Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

The Thiocarbonyl Group in Carbohydrate Chemistry

José Manuel García Fernandez[a]; Carmen Ortiz Mellet[b]
[a] Institute de Investigaciones Químicas, C.S.I.C., Centro de Investigaciones Científicas Isla de la Cartuja, Américo Vespucio s/n, Isla de la Cartuja, Sevilla, Spain [b] Departamento de Química Organica, Facultad de Química, Universidad de Sevilla, Sevilla, Spain

To cite this Article Fernandez, José Manuel García and Mellet, Carmen Ortiz(1996) 'The Thiocarbonyl Group in Carbohydrate Chemistry', Journal of Sulfur Chemistry, 19: 1, 61 — 159
To link to this Article: DOI: 10.1080/01961779608047905
URL: http://dx.doi.org/10.1080/01961779608047905

Sulfur Reports, Volume 19, pp. 61–169
Reprints available directly from the publisher
Photocopying permitted by license only

THE THIOCARBONYL GROUP IN CARBOHYDRATE CHEMISTRY

JOSÉ MANUEL GARCÍA FERNANDEZ[1]
and CARMEN ORTIZ MELLET[2]

[1]*Instituto de Investigaciones Químicas, C.S.I.C., Centro de Investigaciones Científícas Isla de la Cartuja, Américo Vespucio s/n, Isla de la Cartuja, E-41092 Sevilla, Spain*
[2]*Departamento de Química Organica, Facultad de Química, Universidad de Sevilla, Apartado de Correos 553, E-41071 Sevilla, Spain*

(Received 3 January 1996)

Recent developments in the chemistry of thiocarbonyl carbohydrate derivatives are reviewed in this article. Emphasis has been placed on the interactions between the various functional groups that may coexist in a given molecule as well as the synthetic, biological, and technical applications of this family of compounds.

Key words: Thiocarbonyl compounds; sugar isothiocyanates; sugar thioamides; sugar thioesters; sugar thioureas; sugar thiocarbamates; sugar thiocarbonates

CONTENTS

1. INTRODUCTION

More than eighty years have elapsed since Emil Fischer reported the synthesis of the first sugar isothiocyanate and its transformation into sugar thioureas.[1] A vast literature on thiocarbonyl sugar derivatives has accumulated over the years and this subject continues to be a very active field in carbohydrate chemistry. A main reason for this situation is obviously their diversity of reactions and their availability. It should be also noted that thiocarbonyl compounds are close analogs of carbonyl compounds and may thus be useful for structure-activity studies and for studies of enzymic reactivity in connection with naturally occurring, biologically active derivatives.

The purpose of this article is to present the state of the art in the chemistry of such thiocarbonyl-containing sugar derivatives with particular reference to the scope and limitations derived from the presence of the polyfunctional carbohydrate portion. A general review of this type has not been previously written, although more specialized articles, e.g. on the chemistry of sugar thioureas,[2] thiocarbonates,[3] and isothiocyanates,[4] are available. It should be noticed that examples already covered in previous reviews have not been included, unless required. The literature has been surveyed since 1985 up to March 1995. For specific aspects not covered in the last partial revision,[4] highlights on the former literature have also been included. The preparation, properties, and reactions of thiocarbonyl compounds have been the subject of valuable comprehensive[5,6] as well as specialized accounts[7–12] which should be consulted for details.

2. SUGAR ISOTHIOCYANATES

Sugar isothiocyanates are among the most versatile synthetic intermediates in carbohydrate chemistry. The NCS group undergoes many reactions, giving access to a variety of other functional groups which, in turn, may be subjected to further transformations. The strong electrophilic character of the NCS group, its behaviour as a "counter-attack reagent", and its ability to react through the C=S or the C=N bond in cycloaddition reactions makes sugar isothiocyanates important precursors in the synthesis of heterocyclic derivatives of sugars, including nucleoside analogs, *N*-glycosides, and *neo*-glycoconjugates incorporating various types of

aglycon moieties. The synthesis, chemistry and preparative applications of monosaccharide isothiocyanates have been the subject of a previous review.[4]

2.1. *Synthesis of Sugar Isothiocyanates*

The polyfunctionality of carbohydrates imposes some requirements on the synthesis of sugar isothiocyanates such as, in most cases, protection of the reactive hydroxyl groups. For the purpose of this review, three types of isothiocyanate derivatives of sugars will be considered, depending on the position of the NCS group in the molecule: glycosyl isothiocyanates, deoxyisothiocyanato sugars and isothiocyanate conjugates. For a complete list of structures reported up to the closure date of this review, see Tables 1–3.

2.1.1. *Glycosyl Isothiocyanates*

2.1.1.1. *Reaction of a Glycosyl Donor with an Inorganic Thiocyanate.* Since the classic report by Emil Fischer[1] in 1914 in which he described the preparation of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate by treatment of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with silver thiocyanate, the reaction of an *O*-protected glycosyl halide with an inorganic thiocyanate has being widely used for the synthesis of glycosidically linked sugar isothiocyanates (Scheme 1). Early attempts to avoid the use of the expensive silver salt resulted in concomitant formation of the kinetically favoured glycosyl thiocyanate derivative. Although thermal isomerization of the latter to the corresponding isothiocyanate has been reported, the overall yields are, in general, significantly lower.[4]

This problem has been overcome by the use of phase-transfer catalysts which promote *in situ* thiocyanate → isothiocyanate conversion under mild conditions.[13–22] Per-*O*-protected glycosyl bromides have been most often employed as glycosyl donors, although other anomeric leaving groups (e.g. sulfonyloxy, acyloxy) have also been claimed.[18] Inexpensive alkali metal thiocyanates can then be used in the presence of cyclic polyethers or tetraalkylammonium salts as catalysts. The best results are obtained by performing the reaction in polar aprotic solvents (e.g. acetonitrile), using per-*O*-acylglycopyranosyl bromides as precursors.[16,17]

TABLE 1 Glycosyl Isothiocyanates

	M.p.(°C)	*Rotation*		*Ref.*
		$[\alpha]_D$	*Solvent*	
Monosaccharides				
β-D-Arabinofuranosyl				
2,3,4-tri-*O*-benzoyl	149–150	—	—	20
2-Deoxy-α-D-*arabino*-hexopyranosyl				
4,6-di-*O*-acetyl-3-bromo-3-deoxy	amorphous	—	—	27
3,4,6-tri-*O*-acetyl	70–72/syrup	+142/+168.8	$CH_2Cl_2/CHCl_3$	27, 28
3,4,6-tri-*O*-benzoyl	syrup	+84.4	$CHCl_3$	28
3,4,6-tri-*O*-(4-nitrobenzoyl)	amorphous	+73.0	$CHCl_3$	28
2-Deoxy-β-D-*arabino*-hexopyranosyl				
4,6-di-*O*-acetyl-3-bromo-3-deoxy	amorphous	+46	CH_2Cl_2	27
3,4,6-tri-*O*-acetyl	90–92/100–101	–26/–15.7	$CH_2Cl_2/CHCl_3$	27, 28
3,4,6-tri-*O*-benzoyl	syrup	+11.0	$CHCl_3$	28
3,4,6-tri-*O*-(4-nitrobenzoyl)	amorphous	–13.3	$CHCl_3$	28
α-D-Arabinopyranosyl				
2,3,4-tri-*O*-acetyl	syrup/175–178	—	—	20, 95
2,3,4-tri-*O*-benzoyl	foam	–114	$CHCl_3$	16
β-L-Arabinopyranosyl				
2,3,4-trio-*O*-acetyl	syrup	–45.5	$CHCl_3$	19
β-D-Fucopyranosyl				
2,3,4-tri-*O*-acetyl	94	+20	$CHCl_3$	96

(Table continues)

TABLE 1 *(continued)*

	M.p.(°C)	*Rotation*		*Ref.*
		$[\alpha]_D$	*Solvent*	
β-L-Fucopyranosyl				
2,3,4-tri-*O*-acetyl	102–104	—	—	96
2,3,4-tri-*O*-benzoyl	58–60	–174	CH_2Cl_2	36
α-D-Galactopyranosyl				
2,3,4,6-tetra-*O*-benzyl	syrup	+103	$CHCl_3$	26
β-D-Galactopyranosyl				
2,3,4,6-tetra-*O*-acetyl	92–94/97–99	+10	$CHCl_3$	14, 15, 96
3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo	145–150	+110	$CHCl_3$	44
3,6-di-*O*-benzoyl	amorphous	—	—	40
2,3,4,6-tetra-*O*-benzoyl	68–71	+137	$CHCl_3$	34
2,3,6-tri-*O*-benzoyl	150–152	+2	CH_2Cl_2	40
2,3,4,6-tetra-*O*-benzyl	98–99	+5.1	$CHCl_3$	26
D-Gluconyl				
2,3,4,5,6-penta-*O*-acetyl	132–135	—	—	97
α-D-Glucopyranosyl				
2,3,4-tri-*O*-acetyl-6-bromo-6-deoxy	164.5	+16.2	CCl_4	98
3,4,6-tri-*O*-acetyl-2-deoxy-2-thiocyanate	94.5–96	+249	$CHCl_3$	43
2,3,4,6-tetra-*O*-benzyl	syrup	+73	$CHCl_3$	16
2,3,4,6-tetra-*O*-benzyl-5a-carba	103–104	+99	$CHCl_3$	26, 42
β-D-Glucopyranosyl	syrup	+72	MeOH	29, 30, 99
2-acetamido-2-deoxy	syrup	+25	MeOH	31
2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy	161	+9.5	$CHCl_3$	16
2,3,4,6-tetra-*O*-acetyl	113–115	+4.4	$CHCl_3$	1, 14–16, 34

2,3,4-tri-*O*-acetyl	amorphous	+5.0	CH_2Cl_2	41
2,3,6-tri-*O*-acetyl	syrup	–46.0	CH_2Cl_2	41
3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo	103–105	+4	$CHCl_3$	44
2,3,4,6-tetra-*O*-benzyl	syrup	+12	$CHCl_3$	16
2,3,4,6-tetra-*O*-benzoyl	147–148	+17	CH_2Cl_2	35
2,3,4-tri-*O*-benzoyl	foam	–16.2	CH_2Cl_2	41
2,3,6-tri-*O*-benzoyl	197–199	+46	CH_2Cl_2	40
2-Deoxy-α-D-*lyxo*-hexopyranosyl				
3,4,6-tri-*O*-acetyl	syrup	+129	CH_2Cl_2	27
2-Deoxy-β-D-*lyxo*-hexopyranosyl				
3,4,6-tri-*O*-acetyl	syrup	+25	CH_2Cl_2	27
α-D-Mannopyranosyl				
2,3,4,6-tetra-*O*-acetyl	92–94/syrup	+132/+144	$CHCl_3$	16, 26
3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo	syrup	+59	$CHCl_3$	44
α-D-Quinovosyl				
2,3,4-tri-*O*-benzyl	syrup	+118	$CHCl_3$	26
β-D-Quinovosyl				
2,3,4-tri-*O*-benzyl	114–115	–2.6	$CHCl_3$	26
β-L-Quinovosyl				
3,4-di-*O*-acetyl-2-deoxy-2-iodo	62–65	–5	$CHCl_3$	44
α-L-Rhamnopyranosyl				
3,4-di-*O*-acetyl-2-deoxy-2-iodo	syrup	–115	$CHCl_3$	44
2,3,4-tri-*O*-acetyl	106.7–107.3	–185	$CHCl_3$	22
β-L-Rhamnopyranosyl				
2,3,4-tri-*O*-benzoyl	55–57	+182	CH_2Cl_2	36

(Table continues)

TABLE 1 *(continued)*

	M.p.(°C)	*Rotation*		*Ref.*
		$[\alpha]_D$	*Solvent*	
β-D-Ribofuranosyl				
2,3,5-tri-*O*-acetyl	syrup	–3	$CHCl_3$	16, 21
2,3,5-tri-*O*-benzoyl	96–97	—	—	100
3-Deoxy-α-D-*ribo*-hexopyranosyl				
2,4,6-tri-*O*-benzyl	syrup	+110	$CHCl_3$	26
3-Deoxy-β-D-*ribo*-hexopyranosyl				
2,4,6-tri-*O*-benzyl	65–66	+42.5	$CHCl_3$	26
α-D-Ribopyranosyl				
2,3,4-tri-*O*-benzoyl	syrup	–57	CH_2Cl_2	37
β-D-Ribopyranosyl				
2,3,4-tri-*O*-benzoyl	syrup	–187	CH_2Cl_2	37
α-D-Talopyranosyl				
3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo	116–119	+110	$CHCl_3$	44
α-D-*xylo*-Hex-5(5a)-enopyranosyl				
5a-carba-2,3:4,6-di-*O*-isopropylidene	syrup	+260	$CHCl_3$	26
β-D-Xylopyranosyl				
2,3,4-tri-*O*-acetyl	72–73	–31.2	$CHCl_3$	19
Disaccharides				
α-Cellobiosyl				
2,3,6,2′,3′,4′,6′-hepta-*O*-benzyl	syrup	+66.7	$CHCl_3$	26

