Organic LETTERS

Letter

pubs.acs.org/OrgLett

Tn Antigen Mimics Based on sp^2-Iminosugars with Affinity for an anti-MUC1 Antibody

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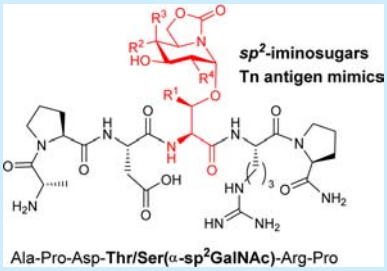
S *Supporting Information*

ABSTRACT: The first examples of amino acid (Ser/Thr)−sp^2-iminosugar glycomimetic conjugates featuring an α-*O*-linked pseudoanomeric linkage are reported. The key synthetic step involves the completely diastereoselective α-glycosylation of Ser/Thr due to strong stereoelectronic and conformational bias imposed by the bicyclic sp^2-iminosugar scaffold. Mucin-related glycopeptides incorporating these motifs were recognized by the monoclonal antibody (mAb) scFv-SM3, with activities depending on both the hydroxylation pattern (Glc/Gal/GlcNAc/GalNAc) of the sp^2-iminosugar and the peptide aglycone structure (Ser/Thr).



Mucin MUC1 is an *O*-glycoprotein overexpressed and aberrantly glycosylated in cancerous cells,[1] where it displays various immunogenic motifs behaving as tumor-associated carbohydrate antigens (TACAs), which interact with anti-MUC1 antibodies.[2] Most of these antibodies recognize a small peptide sequence that comprises Ala-Pro-Asp-Thr-Arg-Pro.[3] Glycosylation of the threonine residue of this epitope with GalNAc gives rise to the Tn determinant (α-O-GalNAc-Ser/Thr),[4] whose presence enhances the binding affinity toward these antibodies,[3,5] offering a potential target for the development of cancer-targeted vaccines.[2,6] Designing Tn analogues with higher immunogenic potential, capable of generating a protective immune response, is a *sine qua non* prerequisite for these channels. Early structural studies revealed that glycosylation was not required for binding, but that GalNAc *O*-glycosylation of threonine induced conformational changes in the peptide[7] that enhanced its interactions with the antibody. We recently reported the X-ray structure of the glycopeptide shown in Figure 1 in complex with the anti-MUC1 monoclonal SM3 antibody,[5] which showed the existence of direct interactions between the sugar moiety and the antibody involving: (i) a hydrogen bond between the hydroxymethyl group and a tyrosine residue and (ii) a hydrophobic contact through the *N*-acetyl group and a tryptophan residue. These findings suggest that glycopeptide

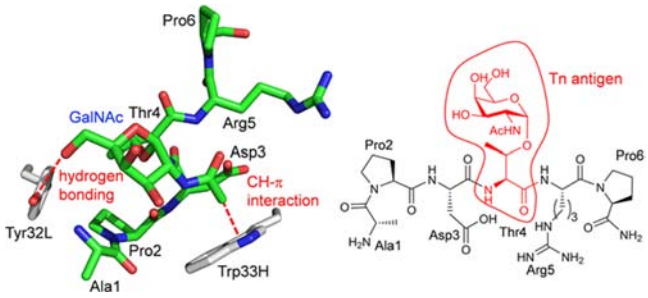


Figure 1. Key binding interactions of glycopeptide Ala-Pro-Asp-Thr(α-*O*-GalNAc)-Arg-Pro with scFv-SM3 antibody, as observed in the X-ray crystal structure (pdb ID: 5a2k, ref 5).

mimetics incorporating Tn antigen surrogates providing favorable interactions with MUC1 antibodies may represent better candidates for anticancer vaccine generation, as far as they still promote the right conformation of the peptide segment. Replacing the α-*O*-GalNAc moiety by an unnatural mimic may not only improve antigen recognition but also increase the stability of the conjugate in biological media. It has been recently demonstrated that improved bioavailability

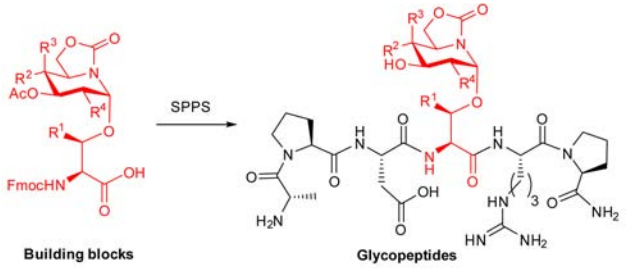
Received: June 30, 2016
Published: July 25, 2016

