

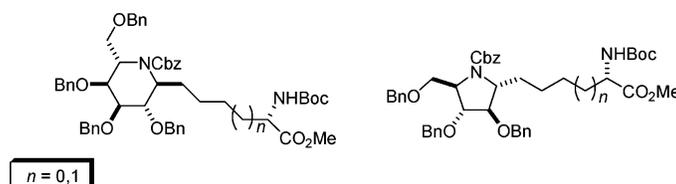
**Cross-Metathesis of C-Allyl Iminosugars with Alkenyl Oxazolidines as a Key Step in the Synthesis of C-Iminoglycosyl α -Amino Acids.¹
A Route to Iminosugar Containing C-Glycopeptides**

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A general access to a novel class of sugar α -amino acids composed of iminofuranose and iminopyranose residues anomerically linked to the glycyl group through an alkyl chain is described. A set of eight compounds was prepared by the same reaction sequence involving as an initial step the Grubbs Ru-carbene-catalyzed cross-metathesis (CM) of various *N*-Cbz-protected allyl *C*-iminoglycosides with *N*-Boc-vinyl- and *N*-Boc-allyloxazolidine. The isolated yields of the CM products (mixtures of *E*- and *Z*-alkenes) varied in the range 40–70%. Each mixture was elaborated by first reducing the carbon-carbon double bond using in situ generated diimide and then unveiling the *N*-Boc glycyl group [CH(BocNH)CO₂H] by oxidative cleavage of the oxazolidine ring by the Jones reagent. All amino acids were characterized as their methyl esters. The insertion of a model *C*-iminoglycosyl-2-aminopentanoic acid into a tripeptide via sequential carboxylic and amino group coupling with *L*-phenylalanine derivatives was carried out as a demonstration of the potential of these sugar amino acids in designed glycopeptide synthesis.

Introduction

Densely hydroxylated chiral pyrrolidines and piperidines, currently known as imino- or azasugars,² be they obtained by chemical synthesis or extracted from natural sources,³ owe their importance in glycomedicine and glycobiology⁴ to their effectiveness and specificity against the action of carbohydrate-processing enzymes such as glycosidases⁵ and glycosyltransferases.^{5a,6} The inhibition of glycoconjugate-associated enzymes such as nucleoside phosphorylases has been recently discovered

as well.⁷ These enzyme-promoted processes are key steps in a multitude of events either beneficial or detrimental for living organisms and which essentially involve cell growth, regulation, and proliferation. Hence, iminosugars that inhibit these enzymes are useful as probes for

(1) The trivial name *C*-iminoglycosyl amino acid has to be used only for compounds featuring the iminosugar fragment linked by the pseudoanomeric center (C1) to the glycyl group (CH(NH₂)CO₂H) through a carbon tether.

(2) (a) Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199. (b) Stütz, A. E. *Iminosugars as Glycosidase Inhibitors; Nojirimycin and Beyond*; Wiley-VCH: Weinheim, Germany, 1999.

(3) (a) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645. (b) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265.

(4) For a basic treatise on this topic, see: *Essentials of Glycobiology*; Varki, A., Cummings, R., Esko, J., Freeze, H., Hart, G., Marth, J., Eds.; Cold Spring Harbor Laboratory Press: Cold Spring Harbor, 1999.

(5) (a) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300. (b) Ossor, A.; Elbein, A. D. *Glycoprotein Processing Inhibitors. In Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH: Weinheim, Germany, 2000; Part II, Vol. 3, p 513. (c) Asano, N. *Curr. Top. Med. Chem.* **2003**, *3*, 471. (d) Lillend, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515.

(6) (a) Compain, P.; Martin, O. R. *Bioorg. Med. Chem.* **2001**, *9*, 3077. (b) Schuster, M.; Blechert, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1809. (c) Bastida, A.; Fernandez-Mayoralas, A.; Arrayas, R. G.; Iradier, F.; Carretero, J. C.; Garcia-Junceda, E. *Chem. Eur. J.* **2001**, *7*, 2390. (d) Compain, P.; Martin, O. R. *Curr. Top. Med. Chem.* **2003**, *3*, 541. (e) Marotte, K.; Ayad, T.; Génisson, Y.; Besra, G. S.; Baltas, M.; Prandi, J. *Eur. J. Org. Chem.* **2003**, 2557.

(7) (a) Miles, R. W.; Tyler, P. C.; Furneaux, R. H.; Bagdassarian, C.; Schramm, V. L. *Biochemistry* **1998**, *37*, 8615. (b) Evans, G. B.; Furneaux, R. H.; Hutchinson, T. L.; Kezar, H. S.; Morris, P. E., Jr.; Schramm, V. L.; Tyler, P. C. *J. Org. Chem.* **2001**, *66*, 5723. (c) Fedorov, A.; Shi, W.; Kicska, G.; Fedorov, E.; Tyler, P. C.; Furneaux, R. H.; Hanson, J. C.; Gainsford, G. J.; Larese, J. Z.; Schramm, V. L.; Almo, S. C. *Biochemistry* **2001**, *40*, 853. (d) Evans, G. B.; Furneaux, R. H.; Hausler, H.; Larsen, J. S.; Tyler, P. C. *J. Org. Chem.* **2004**, *69*, 2217.

studies on structure/function of enzymatic catalysis and serve as leads for the development of new efficient drugs against diabetes,⁸ cancer metastasis,⁹ viral infections,¹⁰ particularly that of the human immunodeficiency virus (HIV),¹¹ tuberculosis,¹² lysosomal storage diseases,¹³ and parasitic protozoa.¹⁴ Aiming at broadening the scope of iminosugars in drug discovery, more recent and increasing interest is being addressed to the design and synthesis of iminosugar C-glycosides of some complexity,¹⁵ i.e., compounds in which the iminosugar is linked through the pseudoanomeric carbon (C1) to another carbohydrate residue or an aglycon moiety by an all-carbon tether. For instance, the attention to aza-C-disaccharides¹⁶ which followed the synthesis of the (1,6)-methylene-linked iminomannose-glucose couple **A** reported by Johnson and co-workers¹⁷ (Figure 1) was supported by the suggestion that the attachment of an aglycon-mimicking sugar unit to an iminosugar would result in increased potency and specificity.^{18,19} Carbon-linked iminosugar-containing nucleosides such as **B** and **C** were reported as well (Figure

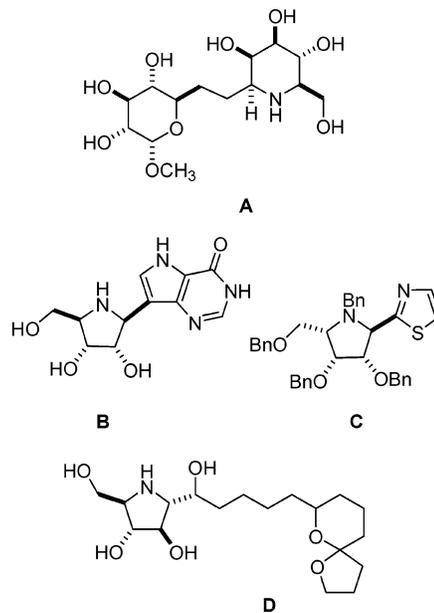


FIGURE 1. Examples of complex iminosugar C-glycosides: **A**, ref 17; **B**, ref 7d; **C**, ref 20; **D**, ref 22.

1). Compound **C** is just an example of various thiazolyl nucleosides with stereochemical diversity in the iminosugar residue which have been recently prepared in our laboratory.²⁰ Noteworthy as a member of a large family of iminosugar C-glycoside natural products is compound **D**, called broussonetine G, isolated by Kusano and co-workers²¹ and whose total synthesis has been recently performed in the Trost laboratory.²²

On the other hand, we are not aware of the existence of carbon-linked iminosugar-containing peptides (C-iminoglycopeptides). These compounds would constitute a new class of unnatural peptides combining hydrolytic stability with inhibitory properties. As the preparation of C-glycopeptides requires easy access to C-glycosyl amino acids,²³ key precursors to their iminosugar-containing analogues are C-iminoglycosyl α -amino acids **I** (Scheme 1). With this goal in mind, Fuchss and Schmidt reported a few years ago²⁴ on the first synthesis of a compound of type **I** called nojirimycinyl C-L-serine because the iminosugar moiety was β -linked to an (S)- α -aminobutanoic acid residue serving as L-serine methylene isostere. The key operation in this synthesis involved the construction of the chiral glycyl group by hydrogenation of an enamide ester group linked to the sugar moiety

(8) Truscheit, E.; Frommer, W.; Junge, B.; Müller, L.; Schmidt, D. D.; Wingender, W. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 744. (b) Horii, S.; Fukase, H.; Matsuo, T.; Kameda, Y.; Asano, N.; Matsui, K. *J. Med. Chem.* **1986**, *29*, 1038. (c) Horii, S.; Fukase, H.; Matsuo, T.; Kameda, Y.; Asano, N.; Matsui, K. *Drugs Future* **1986**, *11*, 1039. (d) Elbein, A. D. *Annu. Rev. Biochem.* **1987**, *56*, 497. (e) Anzeveno, P. B.; Creemer, L. J.; Daniel, J. K.; King, C.-H. R.; Liu, P. S. *J. Org. Chem.* **1989**, *54*, 2539. (f) Andersen, B.; Rassov, A.; Westergaard, N.; Lundgren, K. *Biochem. J.* **1999**, *342*, 545.

(9) Bernacki, R. J.; Niedbala, M. J.; Korytnyk, W. *Cancer Metastasis Rev.* **1985**, *4*, 81. (b) Humphries, M. J.; Matsumoto, K.; White, S. L.; Olden, K. *Cancer Res.* **1986**, *46*, 5215. (c) Spearman, M. A.; Jamieson, J. C.; Wright, J. A. *Exp. Cell. Res.* **1987**, *168*, 116. (d) Tsukamoto, K.; Uno, A.; Shimada, S.; Imokawa, G. *Clin. Res.* **1989**, *37A*, 722. (e) Goss, P. E.; Baptiste, J.; Fernandes, B.; Baker, M.; Dennis, J. W. *Cancer Res.* **1994**, *54*, 1450. (f) Goss, P. E.; Baker, M. A.; Carver, J. P.; Dennis, J. W. *Clin. Cancer Res.* **1995**, *1*, 935. (g) Nishimura, Y.; Satoh, T.; Adachi, H.; Kondo, S.; Takeuchi, T.; Azetaka, M.; Fukuyasu, H.; Lizuka, Y. *J. Med. Chem.* **1997**, *40*, 2626.

(10) (a) Häusler, H.; Kawakami, P.; Mlaker, E.; Severn, W. B.; Wrodnigg, T. M.; Stütz, A. E. *J. Carbohydr. Chem.* **2000**, *19*, 435. (b) Durantel, D.; Branza-Nichita, N.; Carrouee-Durantel, S.; Butters, T. D.; Dwek, R. A.; Zitzmann, N. *J. Virol.* **2001**, *75*, 8987.

(11) (a) Gruters, R. A.; Neeffes, J. J.; Tersmette, M.; de Goede, R. E. Y.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature* **1987**, *330*, 74. (b) Datema, R.; Olafsson, S.; Romero, P. A. *Pharmacol. Ther.* **1987**, *33*, 221. (c) Tymas, A. S.; Berric, E. M.; Ryder, T. A.; Nash, R. J.; Hegarty, M. P.; Taylor, D. L.; Mobberley, M. A.; Davis, J. M.; Bell, E. A.; Jeffries, D. J.; Taylor-Robinson, D.; Fellows, L. E. *Lancet* **1987**, *2*, 1025. (d) Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petrusson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, J. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 9229. (e) Fenouillet, E.; Papandreou, M. J.; Jones, I. M. *Virology* **1997**, *231*, 89.

(12) (a) Davis, B. G.; Brandstetter, T. W.; Hackett, L.; Winchester, B. G.; Nash, R. J.; Watson, A. A.; Griffiths, R. C.; Smith, C.; Fleet, G. W. J. *Tetrahedron* **1999**, *55*, 4489. (b) Shilcock, J. P.; Wheatley, J. R.; Nash, R. J.; Watson, A. A.; Griffiths, R. C.; Butters, T. D.; Muller, M.; Watkin, D. J.; Winkler, D. A.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2735.

(13) Fan, J. Q.; Ishii, S.; Asano, N.; Suzuki, Y. *Nat. Med.* **1999**, *5*, 112.

(14) (a) Li, C. M.; Tyler, P. C.; Furneaux, R. H.; Kicska, G.; Xu, Y. M.; Grubmeyer, C.; Girvin, M. E.; Schramm, V. L. *Nat. Struct. Biol.* **1999**, *6*, 582. (b) Miles, R. W.; Tyler, P. C.; Evans, G. B.; Furneaux, R. H.; Parkin, D. W.; Schramm, V. L. *Biochemistry* **1999**, *38*, 13147.