β-Cellobiosyl				
2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl	191–195	–9.0	CH_2Cl_2	4, 38
2,3,6,2′,3′,4′,6′-hepta-*O*-benzyl	114–115	+28.5	$CHCl_3$	26
β-Chitobiosyl				
N,N′-diacetyl-3,4,3′,4′,6′-penta-*O*-acetyl	157–160	+9	$CHCl_3$	22
D-Gal*p*-β-(1→6)-D-Glc*p*-β-(1→NCS)				
2,3,4,3′,4′,6′-hexa-*O*-acetyl-2′-deoxy-2′-isothiocyanato	amorphous	0.0	CH_2Cl_2	39
D-Gal*p*-β-(1→4)-D-Man*p*-α-(1→NCS)[a]				
3,6,2′,3′,4′,6′-hexa-*O*-acetyl-2-deoxy-2-iodo	57–59	+47	$CHCl_3$	44
D-Glc*p*-α-(1→4)-D-Man*p*-α-(1→NCS)[a]				
3,6,2′,3′,4′,6′-hexa-*O*-acetyl-2-deoxy-2-iodo-	60–62	+120	$CHCl_3$	44
D-Glc*p*-β-(1→4)-D-Man*p*-α-(1→NCS)[a]				
3,6,2′,3′,4′,6′-hexa-*O*-acetyl-2-deoxy-2-iodo	127–129	+33	MeOH	44
β-Lactosyl	—	—	—	33
2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl	157–159/167–169	–18.5	$CHCl_3$	4, 14, 15, 38
α-Maltosyl				
2,3,6,2′,3′,4′,6′-hepta-*O*-benzyl	syrup	+3.1	$CHCl_3$	26

(Table continues)

TABLE 1 *(continued)*

	M.p.(°C)	*Rotation*		*Ref.*
		$[\alpha]_D$	*Solvent*	
β-Maltosyl	—	—	—	29
2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl	120–123	+57.7	CH_2Cl_2	4, 38
2,3,6,2′,3′,4′,6′-hepta-*O*-benzyl	syrup	+2.6	$CHCl_3$	26
β-Melibiosyl				
2,3,4,2′,3′,4′,6′-hepta-*O*-acetyl	syrup	+92.8	CH_2Cl_2	38
2,3,4,3′,4′,6′-hexa-*O*-acetyl-2′-deoxy-2′-isothiocyanato	amorphous	+60.0	CH_2Cl_2	39
Peracetyl Trisaccharides				
β-Chitotriosyl	amorphous	–16.5	$CHCl_3$	22
D-GlcNAc*p*-β-(1→4)[L-Fuc*p*-α-(1→6)]-D-GlcNac*p*-β-(1→NCS)	155–157	–74.2	$CHCl_3$	23
D-Man*p*-β-(1→4)-D-GlcNAc*p*-β-(1→4)-D-GlcNAc*p*-β-(1→NCS)	—	—	—	24

[a]Erroneously named as glucopyranosyl isothiocyanate derivatives in the original reference.

TABLE 2 Deoxyisothiocyanato Sugars

	M.p. (°C)	*Rotation*		*Ref.*
		$[\alpha]_D$	*Solvent*	
Monosaccharides				
α-D-Allofuranose				
5,6-di-*O*-acetyl-3-deoxy-1,2-*O*-isopropylidene-3-isothiocyanato	syrup	+183	CH_2Cl_2	54
3-deoxy-1,2-*O*-isopropylidene-3-isothiocyanato	60–62	+151	CH_2Cl_2	54
3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-isothiocyanato	58–59	+151.1	$CHCl_3$	54
β-D-Fructopyranose				
4,5-di-*O*-acetyl-1-deoxy-2,3-*O*-isopropylidene-1-isothiocyanato	107–109	−19.0	$CHCl_3$	53
1-deoxy-2,3:4,5-di-*O*-isopropylidene-1-isothiocyanato	oil	−65.8	$CHCl_3$	53
α-D-Galactofuranose				
5,6-di-*O*-acetyl-3-deoxy-1,2-*O*-isopropylidene-3-isothiocyanato	syrup	+10.0	CH_2Cl_2	54
3-deoxy-1,2-*O*-isopropylidene-3-isothiocyanato	syrup	+31.3	CH_2Cl_2	54
3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-isothiocyanato	oil	−75.0	$CHCl_3$	54
α-D-Galactopyranose				
6-deoxy-1,2:3,4-di-*O*-isopropylidene-6-isothiocyanato	oil	−83	$CHCl_3$	51, 52
α-D-Galactopyranoside, methyl				
2,3,4-tri-*O*-acetyl-6-deoxy-6-isothiocyanato	syrup	+105	$CHCl_3$	49, 52
2,3,6-tri-*O*-benzyl-4-deoxy-4-isothiocyanato	syrup	+71.0	$CHCl_3$	56
6-deoxy-6-isothiocyanato	120–122	+110	MeOH	52
6-deoxy-6-isothiocyanato-2,3,4-tri-*O*-trimethylsilyl	syrup	+72.8	CH_2Cl_2	60
D-Glucitol				
2,3,4,5,6-penta-*O*-acetyl-1-deoxy-1-isothiocyanato	syrup	+58.8	CH_2Cl_2	49
α-D-Glucofuranose				
5,6-di-*O*-acetyl-3-deoxy-1,2-*O*-isopropylidene-3-isothiocyanato	amorphous	−60.0	$CHCl_3$	54
3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-isothiocyanato	64–65	−75.0	$CHCl_3$	54
6-deoxy-1,2:3,5-di-*O*-isopropylidene-6-isothiocyanato	68	−45	Me_2CO	50
D-Glucopyranose				
1,2,4,6-tetra-*O*-acetyl-3-deoxy-3-isothiocyanato	oil	+55.0	$CHCl_3$	54
1,3,6-tri-*O*-acetyl-4-*O*-benzyl-2-deoxy-2-isothiocyanato	—	—	—	59

(Table continues)

TABLE 2 *(continued)*

	M.p. (°C)	*Rotation*		*Ref.*
		$[\alpha]_D$	*Solvent*	
α-D-Glucopyranose				
1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-isothiocyanato	65–66	+142	$CHCl_3$	45
α-D-Glucopyranoside, methyl				
2,3,4-tri-*O*-acetyl-6-deoxy-6-isothiocyanato	98–99	+129	$CHCl_3$	49, 52
2,3,4-tri-*O*-benzyl-6-deoxy-6-isothiocyanato	syrup	+86.8	$CHCl_3$	56
2,3,6-tri-*O*-benzyl-4-deoxy-4-isothiocyanato	syrup	–7.0	$CHCl_3$	56
6-deoxy-6-isothiocyanato	52–53	+117	Me_2CO	52
6-deoxy-6-isothiocyanato-2,3,4-tri-*O*-trimethylsilyl	syrup	+76.9	CH_2Cl_2	60
β-D-Glucopyranose				
3-*O*-acetyl-1,6-anhydro-4-*O*-benzyl-2-deoxy-2-isothiocyanato	73–75	+200	$CHCl_3$	59
1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-isothiocyanato	72–73	+73	DMF	47
1,6-anhydro-4-*O*-benzyl-2-deoxy-2-isothiocyanato	89–90	+115	$CHCl_3$	59
1,6-anhydro-4-*O*-benzyl-2-deoxy-2-isothiocyanato-3-*O*-*p*-tolylsulfonyl	82–84	+234	$CHCl_3$	59
β-D-Glucopyranoside, benzyl				
2,3,6-tri-*O*-benzyl-4-deoxy-4-isothiocyanato	syrup	–35.6	$CHCl_3$	56
β-D-Glucopyranoside, methyl				
2,3,4-tri-*O*-acetyl-6-deoxy-6-isothiocyanato	syrup	–28	$CHCl_3$	52
6-deoxy-6-isothiocyanato	108–110	–196	MeOH	52
α-D-*glycero*-L-*gluco*-Heptopyranose				
1,3,4,6,7-penta-*O*-acetyl-2-deoxy-2-isothiocyanato	75–76	–121	$CHCl_3$	46
β-D-*glycero*-L-*gluco*-Heptopyranose				
1,3,4,6,7-penta-*O*-acetyl-2-deoxy-2-isothiocyanato	136–138	–23	$CHCl_3$	48
D-*arabino*-Hex-1-enitol				
3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-2-isothiocyanato	syrup	–60	$CHCl_3$	101
D-*erythro*-Hex-3-enopyranoside, ethyl				
2,3,4-trideoxy-2-isothiocyanato-6-*O*-methylsulfonyl	68–69	–105	$CHCl_3$	102, 103
D-*threo*-Hex-3-enopyranoside, ethyl				
2,3,4-trideoxy-2-isothiocyanato-6-*O*-methylsulfonyl	syrup	+375	$CHCl_3$	102, 103
α-D-Mannopyranoside, methyl				
2,3,4-tri-*O*-acetyl-6-deoxy-6-				

(Table continues)

isothiocyanato	114–115	+62	$CHCl_3$	49, 52
6-deoxy-6-isothiocyanato	syrup	+71	Me_2CO	52
6-deoxy-6-isothiocyanato-2,3,4-tri-*O*-trimethylsilyl	syrup	+47.8	CH_2Cl_2	60
Disaccharides				
D-Cellobitol				
2,3,5,6,2′,3′,4′,6′-octa-*O*-acetyl-1-deoxy-1-isothiocyanato	syrup	+25	CH_2Cl_2	49
α-Gentiobioside, ethyl				
3,4,2′,3′,4′,6′-hexa-*O*-acetyl-2-deoxy-2-isothiocyanato	151	+90.6	CH_2Cl_2	64
2′,3′,4′,6′-tetra-*O*-acetyl-3,4-di-*O*-benzoyl-2-deoxy-2-isothiocyanato	125	+48.3	CH_2Cl_2	64
α-Melibioside, ethyl				
3,4,2′,3′,4′,6′-hexa-*O*-acetyl-2-deoxy-2-isothiocyanato	—	—	—	39
2′,3′,4′,6′-tetra-*O*-acetyl-3,4-di-*O*-benzoyl-2-deoxy-2-isothiocyanato	—	+149	CH_2Cl_2	39
D-Gal*p*-β-(1 → 6)-D-Glc*p*-β-(1 → OEt)				
3′,4′,6′-tri-*O*-acetyl-3,4-di-*O*-benzoyl-2,2′-dideoxy-2,2′-diisothiocyanato	—	+42.9	CH_2Cl_2	39
α-D-Fructofuranose β-D-fructopyranose 1,2′:2,1′-dianhydride				
3,4-di-*O*-acetyl-6-deoxy-6-isothiocyanato 3′,4′,5′-tri-*O*-acetyl	amorphous	−34.0	$CHCl_3$	61
6-deoxy-6-isothiocyanato	*amorphous*	−16.0	MeOH	61
Sucrose				
N-acetyl-2,3,1′,3′,4′-penta-*O*-acetyl-6-amino-6,6′-dideoxy-6′-isothiocyanato 6,4-(cyclic thiocarbamate)	syrup	−26.3	$CHCl_3$	61
2,3,4,1′,3′,4′-hexa-*O*-acetyl-6,6′-dideoxy-6,6′-diisothiocyanato	syrup	+72.7	$CHCl_3$	61
6-amino-6,6′-dideoxy-6′-isothiocyanato 6,4-(cyclic thiocarbamate)	syrup	+150.1	MeOH	61
6,6′-dideoxy-6,6′-diisothiocyanato	syrup	+74.3	MeOH	61
α,α′-Trehalose				
N-acetyl-2,3,2′,3′,4′-penta-*O*-acetyl-6-amino-6,6′-dideoxy-6′-isothiocyanato 6,4-(cyclic thiocarbamate)	amorphous	+12.0	CH_2Cl_2	61
2,3,4,2′,3′,4′-hexa-*O*-acetyl-6,6′-dideoxy-6,6′-diisothiocyanato	75–77	+113.8	$CHCl_3$	61
6-amino-6,6′-dideoxy-6′-isothiocyanato 6,4-(cylic thiocarbamate)	amorphous	+10	MeOH	61
6,6′-dideoxy-6,6′-diisothiocyanato	amorphous	+100.7	MeOH	61

(Table continues)

TABLE 2 *(continued)*

	M.p. (°C)	*Rotation*		*Ref.*
		$[\alpha]_D$	*Solvent*	
2,3,4,2′,3′,4′-hexa-*O*-(trimethylsilyl)-6,6′-dideoxy-6,6′-diisothiocyanato	106–108	+85.1	CH_2Cl_2	62
Oligosaccharides				
Cyclomaltoheptaose				
6^I-Deoxy-6^I-isothiocyanato	amorphous	+112	Pyridine	63
Heptakis(6-deoxy-6-isothiocyanato)	>255 (dec.)	+46	Me_2SO	61
Cyclomaltohexaose				
Hexakis(6-deoxy-6-isothiocyanato)	>255 (dec.)	+20	Me_2SO	61
Cyclomaltooctaose				
Octakis(6-deoxy-6-isothiocyanato)	>240 (dec.)	+85	Me_2SO	61

