Design and Synthesis of a Novel Class of Sugar-Peptide Hybrids: *C*-Linked Glyco β-Amino Acids through a Stereoselective "Acetate" Mannich Reaction as the Key Strategic Element

Claudio Palomo,*,† Mikel Oiarbide,† Aitor Landa,† M. Concepción González-Rego,†
Jesús M. García,‡ Alberto González,‡ José M. Odriozola,‡
Manuel Martín-Pastor,§ and Anthony Linden‖

*Contribution from the Departamento de Química Orgánica I, Facultad de Química,
Universidad del País Vasco, Apdo. 1072, 20080 San Sebastián, Spain;
Departamento de Química Aplicada, Universidad Pública de Navarra, Campus de Arrosadía,
31006 Pamplona, Spain; Unidade de Resonancia Magnetica, R.I.A.I.D.T., CACTUS,
Universidad de Santiago de Compostela, 15782 A Coruna, Spain; and Organisch-chemisches
Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057, Zürich, Switzerland*

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Abstract: A new type of sugar-amino acid hybrid, which is comprised of a sugar unit (gluco-, galacto-, or mannopyranose) linked through a *C*-glycosidic linkage to the β-position of an α-unsubstituted β-amino acid unit, is presented. It is hypothesized that these new compounds, or the oligomeric peptides derived therefrom, might possess the structural features of β-amino acid oligomers and the chemical and enzymatic resistance of *C*-glycosides to hydrolysis. The synthetic strategy is based on a new Mannich-type reaction between a chiral acetate enolate equivalent and α-amido sulfones derived from the corresponding sugar-*C*-glycoside aldehydes. While the sugar-*C*-glycoside aldehyde partner is prepared from well-established transformations on known sugar precursors, the lithium enolate derived from (1*R*)-endo-2-acetylisoborneol **3** is employed as the key element. This Mannich approach proceeds with essentially perfect diasteromeric control leading to the new β-amino carbonyl adducts in good yields. Further, cleavage of the camphor auxiliary is smoothly performed by oxidative treatment with ammonium cerium nitrate (CAN). Complementarily, direct peptide-type coupling of the β-amino carbonyl Mannich adducts with an α- or β-amino acid residue and subsequent CAN-promoted detachment of the auxiliary yields dipeptide fragments bearing a sugar-containing aliphatic side chain and is a process that can be iterated. A preliminary conformational study based on the combination of experimental NMR data and molecular mechanics and molecular dynamics (MD) of one particular adduct is also provided.

Introduction and Objectives

Carbohydrates and amino acids appear in all cells in some form or another, and sometimes they merge in the same molecule as happens in proteoglycans, glycoproteins, and glycopeptides.[1] These types of compounds have been implicated in fundamental biological processes, in which the glycan and the peptidyl substructures usually have a distinct, often complex function.[2] The limited availability of these structurally complex compounds is an important obstacle that restrains the study of their structural features and mode of action, because biosynthetic approaches to them are lacking, while the chemical synthesis[3] is, at present, a time-consuming and encumbered process.[4] Remarkably, however, the fact is that less complex, and therefore easier to access, mimetic compounds may display a biological activity level similar to that of their native counterparts. In the case of glycopeptides, shorter oligomers have been

* To whom correspondence should be addressed. E-mail: qoppanic@sc.ehu.es.
† Universidad del País Vasco.
‡ Universidad Pública de Navarra.
§ Universidad de Santiago de Compostela (Conformational analysis).
‖ Universität Zürich (X-ray analysis).

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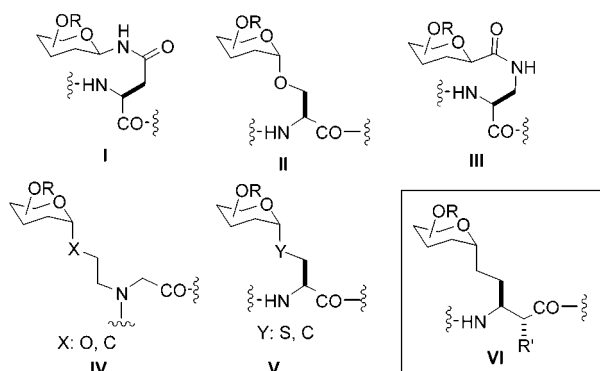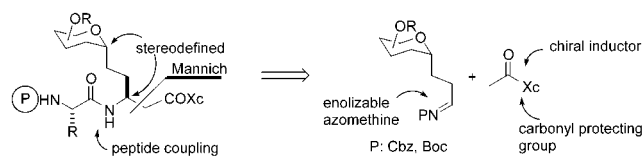
Figure 1. Prototypical sugar-peptide links in native (**I** and **II**) and mimetic (**III**, **IV**, and **V**) glycopetides. The new sugar-amino acids pattern **VI** reported herein is framed.

