C-Glycosyl Tyrosines. Synthesis and Incorporation into *C*-Glycopeptides

Alan J. Pearce,[†] Sharn Ramaya,[†] Simon N. Thorn,[†] Graham B. Bloomberg,[‡] Daryl S. Walter,[§] and Timothy Gallagher*,[†]

School of Chemistry, University of Bristol, Bristol, BS8 1TS, UK, Department of Biochemistry, Medical School, University of Bristol, Bristol, BS8 1TD, UK, and Roche Discovery Welwyn, Welwyn Garden City, AL7 3AY, UK

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The synthesis of the Fmoc-protected *C*-glycosyl tyrosines **1** and **2**, together with two other related *C*-glycosyl tyrosines, has been achieved. Key reactions involved (i) the reaction of a glycal with an organozinc reagent (carrying an aryl iodide function) in the presence of a Lewis acid to establish the *C*-glycosyl linkage and (ii) subsequent cross coupling of the aryl iodide to an alanyl zinc reagent (in the presence of a Pd(0) catalyst) to complete the construction of the α-amino acid moiety. Using solid-phase peptide synthesis methods, two units of the mannosyl derivative **1** (shown as L-Tyr-[*C*-Ac_4-α-D-Man]) have been incorporated (with four units of glycine) into the linear hexapeptide **3** which was then converted to the C_2-symmetric cyclic oligopeptide **4**.

O-Linked glycopeptides represent an extensive and critically important group of glycoconjugates with the *O*-glycosylation of a variety of hydroxylated α-amino acids, in particular serine and threonine, playing a significant role in a number of key cellular processes.[1] To probe and understand the mechanisms of these processes, access to effective molecular tools is a prerequisite, and the emergence of *C*-glycosides[2] as chemically and metabolically stable carbohydrate analogues has led to interest in the potential of the corresponding *C*-glycosyl amino acids. *C*-Glycosides have already been employed to mimic both the conformation (structure)[3] and biological profile (function)[4] of a variety *O*-glycoconjugates. *C*-Glycosyl amino acids, which could be readily incorporated into larger and biologically more relevant molecular frameworks (using established peptide methodologies), would provide novel tools for studying those carbohydrate-based interactions associated with *O*-glycopeptides. As a consequence, the synthesis of a series of different *C*-glycosyl amino acids has been described,[5] and more recently, the development and exploitation of these units as components for peptide synthesis has been reported.[6]

In addition to the commonly found serine- and threonine-based linkages, the *O*-glycosylation of phenolic units[7] (tyrosine and substituted phenylglycine derivatives) is frequently encountered. In a very recent paper, Meldal and co-workers[6e] reported a series of phenylalanine-containing *C*-glycosides based on a two-carbon alkyne linkage; however, *C*-glycosyl variants of tyrosine *O*-glycoconjugates have yet to be described. In this paper we report the first synthesis of the *C*-glycosyl tyrosine

[†] School of Chemistry, University of Bristol.

[‡] Medical School, University of Bristol.

[§] Roche Discovery Welwyn.

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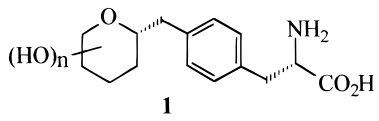
motif represented by general structure **1**. Four structur-



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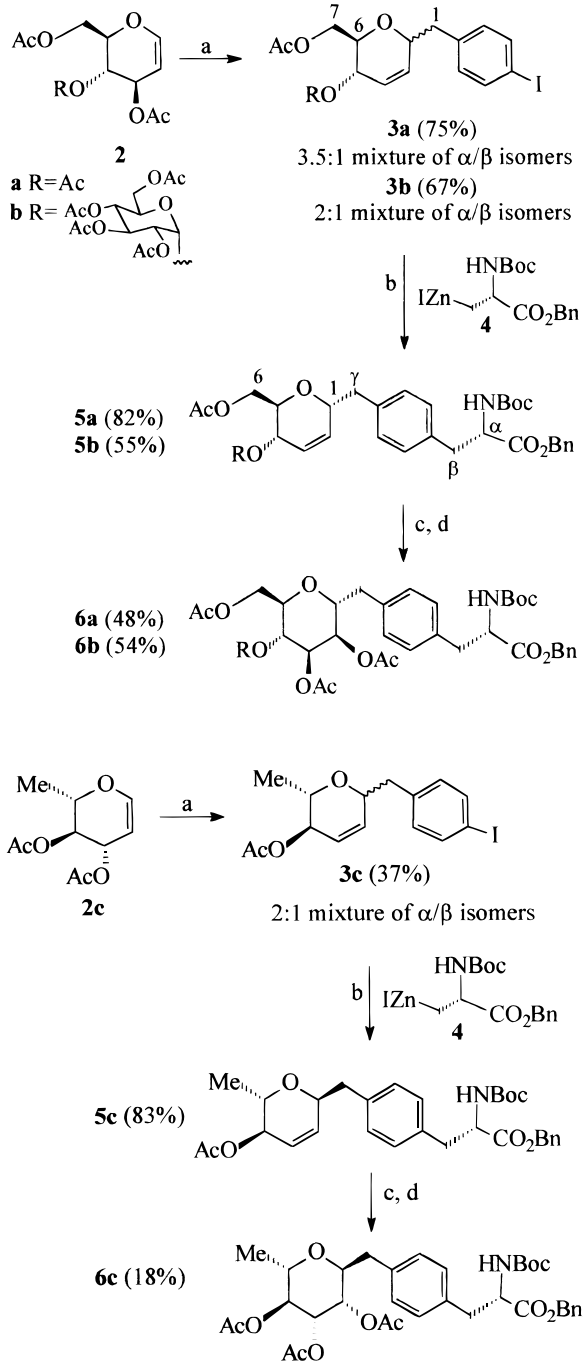
ally distinct *C*-glycosyl tyrosines **6a**, **6b**, **6c**, and **10** have been generated and these derivatives are based on D-mannose, a disaccharide unit, L-rhamnose, and an unsaturated 2,3-dideoxy furanosyl derivative, respectively. We view a primary role for *C*-glycosyl amino acids as building blocks for peptide synthesis, and the successful incorporation of the Fmoc-protected *C*-mannosyl tyrosine **11a** into representative examples of both linear and cyclic oligopeptides, using a combination of solid phase and solution synthesis techniques, is also demonstrated.

An analysis of *C*-glycosyl tyrosines **1** offered various options for synthesis and the route shown in Schemes 1 and 2 represents a convergent and flexible approach to this class of molecule. The crucial *C*-glycoside linkage is established using an organozinc species as a nucleophilic *C*-glycosyl "acceptor",[8] and the synthesis of the *C*-mannosyl tyrosine **6a**, which has been optimized (23% overall yield from **2a**), serves to illustrate all aspects of the strategy that has been developed. Reaction of 3,4,5-tri-*O*-acetyl-D-glucal (**2a**) (in the presence of $BF_3{\cdot}OEt_2$) with the organozinc reagent prepared from 4-iodobenzyl bromide gave **3a** as a 3.5:1 mixture of α and *β* isomers which were separated by chromatography.[9] In a general sense, the α/*β* selectivity associated with this *C*-glycosylation method does depend on the nature of the glycal component, and very high α selectivity has been observed with a number of substrates[8] (see also **9** below). Those factors responsible for determining this α/*β* ratio are, however, unclear, and efforts are underway to both understand and improve the general level of stereocontrol available with this process. With **3a**−**c**, only modest α selectivity was observed (2 to 3.5:1) but the need to separate isomers at this first stage did not constitute a major barrier. The *β*-*C*-glycoside isomers are also available, but we have only pursued the synthesis of *C*-glycosyl tyrosines using the α-anomers as this corresponds to the configuration associated with most of the naturally occurring *O*-glycopeptides of this type.[7]

Scheme 1[a]



[a] Key: (a) 4-$IC_6H_4CH_2ZnBr$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −30 to 0 °C, 0.5 h; (b) **3a**, **3b** (see text) or **3c**, $PdCl_2(o\text{-}Tol_3P)_2$, DMA/THF then **4** in THF, rt to 50 °C, 1 h; (c) NMO, OsO_4 (10 mol %), *tert*-BuOH/Me_2CO/H_2O, rt, 24 h. (d) Ac_2O, DMAP, py, 0 °C, 0.5 h.

Introduction of the α-amino acid moiety into **3a** was achieved using Jackson's method which involved a Pd(0)-mediated coupling with the enantiomerically pure zinc reagent **4**.[10,11] We found, however, that the efficiency of this transformation was sensitive to the conditions used

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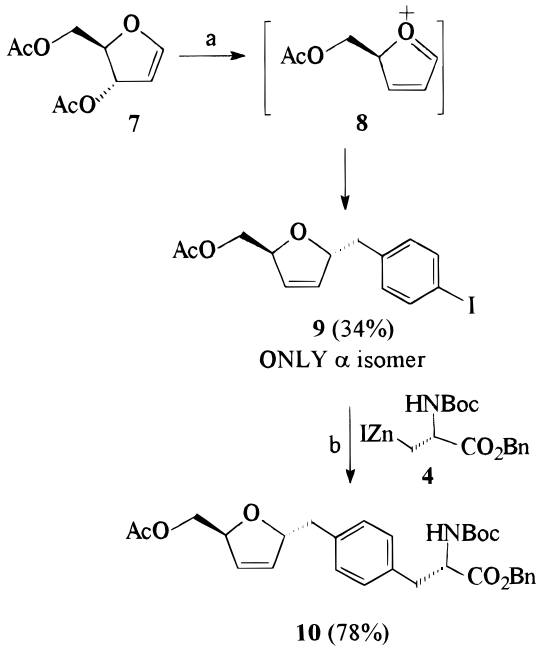
(9) Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic Press: New York, 1973; Chapter 3. The numbering system used for both the *C*-glycoside adducts (**3**, **9**) and the *C*-glycopeptides (**5**, **6**, **10**−**13**) is shown within Scheme 1. Stereochemical assignment of the individual α and *β* isomers associated with **3a** [and **3b** and **3c**] was achieved using ^{13}C and ^1H NMR as previously described for a series of structurally related *C*-glycosides.[8] For **3a** α isomer: *C(6)* 69.5; $J_{5,6}$ 6.8 Hz. For **3a** *β* isomer: *C(6)* δ_C 74.2; $J_{5,6}$ 9.0 Hz. NOE was observed between *C(2)* and *C(6)* in *β*-isomer only (see Scheme 1 for numbering system). For other applications of this method, see: Dawe, R. D.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 522. Orsini, F.; Pelizzoni, F. *Carbohydr. Res.* **1993**, *243*, 183. Moineau, C.; Bolitt, V.; Sinou, D. *J. Chem. Soc., Chem. Commun.* **1995**, 1103. Brakta, M.; Lhoste, P.; Sinou, D. *J. Org. Chem.* **1989**, *54*, 1890. Achmatowicz has noted that the magnitude of $J_{5,6}$ is also diagnostic of the "anomeric" configuration in *C*-glycosides of this type: Achmatowicz, O.; Bukowski, P. *Rocz. Chem.* **1973**, *47*, 99.

Scheme 2[a]



[a] Key: (a) 4-$IC_6H_4CH_2ZnBr$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −30 to 0 °C, 0.5 h. (b) $PdCl_2(o\text{-}Tol_3P)_2$, DMA/THF then **4** in THF, rt to 50 °C, 1 h.

and, in the examples that we have studied, our best yields were obtained when **4** was added to a solution of **3a** already containing the Pd(0) catalyst. These optimized conditions afforded **5a** in 82% yield. Osmium-mediated dihydroxylation of **5a** was highly selective[12] leading to the mannose derivative exclusively, and *O*-acetylation gave the fully protected *C*-mannosyl tyrosine **6a** in 48% overall yield from **5a**.

Since tyrosine is found in nature linked to more elaborate oligosaccharides,[7e] we have applied this strategy to both the synthesis of a structurally more complex *C*-glycosyl amino acid as well as variants derived from alternative monosaccharide precursors. Starting from D-maltal (**2b**), application of the sequence shown in Scheme 1 led to a disaccharide *C*-glycosyl tyrosine variant **6b**. In this instance, it was more convenient to convert the intermediate *C*-glycoside **3b** (as a 2:1 mixture of α and *β*-isomers) to **5b** *prior* to separation of the α- and *β*-C-glycosides. Dihydroxylation of **5b** was completely stereoselective and the fully protected *C*-[Manα1→4Man] analogue **6b** was obtained in ca. 13% (optimized) overall yield from D-maltal. Similarly, starting with L-rhamnal (**2c**), the chemistry shown in Scheme 1 provided the L-configured glycosyl tyrosine **6c**, although in this latter case neither the *C*-glycosylation step nor the final *O*-acetylation procedure has yet been fully optimized.[12]

We were also interested in generating a *C*-glycosyl amino acid based on a pentose derivative. Lewis acid-mediated reaction of crude di-*O*-acetyl-D-arabinal (**7**) with the zinc reagent derived from 4-iodobenzyl bromide gave the *C*-glycoside **9** in 34% isolated yield. This is an acceptable result, bearing in mind that oxonium ion **8** is a likely intermediate in this process, together with the known sensitivity of **7** toward acids.[13] Further, *C*-glycoside **9** was obtained as a single stereoisomer, the structure of which was assigned on the basis of NOE experiments.[14] Pd-Mediated cross coupling of **4** with **9** gave the protected *C*-furanosyl tyrosine **10** in 78% yield (Scheme 2).[15]

To realize the potential of *C*-glycosyl amino acids as tools for probing the structure and function of carbohydrates, including *O*-glycopeptides, an ability to incorporate these structural units within larger and more relevant peptide frameworks is required. With solid-phase peptide synthesis (SPPS) as the method of choice for assembling oligopeptides, including *O*-glycopeptides,[16] our aim was to incorporate *C*-glycosyl tyrosine units within simple, but nonetheless representative examples of both linear and cyclic oligopeptides. We chose the cyclic *C*-glycopeptide **13** as a target since this is closely related to a family of C_2-symmetric peptides [*cyclo*(Gly-X_{aa}-Gly)$_2$][17,18] which have attracted significant interest and offer the additional benefit of simple and well-defined NMR spectra.

To exploit these *C*-glycosyl amino acid components in SPPS, access to the appropriately protected monomers

(10) Jackson, R. F. W.; Wishart, N.; Wood, A.; James, K.; Wythes, M. J. *J. Org. Chem.* **1992**, *57*, 3397. Jackson, R. F. W.; Turner, D.; Block, M. H. *Synlett* **1996**, 862. Dunn, M. J.; Jackson, R. F. W.; Pietruszka, J.; Wishart, N.; Ellis, D.; Wythes, M. J. *Synlett* **1993**, 499. Fraser, J. L.; Jackson R. F. W.; Porter, B. *Synlett* **1994**, 379.