TABLE 3 Isothiocyanate Conjugates

Sugar	*Bridging arm*	*Ref.*
Monosaccharides		
N-Acetylneuraminic acid		
2-aminoalditol-N→	6-isothiocyanatohexyl	91
3-Deoxy-D-*manno*-2-octulosonic acid		
2-aminoalditol-N→	6-isothiocyanatohexyl	91
α-L-Fucopyranoside	*p*-isothiocyanatophenyl	84
α-D-Galactopyranoside		
2-acetamido-2-deoxy	*p*-isothiocyanatophenyl	84
β-D-Galactopyranoside	*p*-isothiocyanatophenyl	65, 84
2-acetamido-2-deoxy	*p*-isothiocyanatophenyl	84
2-acetamido-2-deoxy, 1-aminoalditol-N→	*p*-isothiocyanatophenyl	89
α-D-Glucopyranoside	*p*-isothiocyanatophenyl	65, 84
α-D-Glucopyranoside, methyl		
2-amino-2-deoxy-N→	*p*-isothiocyanatobenzoyl	65
β-D-Glucopyranoside	*p*-isothiocyanatophenyl	65, 84
2-acetamido-2-deoxy	*p*-isothiocyanatophenyl	84
α-D-Mannopyranoside	*p*-isothiocyanatophenyl	84
6-phosphate	*p*-isothiocyanatophenyl	84
β-D-Mannopyranoside	*p*-isothiocyanatophenyl	84
α-L-Rhamnopyranoside	*p*-isothiocyanatophenyl	84
Disaccharides		
Abe*p*-α-(1→3)-D-Man*p* -α-(1→[a]	*p*-isothiocyanatophenyl	81
D-Glc*p* -α-(1→6)-D-Man*p* -α-(1→	2-(*p*-isothiocyanatophenyl)ethyl	85

(Table continues)

β-Lactoside	*p*-isothiocyanatophenyl	84
β-Lactoside	2-(*p*-isothiocyanatophenylthio)ethyl	87
β-Maltoside	*p*-isothiocyanatophenyl	84
D-Man*p*-α-(1→6)-D-Glc*p*-α-(1→	2-(*p*-isothiocyanatophenyl)ethyl	85
D-Man*p*-α-(1→2)-D-Man*p*-α-(1→	*p*-isothiocyanatophenyl	70
D-Man*p*-α-(1→2)-D-Man*p*-α-(1→	2-(*p*-isothiocyanatophenyl)ethyl	85
D-Man*p*-α-(1→6)-D-Man*p*-α-(1→	2-(*p*-isothiocyanatophenyl)ethyl	85
Par*p*-α-(1→3)-D-Man*p*-α-(1→[b]	*p*-isothiocyanatophenyl	82
Tyv*p*-α-(1→3)-D-Man*p*-α-(1→[c]	*p*-isothiocyanatophenyl	80
Trisaccharides		
Chitotriose		
1-aminoalditol-*N*→	*p*-isothiocyanatophenyl	89
2-*O*-(α-D-Glc*p*)-isomaltoside	2-(*p*-isothiocyanatophenyl)ethyl	86
3-*O*-(α-D-Glc*p*)isomaltoside	2-(*p*-isothiocyanatophenyl)ethyl	86
4-*O*-(α-D-Glc*p*)isomaltoside	2-(*p*-isothiocyanatophenyl)ethyl	86
3′-*O*-α-Sialyllactose		
1-aminoalditol-*N*→	*p*-isothiocyanatophenyl	89
1-aminoalditol-*N*→	2-(*p*-isothiocyanatophenyl)ethyl	88
6′-*O*-α-Sialyllactose		
1-aminoalditol-*N*→	2-(*p*-isothiocyanatophenyl)ethyl	88
D-Gal*p*-β-(1→6)-D-Gal*p*-β(1→6)-D-Gal*p*-β-(1→	*p*-isothiocyanatophenyl	75
D-Man*p* -α-(1→2)-[D-Man*p*-α(1→6)]-D-Man*p*-α-(1→	2-(*p*-isothiocyanatophenyl)ethyl	85
Higher Oligosaccharides		
A-Tetrasaccharide		
1-aminoalditol-*N*→	*p*-isothiocyanatophenyl	89
Lacto-*N*-difucohexaose I		
1-aminoalditol-*N*→	*p*-isothiocyanatophenyl	89
1-aminoalditol-*N*→	2-(*p*-isothiocyanatophenyl)ethyl	88
Lacto-*N*-fucopentaose I		
1-aminoalditol-*N*→	*p*-isothiocyanatophenyl	89
Lacto-*N*-fucopentaose II		
1-aminoalditol-*N*→	*p*-isothiocyanatophenyl	89
1-aminoalditol-*N*→	2-(*p*-isothiocyanatophenyl)ethyl	88
Lacto-*N*-fucopentaose III		
1-aminoalditol-*N*→	*p*-isothiocyanatophenyl	89
Lacto-*N*-hexaose		
1-aminoalditol-*N*→	*p*-isothiocyanatophenyl	89
Lacto-*N*-tetraose		
1-aminoalditol-*N*→	*p*-isothiocyanatophenyl	89
Salmonella specific oligosaccharides		
1-aminoalditol-*N*→	2-(*p*-isothiocyanatophenyl)ethyl	68
Polysacchrides		
Aeromonas specific polysaccharides		
KDO-2-aminoalditol-*N*→	6-isothiocyanatohexyl	91
Vibrio anguilarum polysaccharide		
oxidized heptose-6-*NH*→	6-isothiocyanatohexyl	91

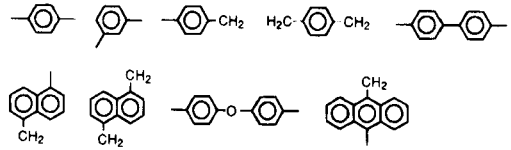
(Table continues)

TABLE 3 *(continued)*

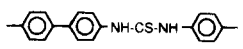
Sugar	*Bridging arm*	*Ref.*
Cellulose -*O*→	$(CH_2)_2$-NH-CS-NH-R-NCS[d]	92
Cellulose -*O*→	$(CH_2)_2$-NCS	92
Cellulose -*O*→	CH_2-CO-NH-R-NCS[e]	92
Cellulose -*O*→	CO-NH-R-NCS[f]	92, 94

[a]Abe = Abequose (3,6-dideoxy-D-*xylo*-hexose).
[b]Tyv = Tyvelose (3,6-dideoxy-D-*arabino*-hexose).
[c]Par = Paratose (3,6-dideoxy-D-*ribo*-hexose).

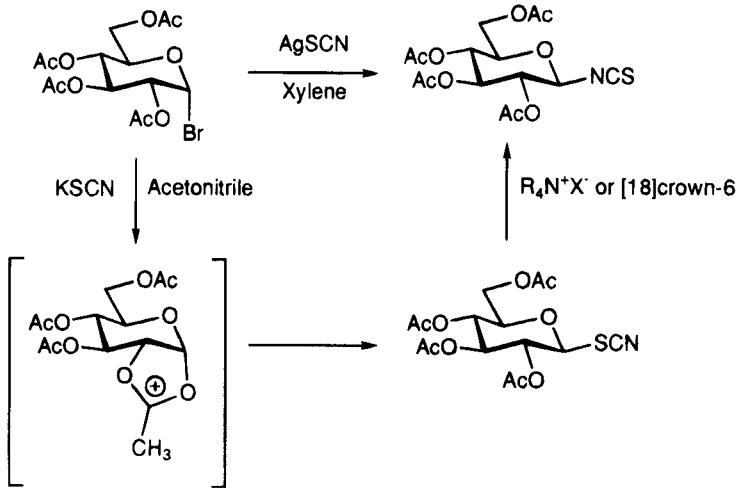
[d]R =



[e]R =



[f]R = -$(CH_2)_5$-



SCHEME 1

Displacement of the halide anion is then assisted by the neighbouring acyl group. Further attack by the thiocyanate anion and subsequent rearrangement into the isomeric isothiocyanate affords per-*O*-acyl glycopyranosyl isothiocyanates having a 1,2-*trans* relative disposition in pure anomeric form (Scheme 1).

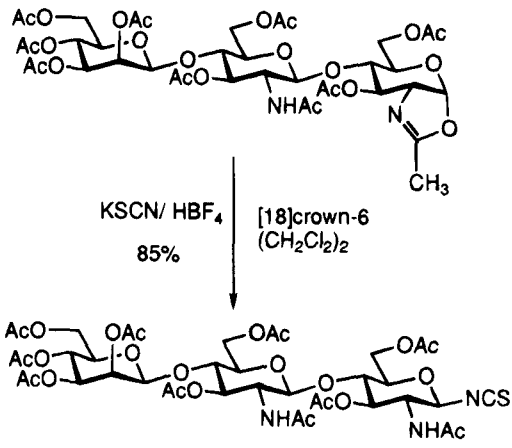
Per-*O*-acetyl- and per-*O*-benzoylglycopyranosyl isothiocyanate derivatives of aldohexoses, 2-amino-2-deoxyaldoses and aldopentoses have been prepared in this way in 60–80% yield. This method has also been successfully applied to the synthesis of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl isothiocyanate from an anomeric mixture of the corresponding D-ribofuranosyl chlorides.[21]

This approach has been extended to the synthesis of oligosaccharide glycosyl isothiocyanates of biological importance. Thus, peracetyl glycosyl isothiocyanate derivatives of lactose, chitobiose and chitotriose have been prepared by reaction of the corresponding glycosyl bromides or chlorides with potassium thiocyanate in benzene[14,15] or by reaction with ammonium thiocyanate in acetonitrile or acetone.[13,22] Two other trisaccharide glycosyl isothiocyanates, structurally related to the oligosaccharide core portion of *N*-linked glycoproteins, have also been synthetized in a similar way and used as key intermediates in the coupling reaction to the amino acid asparagine.[23,24] In the case of the branched trisaccharide GlcNAc-β-(1→4)-[Fuc-α-(1→6)]-GlcNAc-β-(1→NCS), a glycosyl bromide was used as glycosyl donor, while an oxazolinium salt[25] allowed introduction of the NCS functionality in the case of the linear mannosyl chitobiose derivative Man-β-(1→4)-GlcNAc-β-(1→4)-GlcNAc-β-(1→NCS) (Scheme 2).

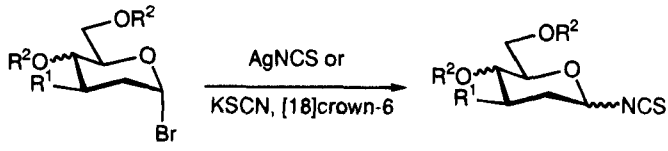
The reaction of glycosyl donors incorporating non-participating protecting groups, e.g. ether groups, with inorganic thiocyanates leads to mixtures of 1,2-*trans* and 1,2-*cis* glycosyl isothiocyanates, the α-anomers being favoured by virtue of the anomeric effect.[16,17,26]

Analogously, treatment of peracetyl 2-deoxy-α-D-glycosyl bromides with silver thiocyanate in toluene afforded mixtures of 2-deoxy-α- and β-D-glycosyl isothiocyanates in 52–60% yield.[27] An improved procedure which uses potassium thiocyanate in the presence of [18]crown-6 in anhydrous acetone has also been reported[28] (Scheme 3).

2.1.1.2. *Isothiocyanation of Glycosylamines* From the variety of preparative methods available for the synthesis of isothiocyanates, the reaction of a



SCHEME 2



	R^1	R^2	α:β
D-*arabino*	OAc	Ac	1.2:1-2:1
D-*arabino*	Br	Ac	1:1
D-*arabino*	OBz	Bz	1:1.2
D-*arabino*	NHBz	Bz	1:3
D-*lyxo*	OAc	Ac	1:1.1

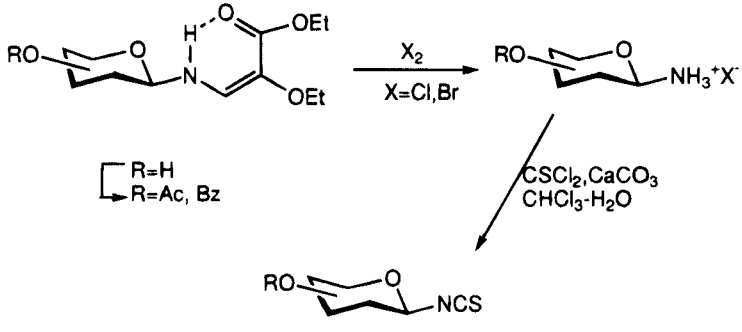
SCHEME 3

primary amine with thiophosgene is probably the most generally useful. Formation of the C–N bond occurs prior to generation of the isothiocyanate group and, therefore, formation of the isomeric thiocyanate is prevented. Also, since glycosylamines only anomerize slowly, a very efficient stereocontrol of the anomeric configuration is generally obtained, regardless of the nature (i.e., participating or non-participating character) of the hydroxyl protecting groups.

