University of Groningen

Synthesis of Health-Promoting Carbohydrates

Verkhnyatskaya, Stella A.

DOI:
[10.33612/diss.158661500](https://doi.org/10.33612/diss.158661500)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):
Verkhnyatskaya, S. A. (2021). *Synthesis of Health-Promoting Carbohydrates*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen. <https://doi.org/10.33612/diss.158661500>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Synthesis of Health-Promoting Carbohydrates

Stella Aleksandrovna Verkhnyatskaya

On the cover:

On the cover, is depicted a galaxy with a central constellation presenting an L-sugar. The idea was inspired by the words “galactose” and “galaxy”, which share a common root. Originally, the word “galaxy” referred to the Milky Way and is derived from the Greek word “γάλα” (gala) that means milk. Galactose is a component of milk sugar and owes its name as well to the Greek word “γάλα”.

Cover Design: S. A. Verkhnyatskaya

Stella Aleksandrovna Verkhnyatskaya
PhD Thesis
Rijksuniversiteit Groningen

The work in this thesis was financially supported by the Rosalind Franklin Fellowship scheme and the European Union through COFUND project 600211

Printed by: Ipskamp Printing B.V.

university of
 groningen

Synthesis of Health-Promoting Carbohydrates

PhD thesis

to obtain the degree of PhD at the
University of Groningen
on the authority of the
Rector Magnificus Prof. C. Wijmenga
and in accordance with
the decision by the College of Deans.

This thesis will be defended in public on

Friday 5 March 2021 at 12.45 hours

by

Stella Aleksandrovna Verkhnyatskaya

born on 21 June 1993
in Nova Kakhovka, Ukraine

Supervisor

Prof. A.J. Minnaard

Co-supervisor

Dr. M.T.C. Walvoort

Assessment Committee

Prof. S. Otto

Prof. M. Sollogoub

Prof. M. Bols

Table of Contents

List of abbreviations	8
Chapter 1	
General Introduction	13
Chapter 2	
Shaping the Infant Microbiome with Non-Digestible Carbohydrates	17
Part 1	
Synthesis and Biological Evaluation of the Di- α -fucosylated β -cyclodextrin	29
Chapter 3	
Direct and Regioselective Di- α -Fucosylation on the Secondary Rim of β -Cyclodextrin	33
Chapter 4	
On the Mechanism of the Regio- and Stereoselective Fucosylation of β -Cyclodextrin	63
Chapter 5	
Digestion, Fermentation, and Pathogen Anti-adhesive Properties of the HMO-mimic di-Fucosyl- β -cyclodextrin	101
Part 2	
Total Synthesis of the Exopolysaccharide repeating unit of <i>Bifidobacterium adolescentis</i>	121
Chapter 6	
Synthesis of the all- <i>trans</i> Hexasaccharide Unit of <i>Bifidobacterium adolescentis</i>	125
Chapter 7	
On the Reactivity and Selectivity of 6-Deoxytalosides in <i>cis</i> -Glycosylation	155
Chapter 8	
Total Synthesis of the Nonasaccharide Repeating Unit of EPS from <i>Bifidobacterium adolescentis</i>	199
Chapter 9	
Summary and Outlook	221
Samenvatting	233

Popular Summary	<i>237</i>
Populaire Samenvatting	<i>241</i>
Популярное Описание	<i>245</i>
List of publications	<i>249</i>
Curriculum Vitae	<i>251</i>
Acknowledgments	<i>253</i>

List of abbreviations

2'-FL	2'-fucosyllactose	CE	capillary electrophoresis
3-FL	3-fucosyllactose	CEL	conformational energy landscape
6dTal	6-deoxy-L-talose	CFU	colony-forming unit
6'-SL	6'-sialyllactose	CIP	contact ion pair
A	acceptor	COSY	correlation spectroscopy
Å	ångström	CPS	capsular polysaccharides
Ac	acetyl	δ	chemical shift
ACN	acetonitrile	d	doublet
All	allyl	D	donor
Alloc	allyl carbonate	DAG	diacetone-D-glucose
AMBER	assisted model building with energy refinement	DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
app t	apparent triplet	DCE	1,2-dichloroethane
APS	Acidic polysaccharides	DCM	dichloromethane
aq	aqueous	dd	double doublet
Ara	arabinose	ddd	double of double doublets
AU	arbitrary unit	DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
(A)XOS	(arabino-)xylo-oligosaccharides	DFL	2',3-di-fucosyllactose
<i>B</i>	boat	DFT	density-functional theory
BHI	brain heart infusion	DF β -CD	di- α -fucosylated β -cyclodextrin
Bn	benzyl	DIBAL	diisobutylaluminium hydride
br s	broad singlet	DIC	<i>N,N</i> -diisopropylcarbodiimide
Bz	benzoyl		
Bzd	benzylidene		
<i>C</i>	chair		
CAN	ceric ammonium nitrate		
Cbz	carboxybenzyl		
CD	cyclodextrin		