(11) For other applications of Pd-mediated cross coupling reactions of organozinc reagents in the synthesis of amino acids, see: Evans, D. A.; Bach, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1326. Walker, M. A.; Kaplita, K. P.; Chen, T.; King, H. D. *Synlett* **1997**, 169. Malan, C.; Morin, C. *Synlett* **1996**, 167.

(12) Fraser-Reid, B.; Molino, B. F.; Magdzinski, L.; Mootoo, D. R. *J. Org. Chem.* **1987**, *52*, 4505. In the case of **6a** we have carried out the dihydroxylation step (and *O*-acetylation) prior to the Pd-mediated coupling of **4** without deleterious effect. However, when applied to the L-rhamnal-derived *C*-glycoside **3c**, while dihydroxylation/acetylation of this intermediate proceeded smoothly, the subsequent attempt at the Pd(0) coupling step (involving **4**) surprisingly failed.

(13) Attempts to rigorously purify **7** by chromatography led to extensive decompositon to give 2-(acetoxymethyl)furan, and **7** was prepared and used directly in crude form. The sensitivity of **7** under acidic *C*-glycosylation conditions has been noted: Byerley, A. L. J.; Kenwright, A. M.; Steel, P. G. *Tetrahedron Lett.* **1996**, *37*, 9092.

(14) The assignment of the stereochemistry of *C*-glycoside **9** is primarily based on NOE experiments and at this time should be viewed as tentative. Irradiation of 1-H (benzylic CH_2) resulted in an enhancement (2%) of 5-H, and irradiation of 6-H resulted in an enhancement (2%) of 2-H. No enhancement of 5-H was observed on irradiation of 2-H.

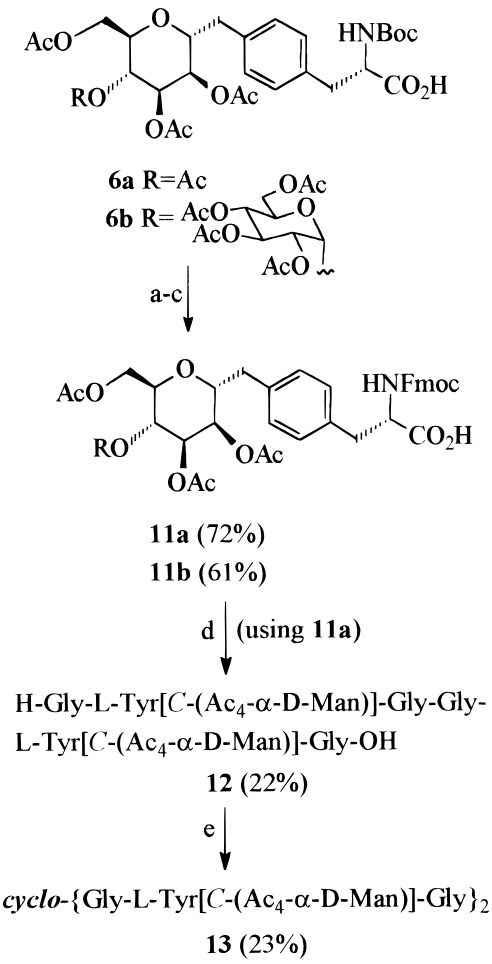
(15) Dihydroxylation of **10** results in a mixture of both *syn*-diol isomers but only a marginal degree of diastereoselectivity was observed, and this has not been pursued.

(16) Kunz, H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 294. Kihlberg J.; Elofsson, M. *Curr. Med. Chem.* **1997**, *4*, 85. Arsequell, G.; Valencia, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2839. For the synthesis of peptides incorporating glycosylated tyrosine units, see: Varga, L.; Horvat, S.; Lemieux, C.; Schiller, P. W. *Int. J. Pept. Protein Res.* **1987**, *30*, 371. Horvat, S.; Varga L.; Horvat, J. *Synthesis* **1986**, 209. Horvat, S.; Varga, L.; Horvat, J.; Pfützner, A.; Suhartono, H.; Rübsamen-Waigmann, H. *Helv. Chim. Acta* **1991**, *74*, 951.

(17) Kopple, K. D.; Go, A.; Logan, R. H.; Savrda, J. *J. Am. Chem. Soc.* **1972**, *94*, 973. Tanizawa, K.; Okumura, K.; Itoh, H.; Hatanaka, Y.; Kanaoka, Y. *Chem. Pharm. Bull.* **1986**, *34*, 4001.

(18) Synthesis of a model cyclic hexapeptide cyclo-[Gly-L-Phe-Gly]$_2$ (**14**) (Schwyzer, R.; Tun-Kyi, A. *Helv. Chim. Acta* **1962**, *45*, 859. Schwyzer, R.; Carrión, J. P.; Gorup, B.; Nolting, H.; Tun-Kyi, A. *Helv. Chim. Acta* **1964**, *47*, 441), which lacks any bulky carbohydrate units, was carried out by cyclization[19] of the corresponding linear hexapeptide (H-Gly-L-Phe-Gly-Gly-L-Phe-Gly-OH) using HOBt/TBTU. In our hands, this reaction proceeded in 41% yield as compared to the cyclization of **12** to give **13** (23% yield). Cyclic hexapeptides are also available via cyclodimerization of a tripeptide unit using azide activation: Kopple, K. D. *J. Pharm. Sci.* **1972**, *61*, 1345. While this method was successfully applied to the synthesis of the model cyclic hexapeptide (cyclo-[Gly-L-Phe-Gly]$_2$) **14**, it is known that the presence and position of a bulky aryl amino acid component within the tripeptide unit does influence the yield of this reaction (Konishi, M.; Yoshida, N.; Izumiya, N. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2801). We were not able to prepare the cyclic *C*-glycopeptide derivative **13** using this dimerization methodology and details of the synthesis and characterization of the precursor linear tripeptide {H-L-Tyr[*C*-(Ac_4-α-D-Man)]-Gly-Gly-$NHNH_2$} and of **14** are available in the Supporting Information.

Scheme 3[a]



[a] Key: (a) H_2, 10% Pd/C, MeOH, rt, 1 h. (b) TFA, CH_2Cl_2, rt, 1 h. (c) FmocOSuc, Et_3N, MeCN/H_2O, rt, 0.75 h. (d) SPPS (see Supporting Information). (e) HOBt, DIEA, TBTU (2-(1*H*-benzotriazol-1-yl)-1,1,3,3,-tetramethyluronium tetrafluoroborate), DMF, rt, 26 h, followed by reverse phase HPLC (see Supporting Information).

is mandatory. The conversion of **6a** and **6b** to the corresponding Fmoc-protected amino acids **11a** (72% overall yield) and **11b** (61% overall yield) was carried out as shown in Scheme 3. Using Fmoc-Gly-PEG-PS(HMP) resin, and starting with the *C*-mannosyl derivative **11a**, we have achieved the synthesis of hexapeptide **12**, containing two units of *C*-mannosyl tyrosine (and four glycine units), which was isolated in 22% yield following purification by reverse phase HPLC. Linear hexapeptide **12** was then converted to cyclic hexapeptide **13** (isolated in 23% yield), a transformation that was conducted in solution using the conditions described by Kessler.[19] This cyclization step[18] did not appear to be significantly impeded by the presence of the bulky *C*-glycosyl units and the C_2-symmetry of the cyclic derivative **13**, which was evident from ^{1}H NMR, and also served to confirm the integrity of the linear precursor **12**.

In summary, *C*-glycosides corresponding to a representative series of tyrosine *O*-glycoconjugates have been synthesized for the first time. We have also demonstrated, using the Fmoc-protected *C*-mannosyl tyrosine **11a**, that these novel *C*-glycosyl amino acids will function as building blocks for the solid-phase synthesis of linear and cyclic *C*-glycopeptides.[20,21] The chemistry described in this paper extends the range of *C*-glycosyl amino acids available, with these derivatives being important both in relation to *O*-glycopeptides (as a means to study the influence of glycosylation on glycopeptide structure) but also as novel amino acids in their own right. The robust nature of the *C*-linkage offers advantages where the naturally occurring *O*-glycoside proves to be sensitive, and work to extend the applications associated with *C*-glycosyl amino acids is continuing.

Experimental Section

For general experimental procedures, including details of HPLC purification methods, and procedures used to generate activated zinc and Pd/C, see Supporting Information.

4-(5,7-Di-*O*-acetyl-2,6-anhydro-1,3,4-trideoxy-*β*-D-*erythro*-hept-3-enitol-1-yl)iodobenzene (*β*-3a) and 4-(5,7-Di-*O*-acetyl-2,6-anhydro-1,3,4-trideoxy-α-D-*erythro*-hept-3-enitol-1-yl)iodobenzene (α-3a). Zinc dust (4.80 g, 0.08 mol) was activated according to general procedure A (see Supporting Information), using dry THF (5 mL), 1,2-dibromoethane (253 μL, 2.94 mmol) and TMSCl (281 μL, 2.21 mmol). A solution of 4-iodobenzyl bromide (10.91 g, 0.04 mol) in dry THF (20 mL) was added dropwise, over 1 h, to the stirred suspension of activated zinc at 0 °C under argon in the dark. After addition, TLC (ethyl acetate−light petroleum, 1:5) indicated no iodide (R_f 0.8) remained, and the mixture was warmed to room temperature and allowed to settle. The zincate solution was transferred away from unreacted zinc via gastight syringe into a flask purged with argon, and the solvent was removed in vacuo (bath temp 35 °C). Dry dichloromethane (20 mL) was added to the residue, and the solution was cooled to −30 °C under argon in the dark. A solution of tri-*O*-acetyl-D-glucal (**2a**) (5.88 g, 0.02 mol) in dry dichloromethane (10 mL) was added to the zincate, followed by $BF_3{\cdot}OEt_2$ (13.3 mL, 0.11 mol). The mixture was immediately warmed to 0 °C and stirred for 15 min, after which time TLC (ethyl acetate−light petroleum, 1:3) indicated no glucal (R_f 0.3) and a major product (R_f 0.4). The reaction mixture was warmed to room temperature, then diluted with dichloromethane (40 mL), and washed with brine (40 mL); and the organic layer was dried (Na_2SO_4) and filtered; and the solvent was removed in vacuo. The residue was purified by flash chromatography (ethyl acetate−light petroleum, 1:3) to afford the title compounds (7.0 g, 75%) as a 3.5:1 mixture of α:*β* isomers as determined by ^{1}H NMR analysis. Further flash chromatography (ethyl acetate−light petroleum, 1:3) afforded pure 4-(5,7-di-*O*-acetyl-2,6-anhydro-1,3,4-trideoxy-*β*-D-*erythro*-hept-3-enitol-1-yl)iodobenzene (*β*-**3a**), as a colorless oil: $[\alpha]_D^{19}$ +90.7 (*c* 1.8, $CHCl_3$); IR (film) 1738vs (C═O), 1486s, 1369s, 1232s (C−O), 1047s, 1007s cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (2 H, d, *J* 8.0, Ar *o*-I), 6.98 (2 H, d, *J* 8.0, Ar *m*-I), 5.77 (1 H, dt, $J_{3,4}$ 10.4, $J_{2,3} = J_{3,5}$ 1.5, 3-H), 5.70 (1 H, dt, $J_{3,4}$ 10.4, $J_{2,4} = J_{4,5}$ 2.0, 4-H), 5.22 (1 H, ddd, $J_{5,6}$ 9.0, $J_{4,5}$ 2.0, $J_{3,5}$ 1.5, 5-H), 4.36 (1 H, m, 2-H), 4.19 (2 H, m, 7-H^{a,b}), 3.70 (1 H, ddd, $J_{5,6}$ 9.0, $J_{6,7b}$ 5.0, $J_{6,7a}$ 3.5, 6-H), 2.87 (1 H, dd, $J_{1a,1b}$ 13.7, $J_{1a,2}$ 6.6, 1-H^a), 2.72 (1 H, dd, $J_{1a,1b}$ 13.7, $J_{1b,2}$ 6.4, 1-H^b), 2.08 (3 H, s, CH_3), 2.07 (3 H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 170.3 (2 × *C*OCH$_3$), 137.3 (Ar *o*-I), 136.9 (C_{ipso}), 131.7 (Ar *m*-I), 131.6 (3-C), 125.6 (4-C), 91.8 (*C*-I), 75.2 (2-C), 74.2 (6-C), 65.5 (5-C), 63.5 (7-C), 40.9 (1-C), 21.0, 20.9 (2 × CO*C*H$_3$); MS (CI) *m*/*z* 431 (M + H$^+$, 15%), 371 [(M + H −

(19) For the application of the HOBt/TBTU method for the "head-to-tail" cyclization of linear hexapeptides, see: Zimmer, S.; Hoffmann, E.; Jung, G.; Kessler, H. *Liebigs. Ann. Chem.* **1993**, 497.

(20) There are a number of incentives for developing the chemistry of cyclic *C*-glycopeptides, other than to prove the viability of *C*-glycosyl amino acids as peptide building blocks. RA-XIV,[7g] a glycosylated tyrosine-containing cyclic peptide displays antitumor activity, and the antibiotic ramoplanose[7k] incorporates an α-linked mannosyl-based trisaccharide. Recently, glucosylated cyclic hexapeptides have also been examined as molecular receptors for amino acids.[21]

(21) Leipert, D.; Nopper, D.; Bauser, M.; Gauglitz, G.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3308.

AcOH)$^+$, 100], 311 [(M + H − 2AcOH)$^+$, 94), 217 (*p*-ITol$^+$, 50), 213 [(M − *p*-ITol)$^+$, 56]; HRMS for $C_{17}H_{20}IO_5$ (M + H$^+$) calcd 431.0356, found 431.0393.