As a matter of fact, the reaction of the readily accessible β-D-glucopyranosylamine with thiophosgene to give β-D-glucopyranosyl isothiocyanate

was already reported by Taverna and Langdon[29,30] in 1973. Similarly, 2-acetamido-2-deoxy-β-D-glucopyranosyl,[31] β-maltosyl[32] and β-lactosyl[33] isothiocyanate have been prepared and used as affinity labels in enzymological studies. However, these fully unprotected glycopyranosyl isothiocyanates have been shown to be unstable[33] and no further chemistry has been reported.

The synthesis of stable, fully protected hexopyranosyl isothiocyanates by the thiophosgene reaction was first reported by Fuentes Mota *et al.*[34–36] The reaction sequence involves a glycosyl enamine, stabilized by a six-membered intramolecular hydrogen bond, as key intermediate. Subsequent *O*-protection and halogenolysis of the enamino group provide a very convenient acces to *O*-protected glycosylamine precursors. Interestingly, no O → N acyl migration has been detected neither during the selective *N*-deprotection step nor in the reaction of the resulting amine hydrohalide with thiophosgene using a three-phase chloroform-water-calcium carbonate system. On the other hand, since the anomeric center is not involved in the final step, the reaction proceeds with total retention of the anomeric configuration (Scheme 4).

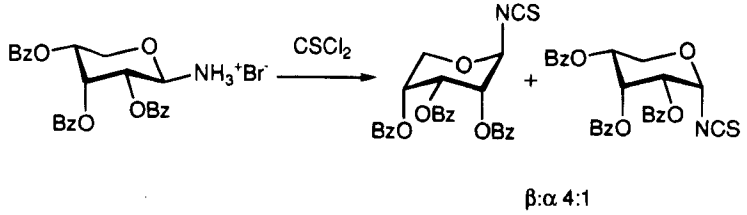


D-*gluco*, D-*galacto*, L-*rhamno*, L-*fuco*

SCHEME 4

Some deviations from this general pattern have, however, been reported in the aldopentose series.[37] Thus, under the above reaction conditions 2,3,4-tri-*O*-benzoyl-β-D-ribopyranosylamine partially anomerized, leading to a 4:1 β:α anomeric mixture of the corresponding tri-*O*-benzoyl ribopyranosyl isothiocyanates. The higher flexibility of the pentopyranose ring, due

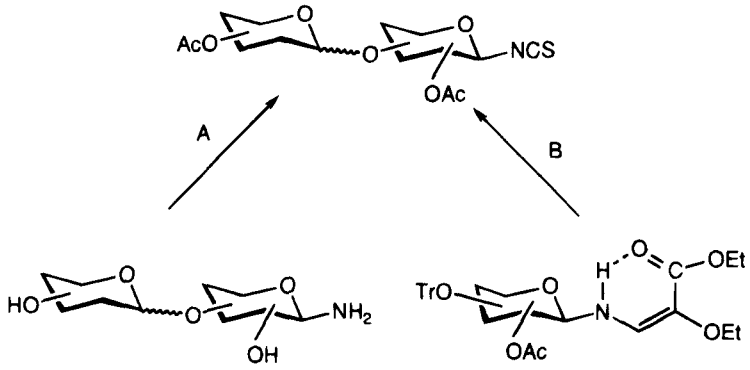
to the absence of a hydroxymethyl substituent at C-5, probably facilitates this process. In agreement with that, the β and α anomers exist in the $^1C_4$ and $^4C_1$ (D) conformation, respectively, with the NCS group in an axial position, fitting the anomeric effect (Scheme 5).



SCHEME 5

Recently, this strategy has been extended to the preparation of oligosaccharide glycosyl isothiocyanates. Two complementary approaches have been investigated involving: (a) direct functionalization of oligosaccharides at the anomeric position and (b) glycosylation of selectively protected glycosyl enamines. In the first case,[38] β-glycosylamines were obtained by reaction of reducing oligosaccharides with ammonium hydrogen carbonate. Further reaction with diethyl ethoxymethylenemalonate, followed by standard *O*-protection, chlorolysis and reaction with thiophosgene lead to the corresponding isothiocyanates in five steps and 50–60% overall yield. The mild reaction conditions and the absence of acidic reagents make this synthetic methodology of virtually general application. In the second approach, the oligosaccharide structure was stepwise built using glycosyl enamines as glycosyl acceptors. Interestingly, the use of 2-azido-2-deoxy glycosyl donors leads to disaccharides incorporating two masked amino groups from which mixed glycosyl isothiocyanate-deoxyisothiocyanato sugars, at different monosaccharide subunits, have been obtained[39] (Scheme 6).

The versatility of the enamine strategy for temporary amine protection in the preparation of glycosyl isothiocyanates has been further illustrated by the synthesis of partially protected glucosyl and galactosyl derivatives.[40,41] Neither O→N nor O→O acyl migration occurred during the halogenolysis and isothiocyanation steps, even in the case of unprotected primary hydroxyl groups.[41] Nevertheless, intramolecular transesterification took place after some time in solution.



β–maltosyl
β–cellobiosyl
β–lactosyl
β–melibiosyl

[2-NCS]-D-Gal*p*-α(1→6)D-Glc*p*
[2-NCS]-D-Gal*p*-β(1→6)D-Glc*p*

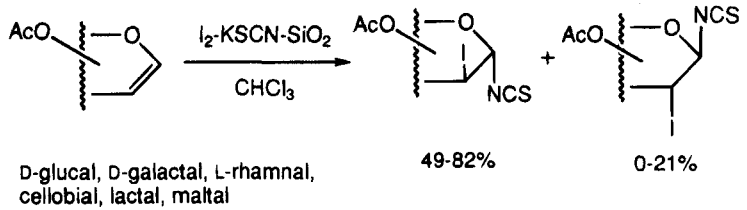
A: 1. $EtOCH{=}C(COOEt)_2$/ MeOH; 2. Ac_2O-pyridine; 3. Cl_2/ $CHCl_3$;4. $CSCl_2$
B: 1. Glycosyl donor/ $AgClO_4$/ $MeNO_2$, drierite; 2. Cl_2/ $CHCl_3$; 3. $CSCl_2$

SCHEME 6

The isothiocyanation of glycosylamines competes, in principle, with two thermodynamically favoured side reactions, namely the tautomerization of the sugar precursor and the condensation of the isothiocyanate formed with unreacted amine. Although thiophosgene is generally preferred, since it provides clean and very fast conversions, other isothiocyanation reagents may also be employed. Recently, Ogawa *et al.*[26,42] reported the use of 1,1′-thiocarbonyldiimidazole for the preparation of carbaglycosyl isothiocyanates from the corresponding non-tautomerizable amines.

2.1.1.3. *Electrophilic Addition to Glycals* The possibility of using glycals, i.e. 1,2-unsaturated sugars, as glycosyl isothiocyanate precursors was already explored by Igarashi and Honma[43] almost thirty years ago. However, formation of a complex mixture of diastereomers as well as of isothiocyanate-thiocyanate isomers was observed with thiocyanogen as reagent, and this approach was abandoned.[4]

In a recent report, Santoyo-González *et al.*[44] reported a very convenient route for the simultaneous introduction of the iodo and isothiocyanate functionalities in a sugar molecule starting from glycals. Electrophilic addition of iodine(I) thiocyanate, generated *in situ* from silica supported KSCN and iodine, to the double bond leads exclusively to *trans*-2-deoxy-2-iodoglycopyranosyl isothiocyanates. In the case of monosaccharide glycals, a mixture of the *trans*-diaxial (major) and *trans*-diequatorial product (minor) was obtained, whereas the *trans*-diaxial *vic*-iodo isothiocyanate was the sole product in the case of disaccharide glycals. The high yield, good stereoselectivity and simplicity of the method make it very attractive for the preparation of highly functionalized sugar derivatives (Scheme 7).

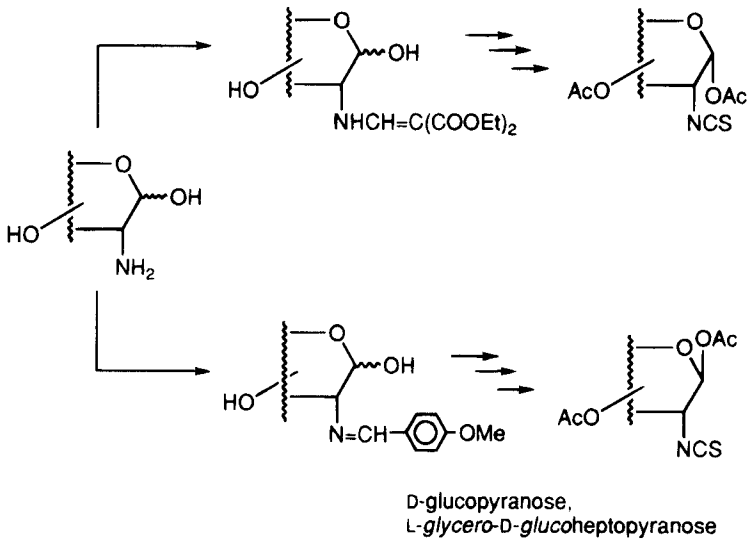


SCHEME 7

2.1.2. *Deoxyisothiocyanato Sugars* Sugars in which a hydroxyl group other than the anomeric one is replaced by the NCS group are discussed under this heading. They are obtained either through allylic rearrangement of unsaturated thiocyanates into isothiocyanates or by isothiocyanation of the amino group in suitable amino sugar precursors. The first approach has been used for the preparation of 2-deoxy-2-isothiocyanato and 3-deoxy-3-isothiocyanato sugars in rather moderate yields.[4]

The second synthetic methodology is of much more general application. It requires the preparation of per-*O*-protected amino sugars, or the respective hydrohalides, which by reaction with an isothiocyanation reagent afford deoxyisothiocyanato sugars. The utility of this strategy is highly dependent on the development of efficient synthetic routes to the *O*-protected amino sugar precursors. In this respect, the transformation of the amino group of readily available amino sugars into an enamine intermediate has proved to be particularly useful. In the 2-amino-2-deoxyaldopyranose series, the use of the 2,2-(diethoxycarbonyl)vinyl *N*-protecting group

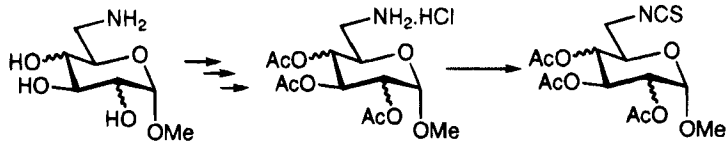
allowed access to the corresponding 1,2-*cis* per-*O*-acyl amino sugar hydrohalides, which upon reaction with thiophosgene furnished isothiocyanates in high overall yield.[45,46] Interestingly, the formation of a Schiff base derivative with 4-methoxybenzaldehyde anchored the opposite anomeric configuration.[47,48] In this way, the peracetylated α- and β-anomers of 2-deoxy-2-isothiocyanato-D-glucopyranose and 2-deoxy-2-isothiocyanato-D-*glycero*-L-*gluco*-heptopyranose have been obtained (Scheme 8).



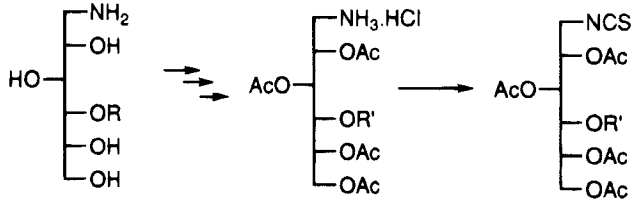
SCHEME 8

The synthetic value of the enamine strategy is additionally underlined by the possibility of access to per-*O*-acylated 6-deoxy-6-isothiocyanato aldopyranosides and 1-deoxy-1-isothiocyanatoalditols.[49] In both cases, the preparation of the starting amines has been reported to be unsuccessful by other methodologies due to acyl migration to the more basic primary amino group. Nevertheless, chlorolysis of per-*O*-acetyl enamines and further reaction with excess thiophosgene afforded the target isothiocyanates in 80–90% yield (Scheme 9).