List of abbreviations

DIPEA	<i>N,N</i> -diisopropylethylamine	GHs	glycosyl hydrolases
DMAP	4-dimethylaminopyridine	GIT	gastrointestinal tract
DMF	dimethylformamide	Glc	glucose
DMSO	dimethylsulfoxide	GlcN	glucosamine
		GlcNAc	<i>N</i> -acetylglucosamine
DMTST	dimethyl(methylthio)sulfonium trifluoromethanesulfonate	GMP	glycomacropeptide
		GOS	galacto-oligosaccharides
DP	degree of polymerization	GROMOS	Groningen molecular simulation
dt	doublettriplet	GTs	glycosyltransferases
DTBMP	2,6-di- <i>tert</i> -butyl-4-methylpyridine	<i>H</i>	half-chair
		HAD	hydrogen bond-mediated aglycon delivery
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide	H-APS	high-molecular weight acidic polysaccharide
EHEC	enterohemorrhagic <i>E. coli</i>	HePS	heteropolysaccharides
EPEC	enteropathogenic <i>E. coli</i>	HILIC	hydrophilic interaction liquid chromatography
EPS	exopolysaccharides		heteronuclear multiple-bond correlation spectroscopy
ESI	electrospray ionization	HMBC	
Et	ethyl	HMO	human milk oligosaccharides
ETEC	enterotoxigenic <i>E. coli</i>	HoPS	homopolysaccharides
FDA	Food and Drug Administration		high-performance anion exchange chromatography
Fmoc	fluorenylmethoxycarbonyl	HPAEC	
FOS	fructo-oligosaccharides	HPLC	high-performance liquid chromatography
Fru	fructose		high resolution mass-spectrometry
Fuc	fucose	HRMS	
Gal	galactose		heteronuclear single-quantum correlation spectroscopy
GaIA	galacturonic acid	HSQC	
GATED	proton decoupling only during relaxation time	IAD	intra-molecular aglycon delivery

Synthesis of Health-Promoting Carbohydrates

IL	interleukin	NOE	nuclear Overhauser effect
<i>J</i>	coupling constant		
Lev	levulinoyl	NOESY	nuclear Overhauser effect spectroscopy
LG	leaving group	NPS	neutral polysaccharides
LNnT	lacto- <i>N</i> -neotetraose	p	quintet
m	multiplet	PAD	pulsed amperometric detection
MALDI-TOF	matrix-assisted laser desorption/ionization - time of flight	PBMC	peripheral blood mononuclear cells
Man	mannose	PBS	phosphate buffered saline
MD	molecular dynamics	PDX	polydextrose
Me	methyl	Ph	phenyl
MFβ-CD	monofucosylated β-CD	Pic	picolinyll
MM	molecular mechanics	Pico	picoloyl
MRS	de Man, Rogosa and Sharpe agar	Piv	pivaloyl
MS	mass-spectrometry	PMB	<i>para</i> -methoxybenzyl
MS4Å	molecular sieves – 4 Ångström	PME	particle mesh Ewald
Ms	mesyl	PMF	potential of mean force
<i>m/z</i>	mass over charge ratio	PMP	<i>para</i> -methoxyphenyl
MTBE	methyl- <i>tert</i> -butylether	POS	pectin oligosaccharides
NACs	near attack conformations	pyr	pyridine
Nap	2-naphthylmethyl	q	quartet
NBS	<i>N</i> -bromosuccinimide	QM	quantum mechanics
NDC	non-digestible carbohydrate	RDS	rapidly digestible starch
NDP	nucleotide diphosphate	RF	reaction field
NEC	necrotizing enterocolitis	R _f	retention factor
NIS	<i>N</i> -iodosuccinimide	Rha	rhamnose
NMR	nuclear magnetic resonance	RI	refractive Index
		RMSD	root mean squared deviation
		RP	reverse phase

List of abbreviations

RS	resistant starch	TDS	total digestible starch
R_t	retention times	TES	triethylsilane
RT	room temperature	Tf	triflate
s	singlet	TFA	trifluoroacetic acid
SB-POS	sugar beet pulp pectin oligosaccharides	Th	T helper
SCFA	short-chain fatty acids	THF	tetrahydrofuran
SD	standard deviation	TLC	thin layer chromatography
SDS	slowly digestible starch	TMS	trimethylsilyl
Sia	sialic acid	TNF	tumor necrosis factor
SIEM	standard ileal efflux medium	TOCSY	total correlation spectroscopy
SM	starting material	Tol	<i>para</i> -methylphenyl
S_N	substitution nucleophilic	Tr	trityl
SSIP	solvent separated ion pair	TS	transition state
t	triplet	Ts	tosyl
TBAB	tetra-n-butylammonium bromide	TTBP	2,4,6-tri- <i>tert</i> -butylpyrimidine
TBAI	tetra-n-butylammonium iodide	(UP)LC	(ultra high performance) liquid chromatography
TBS	<i>tert</i> -butyldimethylsilyl	UV	ultraviolet
td	triplet of doublets	Xyl	xylose