Continued elution gave 4-(5,7-di-*O*-acetyl-2,6-anhydro-1,3,4-trideoxy-α-D-*erythro*-hept-3-enitol-1-yl)iodobenzene (α-**3a**), as a colorless oil: $[\alpha]_D^{19}$ +61.7 (*c* 1.0, $CHCl_3$); IR (film) 1739vs (C═O), 1485s, 1370s, 1233s (C−O), 1046s, 1007s cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (2 H, d, *J* 8.0, Ar *o*-I), 7.00 (2 H, d, *J* 8.0, Ar *m*-I), 5.89 (1 H, ddd, $J_{3,4}$ 10.4, $J_{2,3}$ 2.0, $J_{3,5}$ 1.5, 3-H), 5.81 (1 H, dt, $J_{3,4}$ 10.4, $J_{2,4} = J_{4,5}$ 2.0, 4-H), 5.12 (1 H, m, 5-H), 4.42 (1 H, ddt, $J_{1a,2}$ 8.0, $J_{1b,2}$ 6.0, $J_{2,3} = J_{2,4}$ 2.0, 2-H), 4.22 (1 H, dd, $J_{7a,7b}$ 11.9, $J_{6,7a}$ 6.8, 7-H^a), 4.13 (1 H, dd, $J_{7a,7b}$ 11.9, $J_{6,7b}$ 3.5, 7-H^b), 4.00 (1 H, td, $J_{5,6} = J_{6,7a}$ 6.8, $J_{6,7b}$ 3.5, 6-H), 2.95 (1 H, dd, $J_{1a,1b}$ 14.0, $J_{1a,2}$ 8.0, 1-H^a), 2.77 (1 H, dd, $J_{1a,1b}$ 14.0, $J_{1b,2}$ 6.0, 1-H^b), 2.10 (3 H, s, C*H*$_3$), 2.07 (3 H, s, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 170.4 (2 × *C*OCH$_3$), 137.5 (Ar *o*-I), 137.4 (C$_{ipso}$), 132.3 (3-C), 131.4 (Ar *m*-I), 124.2 (4-C), 91.8 (*C*-I), 72.6 (2-C), 69.5 (6-C), 65.0 (5-C), 62.9 (7-C), 39.0 (1-C), 21.1, 20.8 (2 × CO*C*H$_3$); MS (CI) *m*/*z* 431 (M + H$^+$, 1%), 371 [(M + H − AcOH)$^+$, 42], 311 [(M + H − 2AcOH)$^+$, 100), 217 (*p*-ITol$^+$, 38), 213 [(M − *p*-ITol)$^+$, 20]; HRMS for $C_{17}H_{20}IO_5$ (M + H$^+$) calcd 431.0356, found 431.0358.

***N*$^\alpha$-(*tert*-Butoxycarbonyl)-*C*-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-L-tyrosine benzyl ester (5a).** Zinc dust (1.71 g, 0.03 mol) was activated according to general procedure A, using dry THF (1.5 mL), 1,2-dibromoethane (90 μL, 1.04 mmol), and TMSCl (100 μL, 0.79 mmol). A solution of Boc-L-Ala(I)-OBn[10] (3.53 g, 8.71 mmol) in dry THF (4.5 mL) was added to the stirred suspension of activated zinc at 35 °C under argon in the dark. After 2 h, TLC (ethyl acetate−light petroleum, 1:3) indicated no iodide (R_f 0.8) remained, and the mixture was cooled to room temperature and allowed to settle. Bis(tri-*o*-tolylphosphine)palladium dichloride (236 mg, 0.33 mmol) was added to a stirred solution of (α-**3a**) (0.94 g, 2.18 mmol) in dry *N*,*N*-dimethylacetamide (3 mL) and dry THF (1 mL) at room temperature under argon. After 15 min, the zincate solution was transferred away from unreacted zinc via gastight syringe and added to the yellow iodobenzene mixture. After 1 h of stirring at room temperature, the mixture was heated to 50 °C. After 2 h, TLC (ethyl acetate−light petroleum, 1:3) indicated no iodobenzene (R_f 0.5) and a major product (R_f 0.2), and the green reaction mixture was allowed to cool to room temperature. Ethyl acetate (100 mL) was added, the mixture was filtered through Celite into a separating funnel, then washed with saturated aqueous NH_4Cl (15 mL), brine (15 mL), dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography (eluent gradient, light petroleum to ethyl acetate−light petroleum, 2:3) to afford *N*$^\alpha$-(*tert*-butoxycarbonyl)-*C*-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-L-tyrosine benzyl ester (**5a**) (1.0 g, 82%), as a colorless oil: $[\alpha]_D^{26}$ +27.4 (*c* 1.0, $CHCl_3$); IR (film) 3375br (N−H), 2977w, 1744vs (C═O), 1715vs (C═O), 1500m, 1358m, 1237s (C−O), 1166s, 1050m cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.28 (5 H, m, Ph), 7.10 (2 H, d, *J* 7.8, Ar), 6.98 (2 H, d, *J* 7.8, Ar), 5.87 (1 H, ddd, $J_{2,3}$ 10.5, $J_{1,2}$ 2.4, $J_{2,4}$ 1.6, 2-H), 5.79 (1 H, dt, $J_{2,3}$ 10.5, $J_{1,3} = J_{3,4}$ 2.0, 3-H), 5.20−5.08 (3 H, m, PhC*H*$_2$, 4-H), 5.03 (1 H, br d, $J_{NH,CH\alpha}$ 8.0, N*H*), 4.61 (1 H, dt, $J_{NH,CH\alpha}$ 8.0, $J_{CH\alpha,CH\beta} = J_{CH\alpha,CH\beta'}$ 6.0, α-H), 4.41 (1 H, m, $J_{1,CH\gamma}$ 8.0, $J_{1,CH\gamma'}$ 6.3, $J_{1,3}$ 2.0, 1-H), 4.23 (1 H, dd, $J_{6a,6b}$ 11.8, $J_{5,6a}$ 6.6, 6-H^a), 4.15 (1 H, dd, $J_{6a,6b}$ 11.8, $J_{5,6b}$ 3.4, 6-H^b), 3.99 (1 H, td, $J_{4,5} = J_{5,6a}$ 6.6, $J_{5,6b}$ 3.4, 5-H), 3.10 (1 H, dd, $J_{CH\beta,CH\beta'}$ 8.0, $J_{CH\alpha,CH\beta}$ 6.0, β-H), 3.03 (1 H, dd, $J_{CH\beta,CH\beta'}$ 8.0, $J_{CH\alpha,CH\beta'}$ 6.0, β′-H), 3.00 (1 H, dd, $J_{CH\gamma,CH\gamma'}$ 13.8, $J_{1,CH\gamma}$ 8.0, γ-H), 2.77 (1 H, dd, $J_{CH\gamma,CH\gamma'}$ 13.8, $J_{1,CH\gamma'}$ 6.3, γ′-H), 2.09 (3 H, s, COC*H*$_3$), 2.06 (3 H, s, COC*H*$_3$), 1.41 (9 H, s, (C*H*$_3$)$_3$C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6 (*C*OCH$_2$), 170.7, 170.3 (2 × *C*OCH$_3$), 155.0 (O*C*ON), 136.2, 135.1, 134.0, 132.4 (2-C), 129.3, 128.5, 128.42, 128.4, 128.0, 123.9 (3-C), 79.8 ((CH$_3$)$_3$*C*), 72.9, 69.4, 67.0, 65.0, 62.9, 54.3 (α-C), 39.1, 37.7 (β-C, γ-C), 28.2 ((*C*H$_3$)$_3$C), 21.0, 20.7 (2 × CO*C*H$_3$); MS (FAB$^+$) *m*/*z* 582 (M + H$^+$, 10%), 482 [(M + H − Boc)$^+$, 40], 213 (10), 91 (C$_7$H$_7^+$, 100); HRMS for $C_{32}H_{40}NO_9$ (M + H$^+$) calcd 582.2703, found 582.2672.

***N*$^\alpha$-(*tert*-Butoxycarbonyl)-*C*-(4,6-di-*O*-acetyl-α-D-mannopyranosyl)-L-tyrosine Benzyl Ester.** *N*-Methylmorpholine *N*-oxide (247 mg, 2.11 mmol) and then OsO_4 (2.5 wt % in *tert*-BuOH, 2.20 mL, 0.18 mmol) were added to a stirred solution of *N*$^\alpha$-(*tert*-butoxycarbonyl)-*C*-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-L-tyrosine benzyl ester (**5a**) (1.0 g, 1.76 mmol) in acetone−water (5:1, 15 mL) at room temperature. After 24 h, TLC (ethyl acetate−light petroleum, 3:2) indicated no starting material (R_f 0.8) and product (R_f 0.2). Sodium metabisulfite (70 mg, 0.37 mmol) in water (2 mL) was added, and the mixture was stirred vigorously for 0.5 h. Ethyl acetate (15 mL) was added, and the mixture was filtered through Celite into a separating funnel and washed with brine (2 mL). The aqueous layer was extracted with ethyl acetate (3 × 15 mL), dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography (eluent gradient, ethyl acetate−light petroleum, 2:1 to ethyl acetate) to afford *N*$^\alpha$-(*tert*-butoxycarbonyl)-*C*-(4,6-di-O-acetyl-α-D-mannopyranosyl)-L-tyrosine benzyl ester (628 mg, 58%), as a colorless oil. $[\alpha]_D$25 +20.8 (*c* 1.0, $CHCl_3$); IR (film) 3350br, 2933w, 1734vs (C═O), 1694s (C═O), 1523m, 1368m, 1239s (C−O), 1167m, 1055s cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.30 (5 H, m, Ph), 7.10 (2 H, d, *J* 7.2, Ar), 6.97 (2 H, d, *J* 7.2, Ar), 5.16 (1 H, d, *J* 12.3, PhC*H*H′), 5.10 (1 H, d, *J* 12.3, PhCH*H*′), 4.99 (2 H, m, 4-H and N*H*), 4.59 (1 H, dt, $J_{\alpha,NH}$ 8.0, $J_{\alpha,\beta} = J_{\alpha,\beta'}$ 6.0, α-H), 4.37 (1 H, dd, $J_{6a,6b}$ 12.0, $J_{5,6a}$ 7.0, 6-H^a), 4.15 (1 H, m, 1-H), 4.08 (1 H, dd, $J_{6a,6b}$ 12.0, $J_{5,6b}$ 3.0, 6-H^b), 3.98−3.92 (2 H, m, 5-H and 3-H), 3.81 (1 H, t, $J_{1,2} = J_{2,3}$ 3.7, 2-H), 3.11−2.99 (2 H, m, β-H, β′-H), 2.97−2.84 (2 H, m, γ-H, γ′-H), 2.12 (3 H, s, COC*H*$_3$), 1.97 (3 H, s, COC*H*$_3$), 1.41 (9 H, s, (C*H*$_3$)$_3$C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7 (*C*OCH$_2$), 171.2, 170.8 (2 × *C*OCH$_3$), 155.1 (O*C*ON), 136.2, 135.1, 134.1, 129.5, 129.3, 129.2, 129.0, 128.6, 79.9 ((CH$_3$)$_3$*C*), 76.6, 70.7, 70.6, 70.1, 69.6, 67.1 (1-C, 2-C, 3-C, 4-C, 5-C, PhCH$_2$), 62.4 (6-C), 54.4 (α-C), 37.7, 35.4 (β-C, γ-C), 28.2 ((*C*H$_3$)$_3$C), 21.0, 20.7 (2 × CO*C*H$_3$); MS (EI) *m*/*z* 498 [(M − BocNH$_2$)$^+$, 20%), 247 (C$_{10}$H$_{15}$O$_7$+, 40), 91 (C$_7$H$_7$+, 100), 57 (C$_4$H$_9$+, 75); HRMS for $C_{27}H_{30}O_9$ (M − BocNH$_2$)$^+$ calcd 498.1890, found 498.1893.

***N*$^\alpha$-(*tert*-Butoxycarbonyl)-*C*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-L-tyrosine Benzyl Ester (6a).** Acetic anhydride (0.48 mL, 5.09 mmol) was added dropwise over 1 min to a stirred solution of *N*$^\alpha$-(*tert*-butoxycarbonyl)-*C*-(4,6-di-*O*-acetyl-α-D-mannopyranosyl)-L-tyrosine benzyl ester (628 mg, 1.02 mmol) and DMAP (6.2 mg, 0.05 mmol) in dry pyridine (7 mL) at 0 °C under nitrogen. After 25 min, TLC (ethyl acetate−light petroleum, 2:1) indicated no diol (R_f 0.2) and product (R_f 0.6), and the reaction was quenched by the addition of water (2 mL). The mixture was allowed to warm to room temperature, brine (2 mL) was added, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). Combined extracts were washed with 2 M hydrochloric acid (7 × 5 mL), dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo (toluene azeotrope × 3). The residue was purified by flash chromatography (eluent gradient, ethyl acetate−light petroleum, 2:3 to ethyl acetate−light petroleum, 1:1) to afford *N*$^\alpha$-(*tert*-butoxycarbonyl)-*C*-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)-L-tyrosine benzyl ester (**6a**) (591 mg, 83%), as a colorless solid: mp 53−55 °C; analytical chiral HPLC (R$_t$ 23.0 min); $[\alpha]_D^{28}$ +6.6 (*c* 1.6, $CHCl_3$); IR (KBr) 3370br (N−H), 2976w, 1746vs (C═O), 1716s (C═O), 1515m, 1368s, 1228vs (C−O), 1165s, 1050s cm^{-1}; UV (CH_2Cl_2) 229 (ϵ/dm^3 mol^{-1} mL^{-1} 2 200), 263 (650), 259 (650) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.29 (5 H, m, Ph), 7.10 (2 H, d, *J* 8.0, Ar), 7.00 (2 H, d, *J* 8.0, Ar), 5.35 (1 H, dd, $J_{3,4}$ 9.0, $J_{2,3}$ 3.2, 3-H), 5.22 (1 H, t, $J_{1,2} = J_{2,3}$ 3.2, 2-H), 5.21 (1 H, t, $J_{3,4} = J_{4,5}$ 9.0, 4-H), 5.16 (1 H, d, *J* 12.0, PhC*H*H′), 5.10 (1 H, d, *J* 12.0, PhCH*H*′), 4.97 (1 H, br d, $J_{NH,CH\alpha}$ 8.3, N*H*), 4.61 (1 H, m, α-H), 4.29 (1 H, dd, $J_{6a,6b}$ 12.0, $J_{5,6a}$ 6.6, 6-H^a), 4.18 (1 H, ddd, $J_{1,CH\gamma}$ 8.8, $J_{1,CH\gamma'}$ 5.9, $J_{1,2}$ 3.2, 1-H), 4.08 (1 H, dd, $J_{6a,6b}$ 12.0, $J_{5,6b}$ 3.0, 6-H^b), 4.02 (1 H, ddd, $J_{4,5}$ 9.0, $J_{5,6a}$ 6.6, $J_{5,6b}$ 3.0, 5-H), 3.05−3.00 (3 H, m, β-H, β′-H, γ-H), 2.88 (1 H, dd, $J_{CH\gamma,CH\gamma'}$ 14.5, $J_{1,CH\gamma'}$ 5.9, γ′-H), 2.09 (6 H, s, 2 × COC*H*$_3$), 2.04 (3 H, s, COC*H*$_3$), 2.01 (3 H, s, COC*H*$_3$), 1.41 (9 H, s, (C*H*$_3$)$_3$C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.7, 170.2, 170.1, 169.7 (5 × O*C*O), 155.1 (O*C*ON), 135.25, 135.2, 134.4, 129.6, 129.2, 128.6, 128.55, 128.5, 80.0 ((CH$_3$)$_3$*C*), 75.8, 70.8, 70.0, 68.8, 67.1, 67.0, 62.4 (6-C), 54.4 (α-

C), 37.8, 35.0 (β-C, γ-C), 28.3 (($CH_3)_3C$), 20.9, 20.8, 20.75, 20.7 (4 × $COCH_3$); MS (FAB$^+$) *m*/*z* 700 (M + H$^+$, 10%), 600 [(M + H − Boc)$^+$, 100]. Anal. Calcd for $C_{36}H_{45}NO_{13}$: C, 61.8; H, 6.5; N, 2.0. Found: C, 61.7; H, 6.3; N, 2.2.

