containing 0.25 g of KI, a 10% solution of $Na_2S_2O_3$ (10 mL), and water (10 mL). The resulting solution was dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to afford the corresponding NCA.

(4*S*)-3-Benzyl-4-[(1*S*,5*S*)-5-carbamoyloxymethyl-3,3-dimethyl-2,4-dioxacyclopentane-1-yl]oxazolidine-3,5-dione (16): yield 0.33 g (90%); mp 120−124 °C; $[\alpha]^{25}_D = -24.6$ (c = 0.5, DMSO); IR (KBr) 3456, 3353 (NH_2), 1835, 1764, 1707 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.33−7.32 (m, 5H), 5.28 (m, 2H), 5.03 (d, 1H, J = 15.0 Hz), 4.42 (d, 1H, J = 15.0 Hz), 4.39−4.34 (m, 1H), 4.32−4.19 (m, 3H), 4.11−4.04 (m, 1H), 1.40 and 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 165.6, 156.5, 152.1, 134.3, 128.9, 128.4, 110.6, 77.2, 75.9, 64.0, 60.7, 46.9, 26.8, 26.7. Anal. Calcd for $C_{17}H_{20}N_2O_7$ (364.35): C, 56.04; H, 5.53; N, 7.64. Found: C, 55.68; H, 5.71; N, 7.86.

Bis NCA 31. The general procedure was followed starting from 0.45 g of **30**: yield 0.47 g (98%); ^1H NMR ($CDCl_3$, δ) 7.35−7.25 (m, 10H), 5.02 (d, 2H, J = 15.0 Hz), 4.55 (d, 2H, J = 4.4 Hz), 4.38 (d, 2H, J = 15.0 Hz), 1.33 (s, 6H); ^{13}C NMR ($CDCl_3$, δ) 166.2, 151.8, 134.3, 129.0, 128.6, 128.5, 111.8, 61.3, 47.0, 26.6.

5-(Benzylamino)-5-deoxy-1-*O*-methyl-2,3-di-*O*-isopropylidene-*β*-D-allofuranuronic acid NCA (36): yield 0.33 g (91%); oil; IR (film) 1843 (CO), 1778 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.35−7.20 (m, 5H), 5.11 (dd, 1H, J = 2.2 Hz, J' = 5.9 Hz), 5.09 (d, 1H, J = 15.7 Hz), 5.00 (s, 1H), 4.57 (d, 1H, J = 5.9 Hz), 4.44 (dd, 1H, J = 2.2 Hz, J' = 6.3 Hz), 4.36 (d, 1H, J = 13.7 Hz), 4.21 (d, 1H, J = 6.3 Hz), 3.16 (s, 3H), 1.45 (s, 3H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 165.7, 152.1, 134.3, 129.1, 128.4, 127.5, 113.4, 110.1, 88.1, 84.3, 80.2, 61.1, 56.0, 46.6, 26.6, 25.0; EIMS m/z 364 (M + 1).

(2*R*,3*R*,4*S*,5*S*,6*R*)-6-((4′*R*)-3-Benzyloxazolidine-2,3-dione-4-yl)-2,3,4,5-tetrahydroxy-2,3:4,5-bis(di-*O*-isopropilidene)-pyran (50): yield 0.40 g (95%); oil; IR (film) 1848, 1778 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.5−7.2 (m, 5H), 5.62 (d, 1H, J = 5.0 Hz), 5.06 (d, 1H, J = 14.6 Hz), 4.62 (dd, 1H, J = 8.0 Hz, J' = 2.7 Hz), 4.5−4.2 (m, 3H), 4.34 (d, 1H, J = 14.6 Hz), 4.2−4.0 (m, 1H), 1.52, 1.37, 1.34 and 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 165.6, 152.4, 134.4, 129.0, 128.9, 128.5, 110.2, 109.3, 96.2, 70.4, 70.1, 69.8, 68.8, 57.1, 47.5, 26.0, 25.4, 24.7, 24.4; EIMS m/z (M^+) 419.

General Procedure for the Coupling of NCAs with α-Amino Acid Esters. To a solution of the corresponding NCA (1 mmol) in the corresponding solvent (10 mL) was added the α-amino acid ester (2 mmol), and the resulting mixture stirred at room temperature for 24 h. Then diethyl ether (40 mL) was added, and the organic layer was washed with 0.1 N HCl (2 × 50 mL) and a saturated solution of $NaHCO_3$ (2 × 50 mL) and dried over $MgSO_4$ and the solvent evaporated under reduced pressure to afford the corresponding peptide, which was purified by column chromatography.