(15) Martin, O. R. Toward Azaglycoside Mimics: Aza-C-glycosyl Compounds and Homoazaglycosides. In *Carbohydrate Mimics. Concepts and Methods*; Chapleur, Y., Ed.; Wiley-VCH: Weinheim, Germany, 1998; p 259.

(16) Robina, I.; Vogel, P. *Synlett* **2005**, *5*, 675.

(17) (a) Johnson, C. R.; Miller, M. W.; Golebiowski, A.; Sundram, H.; Ksehati, M. B. *Tetrahedron Lett.* **1994**, *35*, 8991. (b) Johns, B. A.; Pan, Y. T.; Elbein, A. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 4856.

(18) Legler, G. The Catalytic Efficiency of Glycoside Hydrolases and Models of the Transition State Based on Substrate Related Inhibitors. In *Carbohydrate Mimics. Concepts and Methods*; Chapleur, Y., Ed.; Wiley-VCH: Weinheim, Germany, 1998; p 463.

(19) It is worth recalling that also Wong and co-workers were at the forefront of azasugar-containing disaccharide and nucleoside synthesis "...in an effort to develop specific glycosidase inhibitors, as many glycosidases which recognize the same glycon moiety may differ only with the substrate aglycon portion and the type of glycosidic linkage". However, the compounds prepared by the Wong group featured an aminomethyl bridge between the two molecular residues. See: Wong, C.-H.; Provencher, L. Porco, J. A., Jr.; Jung, S.-H.; Wang, Y.-F.; Chen, L.; Wang, R.; Steensma, D. H. *J. Org. Chem.* **1995**, *60*, 1492.

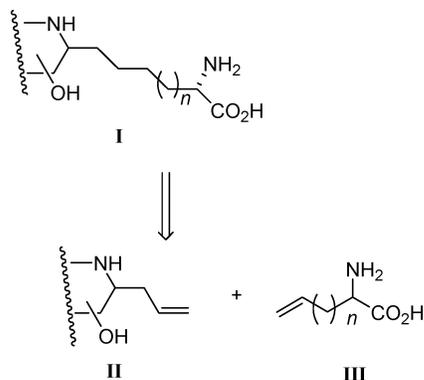
(20) (a) Dondoni, A.; Giovannini, P. P.; Perrone, D. *J. Org. Chem.* **2002**, *67*, 7203. (b) Dondoni, A.; Perrone, D. *Tetrahedron* **2003**, *59*, 4261.

(21) Shibano, M.; Tsukamoto, D.; Kusano, G. *Heterocycles* **2002**, *57*, 1539.

(22) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5987.

(23) Dondoni, A.; Marra, A. *Chem. Rev.* **2000**, *100*, 4395.

(24) Fuchss, T.; Schmidt, R. R. *Synthesis* **2000**, 259.

SCHEME 1. Retrosynthetic Plan to Carbon-Linked Iminosugar α -Amino Acids


through a methylene bridge. This reaction afforded a 6:1 mixture of the two aminoester epimers in good overall yield (81%). However, the efficiency of this approach cannot be generalized since the stereochemical outcome may vary substantially by changing the iminosugar residue²⁵ and the length of the side chain. This constitutes a substantial drawback in the preparation of collections of *C*-glycosyl amino acids with a stereochemical uniformity. Hence, we report here our own method which stems from a simple disconnection of **I** and is centered on the cross-metathesis (CM)²⁶ of alkenes **II** and **III** featuring an iminosugar residue and a glycyl group respectively (Scheme 1). The transformation of the resulting CM product into **I** will simply require the reduction of the newly formed carbon–carbon double bond connecting the two functionalized moieties. The unveiling of the glycyl group might be required in case that a protected form or a synthetic equivalent had been employed. This method avoids the problems that are encountered in synthetic approaches involving the construction of the two key stereocenters, i.e., the pseudoanomeric carbon of the sugar fragment and the carbon bearing the amino group in the glycyl moiety. This work represents an extension to iminosugars of our recent CM-centered synthesis of *C*-glycosyl amino acids.²⁷

Results and Discussion

Preparation of Alkenes for CM Reactions. In the context of a program directed at the synthesis of a variety of *C*-iminoglycoconjugates, we have developed a general method that allows furanose and pyranose derived *N*-benzyl hydroxylamines (hidden polyhydroxyalkyl nitrones) to be transformed into five- and six-membered iminosugars bearing a reactive carbon-linked functional group at C1 such as formyl, ethynyl, and allyl.^{20b} As these groups provide easily exploitable reactivity, they can serve to introduce the iminosugar fragment into a variety of substrates by suitable carboligation methods. Accordingly a set of *C*-formyl iminosugars was recently submitted to a Wittig-type reaction with a sugar phosphorane

(25) Fuchss, T.; Schmidt, R. R. *Synthesis* **1998**, 753.

(26) For recent reviews, see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (b) Louie, J.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 247. (c) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 1900. (d) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117.

(27) Dondoni, A.; Giovannini, P. P.; Marra, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2380

TABLE 1. Conversion of *N*-Benzyl Iminosugars **1a–d into *N*-Benzyloxycarbonyl Iminosugars **2a–d****

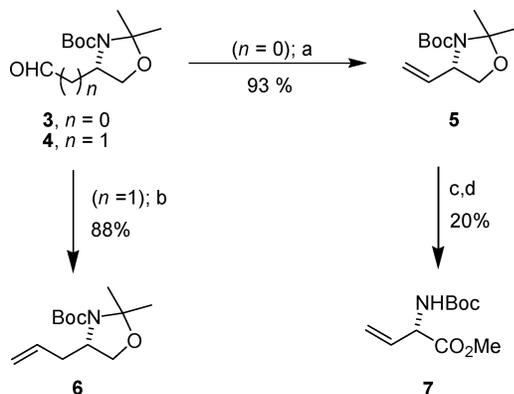
Reaction scheme: **1a–d** (with *N*-Bn group) $\xrightarrow[2) \text{ CbzCl}]{1) \text{ CAN}}$ **2a–d** (with *N*-Cbz group).

Iminosugar	Yield ^a (%)
	1a R = Bn
	2a R = Cbz (65)
	1b R = Bn
	2b R = Cbz (58)
	1c R = Bn
	2c R = Cbz (45)
	1d R = Bn
	2d R = Cbz (35)

^a Isolated yield.

and the alkenes thus obtained transformed into aza-*C*-disaccharides.^{20a} In analogy to that, we planned to take advantage of the easy access to known²⁰ *C*-allyl iminosugars **1a–c** (Table 1) and the new member **1d** and submit these alkenes to the CM with alkenes of type **III** according to the retrosynthetic plan shown in Scheme 1. However, recent reports from other laboratories²⁸ pointed out that the CM was incompatible with the endocyclic *N*-Bn group, very likely because of the coordinating ability of the latter with the Ru–carbene catalyst. Hence, we followed a similar stratagem to that of Martin and co-workers^{28b} and converted the tertiary amines **1a–d** into the less coordinating benzyloxycarbonyl (Cbz) derivatives **2a–d**. This transformation was carried out by a reaction sequence consisting of removing the benzyl group by cerium ammonium nitrate (CAN) followed by treatment with benzyl chloroformate in the presence of a base. In all cases the overall yield of this *N*-dealkylation–carbamoylation sequence was rather low very likely because of the inefficiency of the CAN-promoted dealkylation.^{28b} We considered this drawback largely compensated by the advantages associated with the inexpensive and easy preparation in a multigram scale of the *N*-benzyl derivatives **1a–d**. However, the use of the more easily dealkylable *N*-naphthalenemethyl (NAP)-protected analogues according to the work of Martin and co-workers^{28b} might provide access to *N*-Cbz *C*-allyl iminosugars **2a–d** more effectively.

(28) (a) Hu, Y.-J.; Roy, R. *Tetrahedron Lett.* **1999**, *40*, 3305 (b) Godin, G.; Compain, P.; Martin, O. R. *Org. Lett.* **2003**, *5*, 3269. (c) Vernall, A. J.; Abell, A. D. *Aldrichim. Acta* **2003**, *36*, 93.

SCHEME 2. Synthesis of Alkenes Bearing Masked and Unmasked Glycyl Groups^a

^a Reagents and conditions: (a) see ref 30; (b) $\text{Ph}_3\text{PCH}_2\text{Br}$, KHMDS, THF, -78°C to rt; (c) Jones' reagent (1 M), acetone, 0°C to rt; (d) CH_2N_2 , Et_2O , MeOH, 0°C .

The alkenes **5** and **6** that we intended to use in the CM with C-allyl iminosugars **2a–d** were bearing the N-Boc-2,2-dimethyloxazolidine residue. This represented a convenient masked glycyl group that proved to be stable under a variety of reaction conditions yet readily convertible to amino acid by a one pot cleavage–oxidation procedure²⁹ (Scheme 2). The known N-Boc-vinyloxazolidine **5**³⁰ and the hitherto unreported allyl homologue **6** were prepared in very good yields by olefination of the known aldehydes **3**³¹ and **4**,³² respectively, with the ylide generated in situ from $\text{Ph}_3\text{PMeBr}/\text{KHMDS}$. As the formation of **5** in high optical purity had been earlier established,³⁰ the same result was assumed with enough confidence for **6** since this was generated from the enantiomerically pure and configurationally stable aldehyde **4**. To compare the reactivity of **5** with that of a free glycyl containing alkene, we also prepared the N-Boc-vinyl glycinate **7**. This compound was obtained in a straightforward way from **5**, albeit in low yield (20%), by oxidative cleavage of the oxazolidine ring by the Jones reagent (CrO_3 , $\text{H}_2\text{SO}_4\text{–H}_2\text{O}$) and esterification by diazomethane.

CM Reactions and Synthesis of C-Iminoglycosyl α -Amino Acids. At the outset of this work we were quite disappointed at not being able to carry out a model CM of two alkenes of type **II** and **III** under the optimized conditions established in our earlier C-glycosyl amino acid synthesis.²⁷ Specifically, only traces of the CM product **9a** were detected by MALDI TOF analysis of the crude reaction mixture formed on mixing the β -linked C-allyl iminosugar **2a**, the N-Boc-vinyloxazolidine **5** (2 equiv) and the Grubbs 1,3-dimesityl-4,5-dihydroimidazol-

2-ylideneruthenium carbene **8**³³ (0.2 equiv) in CCl_4 at 100°C (sealed vial) for 3.5 h. Our own experimentation and the data from a recent communication by Martin and co-workers^{28b} led us to establish appropriate conditions for a satisfactory CM reaction. Hence, the above model reaction between **2a** and **5** was performed under milder conditions in CH_2Cl_2 at 40°C for 18 h with a higher excess (3 equiv) of the vinyloxazolidine **5** and 20 mol % of the Ru–carbene catalyst **8** (Scheme 3). This reaction afforded the desired CM olefin **9a** (*E,Z* mixture) in 50% isolated yield by column chromatography. In addition, the unchanged reactants **2a** and **5** were partly recovered (15–20%) while the remaining material was composed of a complex mixture of products. The elaboration of **9a** was effectively carried out by first reducing the carbon–carbon double bond by in situ generated diimide from tosylhydrazine and sodium acetate and then by submitting the product **10a** to the oxidative cleavage of the oxazolidine ring by the Jones reagent. The use of diimide left unaffected the Bn and Cbz protective groups which would instead be removed by Pd-catalyzed hydrogenation. The α -amino acid **11a** obtained in this way was isolated and characterized as its methyl ester **12a**. The configuration of the stereocenter of the glycyl group was assigned as that for the oxazolidine ring in the reactant **5** on the basis of the reasonable assumption that the above reaction sequence leading to **11a** occurs without disrupting the integrity of any stereocenter. This assumption was corroborated by the recovery of the unaltered reactants **2a** and **5** in the CM step and the lack of formation of epimers of **11a**. In addition, the one-step oxidative cleavage of the N-Boc-2,2-dimethyloxazolidine ring is well-documented to occur with preservation of the configuration of its stereocenter.^{27,29} Although we were quite gratified by the successful synthesis of **11a**, we wondered whether the yield could be improved by a more effective olefin CM. As we thought that the sluggish reaction of **2a** with **5** was due to the bulky and rigid N-Boc oxazolidine ring flanking the carbon–carbon double bond, the CM was carried out using the more flexible N-Boc vinylglycinate **7**. Unfortunately this change failed to provide the desired improvement as the CM product **13a** was obtained in slightly lower yield (40%) than **9a**. The only advantage that we could see in this route was the straightforward entry to the ester **12a** by diimide reduction of the carbon–carbon double bond. In the event, saponification of this ester into the free acid **11a** had to be carried out in order to construct a suitable building block for peptide synthesis from the C-terminus. This transformation was simply performed by treating the ester overnight at room temperature with NaOH in ethanol.³⁴ However, an optimized synthesis of the vinyl glycinate **7** from a readily available starting material is needed in order to make this route superior to that employing the masked equivalent **5**.