4-[(2′,3′,4′,6′-Tetra-*O*-acetyl-α-D-glucopyranosyl)-(1′→5)-(7-*O*-acetyl-2,6-anhydro-1,3,4-trideoxy-α,β-D-*erythro*-hept-3-enitol-1-yl)]iodobenzene (3b). Zinc dust (1.78 g, 0.03 mol) was activated according to general procedure A, using dry THF (2.0 mL), 1,2-dibromoethane (94 μL, 1.09 mmol) and TMSCl (104 μL, 0.82 mmol). A solution of 4-iodobenzyl bromide (4.05 g, 13.64 mmol) in dry THF (10 mL) was added dropwise over 1 h to the stirred suspension of activated zinc at 0 °C, under argon in the dark. After an additional 0.5 h at 0 °C, TLC (ethyl acetate−light petroleum, 1:5) indicated no iodide (R_f 0.8) remained, and the mixture was warmed to room temperature and allowed to settle. The zincate solution was transferred away from unreacted zinc via gastight syringe into a flask purged with argon, and the solvent was removed in vacuo (bath temp 35 °C). Dry dichloromethane (10 mL) was added to the residue, and the solution was cooled to −30 °C under argon in the dark. A solution of hexa-*O*-acetyl-D-maltal (**2b**) (4.49 g, 8.02 mmol) in dry dichloromethane (10 mL) was added to the zincate, followed by $BF_3.OEt_2$ (4.93 mL, 0.04 mol). The mixture was warmed to 0 °C after 10 min and stirred for an additional 0.5 h, after which time TLC (ethyl acetate−light petroleum, 1:1) indicated no maltal (R_f 0.5) and a major product (R_f 0.6). The reaction mixture was warmed to room temperature, diluted with dichloromethane (40 mL), washed with brine (30 mL); the organic (upper) layer was dried (Na_2SO_4) and filtered; and the solvent was removed in vacuo. The residue was purified by flash chromatography (60H; eluent gradient, 15−35% ethyl acetate in light petroleum) to afford 4-[(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-glucopyranosyl)-(1′→5)-(7-*O*-acetyl-2,6-anhydro-1,3,4-trideoxy-α,β-D-*erythro*-hept-3-enitol-1-yl)]iodobenzene (**3b**) (3.92 g, 67%) as an inseparable 2:1 mixture of α/β isomers as determined by ^{1}H NMR analysis, as a colorless foam: IR (KBr) 1748vs (C═O), 1368m, 1226vs (C−O), 1038s cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (1.3 H, d, *J* 8.3, Ar$_\alpha$ *o*-I), 7.60 (0.7 H, d, *J* 8.3, Ar$_\beta$ *o*-I), 7.00 (1.3 H, d, *J* 8.3, Ar$_\alpha$ *m*-I), 6.97 (0.7 H, d, *J* 8.3, Ar$_\beta$ *m*-I), 5.89 (0.7 H, ddd, $J_{3,4}$ 10.5, $J_{2,3}$ 2.6, $J_{3,5}$ 2.0, 3-H$_\alpha$), 5.77 (1 H, m, 4-H$_\alpha$, 3-H$_\beta$), 5.67 (0.3 H, dt, $J_{3,4}$ 10.5, $J_{2,4}$ = $J_{4,5}$ 2.0, 4-H$_\beta$), 5.47 (0.7 H, dd, $J_{2',3'}$ 10.3, $J_{3',4'}$ 9.5, 3′-H$_\alpha$), 5.41 (0.3 H, dd, $J_{2',3'}$ 10.3, $J_{3',4'}$ 9.5, 3′-H$_\beta$), 5.32 (0.7 H, d, $J_{1',2'}$ 3.9, 1′-H$_\alpha$), 5.27 (0.3 H, d, $J_{1',2'}$ 4.0, 1′-H$_\beta$), 5.07 (0.7 H, t, $J_{3',4'}$ = $J_{4',5'}$ 9.5, 4′-H$_\alpha$), 5.05 (0.3 H, t, $J_{3',4'}$ = $J_{4',5'}$ 9.5, 4′-H$_\beta$), 4.85 (0.7 H, dd, $J_{2',3'}$ 10.3, $J_{1',2'}$ 3.9, 2′-H$_\alpha$), 4.82 (0.3 H, dd, $J_{2',3'}$ 10.3, $J_{1',2'}$ 4.0, 2′-H$_\beta$), 4.40−4.03 (7 H, m, 2-H$_{\alpha,\beta}$, 5-H$_{\alpha,\beta}$, 5′-H$_{\alpha,\beta}$, 6′-H$^a_{\alpha,\beta}$, 6′-H$^b_{\alpha,\beta}$, 7-H$^a_{\alpha,\beta}$, 7-H$^b_{\alpha,\beta}$), 3.97 (0.7 H, td, $J_{5,6}$ = $J_{6,7a}$ 7.0, $J_{6,7b}$ 5.0, 6-H$_\alpha$), 3.62 (0.3 H, ddd, $J_{5,6}$ 8.4, $J_{6,7b}$ 5.7, $J_{6,7a}$ 2.4, 6-H$_\beta$), 2.94 (0.7 H, dd, $J_{1a,1b}$ 13.9, $J_{1a,2}$ 8.6, 1-H$^a_\alpha$), 2.84 (0.3 H, dd, $J_{1a,1b}$ 13.8, $J_{1a,2}$ 6.6, 1-H$^a_\beta$), 2.75 (0.7 H, dd, $J_{1a,1b}$ 13.9, $J_{1b,2}$ 6.0, 1-H$^b_\alpha$), 2.70 (0.3 H, dd, $J_{1a,1b}$ 13.8, $J_{1b,2}$ 6.2, 1-H$^b_\beta$), 2.09−2.01 (15 H, 8 × s observed but not all signals were cleanly resolved, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7−169.5 (10 × C observed, but not all signals were not fully resolved, $COCH_3$), 137.4 (Ar$_\alpha$ *o*-I), 137.2 (Ar$_\beta$ *o*-I), 136.8 (C$_{ipso}$), 132.4 (3-C$_\alpha$), 131.7 (3-C$_\beta$), 131.3 (Ar$_{\alpha,\beta}$ *m*-I), 124.9 (4-C$_\beta$), 123.9 (4-C$_\alpha$), 94.3 (1′-C$_\alpha$), 94.1 (1′-C$_\beta$), 91.8 (*C*-I$_{\alpha,\beta}$), 74.9 (2-C$_\beta$), 74.7 (6-C$_\beta$), 72.8 (2-C$_\alpha$), 70.8, 70.75 (2′-C$_\alpha$, 2′-C$_\beta$), 70.1, 70.0, 69,9, 69.8, 68.1, 68.0, (3′-C$_{\alpha,\beta}$, 5-C$_{\alpha,\beta}$, 5′-C$_{\alpha,\beta}$, 6-C$_\alpha$), 68.3 (4′-C$_\alpha$), 68.2 (4′-C$_\beta$), 63.7, 63.4, 61.8, 61.7 (6′-C$_{\alpha,\beta}$, 7-C$_{\alpha,\beta}$), 40.8 (1-C$_\beta$), 38.9 (1-C$_\alpha$), 21.0, 20.9, 20.8, 20.7, 20.63, 20.6 (10 × C, $COCH_3$); MS (FAB+) *m*/*z* 741 (M + Na$^+$, 13%), 719 (M + H$^+$, 2), 169 (100); HRMS for $C_{29}H_{36}IO_{13}$ (M + H$^+$) calcd 719.1202, found 719.1201.

***N*$^\alpha$-(*tert*-Butoxycarbonyl)-*C*-[(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-glucopyranosyl)-(1′→4)−(6-*O*-acetyl-2,3-dideoxy-β-D-*erythro*-hex-2-enopyranosyl)]-L-tyrosine Benzyl Ester and *N*$^\alpha$-(*tert*-butoxycarbonyl)-*C*-[(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-glucopyranosyl)-(1′→4)-(6-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)]-L-tyrosine Benzyl Ester (5b).** Zinc dust (1.71 g, 0.03 mol) was activated according to general procedure A, using dry THF (1.5 mL), 1,2-dibromoethane (90 μL, 1.04 mmol), and TMSCl (100 μL, 0.79 mmol). A solution of Boc-L-Ala(I)-OBn[10] (3.5 g, 8.63 mmol) in dry THF (4.5 mL) was added to the stirred suspension of activated zinc at 35 °C under argon in the dark. After 2.5 h, TLC (ethyl acetate−light petroleum, 1:3) indicated no iodide (R_f 0.8) remained, and the mixture was cooled to room temperature and allowed to settle. Bis(tri-*o*-tolylphosphine)palladium dichloride (236 mg, 0.33 mmol) was added to a stirred solution of 4-[(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-glucopyranosyl)-(1′→5)-(7-*O*-acetyl-2,6-anhydro-1,3,4-trideoxy-α,β-D-*erythro*-hept-3-enitol-1-yl)]iodobenzene (**3b**) (1.50 g, 2.09 mmol) in dry *N*,*N*-dimethylacetamide (3 mL) and dry THF (1 mL) at room temperature under argon. After 15 min, the zincate solution was transferred away from unreacted zinc via gastight syringe and added to the yellow iodoarene mixture. After stirring at room temperature for 0.5 h the mixture was heated to 55 °C. After 2 h, TLC (ethyl acetate−light petroleum, 2:3) indicated no iodobenzene (R_f 0.3) and a major product (R_f 0.2), and the green reaction mixture was allowed to cool to room temperature. Ethyl acetate (100 mL) was added; the mixture was filtered through Celite into a separating funnel and then washed with saturated aqueous NH_4Cl (15 mL), brine (15 mL), dried (Na_2SO_4), and filtered; and the solvent was removed in vacuo. The residue was purified by flash chromatography (eluent gradient, ethyl acetate−light petroleum, 1:4 to 1:1) to afford the title compounds (1.46 g, 81%) as a 2:1 mixture of α/β isomers as determined by ^{1}H NMR analysis. Flash chromatography (60H; eluent gradient, 15−50% ethyl acetate in light petroleum) afforded the minor β-isomer (*N*$^\alpha$-(*tert*-butoxycarbonyl)-*C*-[(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-glucopyranosyl)-(1′→4)−(6-*O*-acetyl-2,3-dideoxy-β-D-*erythro*-hex-2-enopyranosyl)]-L-tyrosine benzyl ester) (480 mg) as a colorless foam: analytical RPHPLC (0−15 min, linear gradient of 60−100% solvent B in solvent A, R_t 10.2 min); $[\alpha]_D^{30}$ +105.1 (*c* 1.0 in $CHCl_3$); IR (KBr) 3376br (N−H), 2976w, 1748vs (C═O), 1716s (C═O), 1368m, 1229vs (C−O), 1166m, 1040s cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.29 (5 H, m, Ph), 7.08 (2 H, d, *J* 7.8, Ar), 6.96 (2 H, d, *J* 7.8, Ar), 5.76 (1 H, m, 2-H), 5.65 (1 H, m, 3-H), 5.41 (1 H, t, $J_{2',3'}$ = $J_{3',4'}$ 10.0, 3′-H), 5.28 (1 H, d, $J_{1',2'}$ 3.9, 1′-H), 5.17 (1 H, d, *J* 12.2, PhC*H*H′), 5.11 (1 H, d, *J* 12.2, PhCH*H*′), 5.06 (1 H, t, $J_{3',4'}$ = $J_{4',5'}$ 10.0, 4′-H), 4.98 (1 H, d, $J_{NH,CH\alpha}$ 7.7, N*H*), 4.82 (1 H, dd, $J_{2',3'}$ 10.0, $J_{1',2'}$ 3.9, 2′-H), 4.61 (1 H, dt, $J_{NH,CH\alpha}$ 7.7, $J_{CH\alpha,CH\beta}$ = $J_{CH\alpha,CH\beta'}$ 6.0, α-H), 4.38 (1 H, dd, $J_{6a,6b}$ 12.0, $J_{5,6a}$ 2.4, 6-H^a), 4.28 (1 H, m, 1-H), 4.27−4.05 (5 H, m, 4-H, 5′-H, 6-H^b, 6′-H^a, 6′-H^b), 3.64 (1 H, ddd, *J* 8.3, *J* 5.9, $J_{5,6a}$ 2.4, 5-H), 3.08 (1 H, dd, $J_{CH\beta,CH\beta'}$ 14.0, $J_{CH\alpha,CH\beta}$ 6.0, β-H), 3.03 (1 H, dd, $J_{CH\beta,CH\beta'}$ 14.0, $J_{CH\alpha,CH\beta'}$ 6.0, β′-H), 2.92 (1 H, dd, $J_{CH\gamma,CH\gamma'}$ 13.5, $J_{1,CH\gamma}$ 6.6, γ-H), 2.66 (1 H, dd, $J_{CH\gamma,CH\gamma'}$ 13.5, $J_{1,CH\gamma'}$ 7.3, γ′-H), 2.10, 2.09, 2.03, 2.02, 2.01 (5 × 3 H, s, OCH_3), 1.41 (9 H, s, ($CH_3)_3$C);^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (*C*OCH$_2$), 170.9, 170.7, 170.3, 170.1, 169.6 (5 × *C*OCH$_3$), 155.1 (O*C*ON), 135.9, 135.3, 134.1, 132.1 (2-C), 129.8, 129.5, 129.4, 128.65, 128.6, 124.5 (3-C), 94.1 (1′-C), 80.0 (($CH_3)_3C$), 75.4 (1-C), 74.8 (5-C), 70.8 (2′-C), 70.2 (4-C), 69.9 (3′-C), 68.3 (4′-C), 68.1 (5′-C), 67.1 (Ph*C*H$_2$), 63.9 (6-C), 61.8 (6′-C), 54.5 (α-C), 41.1 (γ-C), 37.9 (β-C), 28.3 (($CH_3)_3$C), 20.9−20.1 (5 × C, COCH_3, signals not fully resolved); MS (ESI$^+$) *m*/*z* 892.4 (M + Na$^+$, 25%), 870.4 (M + H$^+$, 15), 770.3 [(M + H$_2$ − Boc)$^+$, 100]; HRMS for $C_{39}H_{48}NO_{15}$ (M + H$_2$ − Boc)$^+$: calcd 770.3024, found 770.3054.