Figure 2. Main features of the synthetic strategy.

documented to have significant activity.[5] In addition, some isosteres have demonstrated greater stability[6] and bioavailability,[7] thus increasing the chances for potential therapeutic use. Of interest are the new glycan-peptide links designed to substitute the chemically and enzymatically labile *O*- or *N*-glycosyl bond found in native glycopeptides (Figure 1).[8]

On the other hand, structures comprised of a β-amino acid oligomeric backbone, that is, β-peptides, have emerged as promising tools for extending the understanding of protein structure and stabilization into the realm of folded, nonbiological polymers.[9] Like α-peptides, β-peptides have been shown to fold into helices, sheets, and turns which are the main structural elements of proteins, and, in some instances, it has been found that they possess even higher biological activity than their parent α-peptides.[10] Additionally, β-peptides show greater resistance to peptidases and proteases, a property that is of interest in pharmaceutical drug development.[9,10] From these precedents, it could be anticipated that glycoconjugates comprised of a sugar and a β-peptide unit, both linked through a *C*-glycosyl bond, may constitute interesting targets for study. Here we report the first synthetic approach to this new type of glycoconjugates **VI** which relies on a stereoselective Mannich reaction as the key strategic element.

Results and Discussion

Synthetic Plan and Challenges. A satisfactory approach to *C*-glyco β-amino acids has at least three requirements: (1) it must be chemically efficient, starting from readily affordable
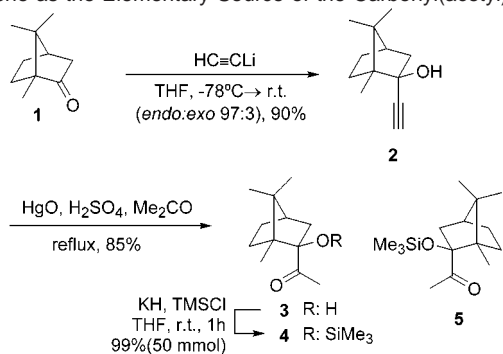
C-glycosides; (2) the stereochemistry during the process of C–C bond formation at both the anomeric and the *C*-β positions must be fully controlled; and (3) it would be desirable to obtain monomeric *C*-glycosyl β-amino acid units that are directly amenable to a further peptide-type coupling step, while keeping the functional group protection/deprotection events at a minimum.

To adhere well to the above requirements, we envisaged the strategy depicted in Figure 2. The key element of the route is the Mannich reaction of a chiral acetate enolate or equivalent with the corresponding azomethine function.[11] This reaction, when compared with other approaches to β-amino carbonyls, inter alia β-amino acids,[12] makes it possible to create the C–C bond and the new stereogenic center(s) in a single synthetic operation. Despite this synthetic potential[11] and the recent advances in the area of diastereoselective,[13] enantioselective,[14] and direct[15] methods, there are two inherent problems that hamper the use of the Mannich reaction to increase the pool of available β-amino acids: the tendency of enolizable aldehyde-derived azomethines to undergo α-deprotonation rather than addition,[16] and the lack of efficient stereocontrol during the C–C bond formation process, especially in reactions involving acetate

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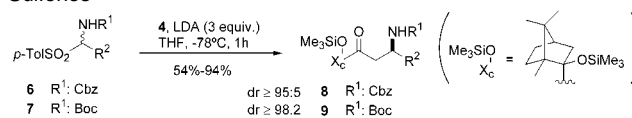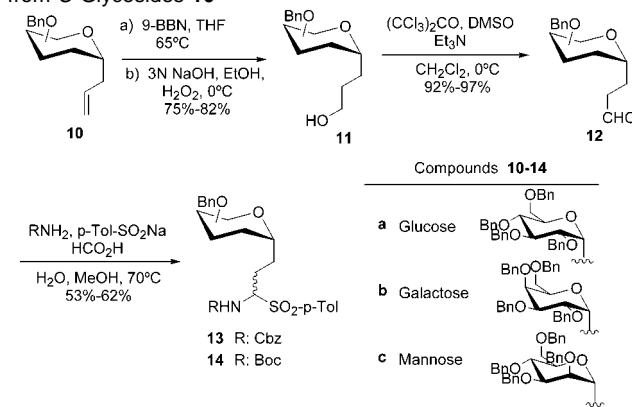
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Scheme 1. Preparation of Reagent **4** from (1*R*)-(+)-Camphor and Acetylene as the Elementary Source of the Carbonyl(acetyl) Group