DOI: 10.1021/acs.orglett.6b01899
Org. Lett. 2016, 18, 3890−3893

through backbone modification is an important advantage for efficient vaccine generation.[8] The challenge of glycone alteration is not trivial, since classical iminosugar-, thiosugar-, or carbasugar-type glycoside analogues suffer from either low stability or high synthetic complexity, especially when α-*O*-linked acetamidosugar-like structures are considered. Here we show that glycomimetics of the sp^2-iminosugar family represent a viable alternative for designing α-*O*-linked glycopeptidomimetics and demonstrate the value of 2-acetamido-2-deoxy-sp^2-iminosugar Tn antigen analogues as anti-MUC1 antibody binders.

Piperidine-oxazolidinone bicyclic sp^2-iminosugars have been shown to behave as true chemical mimics of the parent monosaccharides susceptible of being engaged in glycosylation reactions to afford stable glycoside-type conjugates.[9] Conjugates **1′**−**8′** (Scheme 1) were synthesized using solid-phase

Scheme 1. Solid Phase Peptide Synthesis (SPPS) of Glycopeptides 1′−8′ Incorporating Tn Antigen Mimics



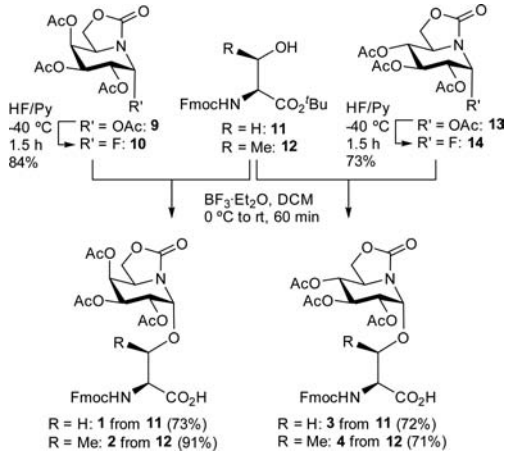
	R^1	R^2	R^3	R^4
1	H	H	OAc	OAc
2	Me	H	OAc	OAc
3	H	OAc	H	OAc
4	Me	OAc	H	OAc
5	H	H	OAc	NHAc
6	Me	H	OAc	NHAc
7	H	OAc	H	NHAc
8	Me	OAc	H	NHAc

	R^1	R^2	R^3	R^4	Sequence
1′	H	H	OH	OH	Ala-Pro-Asp-Ser(α-sp^2Gal)-Arg-Pro
2′	Me	H	OH	OH	Ala-Pro-Asp-Thr(α-sp^2Gal)-Arg-Pro
3′	H	OH	H	OH	Ala-Pro-Asp-Ser(α-sp^2Glc)-Arg-Pro
4′	Me	OH	H	OH	Ala-Pro-Asp-Thr(α-sp^2Glc)-Arg-Pro
5′	H	H	OH	NHAc	Ala-Pro-Asp-Ser(α-sp^2GalNAc)-Arg-Pro
6′	Me	H	OH	NHAc	Ala-Pro-Asp-Thr(α-sp^2GalNAc)-Arg-Pro
7′	H	OH	H	NHAc	Ala-Pro-Asp-Ser(α-sp^2GlcNAc)-Arg-Pro
8′	Me	OH	H	NHAc	Ala-Pro-Asp-Thr(α-sp^2GlcNAc)-Arg-Pro

techniques from the corresponding unnatural building blocks (*vide infra*). In these derivatives, the GalNAc residue of the natural Tn antigen has been replaced by an sp^2-iminosugar variant with either the D-gluco or D-galacto configurational pattern. Note that the oxygen atom equivalent to O6 is now part of a cyclic carbamate, limiting the conformational flexibility and thus potentially reducing the entropic penalty associated with binding to a receptor partner. The carbonyl oxygen is also in a fixed orientation, providing a potential hydrogen bond acceptor center. The series has been purposely conceived to probe the effect of the configuration at C4 and the presence of the acetamido group in the glycone portion and the influence of the glycosylated amino acid (threonine vs serine) in the aglycone segment in the conformational and SM3 mAb recognition properties of the new glycopeptidomimetics.