Continued elution gave *N*$^\alpha$-(*tert*-butoxycarbonyl)-*C*-[(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-glucopyranosyl)-(1′→4)-(6-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)]-L-tyrosine benzyl ester (**5b**) (950 mg), as a colorless foam: analytical RPHPLC (0−15 min, linear gradient of 60−100% solvent B in solvent A, R_t 9.6 min); $[\alpha]_D^{30}$ +63.8 (*c* 2.6, $CHCl_3$); IR (KBr) 3378br (N−H), 2977w, 1748vs (C═O), 1716s (C═O), 1368m, 1228vs (C−O), 1166m, 1040s cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.30 (5 H, m, Ph), 7.11 (2 H, d, *J* 7.9, Ar), 6.97 (2 H, d, *J* 7.9, Ar), 5.86 (1 H, ddd, $J_{2,3}$ 10.5, $J_{1,2}$ 2.4, $J_{2,4}$ 1.5, 2-H), 5.75 (1 H, dt, $J_{2,3}$ 10.5, $J_{1,3}$ = $J_{3,4}$ 2.0, 3-H), 5.48 (1 H, dd, $J_{2',3'}$ 10.3, $J_{3',4'}$ 9.6, 3′-H), 5.32 (1 H, d, $J_{1',2'}$ 4.0, 1′-H), 5.18 (1 H, d, *J* 12.2, PhC*H*H′), 5.12 (1 H, d, *J* 12.2, PhCH*H*′), 5.08 (1 H, t, $J_{3',4'}$ = $J_{4',5'}$ 9.6, 4′-H), 4.99 (1 H, d, $J_{NH,CH\alpha}$ 7.0, N*H*), 4.86 (1 H, dd, $J_{2',3'}$ 10.3, $J_{1',2'}$ 4.0, 2′-H), 4.60 (1 H, m, α-H), 4.37 (1 H, m, 1-H), 4.31−4.06 (6 H, m, 4-H, 5′-H, 6-H^a, 6-H^b, 6′-H^a, 6′-H^b), 3.96 (1 H, dt, *J* 7.0, *J* 5.0, 5-H), 3.13−3.00 (2 H, m, β-H, β′-H), 2.98 (1 H, dd, $J_{CH\gamma,CH\gamma'}$ 13.7, $J_{1,CH\gamma}$ 8.0, γ-H), 2.75 (1 H, dd, $J_{CH\gamma,CH\gamma'}$ 13.7, $J_{1,CH\gamma'}$

6.4, γ′-H), 2.10, 2.09, 2.08, 2.04, 2.03 (5 × 3 H, s, COCH_3), 1.41 (9 H, s, (CH_3)$_3$C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7 (*C*OCH$_2$), 170.7, 170.6, 170.2, 170.1, 169.6 (5 × *C*OCH$_3$), 155.0 (O*C*ON), 136.4, 135.2, 134.1, 132.6 (2-C), 129.4, 128.6, 128.5, 128.4, 128.0, 123.7 (3-C), 94.3 (1′-C), 79.9 ((CH$_3$)$_3$*C*), 73.2 (1-C), 70.8 (2′-C), 70.0, 69.95, 69.9, 68.0 (3′-C, 4-C, 5-C, 5′-C), 68.3 (4′-C), 67.1 (Ph*C*H$_2$), 63.5, 61.8 (6-C, 6′-C), 54.4 (α-C), 39.2, 37.9 (*β*-C, γ-C), 28.3 ((*C*H$_3$)$_3$C), 20.8−20.1, (5 × C, CO*C*H$_3$, signals not cleanly resolved); MS (ESI$^+$) *m*/*z* 892.4 (M + Na$^+$, 56%), 870.4 (M + H$^+$, 10), 770.3 [(M + H$_2$ − Boc)$^+$, 100]; HRMS for $C_{39}H_{48}NO_{15}$ (M + H$_2$ − Boc)$^+$ calcd 770.3024, found, 770.3018.

***N*^{α}-(*tert*-Butoxycarbonyl)-*C*-[(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-glucopyranosyl)-(1′→4)-(2,3,6-tri-*O*-acetyl-α-D-mannopyranosyl)]-L-tyrosine Benzyl Ester (6b).** *N*-Methylmorpholine *N*-oxide (67 mg, 0.57 mmol) and then OsO_4 (2.5 wt % in *tert*-BuOH, 595 μL, 0.05 mmol) were added to a stirred solution of *N*^{α}-(*tert*-butoxycarbonyl)-*C*-[(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-glucopyranosyl)−(1′→4)-(6-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)]-L-tyrosine benzyl ester (**5b**) (413 mg, 0.47 mmol) in acetone−water (5:1, 6 mL) at room temperature. After 24 h, TLC (ethyl acetate−light petroleum, 3:1) indicated no starting material (R_f 0.7) and product (R_f 0.2). Sodium metabisulfite (9 mg, 0.05 mmol) in water (1.0 mL) and Florisil (60−100 mesh, 50 mg) were added, and the mixture was stirred vigorously for 0.5 h. Ethyl acetate (50 mL) and brine (10 mL) were added, and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined extracts were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The residue was dissolved in dry pyridine (5 mL) and cooled to 0 °C under nitrogen. DMAP (3 mg, 0.02 mmol) was added, followed by dropwise addition of acetic anhydride (0.23 mL, 2.44 mmol) over 1 min. After 0.5 h of stirring at 0 °C, the reaction mixture was warmed to room temperature. After 0.5 h at room temperature, the mixture was cooled to 0 °C and quenched by the addition of water (2 mL). After the reaction mixture was warmed to room temperature, brine (3 mL) was added and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined extracts were washed with 2 M hydrochloric acid (7 × 5 mL), dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo (toluene azeotrope × 3). The residue was purified by flash chromatography (ethyl acetate−light petroleum, 1:1) to afford *N*^{α}-(*tert*-butoxycarbonyl)-*C*-[(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-glucopyranosyl)-(1′→4)-(2,3,6-tri-*O*-acetyl-α-D-mannopyranosyl)]-L-tyrosine benzyl ester (**6b**) (252 mg, 54%), as a colorless foam: [α]$_D^{30}$ +50.8 (*c* 2.1, $CHCl_3$); IR (KBr) 3396br (N−H), 2975w, 1748vs (C═O), 1716s (C═O), 1369s, 1239vs (C−O), 1166m, 1041vs cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.29 (5 H, m, Ph), 7.13 (2 H, d, *J* 7.6, Ar), 7.00 (2 H, d, *J* 7.6, Ar), 5.47 (1 H, d, $J_{1′,2′}$ 4.1, 1′-H), 5.45 (1 H, t, $J_{2′,3′} = J_{3′,4′}$ 10.0, 3′-H), 5.27 (1 H, dd, $J_{3,4}$ 7.8, $J_{2,3}$ 3.0, 3-H), 5.18 (1 H, t, $J_{1,2} = J_{2,3}$ 3.0, 2-H), 5.17 (1 H, d, *J* 12.2, PhC*H*H′), 5.11 (1 H, d, *J* 12.2, PhCH*H*′), 5.08 (1 H, t, $J_{3′,4′} = J_{4′,5′}$ 10.0, 4′-H), 5.00 (1 H, d, $J_{NH,CHα}$ 7.8, N*H*), 4.92 (1 H, dd, $J_{2′,3′}$ 10.0, $J_{1′,2′}$ 4.1, 2′-H), 4.60 (1 H, dt, $J_{NH,CHα}$ 7.8, $J_{CHα,CHβ} = J_{CHα,CHβ′}$ 6.0, α-H), 4.35−4.22 (3 H, m, 6-H^a, 6-H^b, 6′-H^a), 4.14−4.01 (5 H, m, 1-H, 4-H, 5-H, 5′-H, 6′-H^b), 3.09 (1 H, dd, $J_{CHβ,CHβ′}$ 14.0, $J_{CHα,CHβ}$ 6.0, *β*-H), 3.05−2.99 (2 H, m, $J_{CHγ,CHγ′}$ 14.2, *β*′-H, γ-H), 2.90 (1 H, dd, $J_{CHγ,CHγ′}$ 14.2, $J_{1,CHγ′}$ 5.6, γ′-H), 2.10, 2.08 (2 × 3 H, s, COCH_3), 2.05 (6 H, s, 2 × COCH_3), 2.04, 2.03, 2.02 (3 × 3 H, s, COCH_3), 1.42 (9 H, s, (CH_3)$_3$C); $δ_H$ (400 MHz, C_6D_6) 7.15−6.84 (9 H, m, Ar), 5.90 (1 H, t, $J_{2′,3′} = J_{3′,4′}$ 10.0, 3′-H), 5.66 (1 H, d, $J_{1′,2′}$ 4.4, 1′-H), 5.49 (1 H, dd, $J_{3,4}$ 8.0, $J_{2,3}$ 3.0, 3-H), 5.39 (1 H, t, $J_{1,2} = J_{2,3}$ 3.0, 2-H), 5.36 (1 H, t, $J_{3′,4′} = J_{4′,5′}$ 10.0, 4′-H), 5.08 (1 H, dd, $J_{2′,3′}$ 10.0, $J_{1′,2′}$ 4.4, 2′-H), 5.02 (1 H, d, $J_{NH,CHα}$ 8.4, N*H*), 4.95 (1 H, d, *J* 12.4, PhC*H*H′), 4.85 (1 H, d, *J* 12.4, PhCH*H*′), 4.70 (1 H, ddd, $J_{NH,CHα}$ 8.4, $J_{CHα,CHβ′}$ 6.6, $J_{CHα,CHβ}$ 5.9, α-H), 4.40 (1 H, dd, $J_{6a,6b}$ 12.1, $J_{5,6a}$ 5.5, 6-H^a), 4.36−4.29 (3 H, m, 5′-H, 6′-H^a, 6′-H^b), 4.25 (1 H, dd, $J_{6a,6b}$ 12.1, $J_{5,6b}$ 3.0, 6-H^b), 4.18 (1 H, t, $J_{3,4} = J_{4,5}$ 8.0, 4-H), 4.02 (1 H, m, 1-H), 3.78 (1 H, m, $J_{5,6b}$ 3.0, 5-H), 2.94 (1 H, dd, $J_{CHβ,CHβ′}$ 13.9, $J_{CHα,CHβ}$ 5.9, *β*-H), 2.80 (1 H, dd, $J_{CHβ,CHβ′}$ 13.9, $J_{CHα,CHβ′}$ 6.6, *β*′−H), 2.62 (1 H, dd, $J_{CHγ,CHγ′}$ 14.3, $J_{1,CHγ}$ 8.8, γ-H), 2.46 (1 H, dd, $J_{CHγ,CHγ′}$ 14.3, $J_{1,CHγ′}$ 5.9, γ′-H), 1.94, 1.86, 1.77, 1.76, 1.70, 1.68, 1.58 (7 × 3 H, s, COCH_3), 1.37 (9 H, s, (CH_3)$_3$C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6 (*C*OCH$_2$), 170.5−169.4 (7 × C, signals not cleanly resolved, *C*OCH$_3$), 155.0 (O*C*ON), 135.3, 135.1, 134.3, 129.5, 129.1, 128.5, 128.4, 128.37, 95.8 (1′-C), 79.8 ((CH$_3$)$_3$*C*), 75.1, 71.4, 71.2, 71.0 (1-C, 3-C, 4-C, 5-C), 70.0 (2′-C), 69.6 (2-C), 69.5 (3′-C), 68.4 (5′-C), 68.0 (4′-C), 67.0 (Ph*C*H$_2$), 62.9 (6-C), 61.4 (6′-C), 54.4 (α-C), 37.7 (*β*-C), 35.3 (γ-C), 28.2 ((*C*H$_3$)$_3$C), 20.8, 20.7, 20.65, 20.6, 20.55, 20.5, 20.4 (7 × COCH_3); $δ_C$ (75 MHz, C_6D_6) 171.8 (*C*OCH$_2$), 170.2, 170.1, 170.0, 169.7, 169.6, 169.3 (7 × C, *C*OCH$_3$), 155.3 (O*C*ON), 136.0, 135.8, 134.9, 129.7, 129.6, 128.7, 128.65, 96.4 (1′-C), 79.4 ((CH$_3$)$_3$*C*), 75.8 (1-C), 72.0 (3-C, 4-C), 71.5 (5-C), 70.9 (2′-C), 70.2 (2 × C, 2-C), 70.0 (3′-C), 69.2 (5′-C), 68.9 (4′-C), 66.9 (Ph*C*H$_2$), 63.2 (6′-C), 62.0 (6-C), 55.0 (α-C), 37.9 (*β*-C), 35.2 (γ-C), 28.3 ((*C*H$_3$)$_3$C), 20.8, 20.4, 20.35, 20.3, 20.25, 20.2, 20.1 (7 × COCH_3); MS (FAB$^+$) *m*/*z* 1011 (M + Na$^+$, 30%), 989 (M + H$^+$, 5), 888 [(M + H$_2$ − Boc)$^+$, 100]; HRMS for $C_{43}H_{54}NO_{19}$ (M + H$_2$ − Boc)$^+$ calcd 888.3290, found 888.3296.