Scheme 2. Asymmetric Mannich Reaction with α-Amido Alkyl Sulfones

Scheme 3. Preparation of α-Amido Glycoalkyl Sulfones **13**/**14** from *C*-Glycosides **10**

enolate equivalents.[17] Yet, such transformations have traditionally been among the most challenging to accomplish.[18]

Background. A prior report from these laboratories documented the efficiency of the lithium enolate of methyl ketone **4**, Scheme 1, in successfully addressing the problem of the insufficient stereoselectivity often encountered in the "acetate" aldol addition reaction.[19] On this basis, it seemed reasonable to us that the same enolate system may be equally effective, in terms of stereoselectivity, against azomethine electrophiles. Importantly, the synthesis of the required methyl ketone **4** from (1*R*)-(+)-camphor **1** and acetylene, two commodity chemicals available in bulk, is straightforward and high yielding. Likewise, **5** is also available from (1*S*)-(−)-camphor in the same way.

At the outset of our investigation, however, it was not evident which kind of azomethines would be best suited for this Mannich reaction.[20,21] In addition to the inherent problem associated with the ease of isomerization of enolizable aldehyde-derived azomethines, there is the fact that lithium enolates of acetate are rather inert toward Schiff bases such as *N*-aryl and *N*-trimethylsilylaldimines of benzaldehyde.[22] We have addressed this issue and found that, Scheme 2, α-amido sulfones **6**/**7**, generated from both enolizable and nonenolizable aldehydes, sodium *p*-toluenesulfinate, and benzyl or *tert*-butyl carbamate,
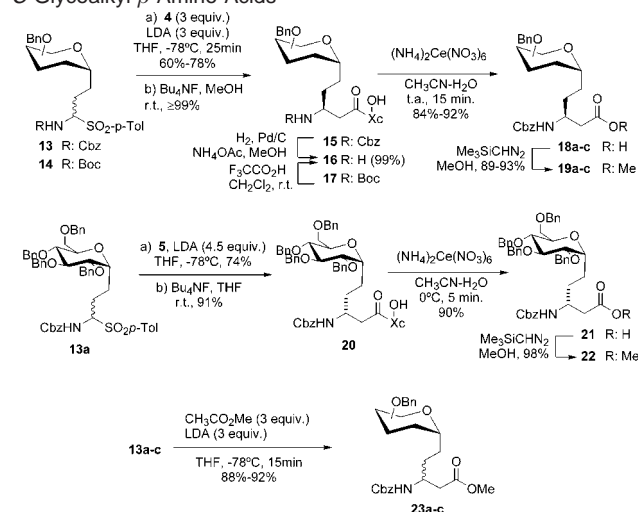
upon reaction with the lithium enolate of **4**, in the presence of a 1 equiv excess of LDA, provided the Mannich adducts **8**/**9** with good yields and essentially complete diastereoselectivity.[23] Concurrent with our investigation, Petrini and co-workers have also demonstrated that these α-amido sulfones are capable of reacting with enolsilanes to give the expected β-amino carbonyl adducts in their racemic form.[24] In a related investigation by Kise and Ueda, it has been shown that *N*-alkoxycarbonyl-1-methoxyamines, upon reaction with metal enolates of chiral carboxylic acid derivatives, provide β-amino esters, albeit in moderate levels of diastereoselectivity.[25]

In the present study, the glucose, galactose, and mannose derivatives **10a**−**c**,[26] Scheme 3, were selected for development, owing to the ample precedents for their preparation in a highly stereocontrolled manner.[27] The formation of α-amido glycoalkyl sulfones from these stereochemically defined sugar derivatives is straightforward. Thus, the hydroboration of the double bond[28] in each compound **10a**−**c**, followed by oxidation of the respective intermediate borane,[29] leads to high yields of crystalline, easy to purify products **11a**−**c**. Further Swern oxidation of the primary alcohol to the corresponding aldehyde[30] **12a**−**c** and reaction of each one with benzyl carbamate and sodium *p*-toluenesulfinate afforded the α-amido glycoalkyl sulfones **13a**−**c** in moderate to good yields. Similarly, compound **14a**

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Scheme 4. Asymmetric Mannich Reaction for the Synthesis of *C*-Glycoalkyl β-Amino Acids

Scheme 5. Strategic Combination of the Asymmetric Mannich Reaction with a Peptide Coupling Process Leading to Either β-Peptides or α,β-Peptides[a]