We have first accomplished the preparation of the corresponding sp^2-iminosugar α-*O*-linked glycosyl amino acid building blocks (**1**−**8** in Scheme 1) ready to be incorporated in solid phase peptide synthesis schemes. For the galactosyl mimics **1** and **2**, the pseudoglycosyl fluoride **10**, obtained in 84% yield as a stable solid from tetraacetate **9**[10] upon reaction with pyridinium poly(hydrogen fluoride) (HF/Py),[11] was chosen as a suitable donor for the key α-glycosylation step (Scheme 2). In the presence of boron trifluoride-diethyl ether ($BF_3{\cdot}Et_2O$) as the glycosylation promotor, compound **10** smoothly reacted with *N*-Fmoc-serine *tert*-butyl ester **11**[12] or

Scheme 2. Synthesis of Building Blocks 1−4



N-Fmoc-threonine *tert*-butyl ester **12**[12] with concomitant cleavage of the *tert*-butyl ester, to give the corresponding *N*-protected pseudoglycosylamino acids **1** and **2** in 73% and 91% yield, respectively. Starting from tetraacetate **13**,[10] a parallel reaction sequence in the α-sp^2Glc series afforded the C4-epimeric pseudoglycosylamino acids **3** and **4**.

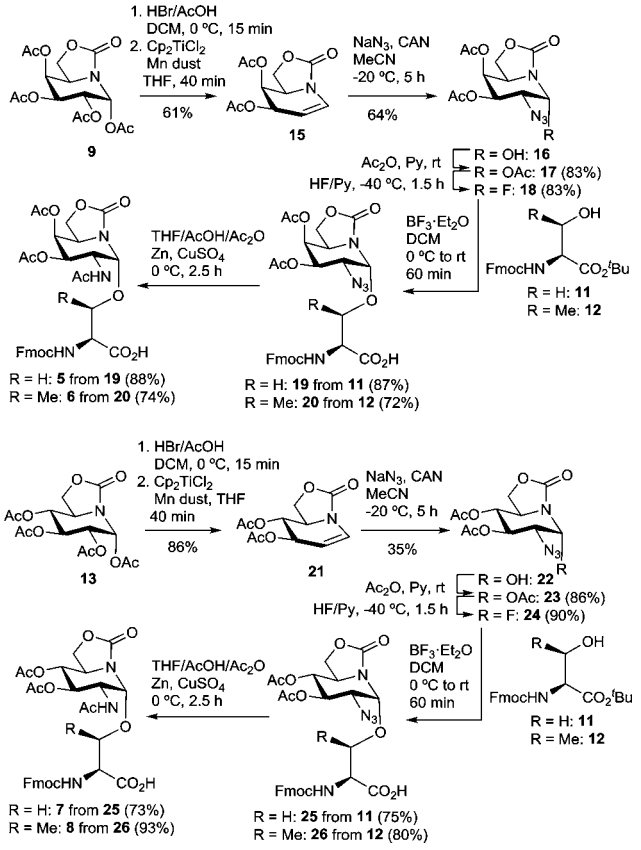
Only the α-anomer was detected in the glycosylation reactions using **10** or **14** as glycosyl donors, which is remarkable considering that the participating character of the acetyl-protecting group at O2 would be expected to favor the β-glycosylation.

The synthesis of building blocks **5** and **6**, bearing sp^2-GalNAc pseudoglycosyl moieties, was achieved starting from tetraacetate **9**, which was converted into the pseudogalactal derivative **15** by reaction with HBr/AcOH and in situ elimination of hydrogen bromide from the resulting pseudoglycosyl bromide intermediate by treatment with Cp_2TiCl_2 and Mn dust (Scheme 3). Compound **15** was subjected to azidonitration with NaN_3 in the presence of ceric ammonium nitrate (CAN) to give, after aqueous workup, the 2-azido-2-deoxy sugar mimic **16**, whose acetylation and further reaction with HF/Py afforded the pseudo-*N*-acetylgalactosaminyl fluoride **18**. Glycosylation of the protected Ser and Thr derivatives **11** and **12** with glycosyl donor **18** provided the α-*O*-linked pseudoglycosides **19** and **20**, respectively, again with complete α-stereoselectivity, which were easily transformed into the target 2-acetamido-2-deoxysugar glycosylamino acid derivatives **5** and **6** by reduction of the azido group and final acetylation. Building blocks **7** and **8**, bearing sp^2-GlcNAc pseudoglycosyl moieties, were obtained from the *gluco*-configured sp^2-iminosugar tetraacetate **13** following a parallel reaction sequence.