4′-(5-*O*-Acetyl-2,6-anhydro-1,3,4,7-tetradeoxy-α-L-*erythro*-hept-3-enitol-1-yl) iodobenzene (α-3c) and 4′-(5-*O*-acetyl-2,6-anhydro-1,3,4,7-tetradeoxy-*β*-L-*erythro*-hept-3-enitol-1-yl) iodobenzene (*β*-3c). Zinc dust (2.95 g, 0.05 mmol) was activated according to general procedure A, using dry THF (2.5 mL), 1,2-dibromoethane (156 μL, 1.81 mmol), and TMSCl (172 μL, 1.36 mmol). A solution of 4-iodobenzyl bromide (6.71 g, 0.02 mmol) in dry THF (10 mL) was added dropwise, over 1 h, to the stirred suspension of activated zinc at 0 °C under argon in the dark. After addition was complete, TLC (ethyl acetate−light petroleum, 1:5) indicated no iodide (R_f 0.8) remained and the mixture was warmed to room temperature and allowed to settle. The zincate solution was transferred away from unreacted zinc via a gastight syringe into a flask purged with argon, and the solvent was removed in vacuo (bath temp 35 °C). Dry dichloromethane (10 mL) was added to the residue, and the solution was cooled to −30 °C under argon in the dark. A solution of 3,4-di-*O*-acetyl-L-rhamnal (**2c**) (2.85 g, 13 mmol) was added to the zincate, followed by BF_3·OEt_2 (6.52 mL, 0.05 mmol). The mixture was immediately warmed to 0 °C and stirred for 15 min, after which time TLC (ethyl acetate−light petroleum, 1:3) indicated no rhamnal (**2c**) (R_f 0.4) and a major product (R_f 0.3). The reaction mixture was warmed to room temperature, then diluted with dichloromethane (20 mL), and washed with brine (30 mL); the organic layer was dried (Na_2SO_4) and filtered; and the solvent was removed in vacuo. The residue was purified by flash chromatography (ethyl acetate−light petroleum, 1:9) to afford (**3c**) (1.8 g, 37%) as a 2:1 mixture of α/*β* isomers as determined by ^{1}H NMR analysis. Further flash chromatography (ethyl acetate−light petroleum, 1:9) afforded pure 4′-(5-*O*-acetyl-2,6-anhydro-1,3,4,7-tetradeoxy-*β*-L-erythro-hept-3-enitol-1-yl)iodobenzene (*β*-**3c**), as a colorless oil. [α]$_D^{26}$ −1.1 (*c* 1.0, $CHCl_3$); IR (film) 1736vs (C═O), 1484s, 1372s, 1238s (C−O), 1043s, 1007s cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (2 H, d, *J* 8.4, Ar *o*-I), 6.99 (2 H, d, *J* 8.4, Ar *m*-I), 5.74 (1 H, ddd, $J_{3,4}$ 10.3, $J_{2,3}$ or $J_{3,5}$ 1.3, $J_{2,3}$ or $J_{3,5}$ 1.7, 3-H), 5.67 (1 H, dt, $J_{3,4}$ 10.3, $J_{4,5}$ and $J_{2,4}$ 1.8, 4-H), 5.02 (1 H, m, 5-H), 4.31 (1 H, m, 2-H), 3.56 (1 H, dq, $J_{5,6}$ 5.7, $J_{6,7}$ 6.2, 6-H), 2.85 (1 H, dd, $J_{1a,1b}$ 13.7, $J_{1a,2}$ 6.7, 1-Ha), 2.68 (1 H, dd, $J_{1a,1b}$ 13.7, $J_{1b,2}$ 6.6, 1-Hb), 2.07 (3 H, s, COCH_3), 1.23 (3 H, d, $J_{6,7}$ 6.2, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6 (*C*OCH$_3$), 137.2 (Ar *o*-I, C_{ipso}), 131.7 (Ar *m*-I), 131.6 (3-C), 126.0 (4-C), 91.8 (*C*-I), 75.1 (2-C), 72.4 (6-C), 71.0 (5-C), 41.3 (1-C), 21.1 (CO*C*H$_3$), 18.4 (*C*H$_3$); MS (EI) *m*/*z* 373 (M + H$^+$, 3%), 217 (*p*-ITol$^+$, 88), 95 [(M − (*p*-ITol) − AcOH)$^+$, 34] HRMS for $C_{15}H_{17}IO_3$ (*M*$^+$) calcd 372.0222, found 372.0237. Anal. Calcd for $C_{15}H_{17}IO_3$: 48.4; H, 4.6. Found: 48.3; H, 4.7.

Continued elution gave 4′-(5-*O*-acetyl-2,6-anhydro-1,3,4,7-tetradeoxy-*β*-L-*erythro*-hept-3-enitol-1-yl)iodobenzene (α-**3c**), as a colorless oil: [α]$_D^{26}$ −107.3 (*c* 1.2, $CHCl_3$); IR (film) 1732vs (C═O), 1484s, 1371s, 1238s (C−O), 1041s, 1007s cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (2 H, d, *J* 8.2, Ar *o*-I), 6.98 (2 H, d, *J* 8.2, Ar *m*-I), 5.82 (1 H, ddd, $J_{3,4}$ 10.4, $J_{2,3}$ or $J_{3,5}$ 1.1, $J_{2,3}$ or $J_{3,5}$ 2.2 3-H), 5.79 (1 H, ddd, $J_{3,4}$ 10.4, $J_{4,5}$ or $J_{2,4}$ 3.1, $J_{4,5}$ or $J_{2,4}$ 1.8 4-H), 4.89 (1 H, m, 5-H), 4.34 (1 H, m, 2-H), 3.93 (1 H, dq, $J_{5,6}$ 5.0, $J_{6,7}$ 6.2, 6-H), 2.94 (1 H, dd, $J_{1a,1b}$ 13.7, $J_{1a,2}$ 7.5, 1-Ha), 2.75 (1 H, dd, $J_{1a,1b}$ 13.7, $J_{1b,2}$ 6.6, 1-Hb), 2.09 (3 H, s, COCH_3), 1.23 (3 H, d, $J_{6,7}$ 6.2, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7 (*C*OCH$_3$), 137.5 (Ar *o*-I, C_{ipso}), 131.4 (Ar *m*-I),

132.7, 123.6 (3-C, 4-C), 91.7 (*C*-I), 71.2 (2-C), 69.5 (5-C), 68.5 (6-C), 39.6 (1-C), 21.2 ($CO\mathit{C}H_3$), 17.0 ($\mathit{C}H_3$); MS (EI) *m*/*z* 373 ($M + H^+$, 3%), 217 (*p*-ITol$^+$, 98) 155 [$(M - p\text{-ITol})^+$, 20], 95 [$(M - (p\text{-ITol}) - AcOH)^+$, 98]. Anal. Calcd for $C_{15}H_{17}IO_3$: C, 48.4; H, 4.6. Found: C, 48.3; H, 4.5.

N$^\alpha$-(*tert*-Butoxycarbonyl)-*C*-(4-*O*-acetyl-2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranosyl)-L-tyrosine Benzyl Ester (5c). Zinc dust (586 mg, 8.7 mmol) was activated according to general procedure A, using dry THF (0.5 mL), 1,2-dibromoethane (29 μL, 0.35 mmol), and TMSCl (33 μL, 0.26 mmol). A solution of Boc-L-Ala(I)-OBn[10] (1.18 g, 2.9 mmol) in dry THF (1.5 mL) was added to the stirred suspension of activated zinc at 35 °C under argon in the dark. After 2 h, TLC (ethyl acetate−light petroleum, 1:3) indicated no iodide (R_f 0.8) remained, and the mixture was cooled to room temperature and allowed to settle. Bis(tri-*o*-tolylphosphine)palladium dichloride (79 mg, 0.11 mmol) was added to a stirred solution of 4′-(5-*O*-acetyl-2,6-anhydro-1,3,4,7-tetradeoxy-α-L-*erythro*-hept-3-enitol-1-yl)iodobenzene (**3c**) (270 mg, 0.73 mmol) in dry *N*,*N*-dimethylacetamide (1 mL) and dry THF (0.5 mL) at room temperature under argon. After 15 min, the zincate solution was transferred away from the unreacted zinc via gastight syringe and added to the yellow iodoarene mixture. After 1 h of stirring at room temperature, the mixture was heated to 50 °C. After 2 h, TLC (ethyl acetate−light petroleum, 1:3) indicated no iodobenzene (R_f 0.4) and a major product (R_f 0.3), and the green reaction mixture was allowed to cool to room temperature. Ethyl acetate (30 mL) was added, the mixture was filtered through Celite into a separating funnel, and the organic extract was washed with saturated aqueous NH_4Cl (5 mL) and brine (5 mL). The organic extracts were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography (eluent gradient, light petroleum−ethyl acetate 1:5 to 1:3) to afford *N*$^\alpha$-(*tert*-butoxycarbonyl)-*C*-(4-*O*-acetyl-2,3-dideoxy-α-L-erythro-hex-2-enopyranosyl-L-tyrosine benzyl ester (**5c**) (314 mg, 83%) as a colorless oil: $[\alpha]_D^{26}$ −2.5 (*c* 1.6, $CHCl_3$); IR ($CHCl_3$) 3436br (N−H), 2975s, 1712vs (C═O), 1509m, 1369m, 1257s (C−O), 1164s, 1048m cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.29 (5 H, m, Ph), 7.09 (2 H, d, *J* 7.7, Ar), 6.98 (2 H, d, *J* 7.7, Ar), 5.85 (1 H, ddd, $J_{2,3}$ 11.9, $J_{1,2}$ or $J_{2,4}$ 1.6, $J_{1,2}$ or $J_{2,4}$ 1.1, 2-H), 5.76 (1 H, ddd, $J_{2,3}$ 11.9, $J_{1,3}$ or $J_{3,4}$ 1.1, $J_{1,3}$ or $J_{3,4}$ 2.9, 3-H), 5.19−5.08 (2 H, m, Ph$\mathit{C}H_2$), 4.98 (1 H, br, d, $J_{NH,CH\alpha}$ 7.6, NH), 4.91 (1 H, m, 4-H), 4.61 (1 H, m, α-H), 4.32 (1 H, m, 1-H), 3.94 (1 H, dq, $J_{4,5}$ 5.3, $J_{5,6}$ 6.4, 5-H), 3.05 (2 H, m, β-H, β′-H), 2.99 (1 H, dd, $J_{1,CH\gamma}$ 7.2, $J_{CH\gamma,CH\gamma'}$ 13.6, γ-H), 2.75 (1 H, dd, $J_{1,CH\gamma'}$ 7.2, $J_{CH\gamma CH\gamma'}$ 13.6, γ′-H), 2.10 (3 H, s $CO\mathit{C}H_3$), 1.41 (9 H, s, $(CH_3)_3C$), 1.26 (3 H, d, *J* 6.4, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7 ($\mathit{C}OCH_2$), 170.7 ($\mathit{C}OCH_3$), 155.0 (O*C*ON), 136.3, 135.2, 134.0, 133.0 (2-C or 3-C), 129.4, 128.5, 128.6, 123.3 (2-C or 3-C), 79.9 ($(CH_3)_3\mathit{C}$), 71.6, 69.7 (1-C), 68.4 (4-C), 67.4 (5-C), 54.4, 39.8 (β-C), 37.9 (γ-C), 28.3 ($(\mathit{C}H_3)_3C$), 21.2 ($CO\mathit{C}H_3$), 17.1 ($\mathit{C}H_3$); MS (FAB$^+$) *m*/*z* 523 (M^+, 10%), 425 [$(M + H - BOC)^+$, 44].

N$^\alpha$-(*tert*-Butoxycarbonyl)-*C*-(4-*O*-acetyl-α-L-rhamnopyranosyl)-L-tyrosine Benzyl Ester. *N*-Methylmorpholine *N*-oxide (27 mg, 0.19 mmol) and then OsO_4 (2.5wt % in *tert*-BuOH, 0.24 mL, 0.03 mmol) were added to a stirred solution of *N*$^\alpha$-(*tert*-butoxycarbonyl)-*C*-(4-*O*-acetyl-2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranosyl-L-tyrosine benzyl ester (**5c**) (100 mg, 0.19 mmol) in acetone−water (5:1, 1.5 mL) at room temperature. After 24 h, TLC (ethyl acetate−light petroleum, 3:2) indicated no starting material (R_f 0.6) and product (R_f 0.2). Sodium metabisulfite (7.3 mg, 0.04 mmol) in water (0.2 mL) was added, and the mixture was stirred vigorously for 30 min. Ethyl acetate (2 mL) was added, and the mixture was filtered through Celite into a separating funnel and washed with brine (1 mL). The aqueous layer was extracted with ethyl acetate (3 × 1.5 mL), dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography (eluent gradient, ethyl acetate−light petroleum 2:1 to 5:1) to afford *N*$^\alpha$-(*tert*-butoxycarbonyl)-C-(4-*O*-acetyl-α-L-rhamnopyranosyl)-L-tyrosine benzyl ester (62 mg, 58%), as a colorless foam: $[\alpha]_D^{33}$ −13.7 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 3435br, 2924w, 1732vs (C═O), 1701s (C═O), 1521m, 1369m, 1244s (C−O), 1167m cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.34 (5 H, m, Ph), 7.08 (2 H, d, *J* 7.1, Ar), 6.98 (2 H, d, *J* 7.1, Ar), 5.20 (1H, d, *J* 12.5, PhCH*H*), 5.10 (1H, d, *J* 12.5, PhCH*H*), 5.02 (1H, bd, *J* 7.5, NH), 4.85 (1H, t, $J_{3,4} = J_{4,5}$ 8.3, 4-H), 4.61 (1H, m, α-H), 4.40 (1H, br, OH), 4.15 (1H, m, 1-H), 3.93 (1 H, dq, $J_{4,5}$ 8.3, $J_{5,6}$ 6.0, 5-H), 3.82 (2H, m, 2-H 3-H), 3.23 (1H, br, OH), 3.05 (2H, m, β-H β′-H), 2.95 (1H, dd, $J_{1,CH\gamma}$ 7.7, $J_{CH\gamma,CH\gamma'}$ 14.1, γ-H), 2.90 (1 H, dd, $J_{1,CH\gamma'}$ 7.0, $J_{CH\gamma,CH\gamma'}$ 14.1, γ′-H), 2.14 (3H, s, $CO\mathit{C}H_3$), 1.41 (9H, s, $(CH_3)_3C$), 1.21 (3H, d, *J* 6.0, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 170.2 (2 × O*C*O), 155.1 (O*C*ON), 136.3, 135.2, 134.2, 129.6, 129.1, 128.6, 80.1 ($(CH_3)_3\mathit{C}$), 76.6, 75.8, 70.6, 70.2, 67.9, 67.2, 54.5 (α-C), 37.6, 35.3 (β-C, γ-C), 29.7 ($(\mathit{C}H_3)_3C$), 28.3 ($CO\mathit{C}H_3$), 17.7 CH_3; MS (CI) *m*/*z* 458 ($M + H - Boc)^+$; HRMS for $C_{30}H_{38}NO_9$ $(M - H)^+$ calcd 556.2548, found 556.2547.