Tripeptide product 40: yield 0.50 g (87%); mp 108−110 °C; $[\alpha]^{25}_D = -34.0$ (c = 0.5, CH_2Cl_2); IR (KBr) 3318 (NH), 1746, 1682, 1652 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.80 (d, 1H, J = 7.9 Hz), 7.38−7.27 (m, 5H), 6.52 (d, 1H, J = 8.4 Hz), 5.05 (d, 1H, J = 6.0 Hz), 4.92 (s, 1H), 4.59 (d, 1H, J = 6.0 Hz), 4.60−4.40 (m, 2H), 4.17 (d, 1H, J = 9.0 Hz), 3.74 (d, 1H, J = 12.9 Hz), 3.72 (s, 3H), 3.63 (d, 1H, J = 12.9 Hz), 3.28 (s, 3H), 3.23 (d, 1H, J = 9.0 Hz), 1.76−1.45 (m, 6H), 1.42 and 1.28 (s, 3H), 1.04−0.9 (m, 12H); ^{13}C NMR ($CDCl_3$, δ) 173.0, 171.7, 171.3, 138.9, 128.7, 128.0, 127.5, 112.3, 110.3, 87.1, 85.0, 81.6, 65.5, 55.7, 52.9, 52.2, 51.1, 50.7, 41.2, 40.3, 26.4, 25.0, 24.7, 22.8, 22.7, 21.9. Anal. Calcd for $C_{30}H_{47}N_3O_8$ (577.72): C, 62.37; H, 8.20; N, 7.27. Found: C, 62.62; H, 8.48; N, 7.41.

Tripeptide Product 41. To a solution of **40** (0.29 g, 0.5 mmol) and $(Boc)_2O$ (0.45 g, 2 mmol) in ethanol (13 mL) was added 10% $Pd(OH)_2$ on charcoal (0.030 g), and the mixture was kept under hydrogen (1 atm). The reaction mixture was stirred at room temperature until the dissappearance of the starting material as monitored by TLC (24 h). Then, the suspension was filtered through a pad of Celite and evaporated to yield **41**, which was purified by column chromatography and further crystallization from EtOAc/Hex: yield 0.21 g (71%); mp 128−130 °C; $[\alpha]^{25}_D = -28.6$ (c = 1.0, CH_2Cl_2); IR (KBr) 3293 (NH), 1748, 1720, 1655, 1649 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 6.65 (d, 1H, J = 8.4 Hz), 6.52 (d, 1H, J = 8.2 Hz), 6.10 (d, 1H, J = 8.1 Hz), 4.92 (s, 1H), 4.85 (d, 1H, J = 3.9 Hz), 4.68 (d, 1H, J = 5.9 Hz), 4.58−4.45 (m, 3H), 4.30−4.24 (m, 1H), 3.71 (s, 3H), 3.37 (s, 3H), 1.69−1.51 (m, 6H), 1.45 (s, 9H), 1.45 (s, 3H), 1.29 (s, 3H), 1.25−0.87 (m, 12H); ^{13}C NMR ($CDCl_3$, δ) 172.9, 171.3, 169.6, 155.7, 112.7, 110.0, 87.1, 85.3, 81.9, 80.7, 56.9, 55.8, 52.2, 51.3, 50.7, 41.2, 40.6, 28.2, 26.4, 25.0, 24.6, 24.5, 22.9, 22.8, 21.9, 21.7. Anal. Calcd for $C_{28}H_{49}N_3O_{10}$ (587.71): C, 57.22; H, 8.40; N, 7.15. Found: C, 57.25; H, 8.70; N, 7.17.