The outstanding α-selectivity observed in the glycosylation with sp^2-iminosugar donors, irrespective of the equatorial substituent present at C2 (acetate or azide), was analyzed theoretically. The reaction profiles for α- and β-glycosylation were calculated starting from abbreviated models of the iminium cation intermediates (**Ia** or **Ib**) and methanol as a model nucleophile. For the C2-azide substituted model, the reaction between the iminium cation **Ib** and methanol was enthalpically barrierless for the α approximation (no transition structure could be located), due to the minor reorganization required to achieve the chairlike conformation in adduct **IVb_α**. Conversely, an activation barrier of $\Delta G^{\ddagger} \approx 10$ kcal mol^{-1} was calculated for the β approximation, originated by the greater distortion of the cation structure needed to achieve the

DOI: 10.1021/acs.orglett.6b01899
Org. Lett. 2016, 18, 3890−3893

Scheme 3. Synthesis of Building Blocks 5−8



transition structure **IIIb_*β*‡** leading to adduct **IVb_*β***, which in turn is ∼10 kcal mol^{-1} less stable than the *α* epimer **IVb_*α***. Of note, the bicyclic *sp*^{2}-iminosugar scaffold imposes a twist-boat conformation in the six-membered ring along this pathway, in agreement with previous observations for *sp*^{2}-iminosugar *β*-thioglycosides by NMR spectroscopy.[13] Relaxation of this strained conformation to a chairlike one (**IVb_*β*′**) does not stabilize the adduct due to the loss of anomeric hyperconjugation. The conformationally relaxed *α* anomer is further stabilized by strong anomeric effects[14] induced by the *sp*^{2}-iminosugar moiety as demonstrated by NBO calculations[15] (Figure 2). The same trend is observed in the final glycosylation products after proton release as shown in the Supporting Information (SI). A very similar behavior was observed for the C2-acetyl substituted cation **Ia**, despite the anchimeric assistance expected for the neighboring AcO group (SI).

Considering that complete *α*-glycoslylation has been scarcely reported,[16] these results demonstrate the privileged architecture of *sp*^{2}-iminosugars to deploy strong conformational and stereoelectronic bias for the complete stereocontrol of glycosylation reactions, avoiding the need for chromatographic separation of the *α*- and *β*-anomers inherent to most glycosylation methods, particularly in *α*-*O*-glycopeptide synthesis.

The eight protected *α*-*O*-linked glycosylamino acid mimics **1**−**8** were subsequently engaged in automatic solid phase peptide synthesis (SPPS) to obtain the target *α*-*O*-pseudoglycohexapeptides. Incorporation of **1**−**8** in the peptide sequence was effected manually to increase the yield of this coupling step. After completion, the compounds were cleaved from the resin

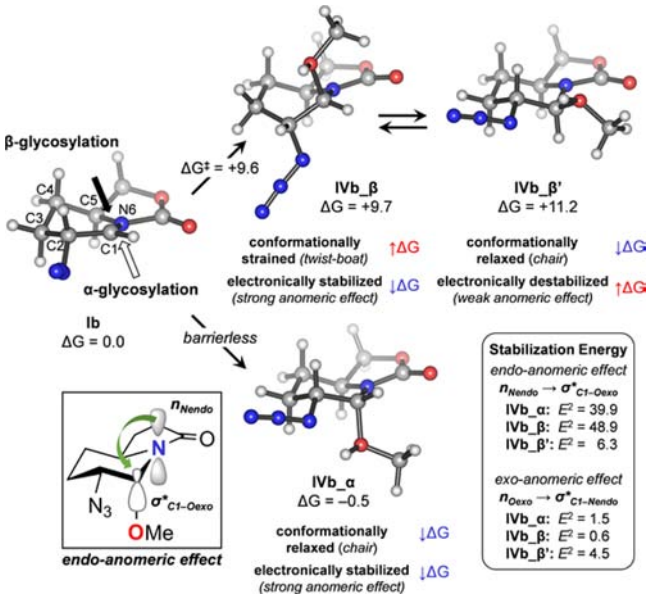


Figure 2. Model glycosylation reactions calculated with PCM(H_2O)/M06-2X/def2-TZVPP. Free energies (ΔG) and hyperconjugative interactions (E^2) are given in kcal mol^{-1}. The NBO orbitals involved in the *endo*-anomeric hyperconjugation are shown in the inset.

using trifluoroacetic acid (TFA), with simultaneous removal of all the acid-labile side-chain protecting groups. Purification by preparative HPLC gave **1′**−**8′** in good overall yields (Scheme 1 and SI).