***N*$^\alpha$-(*tert*-Butoxycarbonyl)-*C*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-L-tyrosine Benzyl Ester (6c).** Acetic anhydride (0.08 mL, 0.83 mmol) was added dropwise over 1 min to a stirred solution of *N*$^\alpha$-(*tert*-butoxycarbonyl)-*C*-(4-*O*-acetyl-α-L-rhamnopyranosyl)-L-tyrosine benzyl ester (92 mg, 0.17 mmol) and DMAP (1 mg, 0.01 mmol) in dry pyridine (1.0 mL) at 0 °C under nitrogen. After 1 h at 0 °C, TLC (ethyl acetate−light petroleum, 2:3) indicated no diol (R_f 0.2) and product (R_f 0.4), and the reaction was quenched by the addition of water (0.5 mL). The reaction mixture was allowed to warm to room temperature, brine (0.5 mL) was added, and the aqueous layer was extracted with ethyl acetate (3 × 3 mL). Combined extracts were washed with 2 M hydrochloric acid (5 × 1.0 mL), dried (Na_2SO_4), and filtered and the solvent was removed in vacuo (toluene azetrope × 3). The residue was purified by flash chromatography (ethyl acetate-light petroleum, 2:3) to afford *N*$^\alpha$-(*tert*-butoxycarbonyl)-*C*-(2,3,4-tri-*O*-acetyl-α-L-mannopyranosyl)-L-tyrosine benzyl ester (**6c**) (33 mg, 31%), as a colorless foam: $[\alpha]_D^{26}$ +1.0 (*c* 1.9, $CHCl_3$); IR ($CHCl_3$) 3685br (N−H), 3436 (N−H), 1742vs (C═O), 1709 (C═O), 1499m, 1369s, 1256s (C−O), 1164s, 1050m cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.29 (5 H, m, Ph), 7.10 (2 H, d, *J* 7.8, Ar), 6.99 (2 H, d, *J* 7.8, Ar), 5.32 (1 H, dd, $J_{2,3}$ 3.2, $J_{3,4}$ 9.4 3-H), 5.30 (1 H, t, $J_{2,3} = J_{1,2}$ 3.2, 2-H), 5.19−5.04 (3 H, m, 4-H, Ph$\mathit{C}H_2$), 4.98 (1 H, br, d, $J_{NH,CH\alpha}$ 8.1, NH), 4.61 (1 H, m, α-H), 4.10 (1 H, m, 1-H), 3.90 (1 H, dq, $J_{4,5}$ 5.6, $J_{5,6}$ 6.2, 5-H), 3.07−2.99 (2 H, m, β-H, β′-H), 3.04 (1 H, dd, $J_{1,CH\gamma}$ 5.1, $J_{CH\gamma,CH\gamma'}$ 14.0, γ-H), 2.90 (1 H, dd, $J_{1,CH\gamma'}$ 6.6, $J_{CH\gamma,CH\gamma'}$ 14.0, γ′-H), 2.10, 2.09, 2.02 (3 × 3 H, s, $CO\mathit{C}H_3$), 1.41 (9 H, s, $(\mathit{C}H_3)_3C$), 1.22 (3 H, d, *J* 6.2, 6-$C\mathit{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 170.7, 170.2, 170.1 (4 × O*C*O), 155.1 (O*C*ON), 135.25, 135.2, 134.4, 129.7, 129.1, 128.6, 128.55, 128.5, 80.0 ($(CH_3)_3\mathit{C}$), 76.2 (1-C), 71.5, 70.3 ($PhCH_2$, 4-C), 69.2 (3-C), 68.5 (2-C), 67.1 (5-C), 54.4 (α-C), 37.8, 35.1 (β-C, γ-C), 28.3 ($(\mathit{C}H_3)_3C$), 20.98, 20.89, 20.78 (3 × $CO\mathit{C}H_3$), 17.6 CH_3; MS (FAB$^+$) *m*/*z* 664 [$(M + Na)^+$, 100%]; HRMS for $C_{34}H_{43}NO_{11}$ $(M)^+$ calcd 641.2834, found 641.2838.

4-(6-*O*-Acetyl-2,5-anhydro-1,3,4-trideoxy-α-D-*glycero*-hex-3-enitol-1-yl)iodobenzene (9). Zinc dust (247 mg, 3.78 mmol) was activated according to general procedure A, using dry THF (0.75 mL), 1,2-dibromoethane (13 μL, 0.15 mmol), and TMSCl (14.5 μL, 0.11 mmol). A solution of 4-iodobenzyl bromide (562 mg, 1.89 mmol) in dry THF (2.5 mL) was added, dropwise over 1 h, to the stirred suspension of activated zinc at 0 °C under argon in the dark. After addition, the mixture was stirred for an additional 0.5 h and then warmed to room temperature and allowed to settle. The zincate solution was transferred away from unreacted zinc via gastight syringe into a flask purged with argon, and the solvent was removed in vacuo (bath temp 35 °C). Dry dichloromethane (5 mL) was added to the residue, and the solution was cooled to −30 °C under argon in the dark. A solution of di-*O*-acetyl-D-arabinal (**7**)[22] (223 mg, 1.11 mmol) in dry dichloromethane (1.5 mL) was added to the zincate, followed by $BF_3{\cdot}OEt_2$ (0.41 mL, 3.33 mmol). After 10 min, the reaction mixture was warmed to 0 °C and stirred for 0.5 h, after which time TLC (ethyl acetate−light petroleum, 1:2) indicated no arabinal (R_f 0.1) and a major product (R_f 0.5). The reaction mixture was warmed to room temperature, diluted with dichloromethane (10 mL), then

(22) Cheng, J. C.-Y.; Hacksell U.; Davies, G. D. *J. Org. Chem.* **1985**, *50*, 2778.

washed with brine (5 mL), dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography (ethyl acetate−light petroleum, 1:5) to afford 4-(6-*O*-acetyl-2,5-anhydro-1,3,4-trideoxy-α-D-glycero-hex-3-enitol-1-yl) iodobenzene (**9**) (153 mg, 34%), as a colorless oil: $[\alpha]_D^{27}$ −146.3 (*c* 1.6 in $CHCl_3$); IR (KBr) 2923w, 2851w, 1736vs (C═O), 1484m, 1231s (C−O), 1088s, 1038s, 1007s cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (2 H, d, *J* 8.2, Ar *o*-I), 6.95 (2 H, d, *J* 8.2, Ar *m*-I), 5.85 (1 H, dt, $J_{3,4}$ 6.2, $J_{2,3} = J_{3,5}$ 2.0, 3-H), 5.71 (1 H, dt, $J_{3,4}$ 6.2, $J_{2,4} = J_{4,5}$ 2.0, 4-H), 5.10 (1 H, dtt, $J_{2,5}$ 7.5, $J_{1a,2} = J_{1b,2}$ 6.0, $J_{2,3} = J_{2,4}$ 2.0, 2-H), 4.91 (1 H, dddt, $J_{2,5}$ 7.5, $J_{5,6b}$ 6.0, $J_{5,6a}$ 4.0, $J_{3,5} = J_{4,5}$ 2.0, 5-H), 4.11 (1 H, dd, $J_{6a,6b}$ 11.6, $J_{5,6a}$ 4.0, 6-H[a]), 4.03 (1 H, dd, $J_{6a,6b}$ 11.6, $J_{5,6b}$ 6.0, 6-H[b]), 2.86 (1 H, dd, $J_{1a,1b}$ 13.6, $J_{1a,2}$ 6.0, 1-H[a]), 2.79 (1 H, dd, $J_{1a,1b}$ 13.6, $J_{1b,2}$ 6.0, 1-H[b]), 2.06 (3 H, s, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8 (*C*OCH$_3$), 137.2 (Ar *o*-I), 137.1 (C_{ipso}), 131.6 (Ar *m*-I), 131.4 (3-C), 126.7 (4-C), 91.7 (*C*-I), 86.6 (2-C), 84.1 (5-C), 66.1 (6-C), 41.8 (1-C), 20.9 (CO*C*H$_3$); MS (CI) *m*/*z* 359 (M + H$^+$, 0.2%), 299 [(M + H − AcOH)$^+$, 2], 217 (*p*-ITol$^+$, 15), 83 (100); HRMS for $C_{14}H_{16}IO_3$ (M + H$^+$): calcd 359.0144, found 359.0138.

The assignment of the stereochemistry of *C*-glycoside **9** is primarily based on NOE.[14]

***N*^{α}-α-(*tert*-Butoxycarbonyl)-*C*-(5-*O*-acetyl-2,3-dideoxy-α-D-*glycero*-pent-2-enofuranosyl)-L-tyrosine Benzyl Ester (10).** Zinc dust (205 mg, 3.14 mmol) was activated according to general procedure A, using dry THF (0.5 mL), 1,2-dibromoethane (11 μL, 0.13 mmol), and TMSCl (12 μL, 0.09 mmol). A solution of Boc-L-Ala(I)-OBn[10] (421 mg, 1.04 mmol) in dry THF (0.75 mL) was added to the stirred suspension of activated zinc at 35 °C under argon in the dark. After 2.25 h, TLC (ethyl acetate−light petroleum, 1:3) indicated no iodide (R_f 0.8) remained, and the mixture was cooled to room temperature and allowed to settle. Bis(tri-*o*-tolylphosphine)palladium dichloride (28 mg, 0.04 mmol) was added to a stirred solution of 4-(6-*O*-acetyl-2,5-anhydro-1,3,4-trideoxy-α-D-*glycero*-hex-3-enitol-1-yl)iodobenzene (**9**) (93 mg, 0.26 mmol) in dry *N*,*N*-dimethylacetamide (0.75 mL) and dry THF (0.25 mL) at room temperature under argon. After 15 min, the zincate solution was transferred away from unreacted zinc via gastight syringe and added to the yellow iodobenzene mixture. After 0.5 h of stirring at room temperature, the mixture was heated to 50 °C. After 1.5 h, TLC (ethyl acetate−light petroleum, 1:3) indicated no iodoarene (**9**) (R_f 0.4) and a major product (R_f 0.2), and the green reaction mixture was allowed to cool to room temperature. Ethyl acetate (20 mL) was added; the mixture was filtered through Celite into a separating funnel, then washed with saturated aqueous NH_4Cl (5 mL), brine (5 mL), dried (Na_2SO_4), and filtered; and the solvent was removed in vacuo. The residue was purified by flash chromatography (eluent gradient, ethyl acetate−light petroleum, 1:9 to 2:3) to afford *N*^{α}-(*tert*-butoxycarbonyl)-*C*-(5-*O*-acetyl-2,3-dideoxy-α-D-*glycero*-pent-2-enofuranosyl)-L-tyrosine benzyl ester (**10**) (103 mg, 78%), as a colorless oil: $[\alpha]_D^{30}$ −71.9 (*c* 1.7, $CHCl_3$); IR (film) 3370br, 2978m, 2934w, 1741vs (C═O), 1715vs (C═O), 1515s (C═C), 1367s, 1250vs (C−O), 1165vs, 1087m cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.28 (5 H, m, Ph), 7.07 (2 H, d, *J* 8.0, Ar), 6.97 (2 H, d, *J* 8.0, Ar), 5.85 (1 H, dt, $J_{2,3}$ 6.0, $J_{1,2} = J_{2,4}$ 2.0, 2-H), 5.70 (1 H, dt, $J_{2,3}$ 6.0, $J_{1,3} = J_{3,4}$ 2.0, 3-H), 5.17 (1 H, d, *J* 12.5, PhC*H*H′), 5.10 (1 H, d, *J* 12.5, PhCH*H*′), 5.08 (1 H, ddt, J_{1,CH_γ} 5.5, $J_{1,CH_{\gamma'}}$ 7.3, $J_{1,2} = J_{1,3}$ 2.0, 1-H), 5.02 (1 H, d, $J_{NH,CH\alpha}$ 8.0, N*H*), 4.96 (1 H, dddt, $J_{1,4}$ 7.5, $J_{4,5b}$ 6.0, $J_{4,5a}$ 4.0, $J_{2,4} = J_{3,4}$ 2.0, 4-H), 4.61 (1 H, dt, $J_{NH,CH\alpha}$ 8.0, $J_{CH\alpha,CH\beta} = J_{CH\alpha,CH\beta'}$ 6.0, α-H), 4.13 (1 H, dd, $J_{5a,5b}$ 11.6, $J_{4,5a}$ 4.0, 5-H[a]), 4.04 (1 H, dd, $J_{5a,5b}$ 11.6, $J_{4,5b}$ 6.0, 5-H[b]), 3.08 (1 H, dd, $J_{CH\beta,CH\beta'}$ 14.0, $J_{CH\alpha,CH\beta}$ 6.0, β-H), 3.02 (1 H, dd, $J_{CH\beta,CH\beta'}$ 14.0, $J_{CH\alpha,CH\beta'}$ 6.0, β′-H), 2.94 (1 H, dd, $J_{CH_\gamma,CH_{\gamma'}}$ 13.4, J_{1,CH_γ} 5.5, γ-H), 2.76 (1 H, dd, $J_{CH_\gamma,CH_{\gamma'}}$ 13.4, $J_{1,CH_{\gamma'}}$ 7.3, γ′-H), 2.06 (3 H, s, OC*H*$_3$), 1.41 (9 H, s, (C*H*$_3$)$_3$C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 170.9 (2 × *C*═O), 155.1 (O*C*ON), 136.2, 135.2, 133.9, 131.9 (2-C), 129.6, 129.3, 128.6, 128.5, 128.4, 126.3 (3-C), 87.0 (1-C), 84.0 (4-C), 79.9 ((CH$_3$)$_3$*C*), 67.0 (PhC*H*$_2$O), 66.3 (5-C), 54.5 (α-C), 42.2 (γ-C), 37.9 (β-C), 28.3 ((*C*H$_3$)$_3$C), 20.9 (CO*C*H$_3$); MS (ESI$^+$) *m*/*z* 532 (M + Na$^+$, 100%), 510 (M + H$^+$, 5), 410 [(M + H$_2$ − Boc)$^+$, 60]; HRMS for $C_{24}H_{28}NO_5$ (M + H$_2$ − Boc)$^+$ calcd 410.1967, found 410.1982.

***N*^{α}-(Fluoren-9-ylmethoxycarbonyl)-C-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-L-tyrosine (11a).** A solution of *N*^{α}-(*tert*-butoxycarbonyl)-*C*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-L-tyrosine benzyl ester (**6a**) (439 mg, 0.63 mmol) in dry methanol (4 mL) was added to a vigorously stirred suspension of preactivated Pd/C (10%, 40 mg) (prepared according to general procedure B) in dry MeOH (2 mL) at room temperature under hydrogen (1 atm). After 1 h, the reaction mixture was purged with nitrogen filtered through Celite, and the solvent was removed in vacuo. The crude acid was dissolved in dry dichloromethane (4.25 mL) and cooled to 0 °C under nitrogen. Trifluoroacetic acid (0.75 mL) was added dropwise over 1 min, and the solution was stirred for 0.5 h at 0 °C and then warmed to room temperature. After 1 h at room temperature, TLC (chloroform−ethanol, 3:1) indicated no starting material (R_f 0.6) and product (R_f 0.3, ninhydrin active). Toluene (20 mL) was added, and the solvent was removed in vacuo (toluene azeotrope × 3). The resultant foam was immediately dissolved in water (5 mL) and acetonitrile (5 mL) and stirred at room temperature. A solution of FmocOSu (254 mg, 0.75 mmol) in acetonitrile (2 mL) was added followed by the dropwise addition of Et_3N (263 μL, 1.88 mmol) in order to maintain pH = 8.5−9.0 (monitored via pH meter). After 45 min, pH remained constant and TLC (chloroform−ethanol, 3:1) indicated no starting material (R_f 0.3) and a major product (R_f 0.7). Hydrochloric acid (2 M) was added until pH = 2, and then dichloromethane (20 mL) was added. The aqueous layer was extracted with dichloromethane (2 × 10 mL); combined extracts were washed with brine (5 mL), dried (Na_2SO_4), and filtered; and the solvent was removed in vacuo. The residue was purified by flash chromatography (eluent gradient, chloroform to chloroform−methanol, 9:1) to afford *N*^{α}-(fluoren-9-ylmethoxycarbonyl)-*C*-(2,3,4,6- tetra-*O*-acetyl-α-D-mannopyranosyl)-L-tyrosine (**11a**) (329 mg, 72%), as a colorless foam: analytical RPHPLC (isocratic elution, 55% solvent B in solvent A, R_t 6.5 min); $[\alpha]_D^{26}$ +13.9 (*c* 3.2, $CHCl_3$); IR (KBr) 3436br, 2952w, 1744vs (C═O), 1517w, 1371s, 1229vs (C−O), 1049s cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70−7.45 (8 H, m, Fmoc Ar), 7.40−6.95 (4 H, m, Ar), 5.35 (2 H, m, 3-H and N*H*), 5.22 (1 H, t, $J_{3,4} = J_{4,5}$ 9.0, 4-H), 5.19 (1 H, m, 2-H), 4.68 (1 H, m, α-H), 4.56 (1 H, d, *J* 7.7, Fmoc CH*H*), 4.41 (2 H, m, Fmoc C*H*, CH*H*), 4.29 (1 H, dd, $J_{6a,6b}$ 12.0, $J_{5,6a}$ 6.3, 6-H[a]), 4.20 (1 H, m, 1-H), 4.08 (1 H, dd, $J_{6a,6b}$ 12.0, $J_{5,6b}$ 3.0, 6-H[b]), 4.00 (1 H, m, 5-H), 3.14 (2 H, m, β-H, β′-H), 3.03 (1 H, dd, $J_{CH_\gamma,CH_{\gamma'}}$ 14.0, J_{1,CH_γ} 8.4, γ-H), 2.93 (1 H, dd, $J_{CH_\gamma,CH_{\gamma'}}$ 14.0, $J_{1,CH_{\gamma'}}$ 6.5, γ′-H), 2.09 (6 H, s, 2 × COC*H*$_3$), 2.08, 2.03 (2 × 3 H, s, COC*H*$_3$) (carboxylic acid O*H* not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.3, 170.1, 169.7 (5 × C, O*C*O), 155.5 (O*C*ON), 143.7, 141.3, 129.6, 129.2, 127.8, 127.7, 127.0, 125.0, 120.0 (10 × C, Ar), 77.3, 75.9, 70.7, 69.9, 68.8, 66.9 (1-C, 2-C, 3-C, 4-C, 5-C, Fmoc*C*H$_2$O), 62.4 (6-C), 47.0 (Fmoc*C*H), 34.9 (2 × C, β-C, γ-C), 20.9, 20.75, 20.7, 20.65 (4 × COC*H*$_3$); MS (FAB+) *m*/*z* 754 (M + Na$^+$, 80%), 732 (M + H$^+$, 15), 511 [(M + H − Fmoc)$^+$, 15], 179 ($C_{14}H_{11}$+, 100); HRMS for $C_{39}H_{42}NO_{13}$ (M + H$^+$) calcd 732.2656, found 732.2638.

