Tetrahedron xxx (2015) 1–12

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Oligomers and peptidomimetics consisting of methyl 3-amino-2,3-dideoxyhexopyranosiduronic acids

Emilia Sikorska [a], Dorota Tuwalska [b], Przemysław Karpowicz [a], Elżbieta Jankowska [a], Andrzej Nowacki [a], Beata Liberek [a,*]

[a] Faculty of Chemistry, University of Gdańsk, Wita Stwosza 63, 80-308 Gdańsk, Poland
[b] Faculty of Chemical Engineering and Technology, Department of Analytical Chemistry, Cracow University of Technology, Warszawska 24, 31-155 Cracow, Poland

ARTICLE INFO

Article history:
Received 21 October 2014
Received in revised form 21 January 2015
Accepted 2 February 2015
Available online xxx

Paper dedicated to Professor Zygfryd Smiatacz on the occasion of his 85th birthday

Keywords:
Sugar amino acid
Conformation
MD simulations
CD spectra
Proteasome

ABSTRACT

In search of new foldamers, the synthesis of homo and heterooligomeric tetramers, consisting of methyl 3-amino-2,3-dideoxyhexopyranosiduronic acids, from the respective dimers, is presented. Both the dimers and tetramers were subjected to molecular dynamics simulations, based on NOE interactions. These show the preferred conformations of presented sugar amino acids (SAAs) oligomers. The CD spectra of these oligomers depend on the configuration of the C3 carbon atom bearing the amide chromophore. Next, the syntheses of two peptidomimetics with SAA incorporated into a peptide chain, are presented. A Leu-enkephalin mimetic was subjected to molecular dynamics simulations, which show how a SAA influences the geometry of a peptidomimetic. A Tat1 protein mimetic is demonstrated to display an inhibitory influence on the activity of a proteasome. Its structure is studied on a basis of the CD and FTIR spectra.

1. Introduction

Sugar amino acids (SAAs) are carbohydrates bearing both an amino group and a carboxyl group. Sialic acids, muraminic acid and glycosaminuronic acids are naturally-occurring SAAs. The syntheses and applications of unnatural SAAs have been widely reviewed.[1–6] Oligomerization of synthetic SAAs provides amide-linked oligosaccharides mimetics, which have been intensely explored in search of interesting secondary structures[7–10] and/or biological activities.[11–13] Synthetic SAAs have also been used extensively in mimetic studies of oligonucleotides,[14] cyclodextrins[15] and peptides.[16] In order to improve the biological activity of peptides, mixed oligomers of SAAs and amino acids have been studied.[17,18] Additionally, SAAs have been introduced into the peptide backbone as non-peptide isosters to achieve desirable secondary structures.[19–24]

In our previous papers the syntheses of methyl 3-amino-2,3-dideoxyhexopyranosiduronic acids with α-D-*arabino*, β-D-*arabino*, α-D-*ribo*, and β-D-*ribo* configurations,[25] and their dimers were presented.[26] The syntheses of four homo and heterooligomeric tetramers built of above mentioned methyl 3-amino-2,3-dideoxyhexopyranosiduronic acids are presented here. In search of the rigid and bent secondary structures consisting of SAAs, studies on these tetramers and dimers conformations are performed on the basis of molecular dynamics (MD), supplemented by NMR data, and CD spectroscopy. To examine how the rigid 3-amino-2,3-dideoxy-α-D-*arabino*-hexopyranosiduronic acid influences the geometry and biological activity of peptides, two peptidomimetics with this SAA incorporated into the peptide chains were synthesized. The first is a Leu-enkephaline derivative, and its geometry is studied based on NMR analysis supplemented by MD simulations. The second is a mimetic of an HIV Tat-derived peptide and this was tested as allosteric modulator of the proteasome activity. Its structure is studied on a basis of the CD and FTIR spectra.