The same route was followed for the conversion of the allyl side-chain of three more iminosugars **2b**, **2c**, and **2d** into the α -aminopentanoic acid group (Table 2, entries

(29) (a) Dondoni, A.; Marra, A.; Massi, A. *Chem. Commun.* **1998**, 1741. (b) Dondoni, A.; Massi, A.; Marra, A. *Tetrahedron Lett.* **1998**, 39, 6601. (c) Dondoni, A.; Marra, A.; Massi, A. *J. Org. Chem.* **1999**, 64, 933. (d) Dondoni, A.; Giovannini, P. P.; Marra, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2380. (e) Dondoni, A.; Mariotti, G.; Marra, A.; Massi, A. *Synthesis* **2001**, 2129. (f) Dondoni, A.; Mariotti, G.; Marra, A. *J. Org. Chem.* **2002**, 67, 4475. (f) Dondoni, A.; Catozzi, N.; Marra, A. *J. Org. Chem.* **2004**, 69, 5023.

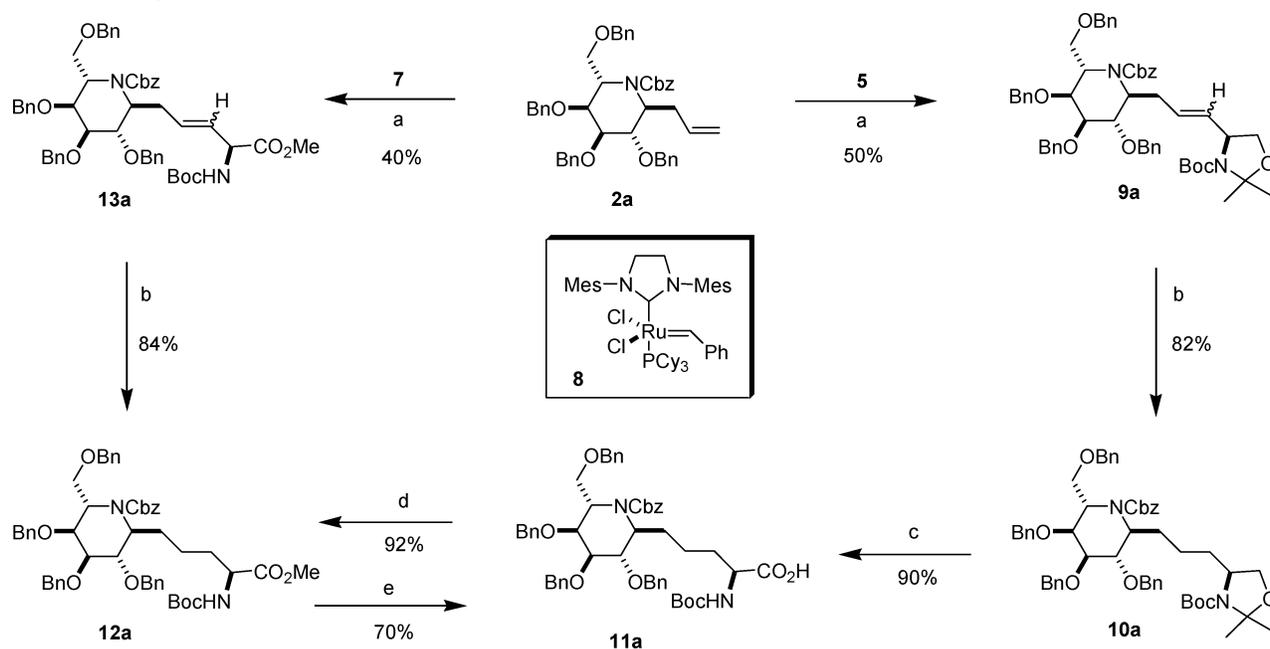
(30) McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synthesis* **1994**, 31

(31) (a) Dondoni, A.; Perrone, D. *Synthesis* **1997**, 527. (b) Dondoni, A.; Perrone, D. *Org. Synth.* **1999**, 77, 64.

(32) Dondoni, A.; Massi, A.; Minghini, E.; Bertolasi, V. *Tetrahedron* **2004**, 60, 2311.

(33) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, 1, 953.

(34) The crude amino acid **11a** obtained from the hydrolysis of **12a** showed identical ^1H NMR spectrum with that of the product derived from **10a**. Moreover, esterification of the above crude acid **11a** afforded **12a** whose ^1H NMR spectrum and optical rotation value were identical with those of the starting material.

SCHEME 3. Synthesis of 11a and 12a^a

^a Reagents and conditions: (a) **8** (20%), CH₂Cl₂, 40 °C; (b) TsNHNH₂, AcONa (1 M), DME, 85 °C; (c) Jones' reagent (1 M), acetone, 0 °C to rt; (d) CH₂N₂, Et₂O, MeOH, 0 °C; (e) NaOH (1 M), EtOH.

2, 4, and 6). In all cases, the key carbon–carbon bond-forming CM was carried out under the conditions of Scheme 3 (CH₂Cl₂, 40 °C, 18 h) and catalyzed by the Grubbs ruthenium–carbene catalyst **8** (20 mol %). Yields of the CM products **9b–d** were in the range 40–45% and unaltered starting reactants were isolated as well. The transformation of alkenes **9b–d** into amino acids (not shown) and then amino esters **12b–d** was carried out as described in Scheme 3. In addition, these amino esters were proved by NMR analysis to be diastereomerically pure, and the configuration of the glycyl group was assigned with high confidence as commented above for **12a**.

Aiming at extending the scope of the above synthetic route, we examined the reaction of **2a** with the *N*-Boc-allyloxazolidine **6** since this would lead to *C*-iminoglycosyl α -amino hexanoic acids. However, the need for new appropriate conditions for CM became apparent. The reaction carried out with a 3-fold excess of the alkene **6** under the same conditions (catalyst, temperature, solvent) employed with the vinyl derivative **5**, afforded a complex mixture of products, none of which resulted by NMR and MALDI TOF analysis to be the desired CM product. Hence, we found that just by inverting the **2a/6** ratio from 1:3 to 2:1 while keeping unaltered the amount of catalyst **8** and the reaction conditions, the CM product **14a** was formed in a rewardingly fair isolated yield (50%) (Table 2, entry 1). Even more productive was the reaction of **6** with **2b** which scored a good 70% yield for the product **14b** (entry 3). On the other hand, the reactions with **2c** and **2d** (entries 5 and 7) afforded the products **14c** and **14d**, respectively (about 50% yields), together with substantial amounts (up to 40%) of self-metathesis products derived by dimerization of the iminosugar moiety. We also observed that the homodimerization of **2d** decreased substantially (around 10%) when the **2d/6** ratio was 1:1. The alkenes **14a–d** were then elaborated

by the usual reactions, namely diimide reduction of the double bond to give the alkyl substituted oxazolidines **15a–d** and oxidative cleavage of the heterocyclic ring to unmasking the target amino acids. These products were isolated and characterized as the *C*-iminoglycosyl *N*-Boc-2-amino hexanoates **16a–d**, all showing NMR spectra consistent with their structure and high diastereomeric purity.

Before closing this section, a short remark is worthwhile. In this and in our earlier work²⁷ on *C*-glycosyl amino acid synthesis, the CM of functionalized olefins, one bearing the sugar and the other the glycyl moiety, affords the product in a moderate yield with an average value of about 50%. While one can appreciate the synthetic utility of this carbon–carbon bond forming reaction, the low efficiency in convergent synthetic approaches involving substituted olefins of some complexity is quite apparent. Hence, an improvement of this step in our syntheses is highly recommended. Unfortunately our efforts to overcome this limitation has been so far unsuccessful.

Synthesis of a Tripeptide with a Pendant *C*-Linked Iminosugar. To validate the utility of this new family of *C*-glycosyl amino acids in peptide synthesis, the incorporation of one of these compounds into a tripeptide was considered as a necessary test (Scheme 4). This operation served to evaluate the reactivity of the *C*-iminoglycosyl amino acid despite the bulkiness of the *O*- and *N*-protected sugar residue and demonstrate the stability of this fragment under the reaction conditions of peptide formation. To this end, we started from crude amino acid **11a** obtained as shown in Scheme 3 by oxidative cleavage of the oxazolidine ring of **10a**. Since this acid was judged to be more than 90% pure by NMR analysis, it was considered suitable for the first amide bond formation by coupling with *L*-phenylalanine methyl ester (H-Phe-OMe). Hence, the one-pot carboxylic group

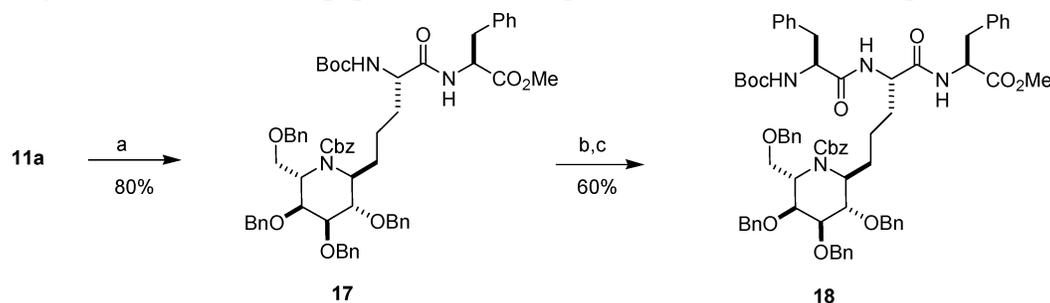
TABLE 2. Synthesis of C-Iminoglycosyl α -Aminopentanoates **12** and α -Aminohexanoates **16**

Entry ^a	Reaction		CM product yield (%) ^b	reduced product yield (%) ^b	aminoester yield (%) ^b
	iminosugar (equiv)	oxazolidine (equiv)			
1	2a (2)	6 (1)	14a (50)	15a (75)	 16a (80)
2	2b (1)	5 (3)	9b (40)	10b (71)	 12b (81)
3	2b (2)	6 (1)	14b (70)	15b (73)	 16b (78)
4	2c (1)	5 (3)	9c (40)	10c (80)	 12c (76)
5	2c (2)	6 (1)	14c (45)	15c (65)	 16c (83)
6	2d (1)	5 (3)	9d (45)	10d (82)	 12d (78)
7	2d (1)	6 (1)	14d (54) ^c	15d (71)	 16d (85)

^a All CM reactions were carried out in CH₂Cl₂ at 40 °C using the Grubbs catalyst **8** (20 mol %). ^b All yields refer to isolated and pure products. In the case of the CM products, the yields were calculated with respect to the initial amount of the minor reactant. ^c Homodimer of **2d** was isolated (40%) when the CM was performed with 2 equiv of iminosugar.

activation with PyBop in the presence of diisopropylethylamine (DIEA) and then treatment with H-Phe-OMe·HCl in CH₂Cl₂ furnished the dipeptide **17** in a rewarding 80% isolated yield by chromatographic purification. Then extension from the *N'*-terminus of this compound was

performed. After Boc removal by treatment with TFA, the coupling of the resultant free amine with *tert*-butoxycarbonyl-L-phenylalanine (Boc-Phe-OH) using PyBop and DIEA afforded the desired tripeptide **18** in 60% overall yield (two steps).

SCHEME 4. Synthesis of Di- and Tripeptides Containing a Carbon-Linked Iminosugar Residue^a

^a Reagents and conditions: (a) H-Phe-OMe·HCl, PyBop, DIEA, CH₂Cl₂, rt; (b) TFA/CH₂Cl₂ (1:4), 0 °C to rt; (c) Boc-Phe-OH, PyBop, DIEA, CH₂Cl₂, rt.

Conclusion

Collectively, a synthetic route to a new family of C-glycosyl amino acids featuring polyhydroxylated piperidine or pyrrolidine rings (iminosugars) has been opened. The main concept in planning this route was the exclusion of steps involving the generation of new stereocenters since these were already in place in the reactants employed. Key to the process were the mild and neutral conditions under which the olefin CM catalyzed by a second generation Grubbs metal-carbene complex proceeded without disrupting the stereochemical integrity of the reactants. Although a small collection of eight amino acids was prepared so far, this path can be profitably followed for the preparation of a large library of compounds whose diversity elements are as follows: (a) the substitution pattern and ring size of the iminosugar, (b) the length of the carbon tether, and (c) the configuration of the pseudoanomeric and glycinyl carbon atoms. Notably, one of the compounds so far prepared was incorporated into a peptide. Thus, this chemistry appears to have great potential as a source of C-glycosylated amino acid precursors to glycopeptides decorated with iminosugar residues.