The binding affinities of the *sp*^{2}-iminosugar glycopeptidomimetics **1′**−**8′** toward single-chain variable fragment (scFv)-SM3 antibody were experimentally evaluated through Bio-Layer Interferometry (BLI) experiments, and the K_D constants are shown in Table 1. This antibody exhibits high affinity

Table 1. Determination of K_D Values of MUC1-*sp*^{2}-Iminosugars with scFv-SM3 mAb by Bio-Layer Interferometry (BLI) Assays

entry	glycopeptide	K_D (M)[a]
1	Ala-Pro-Asp-Thr(*α*-*O*-GalNAc)-Arg-Pro	$3.3 \times 10^{-6} \pm 8.4 \times 10^{-7}$
2	Ala-Pro-Asp-Thr(*α*-*sp*^{2}GalNAc)-Arg-Pro (**6′**)	$1.6 \times 10^{-6} \pm 1.6 \times 10^{-7}$
3	Ala-Pro-Asp-Thr(*α*-*sp*^{2}GlcNAc)-Arg-Pro (**8′**)	$2.0 \times 10^{-6} \pm 3.0 \times 10^{-7}$
4	Ala-Pro-Asp-Thr(*α*-*sp*^{2}Gal)-Arg-Pro (**2′**)	$4.1 \times 10^{-6} \pm 1.1 \times 10^{-6}$
5	Ala-Pro-Asp-Thr(*α*-*sp*^{2}Glc)-Arg-Pro (**4′**)	–

[a]BLI data and fitting curves are represented in the SI.

toward the parent natural antigen Ala-Pro-Asp-Thr(*α*-*O*-GalNAc)-Arg-Pro,[3] which was used as a positive control. The data revealed that, at the same pseudoglycopeptide concentration, Thr-linked derivatives (**2′**, **4′**, **6′**, and **8′**) are higher affinity mimics than Ser-linked conjugates (**1′**, **3′**, **5′**, and **7′**), which is in agreement with previous observations in the parent glycopeptide series.[5] The *galacto* configuration is also important for the molecular recognition. In fact, the *α*-*sp*^{2}Gal conjugate (**2′**) showed better affinity than the *α*-*sp*^{2}Glc analogue with an identical amino acid sequence (**4′**). Interestingly, compound *sp*^{2}GalNAc **6′**, incorporating a "true" Tn antigen mimic moiety, showed the best binding properties, with a 2-fold higher affinity toward the SM3 mAb as compared with the natural glycopeptide.

DOI: 10.1021/acs.orglett.6b01899
Org. Lett. 2016, 18, 3890−3893

Our data also showed that the presence of the *N*-acetyl group at C2 (Gal vs GalNAc) has a greater effect on the binding (2.6-fold increase of K_D in **6′** with respect to **2′**) than the absolute configuration at C4 (GlcNAc vs GalNAc, 1.3-fold increase of K_D in **6′** with respect to **8′**). Most importantly, they confirm that the presence of a primary hydroxymethyl group in the sugar-like component is not essential for strong binding to the SM3 mAb, validating the potential of sp^2-iminosugars in the design of MUC1-related α-linked glycopeptide prototypes for cancer-targeted vaccine generation.

In summary, an efficient methodology for the synthesis of glycomimetic sp^2-iminosugar−peptide conjugates has been developed and applied to the preparation of functional Tn antigen mimics. Complete stereoselectivity toward the desired α-*O*-linkage is consistently obtained, which is dictated mainly by the strong anomeric effect occurring in the axially substituted adducts. These novel conformationally locked compounds show anti-MUC1 antibody binding properties comparable to those of the natural Tn antigen, even in the absence of the *N*-acetyl group or axial disposition of the OH group at C4. The superior performance of Thr- over Ser-containing derivatives reinforces the key role of the underlying amino acid in the molecular recognition of glycopeptides. Presumably, these unnatural glycopeptides will not suffer from immune suppression and will be more stable to enzymatic degradation. These properties, together with the extra rigidity imposed by the fused ring of the sp^2-imino sugar, will hopefully lead to stronger and longer-lasting antigenic responses. Efforts are currently underway to incorporate this derivative in an efficacious vaccine.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01899.

Experimental and computational details and copies of NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to MINECO/FEDER (CTQ2015-67727-R and UNLR13-4E-1931 to J.M.P., CTQ2015-70524-R and RYC-2013-14706 to G.J.O., SAF2013-44021-R to C.O.M., and a fellowship to C.D.N.), the European Union (FP7-People-2012-CIG), Grant Agreement Number 333594 (to E.M.S.F.), the European Regional Funds (FEDER and FSE), and the Junta de Andalucía (FQM2012-1467 to J.M.G.F.). G.J.L.B. is a Royal Society University Research Fellow and is thankful for financial support from the MRC. We also thank CESGA, BiFi (Memento cluster) and CITIUS (University of Seville) for supercomputer and technical support.

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DOI: 10.1021/acs.orglett.6b01899
Org. Lett. 2016, 18, 3890−3893