Dipeptide product 43: yield 0.460 g (90%); mp 142−144 °C; $[\alpha]^{25}_D = -54.8$ (c = 1.0, MeOH); IR (KBr) 3452, 3343 (NH, NH_2), 1733, 1720, 1666 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 8.26 (d, 1H, J = 8.6 Hz), 7.32−7.21 (m, 5H), 4.98 (s, 1H), 4.91−4.84 (m, 2H), 4.66 (d, 1H, J = 6.0 Hz), 4.49 (d, 1H, J = 6.0 Hz), 4.46 (dd, 1H, J = 4.1 Hz, J' = 5.9 Hz), 4.17 (dd, 1H, J = 4.1 Hz, J' = 11.6 Hz), 4.03 (m, 2H), 3.96 (d, 1H, J = 13.4 Hz), 3.79 (s, 3H), 3.59 (d, 1H, J = 13.4 Hz), 3.37 (s, 3H), 3.29 (d, 1H, J = 7.0 Hz), 2.41 (s, 2H), 1.43, 1.35, 1.26 and 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 173.0, 170.2, 157.3, 139.6, 128.9, 128.6, 127.8, 113.2, 110.5, 110.2, 87.4, 86.0, 81.9, 78.6, 77.1, 65.4, 64.6, 56.0, 54.7, 53.2, 52.8, 27.8, 27.7, 26.9, 25.4. Anal. Calcd for $C_{27}H_{39}N_3O_{11}$ (581.62): C, 55.76 H, 6.76; N, 7.22. Found: C, 55.63; H, 7.05; N, 7.28.

Methyl 5-(Benzylamino)-5-deoxy-*β*-D-allofuranuronate, 1-*O*-Methyl-2,3-di-*O*-isopropylidene (37). Compound **36** (0.36 g, 1 mmol) was dissolved in MeOH (8 mL), and the solution was stirred at room temperature for 2 h. The evaporation of the solvent afforded crude **37**, which was purified by crystallization from hexane: yield 0.17 g (96%); mp 82−84 °C; $[\alpha]^{25}_D = -10.0$ (c = 1.0, CH_2Cl_2); IR (KBr) 3342 (NH), 1739 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 7.30−7.20 (m, 5H), 4.91 (s, 1H), 4.82 (d, 1H, J = 6 Hz), 4.64 (d, 1H, J = 3.8 Hz), 4.62 (d, 1H, J = 6.0 Hz), 3.96 (d, 1H, J = 13.3 Hz), 3.73 (s, 3H), 3.52 (d, 1H, J = 13.3 Hz), 3.31 (d, 1H, J = 3.8 Hz), 3.30 (s, 3H), 2.66 (m, 1H), 1.44 and 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 172.1, 139.7, 128.1, 127.9, 126.7, 111.8, 110.9, 87.7, 85.9, 82.2, 62.2, 55.4, 51.7, 26.3, 24.8; EIMS m/z $(M + H)^+$ 352, 353. Anal. Calcd for $C_{18}H_{26}NO_6$ (351.4): C, 61.52; H, 7.17; N, 3.98. Found: C, 61.48; H, 7.19; N, 4.06.

Methyl 5-Amino-5-deoxy-*β*-D-allofuranuronate, 1-*O*-Methyl-2,3-di-*O*-isopropylidene 42. To a solution of **37** (0.28 g, 0.8 mmol) in methanol (5 mL) was added 10% palladium on charcoal (10% w/w, 0.03 g), and the mixture was kept under hydrogen (1 atm). The reaction mixture was stirred at room temperature for 4 h. Then, the suspension was filtered through a pad of Celite and evaporated to afford crude compound **42**, which was purified by column chromatography: yield 0.167 g (80%); mp 36−38 °C; $[\alpha]^{25}_D = -44.4$ (c = 1.0, CH_2Cl_2); IR (KBr) 3391 (NH), 1746 cm^{-1} (CO); ^1H NMR ($CDCl_3$, δ) 4.80 (d, 1H, J = 5.7 Hz), 4.79 (s, 1H), 4.56 (d, 1H, J = 4.5 Hz), 4.45 (d, 1H, J = 5.7 Hz), 3.62 (s, 3H), 3.41 (d, 1H, J = 4.5 Hz), 3.21 (s, 3H), 1.84 (s, 2H) 1.34 and 1.18 (s, 3H); ^{13}C NMR ($CDCl_3$, δ) 173.6, 111.9, 110.4, 88.1, 85.7, 81.6, 56.8, 55.2, 51.9, 26.2, 24.6. EIMS m/z 262 (M + 1). Anal. Calcd for $C_{11}H_{19}NO_6$ (261.27): C, 50.57; H, 7.32; N, 5.36. Found: C, 50.78; H, 7.53; N, 5.39.

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Supporting Information Available: Characterization data for **11**, **12**, **19**−**21**, **22a**,**b**, **23a**, *epi*-**23a**, **23b**, **23c**, **24a**,**b**, **25a**,**b**, **26**−**28**, **32**, **38**, **39**, **45**, **51**, and **52**, ORTEP representations of **34**, **39**, and **48**, and NMR spectra of representative compounds (30 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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