Experimental Section

General Methods. All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware. Solvents were dried over standard drying agent³⁵ and freshly distilled prior to use. Reactions were monitored by TLC on silica gel 60 F254 with detection by charring with sulfuric acid, or alcoholic solutions of ninhydrin. Flash column chromatography³⁶ was performed on silica gel 60 (230–400 mesh). Optical rotations were measured at 20 ± 2 °C in the stated solvent; [α]_D values are given in 10⁻¹ deg cm² g⁻¹. Nuclear magnetic resonance (NMR) spectra were recorded on a 300 spectrometer in the stated solvent and at the specified temperature. MALDI-TOF mass spectra were acquired using α-cyano-4-hydroxycinnamic acid as the matrix. Piperidines **1a** and **1b** and pyrrolidine **1c** were synthesized as described.^{20b} Pyrrolidine **1d** is a new compound prepared according to the procedure described in ref 20b. For its characterization see below. Aldehyde **4** was prepared as reported in ref 32.

1,1-Dimethylethyl 4-(S)-2,2-Dimethyl-4-(2-propenyl)-oxazolidine-3-carboxylate (6). Methyltriphenylphosphonium bromide (4.10 g, 11.5 mmol) was suspended in THF (100 mL) at rt and KHMDS (0.5 M in toluene, 22.0 mL, 11.0 mmol) was added. The resulting yellow suspension was stirred at rt

for 60 min and then cooled to -78 °C, and a solution of aldehyde **4** (1.60 g, 6.58 mmol) in THF (20 mL) was added dropwise. The cooling bath was removed and the mixture allowed to reach rt over 2 h. The reaction was quenched with aqueous phosphate buffer (pH 7, 20 mL) and the resulting mixture was extracted with Et₂O (3 × 20 mL). The combined organic extract were dried (Na₂SO₄) and concentrated. The resulting syrup was purified by flash chromatography (8:1 cyclohexane–AcOEt) to give **6** as a colorless oil (1.48 g, 93%): [α]_D = +19.3 (c 1.5, CHCl₃); ¹H NMR (DMSO-*d*₆, 140 °C) δ 5.88–5.72 (m, 1H), 5.12–5.03 (m, 2H), 3.98–3.85 (m, 2H), 3.72 (dd, 1H, *J* = 1.2, 8.0 Hz), 2.80–2.20 (m, 2H), 1.47 (s, 3H), 1.45 (s, 9H), 1.42 (s, 3H); MALDI-TOF MS (241.3) 242.8 (M + H). Anal. Calcd for C₁₄H₂₆NO₃: C, 65.59; H, 10.22; N, 5.46. Found: C, 65.63; H, 10.40; N, 5.37.

Methyl (S)-2-(tert-Butoxycarbonylamino)but-3-enoate (7). To a cooled (0 °C), stirred solution of oxazolidine **5** (0.35 g, 1.54 mmol) in acetone (15 mL) was added freshly prepared 1 M Jones reagent (4.62 mL). The mixture was allowed to warm to room temperature during 30 min and then was stirred for an additional 4 h. To the orange suspension was added dropwise propan-2-ol until a green color was observed, and then the reaction mixture was diluted with AcOEt (50 mL) and washed with brine (3 × 20 mL). The organic phase was dried (Na₂SO₄) and concentrated to afford crude α-amino acid. The methyl ester was prepared by adding ethereal diazomethane to an Et₂O–MeOH (1:1) solution of the above crude α-amino acid cooled at 0 °C. After for 10 min, the solution was evaporated to dryness. The crude residue was purified by flash chromatography (4:1 cyclohexane–AcOEt) to give the title compound **7** (62 mg, 20%) as a colorless oil: [α]_D = +12.2 (c 1.2, CHCl₃); ¹H NMR (CDCl₃) δ 5.92 (ddd, 1H, *J*_{2,3} = 5.5, *J*_{3,4a} = 17.0, *J*_{3,4b} = 10.5 Hz, H-3), 5.35 (ddd, 1H, *J*_{2,4a} = 0.7, *J*_{4a,4b} = 1.5 Hz, H-4a), 5.28 (ddd, 1H, *J*_{2,4b} = 0.7 Hz, H-4b), 5.27–5.17 (m, 1H, NH), 4.94–4.84 (m, 1H, H-2), 3.80 (s, 3H, OMe), 1.47 (s, 9H, Boc); ¹³C NMR (CDCl₃) δ 171.2 (CO), 162.6 (CO), 132 (CH=), 117.4 (CH₂=), 80.1 (C(CH₃)₃), 55.7 (CH), 52.6 (CH₃), 28.3 (C(CH₃)₃); MALDI-TOF MS (215.2) 216.8 (M + H). Anal. Calcd for C₁₀H₁₇NO₄: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.65; H, 8.03; N, 6.78.

General Procedure for the Conversion of N-Benzyl Iminosugars 1a–d into N-Benzyloxycarbonyl Iminosugars 2a–d. To a stirred solution of N-benzyl iminosugar **1** (4.0–5.0 mmol) in a 5:1 mixture of THF–H₂O (260–330 mL) was added ammonium cerium(IV) nitrate (4.0 equiv) in portions. When the reaction was complete, the mixture was treated with an aqueous saturated solution of NaHCO₃, until basic pH was reached, and then extracted with Et₂O. The organic phase was dried (Na₂SO₄) and concentrated. The crude compound was dissolved in CH₃CH₂OH–H₂O (1:1) to obtain a 0.1 M solution, cooled (0 °C), and treated with NaHCO₃ (3 equiv). After 10 min, benzyl chloroformate (3 equiv) was added to the mixture, and the stirring was continued for 1 h at 0 °C. The mixture was partitioned between brine and Et₂O, and then the organic

(35) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 5th ed.; Butterworth-Heinemann: Oxford, 2003.

(36) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

phase was dried (Na_2SO_4) and concentrated. The crude residue was purified by flash chromatography.

(2S,3S,4R,5S,6S)-N-Benzoyloxycarbonyl-6-benzoyloxymethyl-3,4,5-tribenzoyloxy-2-(2-propenyl)piperidine (2a). Chromatography on silica gel (6:1 cyclohexane–AcOEt): syrup (65% yield); $[\alpha]_{\text{D}} = -6.3$ (c 1.7, CHCl_3); $^1\text{H NMR}$ ($\text{DMSO}-d_6$, 140°C) δ 7.38–7.20 (m, 25H), 5.83–5.68 (m, 1H), 5.18 (d, 1H, $J = 11.5$ Hz), 5.05 (d, 1H, $J = 12.5$ Hz), 5.03–4.90 (m, 2H), 4.94 (d, 1H, $J = 12.5$ Hz), 4.61–4.50 (m, 7H), 4.32–4.25 (m, 1H), 4.01 (dd, 1H, $J = 3.0$, 6.5 Hz), 3.93 (t, 1H, $J = 3.0$ Hz), 3.82 (dd, 1H, $J = 5.5$, 10.5 Hz), 3.77 (dd, 1H, $J = 3.5$, 6.5 Hz), 3.74–3.65 (m, 2H), 2.85–2.72 (m, 1H), 2.65–2.54 (m, 1H); MALDI-TOF MS (697.9): 699.0 (M + H), 720.9 (M + Na). Anal. Calcd for $\text{C}_{45}\text{H}_{47}\text{NO}_6$: C, 77.45; H, 6.79; N, 2.01. Found: C, 77.05; H, 6.83; N, 1.98.

(2S,3S,4R,5R,6S)-N-Benzoyloxycarbonyl-6-benzoyloxymethyl-3,4,5-tribenzoyloxy-2-(2-propenyl)piperidine (2b). Chromatography on silica gel (6:1 cyclohexane–AcOEt): syrup (58% yield); $[\alpha]_{\text{D}} = -42.8$ (c 1.2, CHCl_3); $^1\text{H NMR}$ ($\text{DMSO}-d_6$, 140°C) δ 7.40–7.20 (m, 25H), 5.67–5.83 (m, 1H), 5.22–4.92 (m, 4H), 4.74–4.40 (m, 9H), 4.15–4.02 (m, 1H), 3.99 (t, 1H, $J = 6.0$ Hz), 3.92 (dd, 1H, $J = 6.0$, 11.5 Hz), 3.89–3.84 (m, 1H), 3.73–3.64 (m, 2H), 2.60–2.50 (m, 1H), 2.48–2.34 (m, 1H); MALDI-TOF MS (697.9): 698.8 (M + H), 720.8 (M + Na). Anal. Calcd for $\text{C}_{45}\text{H}_{47}\text{NO}_6$: C, 77.45; H, 6.79; N, 2.01. Found: C, 77.20; H, 6.71; N, 2.05.

(2R,3R,4R,5R)-N-Benzoyloxycarbonyl-3,4-dibenzoyloxy-5-benzoyloxymethyl-2-(2-propenyl)pyrrolidine (2c). Chromatography on silica gel (8:1 cyclohexane–AcOEt): syrup (45% yield); $[\alpha]_{\text{D}} = -27.0$ (c 0.6, CHCl_3); $^1\text{H NMR}$ ($\text{DMSO}-d_6$, 160°C) δ 7.40–7.20 (m, 20H), 5.85–5.69 (m, 1H), 5.18 (d, 1H, $J = 11.5$ Hz), 5.13 (d, 1H, $J = 12.0$ Hz), 5.10 (d, 1H, $J = 12.0$ Hz), 5.06–4.95 (m, 2H), 4.58 (d, 1H, $J = 11.5$ Hz), 4.55 (d, 1H, $J = 11.5$ Hz), 4.51–4.40 (m, 4H), 4.24–4.16 (m, 1H), 4.09 (dd, 1H, $J = 4.0$, 9.5 Hz), 3.92–3.82 (m, 2H), 3.54 (t, 1H, $J = 2.5$ Hz), 2.72–2.62 (m, 1H), 2.44–2.35 (m, 1H); MALDI-TOF MS (577.7): 578.5 (M + H), 600.6 (M + Na). Anal. Calcd for $\text{C}_{37}\text{H}_{39}\text{NO}_5$: C, 76.92; H, 6.80; N, 2.42. Found: C, 76.78; H, 6.52; N, 2.28.

(2S,3S,4R,5S)-N-Benzyl-3,4-dibenzoyloxy-5-benzoyloxymethyl-2-(2-propenyl)pyrrolidine (1d). Chromatography on silica gel (10:1 cyclohexane–AcOEt): syrup (64% overall yield from 1-(N-benzylhydroxylamino)-2,3,5-tri-O-benzyl-1-deoxy-D-ribose^{20a}): $[\alpha]_{\text{D}} = -2.7$ (c 1.2, CHCl_3); $^1\text{H NMR}$ (CDCl_3) δ 7.38–7.18 (m, 20H), 5.78–5.66 (m, 1H, H-2'), 5.00–4.90 (m, 2H, H-1'a, H-1'b), 4.67 and 4.54 (2d, 2H, $J = 12.0$ Hz, $\text{CH}_2\text{-Ph}$), 4.59 and 4.53 (2d, 2H, $J = 12.0$ Hz, CH_2Ph), 4.08 and 3.82 (2d, 2H, $J = 14.0$ Hz, NCH_2Ph), 3.98 (dd, 1H, $J_{3,4} = 5.5$, $J_{4,5} = 6.0$ Hz, H-4), 3.92 (dd, 1H, $J_{5,6a} = 6.5$, $J_{6a,6b} = 10.0$ Hz, H-6a), 3.85 (dd, 1H, $J_{5,6b} = 3.0$ Hz, H-6b), 3.71 (dd, 1H, $J_{2,3} = 2.0$ Hz, H-3), 3.55 (ddd, 1H, H-5), 3.08–3.03 (m, 1H, H-2), 2.21–2.13 (m, 1H, H-3'a), 2.04–1.94 (m, 1H, H-3'b); $^{13}\text{C NMR}$ δ 140.7, 139.2, 139.0, 138.8, 135.5, 128.8–126.8 (Ph), 117.3, 80.7, 78.7, 73.4, 72.4, 72.3, 68.4, 66.8, 61.7, 52.9, 37.1); MALDI-TOF MS (533.7): 534.6 (M + H). Anal. Calcd for $\text{C}_{36}\text{H}_{39}\text{NO}_3$: C, 81.02; H, 7.37; N, 2.62. Found: C, 81.13; H, 7.51; N, 2.12.