2. Results and discussion

2.1. Molecular dynamics of dimers

Calculations of the 3D-structure of the titled compounds were performed on a set of NOE derived interproton distance restraints

* Corresponding author. E-mail address: beata.liberek@ug.edu.pl (B. Liberek).

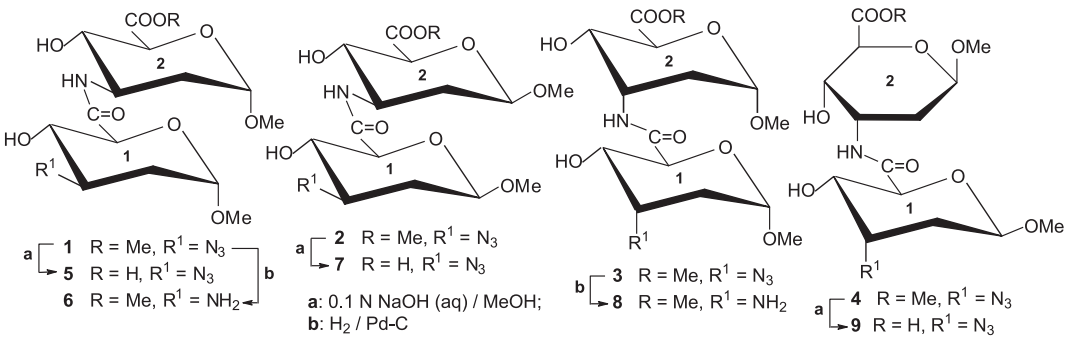
http://dx.doi.org/10.1016/j.tet.2015.02.009
0040-4020/

and the intra-ring coupling constant derived dihedral angle restraints. Both distance and dihedral restraints are a predominant source of structural information in biomolecular structure determination by NMR spectroscopy (for details please see the Supplementary Data).

The superposed conformations of the dimers **1**–**4** (Scheme 1), obtained during simulated annealing (SA) molecular dynamics (MD) with time-averaged restraints (TAV) are shown in Fig. 1. All of the dimers adopt stable conformations (one conformational family per dimer). As the MD investigations show, almost all of the pyranose rings in the dimers adopt the $^4C_1$ chair conformation, except for the methyl (methyl 3-amidohexopyranosid)uronate component 2 of (β-D-*ribo*)$_2$ (**4**)—which adopts the $^0S_2$ twist-boat conformation (Table 1). Such results are fully in agreement with our previous conclusions based solely on ^{1}H NMR spectra.[26]

Table 1
Structural statistics for the set of the conformations of (α-D-*arabino*)$_2$ (**1**), (β-D-*arabino*)$_2$ (**2**), (α-D-*ribo*)$_2$ (**3**) and (β-D-*ribo*)$_2$ (**4**)

Statistic	Dimers			
	1	2	3	4
NOE connectivities:				
Intraresidual	20	21	28	21
Sequential	6	4	7	5
R.m.s differences (Å):				
Heavy atoms	0.369	0.379	0.308	0.209
Atoms N3,C3,C4,C5,C,N	0.018	0.026	0.024	0.040
Hydrogen bonds	–	OH^2–CO^1	OH^1–CO^1 HN^2–OCH_3^2	OH^1–CO^1
Conformation of sugar ring	1: $^4C_1$ 2: $^4C_1$	1: $^4C_1$ 2: $^4C_1$	1: $^4C_1$ 2: $^4C_1$	1: $^4C_1$ 2: $^0S_2$
Radius of gyration (Å)	4.4	4.4	3.8	4.4



Scheme 1. Dimers **1**–**4** and their transformations into 'building blocks' for tetramer synthesis[1].