Aldose and ketose derivatives bearing an isothiocyanate group at a primary carbon atom have also been obtained from cyclic acetal derivatives.[50–53] In this case, introduction of the amino group follows



D-*gluco*, D-*galacto*, D-*manno*



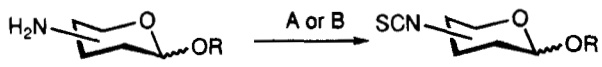
R=H, β-D-Glc*p* R'=Ac, β-D-Glc*p*(OAc)

SCHEME 9

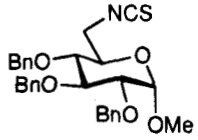
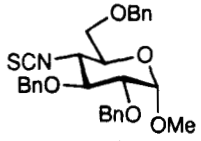
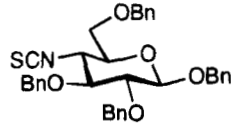
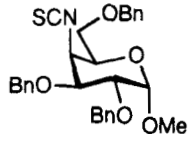
hydroxyl protection and no *N*-protecting group is needed. 6-Deoxy-1,2:3,5-di-*O*-isopropylidene-6-isothiocyanato-α-D-glucofuranose,[50] 6-deoxy-1,2:3,4-di-*O*-isopropylidene-6-isothiocyanato-α-D-galactopyranose,[51,52] and 1-deoxy-2,3:4,5-di-*O*-isopropylidene-1-isothiocyanato-β-D-fructopyranose[53] have been thus prepared in three steps from the corresponding readily accessible selectively *O*-acetalated monosaccharides. An analogous synthetic pathway has been employed[54] in the preparation of the 3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-isothiocyanato derivative of kanosamine (3-amino-3-deoxy-D-glucose) and of its C-3 and C-4 epimers (with D-*allo* and D-*galacto* configuration, respectively).

Recently, the preparation of 6-deoxy-6-isothiocyanato and 4-deoxy-4-isothiocyanato glycopyranoside derivatives incorporating benzyl ether *O*-protecting groups has been reported.[55,56] The amino sugar precursors were obtained from the selectively protected monosaccharides via the corresponding azides. Mukaiyama[57] and Wadsworth-Emmonds[58] isothiocyanation have been used in these cases (Scheme 10).

The stability of monosaccharide derivatives bearing both deoxyisothiocyanato and free hydroxyl groups is dramatically dependent on the config-



(A) 1) CS_2, Et_3N; 2) 2-chloropyridinium iodide, Et_3N
(B) 1) $(EtO)_2P(=O)Cl$, Et_3N; 2) NaH, n-Bu_4NBr, CS_2

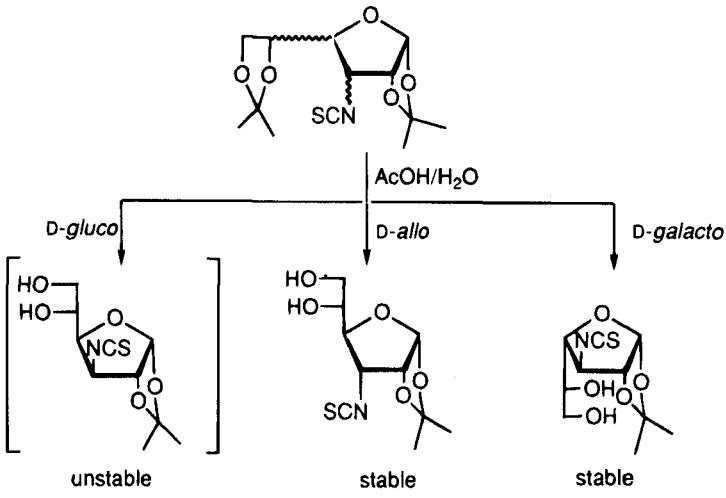
Compound	Reagent	Yield
	A	96%
	B	50%
	B	45%
	B	15%

SCHEME 10

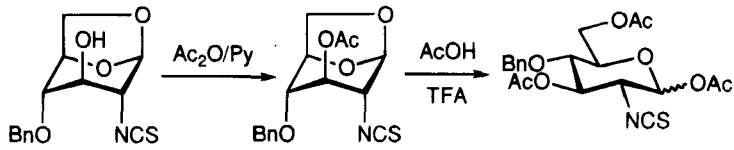
uration and conformation of the sugar template. As a general rule, β- and γ-hydroxy deoxyisothiocyanato sugars undergo spontaneous or base-induced annelation reaction to the corresponding five- and six-membered cyclic thiocarbamates, respectively.[51–54] In some cases, the deoxyisothiocyanato sugar intermediate has been trapped by acetylation.[54]

Stable hydroxy isothiocyanates can, however, be obtained depending on the relative disposition of the functional groups and on conformational bias. Thus, β- and γ-hydroxy isothiocyanates derived from 1,2-*O*-isopropylidene-3-deoxy-3-isothiocyanato-α-D-allofuranose and -galactofuranose[54] (Scheme 11) and from 1,6-anhydro-2-deoxy-2-isothiocyanato-β-D-glucopyranose[59] (Scheme 12) were stable compounds which could undergo

further transformations (e.g. acylation) without affecting the NCS functionality. In all cases, the intramolecular nucleophilic cycloaddition would lead to a five-membered—six-membered *trans*-fused bicyclic system, an unfavourable arrangement.



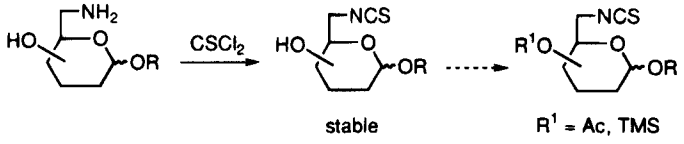
SCHEME 11



SCHEME 12

In contrast to what is observed for reducing 6-deoxy-6-isothiocyanato hexoses, fully unprotected 6-deoxy-6-isothiocyanato aldopyranosides have been found to be stable in the absence of base[51,52] (Scheme 13). The amino sugar precursors can be obtained very efficiently through a three-step synthetic sequence from the commercially available methyl aldopyranosides by direct replacement of the primary hydroxyl group by iodine, nucleophilic displacement by azide anion, and Staudinger reduction of the 6-azido compound. Per-*O*-acyl[52] and per-*O*-trimethylsilyl derivatives[60]

were also prepared after conventional *O*-protecting reactions, although some thiocarbamate formation was observed in the latter derivatization. An alternative synthesis starting from silylated amines has been found more convenient in this case.[60]



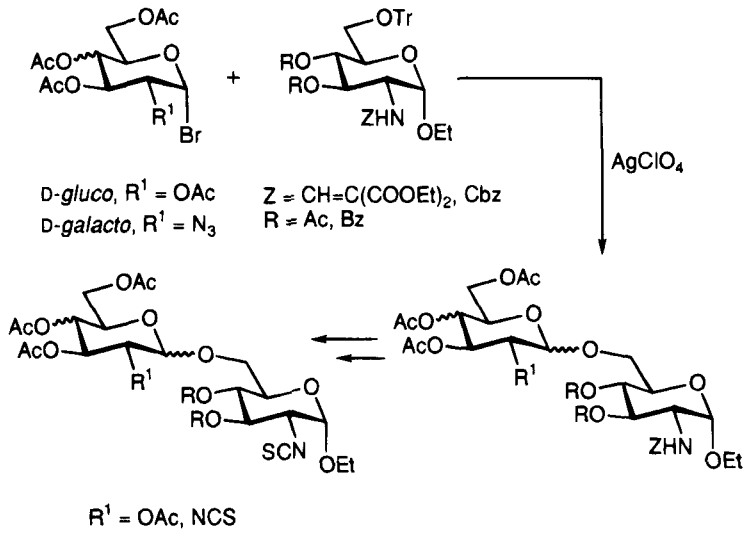
R = Me (α- and β-D-*gluco*, α-D-*galacto*, α-D-*manno*)
or sugar residue (trehalose, sucrose, α-, β-, γ-cyclodextrin)

SCHEME 13

The above results have been extended to the preparation of stable unprotected and *O*-protected sugar isothiocyanates of nonreducing oligosaccharides of economical and biological significance such as α,α′-trehalose, sucrose, and cyclomaltooligosaccharides (α-, β-, and γ-cyclodextrins).[61,62] It is noteworthy that no formation of intermolecular polymeric or cyclic thioureas, or other intramolecular reaction products, was observed during the reaction of the di- or polyamino sugars with thiophosgene, probably due to the rigid conformational bias of the carbohydrate molecules. Recently, the synthesis of 6^I-deoxy-6^I-isothiocyanatocyclomaltoheptaose and its use in the preparation of water soluble β-cyclodextrin derivatives and β-cyclodextrin-glycopeptide conjugates has been presented.[63]

Alternatively, oligosaccharide deoxyisothiocyanato sugars can be obtained through glycosylation reactions using suitably protected amino sugars as glycosyl donors or/and glycosyl acceptors. Using this synthetic strategy, the preparation of a series of ethyl (1→6)-linked 2-deoxy-2-isothiocyanato- and 2,2′-dideoxy-2,2′-diisothiocyanatoglycobiosides has been reported[39,64] (Scheme 14).

2.1.3. *Sugar-isothiocyanate Conjugates* An important family of sugar isothiocyanates comprises compounds in which the NCS group is not directly attached to a sugar carbon atom, but is located in a non-carbohydrate moiety covalently linked to the saccharide core. These compounds, which are valuable synthetic intermediates in the synthesis of sugar-protein conjugates, can be considered themselves as *neo*-glycoconjugates resulting,

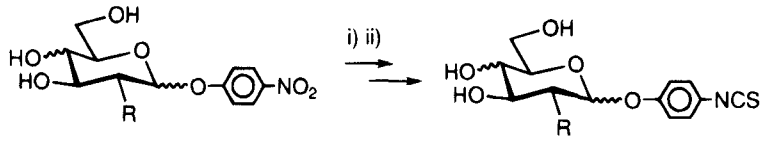


SCHEME 14

formally, from the coupling of a sugar moiety with an alkyl or aryl isothiocyanate, and will be referred to as sugar-isothiocyanate conjugates. The isothiocyanate segment of the molecule is usually called "handle" or "bridging arm" when such conjugates are generated as mere intermediates for the attachment of an oligosaccharide to a macromolecular carrier or a solid matrix.

In 1968, Buss and Goldstein[65] reported a synthesis of monosaccharide-phenyl isothiocyanate conjugates as convenient intermediates for the coupling reaction with proteins, by analogy with the well known use of phenyl isothiocyanate (Edman's reagent) in protein analysis. Crystalline *O*-glycosyl derivatives of 4-hydroxyphenyl isothiocyanate were readily obtained from commercially available *p*-nitrophenyl glycosides by catalytic hydrogenation of the nitro group and reaction of the resulting amine with thiophosgene in aqueous ethanol (Scheme 15). A similar reaction sequence starting from methyl 2-deoxy-2-(*p*-nitrobenzamido)-α-D-glucopyranoside led to a different type of sugar-isothiocyanate conjugate in which the phenyl isothiocyanate residue is not located in the aglycon.

Since this pioneering work, the isothiocyanate procedure has become one of the most popular methods for attaching oligosaccharides to proteins.[66–79] Several modifications have been introduced in order to (a)



i) H_2, cat.; ii) $CSCl_2$

SCHEME 15

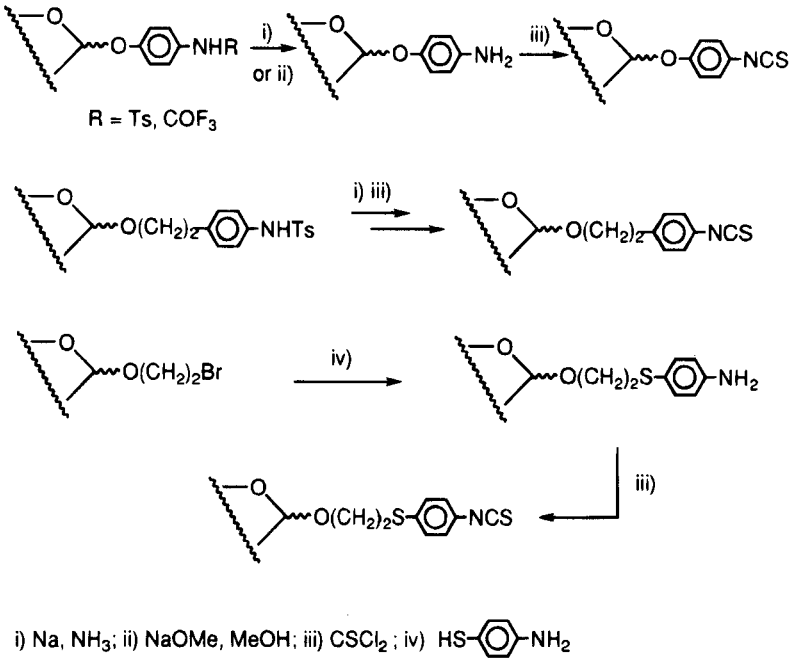
optimize reaction conditions, (b) facilitate the coupling between the oligosaccharide and the bridging arm, and (c) change the nature of the handle to control its immunogenic character.