(2S,3S,4R,5S)-N-Benzoyloxycarbonyl-3,4-dibenzoyloxy-5-benzoyloxymethyl-2-(2-propenyl)pyrrolidine (2d). Chromatography on silica gel (8:1 cyclohexane–AcOEt): syrup (35% yield); $[\alpha]_{\text{D}} = -15.3$ (c 0.8, CHCl_3); $^1\text{H NMR}$ ($\text{DMSO}-d_6$, 120°C) δ 7.40–7.20 (m, 20H), 5.80–5.60 (m, 1H), 5.11 (s, 2H), 5.06–4.98 (m, 2H), 4.71 (d, 1H, $J = 12.0$ Hz), 4.62 (d, 1H, $J = 12.0$ Hz), 4.60 (d, 1H, $J = 12.0$ Hz), 4.58 (d, 1H, $J = 12.0$ Hz), 4.45 (d, 1H, $J = 12.0$ Hz), 4.40 (d, 1H, $J = 12.0$ Hz), 4.31 (dd, 1H, $J = 4.0$, 7.5 Hz), 4.22 (ddd, 1H, $J = 3.0$, 6.5, 7.0 Hz), 4.12 (dd, 1H, $J = 6.5$, 9.5 Hz), 3.94 (dd, 1H, $J = 0.5$, 4.0 Hz), 3.82 (ddd, 1H, $J = 0.5$, 3.5, 9.0 Hz), 3.64 (dd, 1H, $J = 3.0$, 9.5 Hz), 2.58–2.42 (m, 1H), 2.20–2.05 (m, 1H); MALDI-TOF MS (577.7): 578.9 (M + H), 601.0 (M + Na). Anal. Calcd for $\text{C}_{37}\text{H}_{39}\text{NO}_5$: C, 76.92; H, 6.80; N, 2.42. Found: C, 77.10; H, 6.88; N, 2.21.

General Procedure for Cross-Metathesis Reaction of Iminosugar 2 and Alkenes 5 and 7. To a 0.05 M solution of 2 (0.30–0.40 mmol) in dry CH_2Cl_2 were added the olefin 5 or

7 (3 equiv) and the Grubbs catalyst 8 (0.2 equiv). The mixture was heated to 40°C for 18 h while stirring and then cooled to room temperature and concentrated. The crude residue was purified by flash chromatography.

6,10-Anhydro-7,8,9,11-tetra-O-benzyl-6-N-benzoyloxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6-pentadeoxy-1-O,2-N-isopropylidene-L-erythro-L-galacto-undec-3-enitol (9a). Chromatography on silica gel (from 8:1 to 3:1 cyclohexane–AcOEt): syrup (50% yield); compound 9a was a 75/25 mixture of *E/Z* olefins (by $^1\text{H NMR}$ analysis); $^1\text{H NMR}$ (selected data) ($\text{DMSO}-d_6$, 120°C) δ 7.40–7.20 (m, 25H), 5.60–5.28 (m, 2H), 5.07 (d, 0.25H, $J = 12.0$ Hz), 5.03 (d, 0.75H, $J = 12.0$ Hz), 4.98 (d, 0.25H, $J = 12.0$ Hz), 4.92 (d, 0.75H, $J = 12.0$ Hz), 4.36–4.22 (m, 1H), 4.18 (ddd, 1H, $J = 2.5$, 6.0, 6.0 Hz), 4.05 (dd, 0.25H, $J = 3.0$, 6.0 Hz), 4.01 (dd, 0.75H, $J = 3.0$, 6.0 Hz), 3.54 (dd, 0.75H, $J = 3.0$, 9.0 Hz), 3.39 (dd, 0.25H, $J = 3.5$, 8.5 Hz), 1.50 (s, 2.25H), 1.45 (s, 2.25H), 1.40 (s, 6.75H), 1.38 (s, 2.25H); MALDI-TOF MS (897.1): 919.6 (M + Na), 935.5 (M + K). Anal. Calcd for $\text{C}_{55}\text{H}_{64}\text{N}_2\text{O}_9$: C, 73.64; H, 7.19; N, 3.12. Found: C, 73.26; H, 7.48; N, 3.19.

6,10-Anhydro-7,8,9,11-tetra-O-benzyl-6-N-benzoyloxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6-pentadeoxy-1-O,2-N-isopropylidene-L-threo-L-galacto-undec-3-enitol (9b). Chromatography on silica gel (6:1 cyclohexane–AcOEt): syrup (40% yield); compound 9b was a 75/25 mixture of *E/Z* olefins (by $^1\text{H NMR}$ analysis); $^1\text{H NMR}$ (selected data) ($\text{DMSO}-d_6$, 140°C) δ 7.40–7.20 (m, 25H), 5.60–5.40 (m, 2H), 5.10 (s, 2H), 4.23 (ddd, 0.75H, $J = 2.5$, 6.0, 6.0 Hz), 3.57 (dd, 0.75H, $J = 3.0$, 8.5 Hz), 1.55 (s, 0.75H), 1.50 (s, 2.25 H), 1.49 (s, 0.75H), 1.46 (s, 2.25H), 1.42 (s, 2.25H), 1.40 (s, 6.75H); MALDI-TOF MS (897.1): 920.1 (M + Na), 937.0 (M + K). Anal. Calcd for $\text{C}_{55}\text{H}_{64}\text{N}_2\text{O}_9$: C, 73.64; H, 7.19; N, 3.12. Found: C, 73.20; H, 7.08; N, 3.21.

6,9-Anhydro-7,8,10-tri-O-benzyl-6-N-benzoyloxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6-pentadeoxy-1-O,2-N-isopropylidene-D-talo-D-glycero-dec-3-enitol (9c). Chromatography on silica gel (from 6:1 to 3:1 cyclohexane–AcOEt): syrup (40% yield); 9c was a 95/5 mixture of *E/Z* olefins (by $^1\text{H NMR}$ analysis); $^1\text{H NMR}$ (major isomer) ($\text{DMSO}-d_6$, 120°C) δ 7.40–7.20 (m, 20H), 5.54 (ddd, 1H, $J = 5.5$, 7.5, 15.5 Hz), 5.42 (dd, 1H, $J = 6.5$, 15.5 Hz), 5.14 (d, 1H, $J = 12.5$ Hz), 5.06 (d, 1H, $J = 12.5$ Hz), 4.58 (d, 1H, $J = 12.0$ Hz), 4.53 (d, 1H, $J = 12.0$ Hz), 4.49 (d, 1H, $J = 12.0$ Hz), 4.46 (s, 2H), 4.42 (d, 1H, $J = 12.0$ Hz), 4.23 (ddd, 1H, $J = 2.5$, 6.5, 6.5 Hz), 4.17 (s, 1H), 4.06 (dd, 1H, $J = 4.0$, 10.0 Hz), 3.96 (dd, 1H, $J = 6.0$, 9.0 Hz), 3.96 (s, 1H), 3.88–3.80 (m, 2H), 3.58 (dd, 1H, $J = 2.5$, 9.0 Hz), 3.49 (t, 1H, $J = 9.5$ Hz), 2.70–2.59 (m, 1H), 2.32 (ddd, 1H, $J = 7.5$, 10.5, 14.5 Hz), 1.50 (s, 3H), 1.48 (s, 3H), 1.40 (s, 9H); MALDI-TOF MS (776.9): 800.1 (M + Na), 816.3 (M + K). Anal. Calcd for $\text{C}_{47}\text{H}_{56}\text{N}_2\text{O}_8$: C, 72.66; H, 7.26; N, 3.61. Found: C, 72.81; H, 7.35; N, 3.52.

6,9-Anhydro-7,8,10-tri-O-benzyl-6-N-benzoyloxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6-pentadeoxy-1-O,2-N-isopropylidene-D-manno-L-glycero-dec-3-enitol (9d). Chromatography on silica gel (from 6:1 to 3:1 cyclohexane–AcOEt): syrup (45% yield); 9d was a 80/20 mixture of *E/Z* olefins (by $^1\text{H NMR}$ analysis); $^1\text{H NMR}$ (selected data for major isomer) ($\text{DMSO}-d_6$, 120°C) δ 5.50–5.35 (m, 2H), 5.11 (s, 2H), 4.70 (d, 1H, $J = 12.0$ Hz), 4.62 (d, 1H, $J = 12.0$ Hz), 4.44 (s, 2H), 4.30 (dd, 1H, $J = 4.0$, 7.0 Hz), 4.21 (dt, 1H, $J = 3.0$, 6.5 Hz), 4.11 (dd, 1H, $J = 6.5$, 9.5 Hz), 1.52 (s, 3H), 1.50 (s, 9H), 1.49 (s, 3H); MALDI-TOF MS (777.0): 799.8 (M + Na), 816.0 (M + K). Anal. Calcd for $\text{C}_{47}\text{H}_{56}\text{N}_2\text{O}_8$: C, 72.66; H, 7.26; N, 3.61. Found: C, 72.55; H, 7.18; N, 3.73.

Methyl 6,10-Anhydro-7,8,9,11-tetra-O-benzyl-6-N-benzoyloxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6-pentadeoxy-L-erythro-L-galacto-undec-3-enonate (13a). Chromatography on silica gel (from 10:1 to 4:1 cyclohexane–AcOEt): syrup (40% yield); 13a was a 95/5 mixture of *E/Z* olefins (by $^1\text{H NMR}$ analysis); $^1\text{H NMR}$ (major isomer) ($\text{DMSO}-d_6$, 120°C) δ 7.38–7.20 (m, 25H), 6.51 (d, 1H, $J = 7.5$

(Hz), 5.72 (dt, 1H, $J = 6.5, 15.5$ Hz), 5.54 (dd, 1H, $J = 5.5, 15.5$ Hz), 5.04 (d, 1H, $J = 12.5$ Hz), 4.93 (d, 1H, $J = 12.5$ Hz), 4.56 (s, 2H), 4.56 (d, 1H, $J = 12.0$ Hz), 4.53 (s, 2H), 4.50 (d, 1H, $J = 12.0$ Hz), 4.50–4.00 (m, 1H), 4.46 (s, 2H), 4.25 (q, 1H, $J = 5.5$ Hz), 4.0 (dd, 1H, $J = 2.5, 6.0$ Hz), 3.91 (t, 1H, $J = 3.0$ Hz), 3.80 (dd, 1H, $J = 5.0, 10.0$ Hz), 3.74 (dd, 1H, $J = 3.5, 6.0$ Hz), 3.72–3.64 (m, 1H), 3.68 (dd, 1H, $J = 5.5, 10.0$ Hz), 3.60 (s, 3H), 2.80–2.67 (m, 1H), 2.65–2.54 (m, 1H); MALDI-TOF MS (885.0) 886.4 (M + H). Anal. Calcd for $C_{53}H_{60}N_2O_{10}$: C, 71.92; H, 6.83; N, 3.17. Found: C, 72.05; H, 6.71; N, 3.23.

General Procedure for Cross-Metathesis Reaction of Iminosugar 2 and Alkene 6. To a 0.05 M solution of olefin **6** (0.30–0.40 mmol) in dry CH_2Cl_2 were added the iminosugar **2** (see Table 2 for the equiv) and the Grubbs catalyst **8** (0.2 equiv). The mixture was heated to 40 °C for 18 h while stirring and then cooled to room temperature and concentrated. The crude residue was purified by flash chromatography.

7,11-Anhydro-8,9,10,12-tetra-O-benzyl-7-N-benzyl-oxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6,7-hexa-deoxy-1-O,2-N-isopropylidene-L-erythro-L-galacto-dodec-4-enitol (14a). Chromatography on silica gel (from 8:1 to 3:1 cyclohexane–AcOEt): syrup (50% yield); **14a** was a 70/30 mixture of *E/Z* olefins (by 1H NMR analysis); 1H NMR (selected data) (DMSO- d_6 , 120 °C) δ 7.38–7.15 (m, 25H), 5.50–5.28 (m, 2H), 5.04 (d, 0.70H, $J = 12.5$ Hz), 5.01 (d, 0.30H, $J = 12.5$ Hz), 4.92 (d, 0.70H, $J = 12.5$ Hz), 4.90 (d, 0.30H, $J = 12.5$ Hz), 1.44 (s, 2.70H), 1.42 (s, 6.30H); MALDI-TOF MS (911.1) 933.2 (M + Na), 949.2 (M + K). Anal. Calcd for $C_{56}H_{66}N_2O_9$: C, 73.82; H, 7.30; N, 3.07. Found: C, 73.66; H, 7.39; N, 3.25.