[a] (a) (i) **6** (R[1], Cbz; R[2], Et) LDA, THF, −78 °C, 15 min, 94%; (ii) H$_2$, Pd/C (10% w/w), EtAcO, room temperature, 1 h, 98%. (b) (*S*)-BocPheOH, EDC, HOBT, CH$_2$Cl$_2$, 97%. (c) TBAF, THF, room temperature, 20 min, then (NH$_4$)$_2$Ce(NO$_3$)$_6$, CH$_3$CN−H$_2$O, room temperature, 5 min, 90−99%. (d) **24**, EDC, HOBT, CH$_2$Cl$_2$, 95%.

was accessed by reacting **12** with *tert*-butyl carbamate. In every case, the α-amido glycoalkyl sulfones were obtained as mixtures of the corresponding epimers at the newly created stereocenter.

Mannich Reaction. Given the precedent from these laboratories, it was expected that the reaction of the lithium enolate of **4** with these α-amidoglycoalkyl sulfones, Scheme 4, would generate the corresponding β-amino ketones under an analogous stereochemically controlled event. Concordant with our expectations, it was found that the reaction of the lithium enolate of **4** with α-amidoglycoalkyl sulfones **13a−c** proceeds to give Mannich adducts **15a−c** in yields of 78, 75, and 60%, respectively. Likewise, the reaction of the lithium enolate of **4** with **14a** provided **17a** in 70% yield. Most notably, in each case, essentially only one isomer product was formed, as judged by both HPLC and ^{13}C NMR analysis of the respective crude reaction mixture. For stereochemical correlation purposes, the adduct **15a** was selectively *N*-deprotected[31] to give the amino derivative **16** which was identical to that obtained from the *N*-Boc deprotection in **17a**.
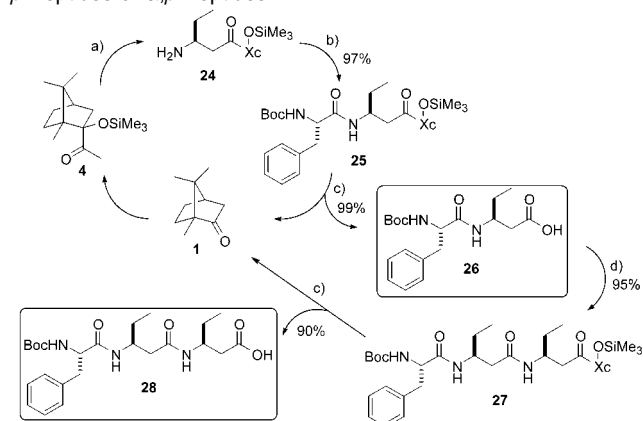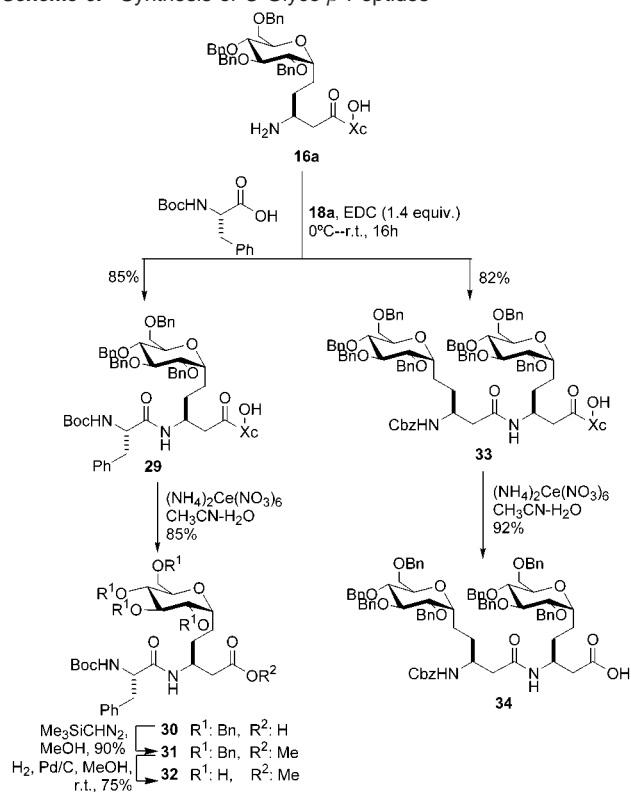
From the virtually perfect stereocontrol observed for this Mannich reaction, which involves two chiral reactants, it seemed of interest to test whether this result corresponds to a matched combination of the reactants and whether the mismatched combination would lead to poorer results. With that aim, the reaction of methyl ketone **5**, the latter derived from (−)-camphor, with **13a** was carried out which afforded adduct **20**, again, as the sole isomer. Therefore, the stereochemistry of this process seems to be fully controlled by the chiral lithium enolate in both possible combinations, and each one of the four possible diastereomeric *C*-glyco β-amino acids (two from the D-sugar series and two from the L-series) is virtually affordable with essentially perfect stereocontrol.