The above commented reaction conditions for the preparation of isothiocyanate derivatives from aminophenyl glycosides are acidic (pH 2) and not suitable for use with acid-sensitive oligosaccharides (e.g. oligosaccharides containing deoxy sugar or sialic acid residues). Nevertheless, isothiocyanates may also be prepared under mild alkaline conditions (pH 8) that would not affect such labile glycosidic linkages. By using this technique, several 3-*O*-(3,6-dideoxyhexosyl)-α-D-mannopyranosyl—phenyl isothiocyanate conjugates related to the *O*-antigenic polysaccharide chains from *Salmonella* bacteria of different serogroups have been prepared.[80–83]

The final sugar-isothiocyanate conjugates are usually employed for protein conjugation without further characterization. In any case, the presence of the phenyl isothiocyanate group can be evidenced by the very characteristic IR broad band centered at 2130 cm^{-1}. Thin layer chromatography (13:8:2 $CHCl_3$/MeOH/H_2O) has proved very useful in both monitoring the reaction and identification of the *p*-nitro-, *p*-amino- and *p*-isothiocyanatophenyl glycosides of mono- and disaccharide derivatives.[84]

The choice of the arm and the mode of attachment to the sugar part of the conjugate depends mainly on the immunogenic requirements of the oligosaccharide to be coupled as a hapten to the protein. The formation of a glycoside stable enough to persist through the oligosaccharide synthesis, from which in a last synthetic step the reactive isothiocyanate functionality can be generated, presents the advantage that it fixes the ring size and the anomeric configuration of the sugar. In addition to the above commented *p*-nitrophenyl glycosides, other aglycons have been

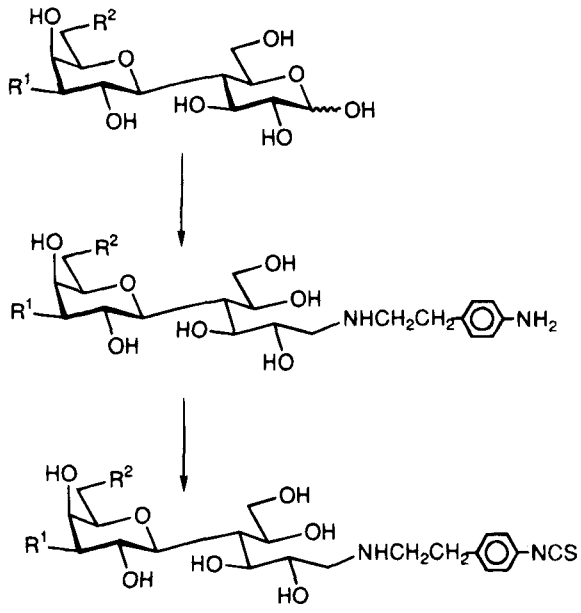
proposed such as 4-(*p*-toluenesulfonamido)phenyl,[76] *p*-trifluoroacetamidophenyl,[80–83] 4-(*p*-toluenesulfonamido)phenethyl[85,86] and 2-bromoethyl groups[87] (Scheme 16).



SCHEME 16

If one can sacrifice the terminal reducing sugar residue, which is usually the case for large haptenic oligosaccharides, reductive amination becomes an attractive coupling method owing to the mildness of the reaction conditions. Smith *et al.*[88] prepared 4-isothiocyanatophenethylamine derivatives of oligosaccharides via reductive amination with 4-aminophenethylamine using sodium borohydride. The isothiocyanation step was performed under reaction conditions compatible with the presence of sialyl and fucosyl subunits using thiophosgene at pH 8 (Scheme 17).

Similar derivatization procedures have been described by other authors. Sodium cyanoborohydride is preferred to sodium borohydride as reducing agent due to the fact that it reduces the Schiff base interme-

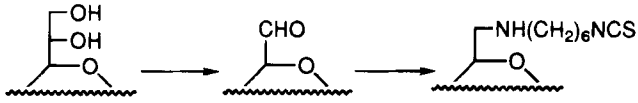


Starting oligosaccharide:
6'-sialyllactose: R^1 = H; R^2 = NeuAc-α-(2→)
3'-sialyllactose: R^1 = NeuAc-α-(2→); R^2 = H
lacto-*N*-difucohexaose I: R^1 = L-Fuc*p*-α-(1→2)-D-Gal*p*-β-(1→3)
[L-Fuc*p*-α-(1→4)]- D-GlcNAc*p*-β-(1→); R^2 = H
lacto-*N*-fucopentaose II: R^1 = D-Gal*p*-β-(1→3))[L-Fuc*p*-α-(1→4)]-
D-GlcNAc*p*-β-(1→); R^2 = H,

SCHEME 17

diate much more rapidly, thus preventing epimerization at C-2 via Amadori compounds.[68,72] *p*-Trifluoroacetamidoaniline[89,90] (TFAN) and 1,6-hexanediamine[91] have been also employed as bifunctional spacer arms after treatment of the adduct with thiophosgene. The latter spacer, which avoids the introduction of the immunogenic aromatic ring in the conjugate, has been coupled to reducing ketose residues of biological importance such as *N*-acetylneuraminic acid and 3-deoxy-D-*manno*-2-octulosonic acid, as well as to oligosaccharides having these terminal subunits. The (6-isothiocyanatohexyl)amino bridging arm has also been inserted into the core oligosaccharide of bacteria glycolipids allowing

further conjugation to BSA protein.[91] In this case, the isothiocyanate portion of the conjugate is linked to C-6 of a partially oxidized terminal heptosyl residue (Scheme 18).



SCHEME 18

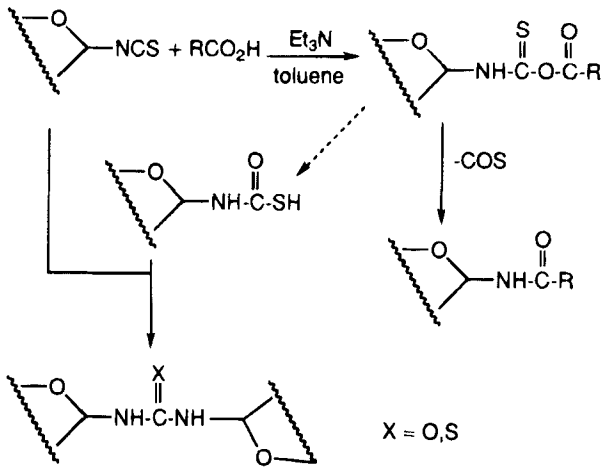
Several cellulose-isothiocyanate polyconjugates have been reported and characterized by their binding capacity with respect to amine and sulfur nucleophiles.[92–94] Functionalization occurred at the cellulose fiber surfaces and a variety of aromatic, aliphatic and mixed type spacers were used.

2.2. *Reactions of Sugar Isothiocyanates*

2.2.1. *Reactions with N-, O-, and S-nucleophiles* The reaction of sugar isothiocyanates with N-, O-, and S-nucleophiles bearing a labile hydrogen atom leads, at least in a first stage, to N-monosubstituted thiocarbamic adducts in which the electronegative residue is linked to the carbon atom of the heteroallene group. The resulting sugar thioureas, thiocarbamates or dithiocarbamates are of interest in view of their synthetic value, especially in the preparation of heterocyclic (N-nucleosides, N-glycosides) derivatives, as well as by the wide spectrum of biological activities of N-glycosyl and, in a more general approach, of N-(sugar radical) thiocarbamoyl derivatives. Nucleophilic addition of amino, hydroxy and mercapto groups to the NCS functionality also plays an important role in the conjugation of sugar isothiocyanates with biomolecules. The literature concerning this important aspect of sugar isothiocyanate reactivity has been partially discussed in several reviews.[2,4,72] The growing interest in these reactions is further corroborated by the wide number of new examples reported in the last decade. A detailed survey of these results has been included in Section 4.

2.2.2. *Condensation with Carboxylic Acids* The triethylamine-catalysed reaction of glycosyl isothiocyanates with carboxylic acids to give glycosylamides was first investigated by Khorlin *et al.*[104,105] and subsequently

applied[106] to the condensation with benzyl *N*-(benzyloxycarbonyl)-L-aspartate. The potentiality of this method in the construction of the D-Glc*p*NAcβ-(1→Asn) *N*-glycosidic linkage, analogous to that existing in natural *N*-glycoproteins, suffers from the simultaneous formation of undesired side products. The reaction proceeds through sequential addition-elimination as shown in Scheme 19. However, concomitant dissociation of the mixed dianhydride intermediate may occur resulting, after recombination with a second isothiocyanate molecule, in the formation of *N,N'*-bis(glycosyl)urea and thiourea. Nevertheless, yields higher than 70% of the desired glycosylamide can be achieved by working under strict exclusion of water and using 0.1 molar equiv of Et_3N, thus comparing advantageously with other *N*-glycopeptide synthetic methodologies.[107,108] These optimal reaction conditions have been recently applied to the preparation of trisaccharide-asparagine conjugates from the corresponding glycosyl isothiocyanates.[23,24]



SCHEME 19

The condensation of several glycosyl isothiocyanates with monomethyl nonanedicarboxylate has been analogously achieved.[96,109] The resulting glycosylamides were further coupled with 6^1-amino-6^1-deoxycyclomaltoheptaose with the aim to obtain receptor-bound systems with enhanced transport properties.

2.2.3. *Desulfurization Reactions* Desulfurization of glycosyl isothiocyanates with tributyltin hydride at room temperature in the absence of a free-radical initiator affords glycosyl isocyanides in 58–76% yield.[19] The outcome of the reaction may strongly depend on the reagent ratio and the presence of moisture, since formation of the corresponding glycosyl thioformamides has been reported by other authors[110] under, apparently, identical reaction conditions, as discussed in Section 3.1.

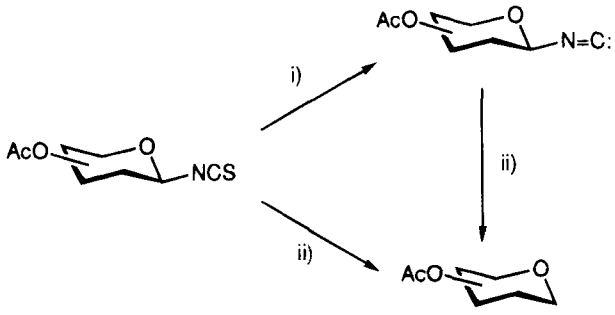
Under more strenuous conditions and in the presence of azobis(isobutyronitrile) (AIBN) as free-radical initiator, reduction of isothiocyanates led to the formation of 1,5-anhydroalditols, via glycosyl isocyanide intermediates, in virtually quantitative yield[19] (Scheme 20).

Hassel and Müller[111,112] have reported the preparation of glycosyl isocyanide dichlorides by chlorination of mono- and disaccharide peracetyl glycosyl isothiocyanates. Interestingly, via these highly reactive intermediates the isothiocyanate group can be transformed into a variety of other functionalities and heterocyclic derivatives, thus widening the already broad spectrum of synthetic applications of sugar isothiocyanates (Scheme 21).

2.3. *Spectroscopic Properties*

The main spectroscopic features of sugar isothiocyanates are the characteristic strong IR absorption and ^{13}C NMR chemical shift of the isothiocyanate functionality (ν_{NCS} and δ_{NCS}, respectively). The first one appears as a strong wide band in the range 2150–1990 cm^{-1} and has been extensively used both for structural confirmation and monitoring of reactions involving sugar isothiocyanate derivatives.[4] The second one is observed at 146–141 ppm for glycosyl isothiocyanates,[27,34–38,40,41,44] whereas it is upfield shifted by 10 ppm in the case of sugars bearing the isothiocyanate group at a primary carbon atom.[49,51–53,6] Secondary deoxyisothiocyanato sugars show the corresponding δ_{NCS} at an intermediate position, although it may be more sensitive to structural changes.[54]

Replacement of a hydroxyl group by an isothiocyanate group in a carbohydrate molecule additionally affects the ^{13}C resonance of the carbon atom directly attached to the heteroallene functionality, which is upfield shifted by 15 ppm as compared to the parent sugar or the corresponding *O*-protected derivatives. Analogously, the ^{1}H resonances of the α-located protons are upfield shifted by 1 ppm.[16,34,39,52–54,56,61,64] However, it must be stressed that similar spectroscopic characteristics may be present in the homologous



i) $^{n}Bu_3SnH$, Et_2O, r.t.; ii) $^{n}Bu_3SnH$, AIBN, toluene, reflux

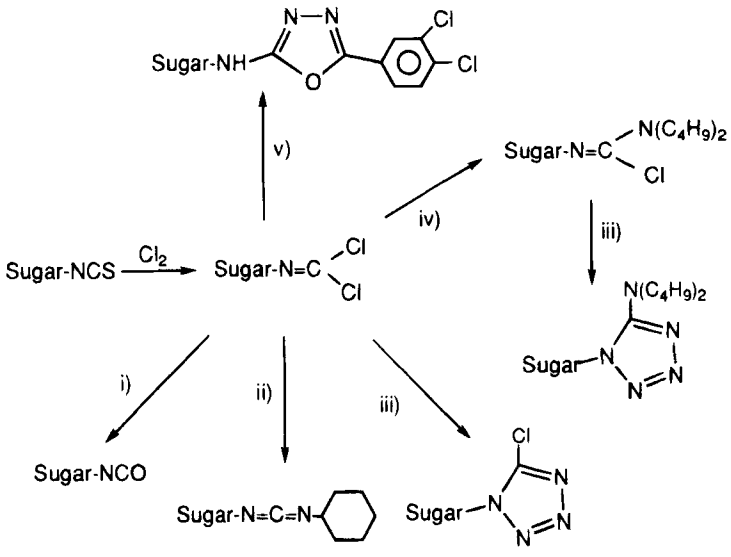
	Yield (%)	
	Isocyanide	1,5-Anhydroalditol
D-Glc*p*	76	89
D-Gal*p*	61	82
D-Glc*p*NAc	59	94
L-Ara*p*	69	85
D-Xyl*p*	58	82

SCHEME 20

amines or ammonium salts, thus becoming of poor diagnostic value when these derivatives are used as direct precursors of sugar isothiocyanates.