7,11-Anhydro-8,9,10,12-tetra-O-benzyl-7-N-benzyl-oxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6,7-hexa-deoxy-1-O,2-N-isopropylidene-L-threo-L-galacto-dodec-4-enitol (14b). Chromatography on silica gel (from 6:1 to 3:1 cyclohexane–AcOEt): syrup (70% yield); **14b** was a 60/40 mixture of *E/Z* olefins (by 1H NMR analysis); 1H NMR (selected data) (DMSO- d_6 , 140 °C) δ 7.40–7.18 (m, 25H), 5.30–5.50 (m, 2H), 5.10 (s, 1.2H), 5.08 (s, 0.8H), 1.44 (s, 5.4H), 1.42 (s, 3.6H); MALDI-TOF MS (911.1) 932.9 (M + Na), 949.0 (M + K). Anal. Calcd for $C_{55}H_{66}N_2O_9$: C, 73.82; H, 7.30; N, 3.07. Found: C, 73.91; H, 7.15; N, 3.12.

7,10-Anhydro-8,9,11-tri-O-benzyl-7-N-benzyl-oxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6,7-hexa-deoxy-1-O,2-N-isopropylidene-D-talo-D-glycero-undec-4-enitol (14c). Chromatography on silica gel (from 6:1 to 3:1 cyclohexane–AcOEt): syrup (45% yield); **14c** was a 60/40 mixture of *E/Z* olefins (by 1H NMR analysis); 1H NMR (selected data) (DMSO- d_6 , 120 °C) δ 7.40–7.15 (m, 20H), 5.13 (d, 1H, $J = 12.5$ Hz), 5.07 (d, 1H, $J = 12.5$ Hz), 4.16 (d, 1H, $J = 3.5$ Hz), 3.71 (dd, 0.4H, $J = 2.0, 8.5$ Hz), 3.64 (dd, 0.6H, $J = 2.0, 8.5$ Hz), 3.05 (dd, 0.6H, $J = 3.0, 9.5$ Hz), 3.46 (dd, 0.4H, $J = 3.0, 9.5$ Hz), 2.65–2.55 (m, 1H), 2.5–2.12 (m, 3H); MALDI-TOF MS (791.0) 813.9 (M + Na), 829.8 (M + K). Anal. Calcd for $C_{48}H_{58}N_2O_8$: C, 72.89; H, 7.39; N, 3.54. Found: C, 72.71; H, 7.45; N, 3.43.

7,10-Anhydro-8,9,11-tri-O-benzyl-7-N-benzyl-oxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6,7-hexa-deoxy-1-O,2-N-isopropylidene-D-manno-L-glycero-undec-4-enitol (14d). Chromatography on silica gel (7:1 toluene–Et $_2$ O): syrup (54% yield); **14d** was a 80/20 mixture of *E/Z* olefins (by 1H NMR analysis); 1H NMR (selected data for major isomer) (DMSO- d_6 , 120 °C) δ 5.42–5.36 (m, 2H), 5.11 (s, 2H), 4.71 (d, 1H, $J = 12.0$ Hz), 4.63 (d, 1H, $J = 12.0$ Hz), 4.62 (d, 1H, $J = 12.0$ Hz), 4.59 (d, 1H, $J = 12.0$ Hz), 4.43 (s, 2H), 4.28 (dd, 1H, $J = 4.0, 7.0$ Hz), 4.21 (dt, 1H, $J = 3.0, 6.5$ Hz), 4.11 (dd, 1H, $J = 6.5, 9.5$ Hz), 3.88 (dd, 1H, $J = 5.5, 8.5$ Hz), 3.65 (dd, 2H, $J = 2.0, 9.0$ Hz), 1.52 (s, 3H), 1.50 (s, 9H), 1.48 (s, 3H); MALDI-TOF MS (911.1) 813.5 (M + Na), 829.5 (M + K). Anal. Calcd for $C_{48}H_{58}N_2O_8$: C, 72.89; H, 7.39; N, 3.54. Found: C, 72.91; H, 7.27; N, 3.29.

General Procedure for the Reduction of the Double Bond. Synthesis of Oxazolidines 10 and 15. To a 0.05 M

solution of alkene **9** or **14** (0.12–0.16 mmol) in 1,2-dimethoxyethane was added freshly recrystallized toluene-*p*-sulfonylhydrazide (6.0 equiv). To the stirred and warmed (85 °C) solution was added 1 M aq sodium acetate (6.0 equiv) by a syringe-pump apparatus during 4 h. After an additional 1 h at 85 °C the mixture was cooled to room temperature, diluted with water, and extracted with CH_2Cl_2 . The organic phase was dried (Na_2SO_4) and concentrated. The crude residue was purified by flash chromatography.

6,10-Anhydro-7,8,9,11-tetra-O-benzyl-6-N-benzyl-oxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6-penta-deoxy-1-O,2-N-isopropylidene-L-erythro-L-galacto-undecitol (10a). Chromatography on silica gel (4:1 cyclohexane–AcOEt): syrup (82% yield); $[\alpha]_D = -4.4$ (c 0.9, CH_3OH); 1H NMR (DMSO- d_6 , 120 °C) δ 7.38–7.20 (m, 25H), 5.03 (d, 1H, $J = 12.5$ Hz), 4.89 (d, 1H, $J = 12.5$ Hz), 4.57 (s, 2H), 4.57 (d, 1H, $J = 12.0$ Hz), 4.54 (d, 1H, $J = 11.0$ Hz), 4.50 (d, 1H, $J = 12.0$ Hz), 4.48 (d, 1H, $J = 11.0$ Hz), 4.48 (d, 1H, $J = 11.0$ Hz), 4.29–4.21 (m, 1H), 3.95 (dd, 1H, $J = 3.0, 7.0$ Hz), 3.94–3.88 (m, 1H), 3.86 (dd, 1H, $J = 5.2, 10.0$ Hz), 3.80 (dd, 1H, $J = 6.0, 9.0$ Hz), 3.75–3.63 (m, 3H), 3.57–3.47 (m, 1H), 3.53 (dd, 1H, $J = 2.0, 9.0$ Hz), 2.10–1.97 (m, 1H), 1.86–1.72 (m, 1H), 1.68–1.54 (m, 1H), 1.52–1.18 (m, 3H), 1.47 (s, 3H), 1.43 (s, 3H), 1.42 (s, 9H). MALDI-TOF MS (899.1) 922.0 (M + Na), 937.9 (M + K). Anal. Calcd for $C_{55}H_{66}N_2O_9$: C, 73.47; H, 7.40; N, 3.12. Found: C, 73.26; H, 7.48; N, 3.19.

6,10-Anhydro-7,8,9,11-tetra-O-benzyl-6-N-benzyl-oxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6-penta-deoxy-1-O,2-N-isopropylidene-L-threo-L-galacto-undecitol (10b). Chromatography on silica gel (4:1 cyclohexane–AcOEt): syrup (71% yield); $[\alpha]_D = -11.6$ (c 0.9, $CHCl_3$); 1H NMR (DMSO- d_6 , 140 °C) δ 7.38–7.20 (m, 25H), 5.09 (s, 2H), 4.66 (d, 1H, $J = 11.5$ Hz), 4.64 (s, 2H), 4.61 (d, 1H, $J = 11.5$ Hz), 4.55 (d, 1H, $J = 12.0$ Hz), 4.52 (d, 1H, $J = 12.0$ Hz), 4.43 (s, 2H), 4.40–4.46 (m, 1H), 4.00–3.91 (m, 3H), 3.86 (dd, 1H, $J = 2.0, 8.0$ Hz), 3.81 (dd, 1H, $J = 6.0, 8.5$ Hz), 3.74–3.66 (m, 2H), 3.63 (dd, 1H, $J = 12.0, 4.5$ Hz), 3.55 (dd, 1H, $J = 2.0, 8.5$ Hz), 2.80–1.55 (m, 4H), 1.50 (s, 3H), 1.42 (s, 12H), 1.35–1.20 (m, 2H); MALDI-TOF MS (899.1) 921.9 (M + Na), 937.9 (M + K). Anal. Calcd for $C_{55}H_{66}N_2O_9$: C, 73.47; H, 7.40; N, 3.12. Found: C, 73.78; H, 7.56; N, 3.01.

6,9-Anhydro-7,8,10-tri-O-benzyl-6-N-benzyl-oxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6-penta-deoxy-1-O,2-N-isopropylidene-D-talo-D-glycero-decitol (10c). Chromatography on silica gel (3:1 cyclohexane–AcOEt): syrup (80% yield); $[\alpha]_D = -22.0$ (c 0.8, $CHCl_3$); 1H NMR (DMSO- d_6 , 120 °C) δ 7.40–7.20 (m, 20H), 5.13 (d, 1H, $J = 12.5$ Hz), 5.06 (d, 1H, $J = 12.5$ Hz), 4.58 (d, 1H, $J = 12.0$ Hz), 4.53 (d, 1H, $J = 12.0$ Hz), 4.50 (s, 2H), 4.49 (d, 1H, $J = 12.0$ Hz), 4.42 (d, 1H, $J = 12.0$ Hz), 4.17 (s, 1H), 4.05 (dd, 1H, $J = 4.0, 10.0$ Hz), 3.93 (s, 1H), 3.89–3.79 (m, 2H), 3.75 (dd, 1H, $J = 3.0, 10.0$ Hz), 3.74–3.67 (m, 1H), 3.59 (dd, 1H, $J = 2.0, 9.0$ Hz), 3.48 (t, 1H, $J = 9.0$ Hz), 1.92–1.75 (m, 1H), 1.72–1.52 (m, 3H), 1.50 (s, 3H), 1.45 (s, 3H), 1.42 (s, 9H), 1.35–1.15 (m, 2H); MALDI-TOF MS (778.9) 801.9 (M + Na), 817.8 (M + K). Anal. Calcd for $C_{47}H_{58}N_2O_8$: C, 72.47; H, 7.50; N, 3.60. Found: C, 72.18; H, 7.38; N, 3.72.

6,9-Anhydro-7,8,10-tri-O-benzyl-6-N-benzyl-oxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6-penta-deoxy-1-O,2-N-isopropylidene-D-manno-L-glycero-decitol (10d). Chromatography on silica gel (3:1 cyclohexane–AcOEt): syrup (82% yield); $[\alpha]_D = +6.0$ (c 1.6, $CHCl_3$); 1H NMR (DMSO- d_6 , 120 °C) δ 7.40–7.20 (m, 20H), 5.12 (d, 1H, $J = 11.5$ Hz), 5.08 (d, 1H, $J = 11.5$ Hz), 4.72 (d, 1H, $J = 11.5$ Hz), 4.65 (d, 1H, $J = 12.0$ Hz), 4.64 (d, 1H, $J = 11.5$ Hz), 4.61 (d, 1H, $J = 12.0$ Hz), 4.45 (d, 1H, $J = 11.5$ Hz), 4.42 (d, 1H, $J = 11.5$ Hz), 4.30 (dd, 1H, $J = 4.0, 7.0$ Hz), 4.22 (ddd, H, $J = 3.0, 6.5, 6.5$ Hz), 4.17–4.08 (m, 2H), 3.96–3.84 (m, 2H), 3.78–3.68 (m, 2H), 3.63 (dd, 1H, $J = 2.0, 9.0$ Hz), 1.80–1.20 (m, 6H), 1.51 (s, 3H), 1.45 (s, 3H), 1.42 (s, 9H); MALDI-TOF MS (778.9) 802.3 (M + Na), 818.1 (M + K). Anal. Calcd for $C_{47}H_{58}N_2O_8$: C, 72.47; H, 7.50; N, 3.60. Found: C, 72.22; H, 7.48; N, 3.45.

7,11-Anhydro-8,9,10,12-tetra-O-benzyl-7-N-benzyl-oxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6,7-hexadeoxy-1-O,2-N-isopropylidene-L-erythro-L-galactododecitol (15a). Chromatography on silica gel (8:1 toluene-Et₂O): syrup (75% yield); $[\alpha]_D = +6.7$ (c 0.8, CHCl₃); ¹H NMR (DMSO-*d*₆, 120 °C) δ 7.38–7.20 (m, 25H), 5.03 (d, 1H, *J* = 12.5 Hz), 4.58 (s, 2H), 4.57 (d, 1H, *J* = 11.5 Hz), 4.56 (d, 1H, *J* = 11.5 Hz), 4.52 (d, 1H, *J* = 11.5 Hz), 4.50 (d, 1H, *J* = 11.5 Hz), 4.47 (s, 2H), 4.31–4.24 (m, 1H), 3.96 (dd, 1H, *J* = 2.5, 9.5 Hz), 3.92 (t, 1H, *J* = 3.0 Hz), 3.87 (dd, 1H, *J* = 2.5, 5.5 Hz), 3.86–3.82 (m, 1H), 3.76–3.68 (m, 3H), 3.60 (dd, 1H, *J* = 2.0, 8.5 Hz), 3.60–3.51 (m, 1H), 2.15–2.0 (m, 1H), 1.85–1.18 (m, 7H), 1.50 (s, 3H), 1.44 (s, 3H), 1.42 (s, 9H); MALDI-TOF MS (913.1) 935.9 (M + Na), 951.9 (M + K). Anal. Calcd for C₅₆H₆₈N₂O₉: C, 73.66; H, 7.51; N, 3.07. Found: C, 73.71; H, 7.63; N, 3.10.