***N*^{α}-(Fluoren-9-ylmethoxycarbonyl)-*C*-[(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-glucopyranosyl)-(1′→4)-(2,3,6-tri-*O*-acetyl-α-D-mannopyranosyl)]-L-tyrosine (11b).** A solution of *N*^{α}-(*tert*-butoxycarbonyl)-*C*-[(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-glucopyranosyl)-(1′→4)-(2,3,6-tri-*O*-acetyl-α-D-mannopyranosyl)]-L-tyrosine benzyl ester (**6b**) (167 mg, 0.17 mmol) in dry methanol (1 mL) was added to a vigorously stirred suspension of preactivated Pd/C (10%, 20 mg, prepared according to general procedure B) in dry MeOH (1 mL) at room temperature under hydrogen (1 atm). After 0.5 h, the reaction mixture was purged with nitrogen and filtered through Celite, and the solvent was removed in vacuo. The residue was dissolved in dry dichloromethane (1.7 mL) and cooled to 0 °C under nitrogen. Trifluoroacetic acid (0.6 mL) was added dropwise over 1 min; the solution was stirred for 0.5 h at 0 °C and then warmed to room temperature. After 1 h at room temperature, TLC (chloroform−ethanol, 3:1) indicated no starting material (R_f 0.75) and product (R_f 0.4, ninhydrin active). Toluene (15 mL)

was added, and the solvent was removed in vacuo (toluene azeotrope × 3). The resultant oil was immediately dissolved in water (2 mL) and acetonitrile (2 mL) and stirred at room temperature. A solution of FmocOSu (68 mg, 0.20 mmol) in acetonitrile (1 mL) was added followed by the dropwise addition of Et_3N in order to maintain pH = 8.5−9.0 (monitored via pH meter). After 45 min, the pH remained constant and TLC (chloroform−ethanol, 3:1) indicated no starting material (R_f 0.4) and a major product (R_f 0.7). Hydrochloric acid (2 M) was added until pH = 2, and then dichloromethane (10 mL) was added. The aqueous layer was extracted with dichloromethane (2 × 10 mL); combined extracts were washed with brine (5 mL), dried (Na_2SO_4), and filtered; and the solvent was removed in vacuo. The residue was purified by flash chromatography (eluent gradient, chloroform to chloroform−methanol, 9:1) to afford N^{α}-(fluoren-9-ylmethoxycarbonyl)-*C*-[(2′,3′,4′,6′-tetra-*O*-acetyl-α-D-glucopyranosyl)-(1′→4)-(2,3,6-tri-*O*-acetyl-α-D-mannopyranosyl)]-L-tyrosine (**11b**) (105 mg, 61%), as a colorless foam: $[\alpha]_D^{30}$ +56.2 (*c* 2.8, $CHCl_3$); IR (KBr) 3432br, 1747vs (C═O), 1652m, 1371m, 1240vs (C−O), 1041s cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71−6.99 (12 H, m, Ar), 5.46 (1 H, d, $J_{1',2'}$ 4.0, 1′-H), 5.44 (1 H, t, $J_{2',3'} = J_{3',4'}$ 10.0, 3′-H), 5.24 (1 H, br m, 3-H), 5.15 (1 H, br m, 2-H), 5.08 (1 H, t, $J_{3',4'} = J_{4',5'}$ 10.0, 4′-H), 4.91 (1 H, dd, $J_{2',3'}$ 10.0, $J_{1',2'}$ 4.0, 2′-H), 4.56−3.90 (12 H, br m, α-H, 1-H, 4-H, 5-H, 5′-H, 6-$H^{a,b}$, 6′-$H^{a,b}$, Fmoc C*H*, Fmoc CH_2), 3.20−2.80 (4 H, m, β-H, β'-H, γ-H, γ'-H), 2.09, 2.06, 2.04, 2.02, 2.01 (21 H, 5 × s, COCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.5, 170.3, 170.1, 170.0, 169.9, 169.5 (8 × C, *C*═O), 148.1 (O*C*ON), 143.7, 141.1, 135.2, 135.1, 135.0, 129.5, 129.2, 127.6, 127.0, 119.9 (10 × C, Ar), 95.8 (1′-C), 71.4, 71.2, 71.0 (4 × C, 1-C, 3-C, 4-C, 5-C), 70.0, 69.9, 69.6 (2-C, 2′-C, 3′-C), 68.4 (5′-C), 68.0 (4′-C), 67.0 (FmocCH_2O), 63.0, 61.4 (6-C, 6′-C), 56.9 (α-C), 46.9 (Fmoc*C*H), 35.1 (2 × C, γ-C, β-C), 20.9, 20.8, 20.7, 20.65, 20.6, 20.56, 20.5 (7 × CO*C*H_3); MS (FAB^+) *m*/*z* 1058.6 ($M + K^+$, 17%), 1042.5 ($M + Na^+$, 21), 1020.6 ($M + H^+$, 63); HRMS for $C_{51}H_{58}NO_{21}$ ($M + H^+$) calcd 1020.3501, found 1020.3494.

H-Gly-L-Tyr[*C*-(Ac_4-α-D-Man)]-Gly-Gly-L-Tyr[*C*-(Ac_4-α-D-Man)]-Gly-*O*H·TFA (12) and H-L-Tyr[*C*-(Ac_4-α-D-Man)]-Gly-Gly-L-Tyr[*C*-(Ac_4-α-D-Man)]-Gly-OH·TFA. Synthesis was achieved by SPPS according to general procedure C (see Supporting Information), using Fmoc-Gly-PEG-PS (HMP) resin (0.105 mmol). Couplings with N^{α}-(fluoren-9-ylmethoxycarbonyl)-*C*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-L-tyrosine (**11**) were performed using a 2-fold excess, with *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, 1-hydroxybenzotriazole (1.0 equiv), and *N*-methylmorpholine (2.0 equiv) for a fixed coupling time of 1 h. Purification of the crude peptide (48 mg) by preparative RPHPLC {0−30 min, linear gradient of 30−42% solvent B in solvent A (see Supporting Information), eluting at 2.0 mL min^{-1}} afforded H-Gly-L-Tyr[*C*-(Ac_4-α-D-Man)]-Gly-Gly-L-Tyr[*C*-(Ac_4-α-D-Man)]-Gly-OH·TFA (**12**) (29.0 mg, 21%, R_t 20.3 min), as a hygroscopic colorless solid: analytical RPHPLC (0−10 min, linear gradient of 50−80% solvent B in solvent A, R_t 4.6 min); ^1H NMR (300 MHz, DMSO-d_6, partial data) δ 8.67 (1 H, d, *J* 7.9, N*H*), 8.47 (1 H, t, *J* 6.0, N*H*), 8.39 (1 H, t, *J* 6.0, N*H*), 8.15 (1 H, d, *J* 8.2, N*H*), 7.97 (1 H, t, *J* 6.0, N*H*), 7.88 (2 H, br s, NH_2), 7.16 (8 H, m, Ar), 5.34 (2 H, m, 3-H, 3′−H), 5.14 (2 H, m, 2-H, 2′−H), 5.04 (2 H, m, 4-H, 4′−H), 1.95 (12 H, s, 4 × COCH_3), 1.93 (6 H, s, 2 × COCH_3), 1.92 (6 H, s, 2 × COCH_3); MS (ESI^+) *m*/*z* 1230 ($M + H^+$, 20%), 615.5 ($M + 2H^+$, 100); HRMS for $C_{56}H_{73}N_6O_{25}$ ($M + H^+$) calcd 1229.4625, found 1229.4607.

Continued elution gave H-L-Tyr[*C*-(Ac_4-α-D-Man)]-Gly-Gly-L-Tyr[*C*-(Ac_4-α-D-Man)]-Gly-OH·TFA (3.0 mg, 2%, R_t 23.0 min), as a hygroscopic colorless solid: analytical RPHPLC (0−10 min, linear gradient of 50−80% solvent B in solvent A, R_t 4.9 min); MS (ESI^+) *m*/*z* 1173 ($M + H^+$, 85%), 586.9 ($M + 2H^+$, 100); HRMS for $C_{54}H_{70}N_5O_{24}$ ($M + H^+$) calcd 1172.4411, found 1172.4380. Due to the small amount of material available, this product was not characterized further.

cyclo-{Gly-L-Tyr[*C*-(Ac_4-α-D-Man)]-Gly}$_2$ (13). H-Gly-L-Tyr[*C*-(Ac_4-α-D-Man)]-Gly-Gly-L-Tyr[*C*-(Ac_4-α-D-Man)]-Gly-OH·TFA (**12**) (18.0 mg, 0.01 mmol) was dissolved in dry DMF (9.7 mL) and mixed with HOBt (5.9 mg, 0.04 mmol) and TBTU (14.1 mg, 0.04 mmol) at room temperature under nitrogen. Diisopropylethylamine (97 μL) was added, and the solution was stirred. After 26 h, the solvent was removed in vacuo, and ether (10 mL) was added to precipitate a gum. The ether was decanted, and the gum was purified by preparative RPHPLC (0−10 min, isocratic elution of 30% solvent B in solvent A, then 10−20 min, linear gradient of 30−67% solvent B in solvent A, eluting at 3.2 mL min^{-1}) to afford cyclo-{Gly-L-Tyr[*C*-(Ac_4-α-D-Man)]-Gly}$_2$ (**13**) (4 mg, 23%, R_t 18.4 min), as a hygroscopic colorless gum: analytical RPHPLC (0−10 min, linear gradient of 50−80% solvent B in solvent A, R_t 4.5 min); ^1H NMR (400 MHz, DMSO-*d*6) (structure numbered as described by Kopple[17]) δ 8.52 (2 H, d, *J* 6.3, 2(5)-N*H*), 8.46 (2 H, t, *J* 6.0, 3(6)-N*H*), 7.55 (2 H, t, *J* 4.4, 1(4)-N*H*), 7.23−7.10 (8 H, m, Ar), 5.37 (2 H, dd, $J_{3,4}$ 9.0, $J_{2,3}$ 3.0, 3-H), 5.15 (2 H, t, $J_{1,2} = J_{2,3}$ 3.0, 2-H), 5.05 (2 H, t, $J_{3,4} = J_{4,5}$ 9.0, 4-H), 4.25−4.11 (6 H, m, α-H, 5-H, 6-H^a), 4.07 (2 H, ddd, $J_{1,CH\gamma}$ 9.3, $J_{1,CH\gamma'}$ 6.0, $J_{1,2}$ 3.0, 1-H), 3.97 (2 H, m, 6-H^b), 3.84 (2 H, dd, $J_{3(6)-H^a,3(6)-H^b}$ 16.6, $J_{3(6)-H^a,3(6)-NH}$ 6.0, 3(6)-H^a), 3.80 (2 H, dd, $J_{1(4)-H^a,1(4)-H^b}$ 16.6, $J_{1(4)-H^a,1(4)-NH}$ 4.4, 1(4)-H^a), 3.71 (2 H, dd, $J_{1(4)-H^a,1(4)-H^b}$ 16.6, $J_{1(4)-H^b,1(4)-NH}$ 4.4, 1(4)-H^b), 3.50 (2 H, m, 3(6)-H^b), 3.11 (2 H, dd, $J_{CH\gamma,CH\gamma'}$ 14.0, $J_{1,CH\gamma}$ 9.3, γ-H), 3.03 (2 H, $J_{CH\beta,CH\beta'}$ 13.7, $J_{CH\alpha,CH\beta}$ 5.0, β-H), 2.95 (2 H, dd, $J_{CH\gamma,CH\gamma'}$ 14.0, $J_{1,CH\gamma'}$ 6.0, γ'−H), 2.82 (2 H, $J_{CH\beta,CH\beta'}$ 13.7, $J_{CH\alpha,CH\beta'}$ 9.3, β'−H), 2.06 (6 H, s, 2 × OCH_3), 2.05 (6 H, s, 2 × OCH_3), 1.96 (6 H, s, 2 × OCH_3), 1.93 (6 H, s, 2 × OCH_3); MS (ESI^+) *m*/*z* 1211.7 ($M + H^+$, 100%), 1169.5 [$(M + H - C_2H_2O)^+$, 40], 606.3 ($M + 2H^+$, 4).

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Supporting Information Available: General experimental procedures, including details of SPPS and HPLC purification methods, copies of ^1H and ^{13}C NMR spectra, characterization data for cyclic peptide **13** (COSY, VT-NMR, and NH proton dependence, and ESI+ mass data), and synthesis and characterization of {H-L-Tyr[*C*-(Ac_4-α-D-Man)]-Gly-Gly-$NHNH_2$} **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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