The UV spectra of acetylated sugar isothiocyanates show a low intensity absorption at 250–254 nm which allows UV detection in the course of chromatographic separations.[27,41,64] This band is frequently overlapped when stronger chromophores (e.g. benzoyl groups) are present in the molecule.[35–37,40]

The main primary fragmentation of glycosyl isothiocyanates in EI or GI mass spectrometry consists of loss of the NCS radical to give an oxocarbenium cation (*m/z* M - 58). The loss of thiocyanic acid (*m/z* M - 59) is also



i) $MeSO_3H$, chlorobenzene, 110 °C
ii) Cyclohexylamine, Et_3N, toluene, -20 °C
iii) NaN_3, DMF, r.t.
iv) Dibutylamine, toluene, -20 °C
v) 3,4-Dichlorobenzoylhydrazine, DMF, 0 °C

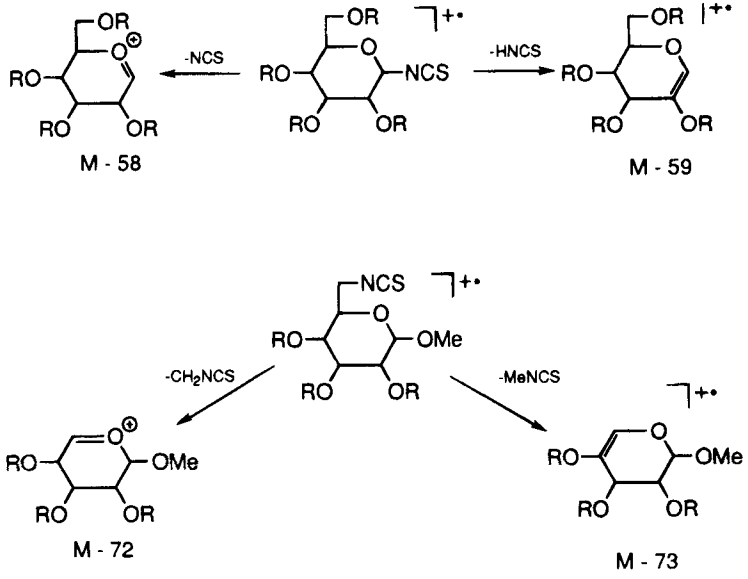
Sugar = peracetylated D-Glc*p*, L-Ara*p*, cellobiosyl

SCHEME 21

frequently observed, whereas the molecular peak is either absent or of very low intensity.[27,36,41,44,64] Significantly, EI mass spectra of peracetyl 6-deoxy-6-isothiocyanato glycopyranosides show intense molecular peaks and loss of CH_2NCS and MeNCS as the main primary fragmentation.[52,53] An analogous fragmentation pathway was observed in the FAB^+ mass spectra of the unprotected derivatives.[52] These data probably reflect the higher stability of deoxy-isothiocyanato sugars as compared to glycosyl isothiocyanates (Scheme 22).

2.4. *Biological Applications*

Fully unprotected glycosyl isothiocyanates have been used as affinity labels in biological studies dealing with active site determination of enzymes hav-



SCHEME 22

ing carbohydrates as putative substrates. Khorlin *et al.*[99,113] have reported the specific irreversible inhibition of sweet-almond β-glucosidase by β-D-glucopyranosyl isothiocyanate. Similarly, 2-acetamido-2-deoxy-D-glucopyranosyl isothiocyanate acts as specific irreversible inhibitor of human and boar *N*-acetyl-β-D-hexosaminidase.[31]

Langdon and coworkers[29,32,114] prepared D-glucosyl and maltosyl isothiocyanates in radioactive (^{14}C) form and applied them to the identification of the glucose transporter protein of the human erythrocyte membrane. Further re-examination of these results[33] showed, however, that the previous data were somehow suspect due to instability of the reagents. Thus, hexosyl isothiocyanates were almost completely destroyed after 10 min incubation at pH 8 and 37 °C.

6-Deoxy-6-isothiocyanato-D-glucose has also been proposed by Ramjeesingh and Khalenberg[50] as potential affinity reagent for the membrane protein of human erythrocytes involved in glucose transport. However, the spontaneous transformation of this isothiocyanate into a cyclic thiocarbamate derivative has also been reported.[52] In turns, the observation that stable, water soluble sugar isothiocyanates can be prepared

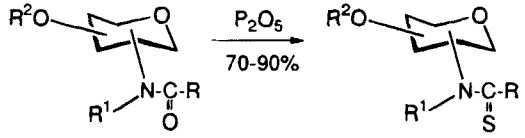
from aldopyranoside derivatives[52,61] may open new channels to their use as efficient labels in enzymological studies.

3. THIOCARBOXYLIC ACID DERIVATIVES

In spite of the long-known influence that replacement of oxygen by sulfur may have in the biological and chemical properties of a sugar molecule[115,116] and the impressive synthetic potential of thionocarboxylic acid derivatives,[12] only a few reports on the synthesis and reactivity of thioacylated carbohydrates appeared before 1985. Since then, the chemistry of this family of compounds has expanded significantly, especially in the last five years, and a rapid development must be expected in the near future fueled by the current biologial and synthetic applications.

3.1. *Sugar Thioamides*

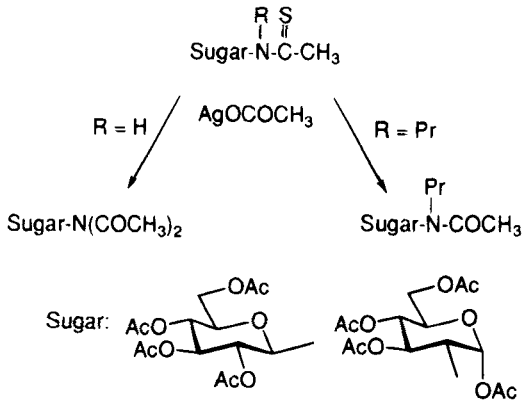
N-Thioacylated amino sugars have been classically obtained from the corresponding *N*-acyl compounds by replacement of oxygen by sulfur with phosphorus pentasulfide[117–121] (Scheme 23). This procedure seems of general applicability for *O*-protected carbohydrate derivatives regardless of the anomeric or non-anomeric character of the amide precursor and the nature of the thioacyl group.[122,123] Nevertheless, formation of bicyclic thiazolines as side products has been observed in the case of 1,2-*trans*-2-acylamido-2-deoxyglycosides.[120] Alternatively, *O*-protected sugar thioacetamides have been obtained by coupling a free amino group with dithioacetic acid in the presence of *N,N'*-dicyclohexylcarbodiimide,[124] and thioformamido derivatives have also been prepared by tributyltin hydride reduction of isothiocyanate precursors.[110]



R= H, Ac, Bz
R^1= H, alkyl
R^2= acyl, acetal, alkyl

SCHEME 23

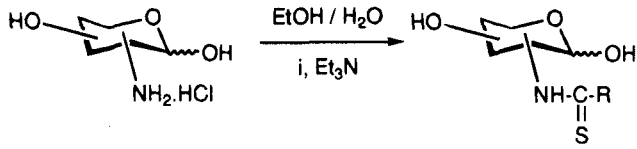
Unlike their oxo counterparts, thioacetamides are readily hydrolyzed under mild basic conditions such as methanolic ammonia, and this provides a convenient route for de-*N*-acetylation in compounds sensitive to strongly basic conditions such as nucleosides.[117,118] Selective *O*-saponification can be achieved with sodium methoxide,[120] whereas the *N*-thioacyl group can be removed in the presence of *O*-acetyl groups by *S*-methylation and subsequent mild acid hydrolysis of the thioimino ether intermediate.[119] Per-*O*-acetyl *N*-sugar acetamides have also been transformed into imides by reaction with silver acetate.[125] Under identical reaction conditions, *N*-alkyl aminosugar thioamides underwent CS→CO transformation to the homologous amides (Scheme 24).



SCHEME 24

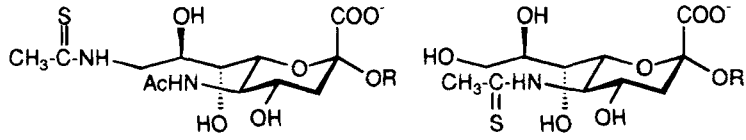
Brossmer and Isecke[126] have reported the direct thioacylation of fully unprotected amino aldoses by using *O*-ethyl thioformate, methyl dithioacetate, and methyl dithiopropionate as the thioacylating reagents. This methodology has been applied to 2-amino-2-deoxy-D-glucose, its 6-phosphate derivative, 2-amino-2-deoxy-D-galactose, and 2-amino-2-deoxy-D-mannose hydrochloride, and further extended to the preparation of thioamido derivatives of sialic acids[127] (Scheme 25).

The exchange of oxygen by sulfur in biologically active *N*-acylamino sugars leads to close analogs which, however, may show remarkable differences in their properties due to the greater bulk and polarizability of the sulfur atom and its decreased ability to form hydrogen bonds. Thus, 2-



i = H-C(=S)-OEt; Me-C(=S)-SMe; Et-C(=S)-SMe
R = H, Me, Et

e.g.:



SCHEME 25

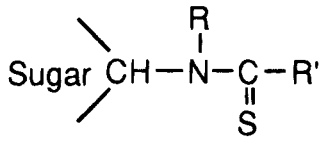
deoxy-2-thioacetamido-D-glucose and D-galactose glycosides are not hydrolyzed by 2-acetamido-2-deoxy-β-D-glucosidase from *Turbatrix aceti*, acting as competitive enzyme inhibitors.[120] An interesting example is the enzymatic synthesis of sialylated neoglycoproteins from C-9 and C-5 modified neuraminic acid derivates containing thioamido groups[127–129] (see Scheme 25). Such analogs have proved to be effective against infection by influenza viruses and promise to be powerful chemotherapeutic agents.

The well-known rotational isomerism of thioamides[130] has been studied in detail for monosaccharide derivatives bearing an thioacetamido substituent at a secondary or primary position.[122,123] As common features, formamido and *N,N*-disubstituted thioamides exist at room temperature as a mixture of unequally populated *Z* and *E* rotamers around the N—C(=S) bond. In contrast, exclusively the *Z* rotamer has been detected in the sugar-NH(C=S)R series for R other than H. In addition, several useful rules for configurational assignment in these compounds have been given on the basis of ^{1}H and ^{13}C NMR spectral parameters (Table 4).

3.2. *Sugar Thioesters and Thiolactones*

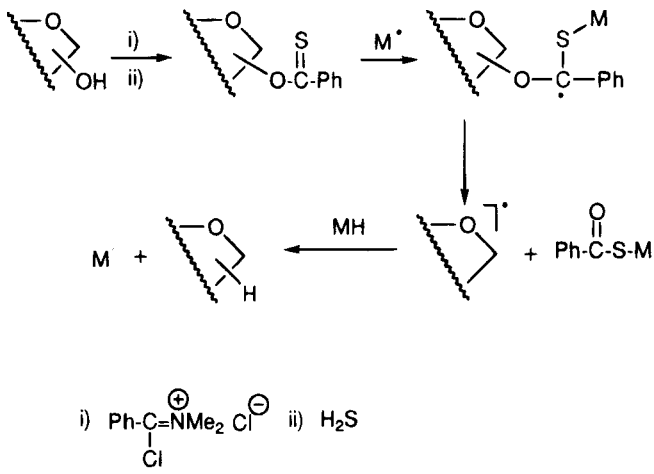
Albeit less popular than thiocarbamic or thiocarbonic *O*-sugar esters, thio-*O*-benzoates have also found application in the radical deoxygenation of carbohydrates under usual Barton-McCombie reaction conditions.[131,132] This method is based on the radical-trapping ability of the thiocarbonyl

TABLE 4 Spectral Parameter Relationships for *Z* and *E* Rotamers of Sugar Thioamides.