Concurrently, it was found that the oxidative cleavage of the acyloin moiety in Mannich adducts **15a−c** with ammonium cerium nitrate (CAN)[32] provided β-amino carboxylic acids **18a−c** and (1*R*)-(+)-camphor[33] as the only detectable products.

Likewise, **20** afforded **21** along with (1*S*)-(−)-camphor. The only case in which this oxidative cleavage failed was for compound **17a**. Apparently, the reaction conditions are too harsh for the *N*-Boc group[34] (vide infra). Separation of each component from the mixture was easily effected by basic aqueous extractions. Alternatively, (1*R*)-(+)-camphor or its enantiomer can also be fully extracted from the mixture by washing the crude products with hexane, while the carboxylic acid, with the exception of a very small amount in some cases, remains behind.

With the purpose of assessing the stereoisomeric purity of the resulting *C*-glyco β-amino acids, all of the compounds **18** and **21** were transformed into their methyl esters **19** and **22**, respectively, and the stereoisomeric composition of each one was tested by comparison of their HPLC chromatograms with those of the epimeric samples **23a−c**, the latter obtained by the reaction of the corresponding α-amido glycoalkyl sulfones **13a−c** with the lithium enolate of methyl acetate. Such tests demonstrated diastereomeric purities higher than 98%.
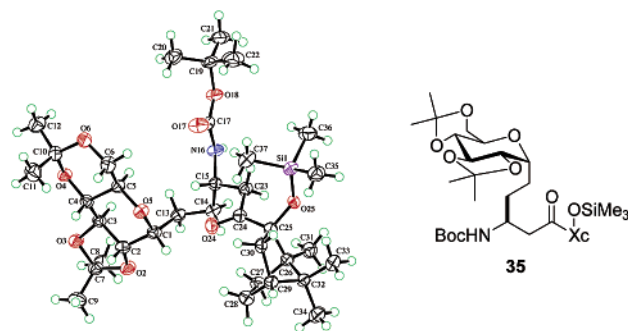
Peptide Synthesis. The excellent diastereoselectivity attained in the present Mannich reaction is of particular interest in that it provides, through *N*-deprotection and subsequent *N*-acylation, a concise route to peptide products. To illustrate this latter aspect, we first elected to use the structurally simple Mannich adduct **24**, Scheme 5, which bears the nonproteinogenic ethyl side chain. This adduct upon acylation with (L)-Boc-*N*-phenylalanine under standard peptide conditions afforded the *N*-acylated product **25** in 97% yield. The smooth release of the camphor moiety in adduct **25** by treatment with CAN proceeded without any byproduct formation to give the α,β-dipeptide **26** in almost quantitative yield. From this result, it was easy to predict that the same process could be realized in an iterative fashion. For example, the α,β-dipeptide **26**, upon coupling with **24**, affords the product **27** in 95% yield, from which the α,β,β-tripeptide **28** is produced in 90% yield along with the recovery of camphor in 87% yield. It is worth noting that in these

(31) (a) Sajiki, H. *Tetrahedron Lett.* **1995**, *36*, 3465−3468. (b) Sajiki, H.; Kuno, H.; Hirota, K. *Tetrahedron Lett.* **1998**, *39*, 7127−7130.
(32) Review: Ho, T.-L. *Synthesis* **1973**, 347−354.
(33) In every case, the starting (1*R*)-(+)-camphor (Aldrich [α]$_D$[25] = +42.2 (*c* = 1, EtOH)) was easily recovered (recovered material, [α]$_D$[25] = +41.5/+42.0 (*c* = 1, EtOH)) in yields of 85−90% by simple aqueous workup.

(34) Under certain reaction conditions, deprotection of *N-tert*-butoxycarbonyl-amines to the free amine by action of CAN has been reported: Hwu, J. R.; Jain, M. L.; Tsay, S.-C.; Hakimelahi, G. H. *Tetrahedron Lett.* **1996**, *37*, 2035−2038.

Scheme 6. Synthesis of *C*-Glyco β-Peptides

Figure 3. An ORTEP[37] drawing of the molecular structure of one of the symmetry-independent molecules of compound **35** (50% probability ellipsoids).

β-amino acid units, and the essentially complete control of the products configuration are some of the features of the present model. From this model, not only the neoglycopolymer total length but also the intersugar distance and the main chain conformation can virtually be modulated.