7,11-Anhydro-8,9,10,12-tetra-O-benzyl-7-N-benzyl-oxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6,7-hexadeoxy-1-O,2-N-isopropylidene-L-threo-D-galactododecitol (15b). Chromatography on silica gel (5:1 cyclohexane-AcOEt): syrup (73% yield); $[\alpha]_D = -13.4$ (c 1.3, CHCl₃); ¹H NMR (DMSO-*d*₆, 140 °C) δ 7.40–7.20 (m, 25H), 5.08 (d, 2H, *J* = 5.0 Hz), 4.70–4.40 (m, 9H), 3.99–3.80 (m, 5H), 3.76–3.58 (m, 4H), 1.85–1.52 (m, 4H), 1.52 (s, 3H), 1.48 (s, 3H), 1.42 (s, 9H), 1.75–1.38 (m, 4H); MALDI-TOF MS (913.1) 936.0 (M + Na), 952.1 (M + K). Anal. Calcd for C₅₆H₆₈N₂O₉: C, 73.66; H, 7.51; N, 3.07. Found: C, 73.72; H, 7.48; N, 3.11.

7,10-Anhydro-8,9,11-tri-O-benzyl-7-N-benzyl-oxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6,7-hexadeoxy-1-O,2-N-isopropylidene-D-talo-D-glycero-undecitol (15c). Chromatography on silica gel (5:1 cyclohexane-AcOEt): syrup (65% yield); compound **15c** was slightly contaminated by **14c** not separable by flash chromatography: ¹H NMR (DMSO-*d*₆, 120 °C) δ 7.40–7.20 (m, 20H), 5.12 (d, 1H, *J* = 12.5 Hz), 5.06 (d, 1H, *J* = 12.5 Hz), 4.57 (d, 1H, *J* = 12.0 Hz), 4.53 (d, 1H, *J* = 12.0 Hz), 4.51 (s, 2H), 4.49 (d, 1H, *J* = 12.0 Hz), 4.44 (d, 1H, *J* = 12.0 Hz), 4.15 (s, 1H), 4.05 (dd, 1H, *J* = 4.0, 10.0 Hz), 3.95 (s, 1H), 3.89–3.79 (m, 2H), 3.77 (dd, 1H, *J* = 3.0, 10.0 Hz), 3.74–3.63 (m, 1H), 3.61 (dd, 1H, *J* = 2.0, 9.0 Hz), 3.52–3.45 (m, 1H), 1.92–1.51 (m, 6H), 1.50 (s, 3H), 1.45 (s, 3H), 1.42 (s, 9H), 1.35–1.15 (m, 2H); MALDI-TOF MS (793.0) 815.9 (M + Na), 831.8 (M + K).

7,10-Anhydro-8,9,11-tri-O-benzyl-7-N-benzyl-oxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6,7-hexadeoxy-1-O,2-N-isopropylidene-D-manno-L-glycero-undecitol (15d). Chromatography on silica gel (5:1 cyclohexane-AcOEt): syrup (71% yield); $[\alpha]_D = +10.8$ (c 1.0, CHCl₃); ¹H NMR (DMSO-*d*₆, 120 °C) δ 7.40–7.20 (m, 20H), 5.12 (d, 1H, *J* = 12.0 Hz), 5.08 (d, 1H, *J* = 12.0 Hz), 4.72 (d, 1H, *J* = 12.0 Hz), 4.64 (d, 1H, *J* = 12.0 Hz), 4.44 (d, 1H, *J* = 12.0 Hz), 4.40 (d, 1H, *J* = 12.0 Hz), 4.30 (dd, 1H, *J* = 4.0, 6.5 Hz), 4.21 (ddd, 1H, *J* = 2.5, 6.5, 6.5 Hz), 4.13 (dd, 1H, *J* = 6.5, 10.0 Hz), 3.96–3.60 (m, 6H), 1.80–1.20 (m, 8H), 1.51 (s, 3H), 1.44 (s, 3H), 1.42 (s, 9H); MALDI-TOF MS (793.0) 815.7 (M + Na), 831.6 (M + K). Anal. Calcd for C₄₈H₆₀N₂O₈: C, 72.70; H, 7.63; N, 3.53. Found: C, 72.56; H, 7.43; N, 3.37.

General Procedure for the Oxidative Cleavage of Oxazolidines 10 and 15. Synthesis of α -Amino Esters 12 and 15 (0.1 mmol) in acetone (2 mL) was added freshly prepared 1 M Jones reagent (0.30 mL). The mixture was allowed to warm to room temperature during 30 min and then was stirred for an additional 3 h. To the orange suspension was added dropwise propan-2-ol until a green color was observed, then the reaction mixture was diluted with CH₂Cl₂ (30 mL) and washed with brine (3 \times 10 mL). The organic phase was dried (Na₂SO₄) and concentrated to afford crude α -amino acids which were employed without any purification. The methyl esters were prepared by adding ethereal diazomethane to an Et₂O-MeOH (1:1) solution of the above crude α -amino acids cooled at 0 °C. After for 10 min, a small amount of AcOH was added to quench any remaining diazomethane, and then the solution

was evaporated to dryness. The crude residue was purified by flash chromatography.

6,10-Anhydro-7,8,9,11-tetra-O-benzyl-6-N-benzyl-oxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6-pentadeoxy-L-erythro-L-galacto-undeconic Acid (11a). From **10a** (See General Procedure Above). Crude **11a**: syrup (~90% yield; 90% pure by ¹H NMR analysis); ¹H NMR (DMSO-*d*₆, 140 °C) δ 7.20–7.40 (m, 25 H), 6.15–6.02 (m, 1H), 5.02 (d, 1H, *J* = 12.5 Hz), 4.91 (d, 1H, *J* = 12.5 Hz), 4.57 (s, 2H), 4.55–4.49 (m, 4H), 4.48 (d, 1H, *J* = 12.0 Hz), 4.45 (d, 1H, *J* = 12.0 Hz), 4.30–4.22 (m, 1H), 3.98–3.88 (m, 3H), 3.83 (dd, 1H, *J* = 5.5, 10.0 Hz), 3.75–3.68 (m, 2H), 3.59–3.50 (m, 1H), 2.15–2.02 (m, 1H), 1.85–1.50 (m, 3H), 1.42 (s, 9H), 1.40–1.20 (m, 4H); MALDI-TOF MS (873.0) 896.6 (M + Na), 912.6 (M + K).

Form 12a. To a solution of **12a** (70 mg, 0.08 mmol) in EtOH (7 mL) was added 1.0 M NaOH (0.25 mL, 0.25 mmol). The solution was stirred for 14 h at rt, then cooled (0 °C) and treated with 1.0 M HCl until pH 3–4. The mixture was diluted with H₂O and extracted with Et₂O (3 \times 15 mL). The combined organic extracts were dried (Na₂SO₄) and then evaporated to dryness to give crude **11a** (~70% yield; 90% pure by ¹H NMR analysis).

Methyl 6,10-Anhydro-7,8,9,11-tetra-O-benzyl-6-N-benzyl-oxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6-pentadeoxy-L-erythro-L-galacto-undecanoate (12a). Chromatography on silica gel (3:1 cyclohexane-AcOEt): syrup (81% yield); $[\alpha]_D = -12.3$ (c 0.7, CH₃OH); ¹H NMR (DMSO-*d*₆, 140 °C) δ 7.38–7.22 (m, 25H), 6.50–6.40 (m, 1H), 5.02 (d, 1H, *J* = 12.5 Hz), 4.90 (d, 1H, *J* = 12.5 Hz), 4.56 (s, 2H), 4.55 (d, 1H, *J* = 12.0 Hz), 4.53–4.53 (m, 4H), 4.48 (d, 1H, *J* = 12.0 Hz), 4.28–4.21 (m, 1H), 3.95–3.88 (m, 3H), 3.82 (dd, 1H, *J* = 5.5, 10.5 Hz), 3.73–3.66 (m, 2H), 3.60 (s, 3H), 3.54–3.45 (m, 1H), 2.12–2.00 (m, 1H), 1.82–1.68 (m, 1H), 1.65–1.50 (m, 2H), 1.42–1.25 (m, 2H), 1.40 (s, 9H); MALDI-TOF MS (887.1) 909.6 (M + Na), 925.6 (M + K). Anal. Calcd for C₅₃H₆₂N₂O₁₀: C, 71.76; H, 7.04; N, 3.16. Found: C, 72.10; H, 7.24; N, 3.02.

Methyl 6,10-Anhydro-7,8,9,11-tetra-O-benzyl-6-N-benzyl-oxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6-pentadeoxy-L-threo-L-galacto-undecanoate (12b). Chromatography on silica gel (3:1 cyclohexane-AcOEt): syrup (81% yield); $[\alpha]_D = -11.4$ (c 0.7, CHCl₃); ¹H NMR (DMSO-*d*₆, 120 °C) δ 7.38–7.15 (m, 25H), 6.50–6.42 (m, 1H), 5.08 (s, 2H), 4.64 (d, 1H, *J* = 12.0 Hz), 4.63 (s, 2H), 4.59 (d, 1H, *J* = 12.0 Hz), 4.54 (d, 1H, *J* = 12.0 Hz), 4.51 (d, 1H, *J* = 12.0 Hz), 4.44–4.38 (m, 1H), 4.42 (s, 2H), 4.00–3.87 (m, 4H), 3.84 (dd, 1H, *J* = 2.0, 7.0 Hz), 3.67 (dd, 1H, *J* = 5.0, 11.5 Hz), 3.64–3.60 (m, 1H), 3.62 (s, 3H), 1.80–1.30 (m, 6H), 1.40 (s, 9H); MALDI-TOF MS (887.1) 909.8 (M + Na), 925.8 (M + K). Anal. Calcd for C₅₃H₆₂N₂O₁₀: C, 71.76; H, 7.04; N, 3.16. Found: C, 71.88; H, 7.15; N, 3.06.

Methyl 6,9-Anhydro-7,8,10-tri-O-benzyl-6-N-benzyl-oxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6-pentadeoxy-D-talo-D-glycero-decanoate (12c). Chromatography on silica gel (3:1 cyclohexane-AcOEt): syrup (76% yield); $[\alpha]_D = -21.8$ (c 0.7, CHCl₃); ¹H NMR (DMSO-*d*₆, 120 °C) δ 7.40–7.20 (m, 20H), 6.45 (d, 1H, *J* = 8.0 Hz), 5.12 (d, 1H, *J* = 12.5 Hz), 5.07 (d, 1H, *J* = 12.5 Hz), 4.58 (d, 1H, *J* = 12.0 Hz), 4.54 (d, 1H, *J* = 12.0 Hz), 4.50 (d, 1H, *J* = 12.0 Hz), 4.48 (d, 1H, *J* = 12.0 Hz), 4.47 (d, 1H, *J* = 12.0 Hz), 4.41 (d, 1H, *J* = 12.0 Hz), 4.15 (s, 1H), 4.03 (dd, 1H, *J* = 4.0, 10.0 Hz), 4.00–3.90 (m, 1H), 3.92 (s, 1H), 3.81 (dd, 1H, *J* = 4.0, 9.0 Hz), 3.75 (dd, 1H, *J* = 3.0, 10.0 Hz), 3.64 (s, 3H), 3.47 (t, 1H, *J* = 9.5 Hz), 1.84–1.75 (m, 1H), 1.70–1.52 (m, 3H), 1.42 (s, 9H), 1.40–1.25 (m, 2H); MALDI-TOF MS (766.9) 790.1 (M + Na), 805.9 (M + K). Anal. Calcd for C₄₅H₅₄N₂O₉: C, 70.47; H, 7.10; N, 3.65. Found: C, 70.89; H, 7.00; N, 3.75.