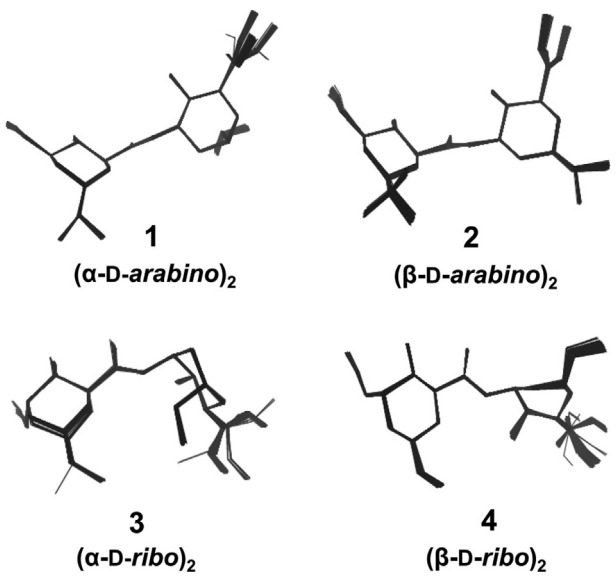


Fig. 1. Superposed conformations of (α-D-*arabino*)$_2$ (**1**), (β-D-*arabino*)$_2$ (**2**), (α-D-*ribo*)$_2$ (**3**), and (β-D-*ribo*)$_2$ (**4**) found by MD SA with time-averaged distance restraints.

The dimers studied using MD differ from each other with a hydrogen bond network. Thus, the structures of the (α-D-*arabino*)$_2$ (**1**) are not stabilized by any hydrogen bonding, whereas the (β-D-*arabino*)$_2$ (**2**) ones are stabilized by the OH^2–CO^1 hydrogen bond (Table 1). In turn, both D-*ribo* dimers (**3** and **4**) possess the OH^1–CO^1 hydrogen bond. In addition, an amide proton of (α-D-*ribo*)$_2$ (**3**), singularly, is engaged in the HN^2–OCH_3^2 hydrogen bond. Consequently, the entire structure of **3** is more compressed than the remaining dimers. The average values of radius of gyration, R_g are equal 3.8 Å and 4.4 Å, for the (α-D-*ribo*)$_2$ (**3**) and the others dimers, respectively (Table 1).

The analysis of ψ^1 ($C4^1$–$C5^1$–C^1–N^2) and ϕ^2 (C^1–N^2–$C3^2$–$C4^2$) dihedral angles indicates only slight differences between the

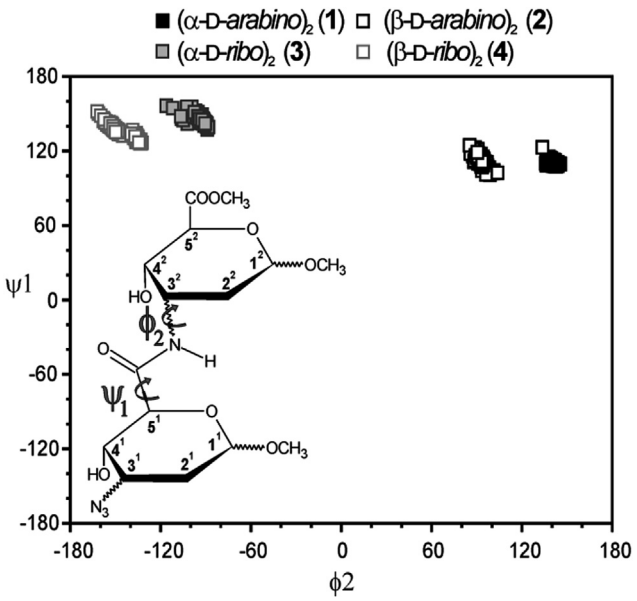


Fig. 2. Scatter plots of the dihedral angles (ψ^1: $C4^1$–$C5^1$–C^1–N^2 and ϕ^2: C^1–N^2–$C3^2$–$C4^2$) of dimers **1**–**4**.

[1] To facilitate the discussion, residues in dimers 1–4 and tetramers 10–13 are identified numerically from the N- to C-terminus. Numbers that identify the residues are drawn inside of each sugar ring.

Please cite this article in press as: Sikorska, E.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.02.009