Determination of the Configuration of the Products. The configuration of the adducts was established by a single-crystal X-ray structure analysis of compound **35** (see Figure 3) and by assuming a uniform reaction mechanism. To date, a general survey of azomethines derived from either enolizable or nonenolizable aldehydes with respect to the generality of this assumption has been gratifying, and diastereoselective Mannich reactions with this methyl ketone appear to proceed with diastereoselection at the 95−98% levels.[23a]

In our and other's experience in the field of sugar derivatives, however, it is not always easy to obtain crystalline samples of sufficient quality for single-crystal X-ray structure analysis. Therefore, we felt it would be of practical convenience to establish some alternative methodology for the assignment of the configuration which would not necessarily depend on any fanciful property, such as crystallinity. In this respect, the protocol developed by Riguera for the assignment of the absolute configuration of chiral amines by NMR spectroscopy[38] seemed attractive. The method relies on the different chemical shift values corresponding to diastereomeric compounds obtained by double derivatization of a given substrate with both (*R*)- and (*S*)-methoxyphenylacetic acid chloride. Accordingly, the corresponding (*R*)- and (*S*)-methoxyphenylacetamides (MPA) of compound **16a** were prepared and analyzed by ^{1}H NMR. As shown in Figure 4, a consistent positive $\Delta\delta^{RS}$ value for the protons at the α site was observed,[39] while a negative $\Delta\delta^{RS}$ value was found for the protons situated at the α′, β′, and γ′ positions. From these observations, and on the basis of the theoretical and empirical rules set by Riguera, a disposition of the L_1 and L_2 portions of the amine can be inferred, which is in accordance with the assumed *S* configuration of the adducts.

Preliminary Conformational Studies. In addition to the observations noted above, it would be instructive to get some structural insight into this new class of β-amino acids, in particular with regard to some relevant parameters such as the

instances the scission promoted by CAN is tolerant of both the Boc protecting group and the amide function,[35] leading to chemically almost pure products. Most notably, this realization implies a dual role for camphor: on one hand, it controls the stereochemistry of the carbon−carbon bond forming process, and, on the other hand, it is an efficient carboxylic acid protecting group (masked in the form of an acyloin moiety). In this way, concomitant peptide synthesis can be approached with the required protection/deprotection steps kept to a minimum.

To gain further insight into the scope of the present model, the synthesis of peptide chains incorporating *C*-glyco β-amino acids was evaluated next. For example, the Mannich adduct **16a**, upon treatment with (L)-*N*-Boc-phenylalanine under standard peptide coupling conditions, furnished compound **29** in 85% yield, Scheme 6. Similarly, the coupling reaction of the adduct **16a** with the *C*-glyco-β-amino acid **18a** afforded the product **33** in 82% yield. Subsequent acyloin cleavage in both **29** and **33** provided the α,β-dipeptide **30** and the β,β-dipeptide product **34** in 85 and 92% yields, respectively. In addition, **30** was transformed into the hydroxyl-free sugar derivative **32** for preliminary conformational studies. Consequently, this development opens the way to further iterative processes en route to the synthesis of a new family of neoglycopolymers,[36] in which the linear backbone is comprised of a β-peptide chain. The wealth of peptide synthesis techniques, the ease of modulation of the peptide chain by incorporating into it new either α- or

(35) Catalytic hydrolysis of α-peptides by the action of CAN at reaction temperatures of about 50 °C has been reported recently: Takarada, T.; Yashiro, M.; Komiyama, M. *Chem.-Eur. J.* **2000**, *6*, 3906−3913.

(36) For a ring-opening metathesis polymerization strategy to linear neoglycopolymers and the biological implications of these compounds, see: (a) Gordon, E. J.; Sanders, W. J.; Kiessling, L. L. *Nature* **1998**, *392*, 30−31. (b) Kanai, M.; Mortell, K. H.; Kiessling, L. L. *J. Am. Chem. Soc.* **1997**, *119*, 9931−9932 and references therein.

(37) Johnson, C. K. *ORTEPII*, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.

(38) (a) López, B.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* **1999**, *121*, 9724−9725. (b) Seco, J. M.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2915−2925.