Methyl 6,9-Anhydro-7,8,10-tri-O-benzyl-6-N-benzyl-oxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6-pentadeoxy-D-manno-L-glycero-decanoate (12d). Chromatography on silica gel (2:1 cyclohexane-AcOEt): syrup (78% yield); $[\alpha]_D = +5.1$ (c 0.6, CHCl₃); ¹H NMR (DMSO-*d*₆, 120 °C) δ 7.40–7.20 (m, 20H), 6.55 (d, 1H, *J* = 6.0 Hz), 5.10 (s, 2H),

4.71 (d, 1H, $J = 12.0$ Hz), 4.63 (d, 1H, $J = 12.0$ Hz), 4.62 (d, 1H, $J = 12.0$ Hz), 4.61 (d, 1H, $J = 12.0$ Hz), 4.44 (d, 1H, $J = 11.5$ Hz), 4.40 (d, 1H, $J = 12.0$ Hz), 4.30 (dd, 1H, $J = 4.0, 7.0$ Hz), 4.21 (ddd, 1H, $J = 2.5, 6.5, 6.5$ Hz), 4.12 (dd, 1H, $J = 6.5, 9.5$ Hz), 4.01–3.91 (m, 2H), 3.74–3.58 (m, 2H), 3.65 (s, 3H), 1.78–1.22 (m, 6H), 1.40 (s, 9H); MALDI-TOF MS (766.9) 789.6 (M + Na), 805.6 (M + K). Anal. Calcd for $C_{45}H_{54}N_2O_9$: C, 70.47; H, 7.10; N, 3.65. Found: C, 70.21; H, 7.28; N, 3.51.

Methyl 7,11-Anhydro-8,9,10,12-tetra-O-benzyl-7-N-benzoyloxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6,7-hexadeoxy-L-erythro-L-galacto-dodeconate (16a). Chromatography on silica gel (4:1 cyclohexane–AcOEt): syrup (80% yield); $[\alpha]_D = -12.1$ (c 1.0, CH_3OH); 1H NMR (DMSO- d_6 , 120 °C) δ 7.38–7.20 (m, 25H), 6.47 (d, 1H, $J = 7.0$ Hz), 5.02 (d, 1H, $J = 12.5$ Hz), 4.90 (d, 1H, $J = 12.5$ Hz), 4.57 (s, 2H), 4.56 (d, 1H, $J = 11.5$ Hz), 4.54 (d, 1H, $J = 11.5$ Hz), 4.51 (d, 1H, $J = 11.5$ Hz), 4.49 (d, 1H, $J = 11.5$ Hz), 4.47 (s, 2H), 4.29–4.21 (m, 1H), 4.00–3.89 (m, 3H), 3.83 (dd, 1H, $J = 5.5, 10.0$ Hz), 3.74–3.67 (m, 2H), 3.63 (s, 3H), 3.55–3.46 (m, 1H), 2.15–1.98 (m, 1H), 1.80–1.65 (m, 1H), 1.65–1.45 (m, 2H), 1.40 (s, 9H), 1.37–1.20 (m, 4H); MALDI-TOF MS (901.1) 923.6 (M + Na), 939.5 (M + K). Anal. Calcd for $C_{54}H_{64}N_2O_{10}$: C, 71.98; H, 7.16; N, 3.11. Found: C, 72.21; H, 7.11; N, 3.23.

Methyl 7,11-Anhydro-8,9,10,12-tetra-O-benzyl-7-N-benzoyloxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6,7-hexadeoxy-L-threo-L-galacto-dodeconate (16b). Chromatography on silica gel (3:1 cyclohexane–AcOEt): syrup (78% yield); $[\alpha]_D = -13.5$ (c 1.0, $CHCl_3$); 1H NMR (DMSO- d_6 , 120 °C) δ 7.38–7.18 (m, 25H), 6.47 (d, 1H, $J = 7.5$ Hz), 5.09 (s, 2H), 4.66 (d, 1H, $J = 11.5$ Hz), 4.63 (s, 2H), 4.60 (d, 1H, $J = 11.5$ Hz), 4.54 (d, 1H, $J = 11.5$ Hz), 4.51 (d, 1H, $J = 11.5$ Hz), 4.45–4.39 (m, 1H), 4.42 (s, 2H), 4.00–3.87 (m, 4H), 3.84 (dd, 1H, $J = 2.0, 7.0$ Hz), 3.67 (dd, 1H, $J = 5.0, 11.5$ Hz), 3.66–3.60 (m, 1H), 3.64 (s, 3H), 1.80–1.50 (m, 4H), 1.42 (s, 9H), 1.35–1.20 (m, 4H); MALDI-TOF MS (901.1) 923.9 (M + Na), 939.8 (M + K). Anal. Calcd for $C_{54}H_{64}N_2O_{10}$: C, 71.98; H, 7.16; N, 3.11. Found: C, 71.47; H, 7.24; N, 3.17.

Methyl 7,10-Anhydro-8,9,11-tri-O-benzyl-7-N-benzoyloxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6,7-hexadeoxy-L-talo-L-glycero-undeconate (16c). Chromatography on silica gel (3:1 cyclohexane–AcOEt): syrup (83% yield); $[\alpha]_D = -21.7$ (c 0.6, $CHCl_3$); 1H NMR (DMSO- d_6 , 120 °C) δ 7.40–7.20 (m, 20H), 6.49 (d, 1H, $J = 8.0$ Hz), 5.13 (d, 1H, $J = 12.0$ Hz), 5.07 (d, 1H, $J = 12.0$ Hz), 4.58 (d, 1H, $J = 12.0$ Hz), 4.54 (d, 1H, $J = 12.0$ Hz), 4.49 (s, 2H), 4.48 (d, 1H, $J = 12.0$ Hz), 4.44 (d, 1H, $J = 12.0$ Hz), 4.15 (s, 2H), 4.04 (dd, 1H, $J = 4.0, 9.5$ Hz), 4.00–3.94 (m, 1H), 3.91 (s, 1H), 3.82 (dd, 1H, $J = 4.0, 9.5$ Hz), 3.75 (dd, 1H, $J = 3.0, 9.5$ Hz), 3.64 (s, 3H), 3.48 (t, 1H, $J = 9.5$ Hz), 1.87–1.74 (m, 1H), 1.7–1.50 (m, 3H), 1.40 (s, 9H), 1.35–1.20 (m, 4H); MALDI-TOF MS (780.9) 803.5 (M + Na), 819.4 (M + K). Anal. Calcd for $C_{46}H_{56}N_2O_9$: C, 70.75; H, 7.23; N, 3.59. Found: C, 70.81; H, 7.17; N, 3.49.

Methyl 7,10-Anhydro-8,9,11-tri-O-benzyl-7-N-benzoyloxycarbonylamino-2-tert-butoxycarbonylamino-2,3,4,5,6,7-hexadeoxy-D-manno-L-glycero-undeconate (16d). Chromatography on silica gel (3:1 cyclohexane–AcOEt): syrup (85% yield); $[\alpha]_D = +5.8$ (c 0.8, $CHCl_3$); 1H NMR (DMSO- d_6 , 120 °C) δ 7.40–7.20 (m, 20H), 6.61–6.48 (m, 1H), 5.12 (d, 1H, $J = 12.0$ Hz), 5.08 (d, 1H, $J = 12.0$ Hz), 4.71 (d, 1H, $J = 12.0$ Hz), 4.64 (d, 1H, $J = 12.0$ Hz), 4.63 (d, 1H, $J = 12.0$ Hz), 4.61 (d, 1H, $J = 12.0$ Hz), 4.44 (d, 1H, $J = 12.0$ Hz), 4.40 (d, 1H, $J = 12.0$ Hz), 4.30 (dd, 1H, $J = 4.0, 6.5$ Hz), 4.21 (ddd, 1H, $J = 2.5, 6.5, 6.5$ Hz), 4.12 (dd, 1H, $J = 6.5, 10.0$ Hz), 4.02–3.90 (m, 2H), 3.72–3.58 (m, 2H), 3.65 (s, 3H), 1.80–1.20 (m, 8H), 1.40 (s, 9H); MALDI-TOF MS (780.9) 803.4 (M + Na), 819.3 (M + K).

Anal. Calcd for $C_{46}H_{56}N_2O_9$: C, 70.75; H, 7.23; N, 3.59. Found: C, 70.61; H, 7.18; N, 3.41.

Dipeptide 17. To a cooled (0 °C), stirred solution of amino acid **11a** (100 mg, 0.11 mmol), 1-phenylalanine methyl ester hydrochloride (30 mg, 0.17 mmol), and (benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate (68 mg, 0.13 mmol) in dry CH_2Cl_2 (1.5 mL) was added *N,N*-diisopropylethylamine (57 μ L, 0.33 mmol). The solution was warmed to rt, stirred for an additional 2 h, and then concentrated. The residue was suspended with AcOEt (15 mL) and washed with H_2O . The organic phase was dried (Na_2SO_4) and concentrated. The crude residue was purified by flash chromatography (2:1 cyclohexane–AcOEt) to give compound **17** (91 mg, 80% yield) as a syrup; $[\alpha]_D = +5.4$ (c 0.8, $CHCl_3$); 1H NMR (DMSO- d_6 , 120 °C) δ 7.65 (d, 1H, $J = 8.0$ Hz), 7.40–7.15 (m, 30H), 6.14 (d, 1H, $J = 8.0$ Hz), 5.01 (d, 1H, $J = 12.5$ Hz), 4.90 (d, 1H, $J = 12.5$ Hz), 4.63–4.41 (m, 9H), 4.28–4.20 (m, 1H), 3.96–3.86 (m, 3H), 3.80 (dd, 1H, $J = 5.5, 10.0$ Hz), 3.73–3.65 (m, 2H), 3.58 (s, 3H), 3.55–3.45 (m, 1H), 3.06 (dd, 1H, $J = 6.0, 14.0$ Hz), 2.97 (dd, 1H, $J = 7.5, 14.0$ Hz), 2.11–1.98 (m, 1H), 1.82–1.69 (m, 1H), 1.64–1.43 (m, 2H), 1.38 (s, 9H), 1.38–1.26 (m, 2H); MALDI-TOF MS (1034.2) 1056.6 (M + Na), 1072.6 (M + K). Anal. Calcd for $C_{62}H_{71}N_3O_{11}$: C, 72.00; H, 6.92; N, 4.06. Found: C, 72.25; H, 6.83; N, 4.16.

Tripeptide 18. To a cooled (0 °C), stirred solution of the above dipeptide **17** (103 mg, 0.10 mmol) in CH_2Cl_2 (2.5 mL) was slowly added a solution of 1/3 TFA- CH_2Cl_2 (2 mL). Stirring was continued at 0 °C for an additional 30 min, the solution was warmed to rt. After 30 min at this temperature the solution was cooled again (0 °C), neutralized with an aqueous saturated solution of Na_2CO_3 , and then extracted with CH_2Cl_2 . The combined organic phases were dried (Na_2SO_4) and concentrated to give the corresponding crude free amine (85 mg) suitable for the next step.

To a cooled (0 °C), stirred solution of the above free amine (85 mg, 0.09 mmol), *tert*-butoxycarbonyl-L-phenylalanine (34 mg, 0.13 mmol), and (benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate (70 mg, 0.13 mmol) in dry CH_2Cl_2 (2 mL) was added *N,N*-diisopropylethylamine (47 μ L, 0.27 mmol). The solution was warmed to rt, stirred for an additional 2 h, and then concentrated. The residue was suspended with AcOEt (15 mL) and washed with H_2O . The organic phase was dried (Na_2SO_4), concentrated. The crude residue was purified by flash chromatography (cyclohexane–AcOEt) to give compound **18** (71 mg, 60% yield from **17**) as a syrup; $[\alpha]_D = -14.0$ (c 0.8, $CHCl_3$); 1H NMR (DMSO- d_6 , 120 °C) δ 7.81 (d, 1H, $J = 8.0$ Hz), 7.52 (d, 1H, $J = 8.0$ Hz), 7.40–7.15 (m, 35H), 6.27 (d, 1H, $J = 8.0$ Hz), 5.01 (d, 1H, $J = 12.5$ Hz), 4.90 (d, 1H, $J = 12.5$ Hz), 4.62–4.40 (m, 9H), 4.34–4.18 (m, 3H), 3.95–3.87 (m, 2H), 3.80 (dd, 1H, $J = 5.5, 10.0$ Hz), 3.74–3.65 (m, 2H), 3.55 (s, 3H), 3.55–3.47 (m, 1H), 3.11–2.73 (m, 4H), 2.15–2.00 (m, 1H), 1.90–1.60 (m, 2H), 1.60–1.30 (m, 3H), 1.28 (s, 9H); MALDI-TOF MS (1181.4) 1203.8 (M + Na), 1219.7 (M + K). Anal. Calcd for $C_{71}H_{80}N_4O_{12}$: C, 72.18; H, 6.83; N, 4.74. Found: C, 72.43; H, 6.91; N, 4.78.

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Supporting Information Available: 1H NMR spectra of compounds **9a–d**, **13a**, and **14a–d**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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