(39) The unambiguous assignment of peaks from the spectra to the α, α′, β′, and γ′ protons was made by means of a HETCOR experiment. See Supporting Information for details.
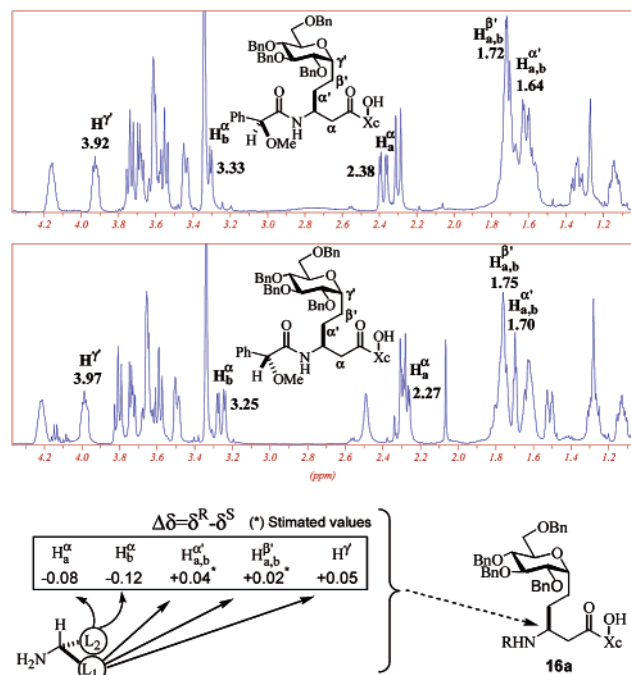
Figure 4. Determination of the absolute configuration of the amine product by chemical shift correlation on MPA-amide derivatives.

Figure 5. Glycopeptide **32** showing the atom numbering used and the definition of torsion angles used for the conformational study.

torsion dihedral angles around the peptide bond. To this end, we adopted the procedure of Seebach and Gusteren[40] who have established that the best understanding of the conformational behavior of a peptide in solution is obtained by a combined analysis of experimental (NMR) and modeling (molecular dynamics, MD) data. Accordingly, we have studied the conformational properties in solution of the sugar-based β dipeptide **32** by NOESY NMR experiments assisted by molecular mechanics and MD calculations. The cluster analysis of the conformations generated during the different MD trajectories allowed the selection of those relevant different structures which populate the trajectory. NOESY intensities were simulated for both the average of each MD trajectory and the single conformations according to the full relaxation matrix approach,[41-43] and plausible models were selected by the ability of the model to reproduce the NOESY experimental data.
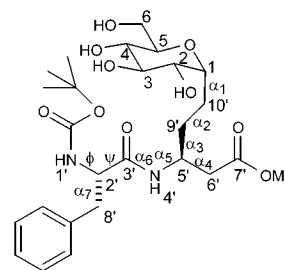
Four starting molecular mechanics minimized models of the glycopeptide were generated for each of the four possible combinations, $Z-Z$, $Z-E$, $E-Z$, and $E-E$, for the two peptidic bonds at atoms N-1' and N-4' (Figure 5) with the glucose pyranose chair of the glycopeptide set in the stable $^4C_1$ conformation. The available conformational space around each minima was explored by a 4 ns long MD calculation, and from these simulations only the $Z-E$ and $E-E$ combinations presented interproton distances and MD average simulated NOEs[41-43] compatible quantitatively with the short distance cross-peaks of the NOESY experiment (Supporting Information Table S1),

while the $Z-Z$ and $E-Z$ completely failed to explain those results.

A cluster analysis of the MD results for the $Z-E$ and $E-E$ trajectories was performed. In each trajectory, the torsion angles defining the backbone structure of the glycopeptide in Figure 5 were analyzed, and a total of four and three different cluster conformers were found independently for the $Z-E$ and $E-E$ conformations, respectively. The molecular mechanics exhaustive optimization of the geometries of each cluster conformation showed that within a $Z-E$ or $E-E$ cluster, the different conformers are close in conformational energy, although the lowest energy conformer of the $E-E$ cluster is 8.9 kJ mol^{-1} more stable than the lowest energy conformer in the $Z-E$ cluster. For both the $Z-E$ and the $E-E$ cluster conformations, the single conformer NOE simulations gave a similarly good agreement with the experimental NOESY intensities for all the nonexchangeable protons, other than the four methylene protons at C-9 and C-10. For all MD simulations, the glucose moiety was found in the initially assumed $^4C_1$ pyranose chair conformation during the complete simulation. A further distinction between the two sets of $Z-E$ and $E-E$ cluster conformers was made by comparing the NOEs of the prochiral methylene protons at C-9 and C-10 (Figure 5), for which overlapping resonances in the spectrum prevented the stereospecific assignment. Only the set of three cluster structures in the $E-E$ peptidic bond configuration was found to be compatible with these extra NOEs, and the values of their torsion angles are given in Table 1.

Because these three conformers have rather similar conformational energies (Table 1) and several transitions among them were observed during the MD trajectory, these results suggest that the glycopeptide **32** has the potential flexibility to adopt a conformational equilibrium among the three cluster structures in solution. The NOE simulations also suggest that in the aforementioned conformational equilibrium, conformer C of Table 1 could represent a major conformation (Supporting Information Table S2). A stereoview of conformer C is given in Figure 6. The analysis of the peptidic torsion angles of the three conformers (Table 1) shows that the ϕ/ψ values are in a region of the Ramachandran plot compatible with a β sheet and an α-helix secondary structure.

Conclusions

New sugar-β-amino acid hybrids[8,44] have been designed, and their synthesis has been approached successfully through a new diastereoselective Mannich reaction model. This model holds

(40) Daura, X.; Gademann, K.; Schäfer, H.; Jaun, B.; Seebach, D.; van Gunsteren, W. F. *J. Am. Chem. Soc.* **2001**, *123*, 2393−2404 and references therein.
(41) Cumming, D. A.; Carver, J. P. *Biochemistry* **1987**, *26*, 6664−6676.
(42) Neuhaus, D.; Williamson, M. P. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*, 2nd ed.; Wiley-VCH: New York, 2000.
(43) Peter, C.; Daura, X.; van Gunsteren, W. F. *J. Biomol. NMR* **2001**, *20*, 297−310.

(44) After the submission of this manuscript, a paper describing sugar-linked β-amino acid esters appeared: Sharma, G. V. M.; Reddy, V. G.; Chander, A. S.; Reddy, K. R. *Tetrahedron: Asymmetry* **2002**, *13*, 21−24.

Table 1. Cluster Conformations Found in the 4 ns MD Trajectory of Glycopeptide **32** with *E*−*E* Peptidic Bond Conformation[a]

cluster conformer	energy (kJ mol^{-1})	torsion angles (deg)								
		$\alpha1$	$\alpha2$	$\alpha3$	$\alpha4$	$\alpha5$	$\alpha6$	$\alpha7$	ϕ	ψ
A	0.0	−60.2	−179.5	−61.2	−61.8	106.3	−178.9	178.0	−84.8	−20.2
B	2.3	−59.0	−176.3	−58.8	−56.3	105.3	−180.0	179.3	−141.9	134.3
C	3.9	39.9	178.6	−59.6	−56.9	138.1	−178.5	179.4	−138.7	52.3

[a] All torsion angles are defined with respect to the four contiguous heavy atoms involved with the lower possible numbering in Figure 5, except α_1, which is defined as H-1−C1−C10′−C9′.
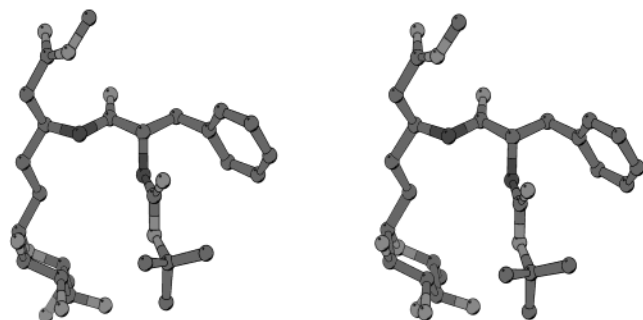
Figure 6. Stereoview of the best conformation glycopeptide **32** found consistent with the NOESY experimental data. This conformation corresponds to conformer C in Table 1.

several interesting features: (i) Mannich adducts of acetate with very high stereochemical purity, perfectly predictable configuration, and a broad range of β-substitution patterns are accessible; (ii) the chiral controller of the process, (1*R*)-(+)-camphor, which is used in stoichiometric quantities, is cheap, almost fully recoverable, and can be reused without loss of efficiency; (iii) all carbon atoms employed in the entire process, including acetylene as the source of acetyl, are integrated into the final products; and (iv) a peptide coupling event can be appropriately fitted into the process. As a result, the synthesis of sugar-peptide hybrids comprised of a β-amino acid backbone and a glycoalkyl side chain has been made viable for the first time. This new class of hybrid compounds, which could be referred to as *C*-glyco β-peptides, may be of interest in pharmaceutical drug design. The synthesis of extended *C*-glyco β-peptide oligomers and studies on their structural features are currently underway. In addition, the potential of these new compounds as glycopeptide mimetics and as multivalent ligands in cell surface processes will be evaluated next.

Supporting Information Available: Complete experimental procedures, determination of stereoisomeric mixtures, analytical and spectral characterization data including copies of spectra and chromatograms, detailed methods of the molecular modeling (PDF), and crystallographic data (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

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