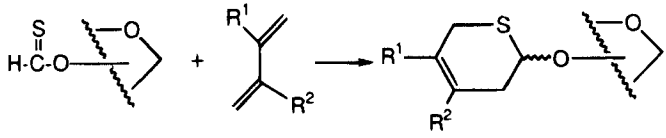
R = R′ = H	*R and/or R′ = alkyl*
$\delta_{H\ sugar}$ (*Z*) > $\delta_{H\ sugar}$ (*E*)	$\delta_{H\ sugar}$ (*Z*) > $\delta_{H\ sugar}$ (*E*)
$\delta_{C\ sugar}$ (*Z*) < $\delta_{C\ sugar}$ (*E*)	$\delta_{C\ sugar}$ (*Z*) < $\delta_{C\ sugar}$ (*E*)
$\delta_{C=S}$ (*Z*) < $\delta_{C=S}$ (*E*)	$\delta_{C=S}$ (*Z*) > $\delta_{C=S}$ (*E*)
δ_{CHS} (*Z*) > δ_{CHS} (*E*)	
$J_{NH,CHS}$ 5.0–6.1 Hz (*Z*)	
$J_{NH,CHS}$ 9.5–14.1 Hz (*E*)	

group, leading to an intermediate carbon radical which fragments into a sugar radical and an *S*-thiobenzoate as despicted in Scheme 26. In the presence of an H-donor, the corresponding deoxy sugar is formed. The driving force of the reaction could be the energy gained on going from thiocarbonyl to carbonyl. The starting thiobenzoates can be prepared in a very convenient manner under neutral conditions by treatment of *N,N*-dimethylbenzamide with phosgene, reaction of the resulting imidoyl chloride with the hydroxyl function, and further in situ treatment with hydrogen sulfide.[131]

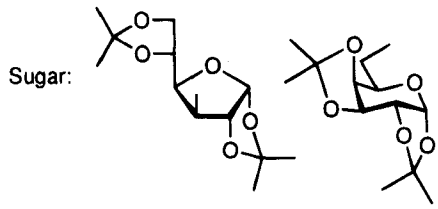


SCHEME 26

Thionoester and thionolactone derivatives of carbohydrates undergo nucleophilic and cycloaddition reactions to give stable thioacetals. Thus, Bognár *et al.*[133,134] reported the synthesis of thiosugar derived disaccharides by Diels-Alder reaction of sugar *O*-thioformates and buta-1,3-dienes (Scheme 27). The starting materials were obtained from the corresponding selectively protected monosaccharides by *O*-thioformylation following the imidoyl chloride procedure with *N,N*-dimethylformamide, phosgene and hydrogen sulfide.



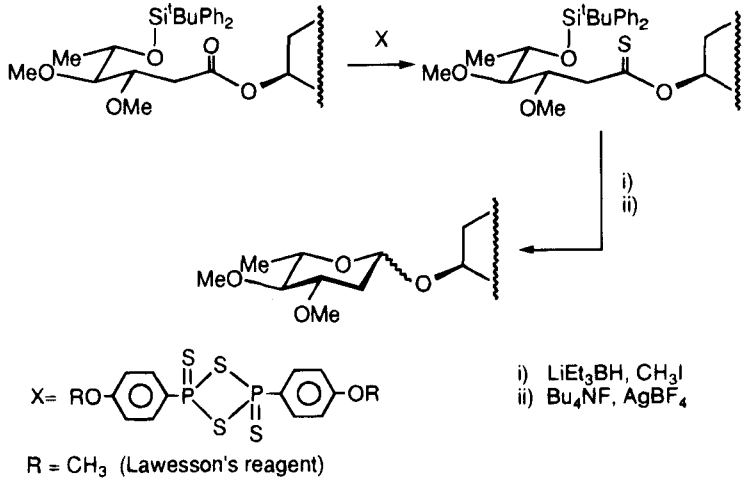
Diene: $R^1 = R^2 = H$; $R^1 = R^2 = Me$; $R^1 = Me_3SiO$, $R^2 = H$



SCHEME 27

Barrett *et al.*[135,136] have exploited the potential of thionoester chemistry in the so-called redox glycosidation strategy. This methodology relies on the ability of the thiocarbonyl group to undergo reductive methylation or desulfurization without cleavage of the masked glycosidic (thionoaldonic esters, Scheme 28) or aglyconic (thionoalduronic esters, Scheme 29) C–O bond. The thioester intermediates were prepared from the corresponding esters by thionation with Lawesson's[137] or Belleau's[138] reagent, the second one being generally more effective.

The unexpected formation of a thionoester derivative had previously been observed in the attempted radical *C*-allylation of a thioacylimidazole derivative in the presence of AIBN, presumably by addition of the 2-cyanopropyl radical at carbon, rather than sulfur, followed by scission of the imidazole moiety[139] (Scheme 30).

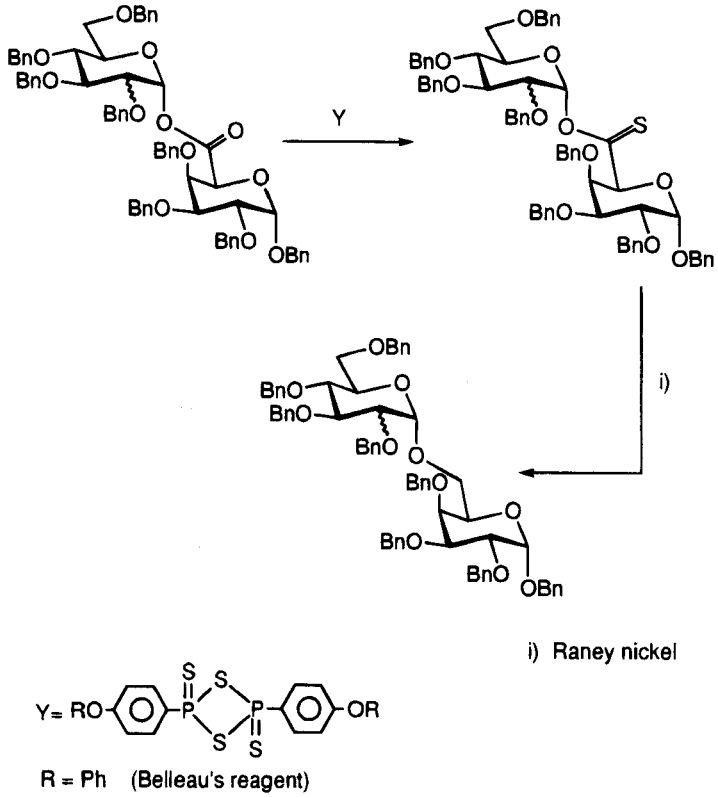


SCHEME 28

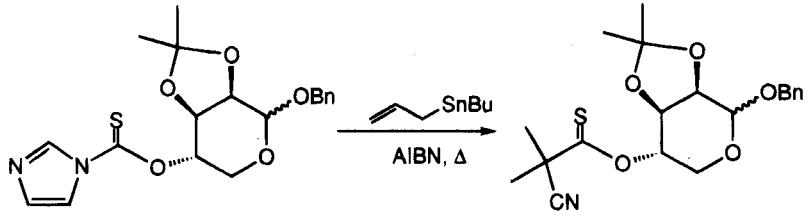
Glyconothio-*O*-lactones were first prepared by thionation of glyconolactone precursors with Lawesson's or Belleau's reagent.[136,140] The yield of the reaction appears, however, to depend upon the substrate and upon the presence of small amounts of impurity. Recently, Vasella *et al.*[141] reported an improved preparation of furanoid and pyranoid aldonothio-*O*-lactones by photolysis of *S*-phenacyl thioglycosides or by thermolysis of *S*-glycosyl thiosulfinates (Scheme 31). The reactivity of the resulting thiocarbonyl compounds towards nuclephiles and their potential as dienophiles in hetero-Diels-Alder reactions and [1,3]-dipolar cycloadditions allows a number of synthetic transformations including the preparation of *O*-, *S*-, and *C*-glycosides, spiroheterocycles and unsaturated derivatives[140–142] (Scheme 31). Additionally, five- and six-membered sugar thionolactones have been converted very efficiently into the corresponding cyclic ethers by radical desulfurization using tri-*n*-butyltin hydride as hydrogen radical donor.[143] The methodology relies upon the propensity of the thiocarbonyl functionality to suffer attack by tin-centered radicals.

4. THIOCARBAMIC ACID DERIVATIVES

The ability of the NCS group to undergo nucleophilic additions is the main characteristic feature of the chemistry of isothiocyanates. Taking into con-

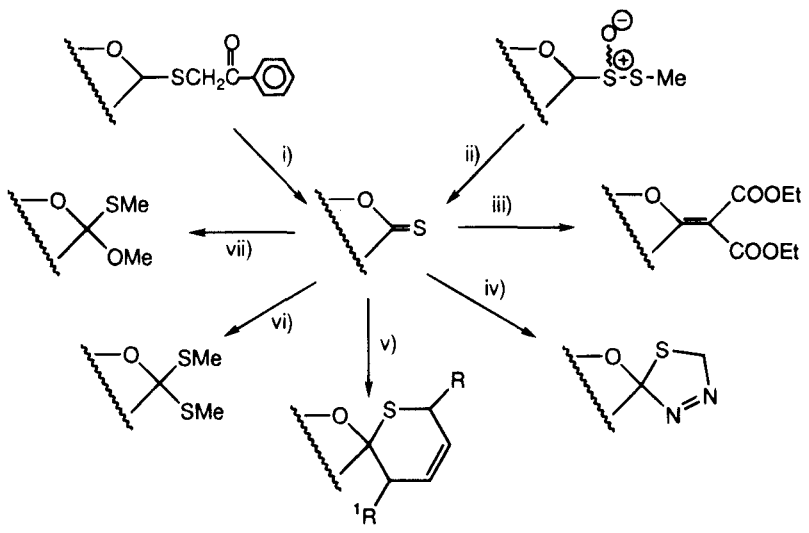


SCHEME 29



SCHEME 30

sideration that a carbohydrate molecule may contain several nucleophilic centers susceptible of selective manipulation, the corresponding thiocarbamic acid derivatives appear as very attractive synthetic intermediates. Either the condensation of sugar isothiocyanates with amines or alcohols



i) hv; ii) Δ 120 °C / 0.05 mbar; iii) $(EtO_2C)_2CN_2$; iv) CH_2N_2
v) diene; vi) MeI / MeLi; vii) MeI, MeOH

SCHEME 31

(see also Section 4.1.1.) or the reverse reaction of sugars or amino sugars with isothiocyanates give rise to the thiocarbamoyl functionality which, in turn, may act as a new reactive center capable to interact with other functional groups present in the molecule in a counterattack-type reaction.[144] The amalgamation of the chemistry of sugars with that of thiocarbamic acid derivatives has led to an extremely fertile research field which, apart from its synthetic potential, finds application in biological, biomedical, and technical areas.

4.1. *Sugar Thioureas*

Three reasons can be put forward, *inter alia*, to justify the growing interest in the synthesis and reactions of sugar thioureas: (a) the high mutual affinity of the functional groups put into reaction, i.e. isothiocyanate and amine, leading to well-defined, frequently crystalline, compounds of high stability, (b) the wide number of technical and biological applications of substituted thiocarbamide derivatives, and (c) the possibility to manipulate the adducts

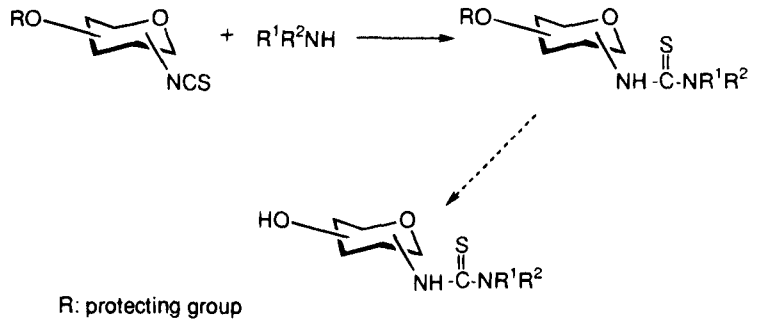
to yield heterocyclic compounds, including *N*-nucleoside and *N*-glycoside analogs. An additional reason is that many biologically active molecules and macromolecules contain amino groups which can be easily conjugated with a carbohydrate portion through thiourea bridges. Improvement of the water solubility and biocompatibility of pharmaceuticals, attachment of haptenic oligosaccharides to proteins, or the preparation of diastereomeric conjugates from enantiomeric mixtures for analytical purposes can then be achieved by relatively simple synthetic procedures.

4.1.1. *Condensation of Sugar Isothiocyanates with Amine Nucleophiles*

4.1.1.1. *Cyclocondensation Reactions* Many new reports have appeared on the reaction of sugar isothiocyanates with amino nucleophiles and, as a matter of fact, this is by far the main synthetic strategy whereby the reactivity of sugar isothiocyanates has been utilized. The condensation with ammonia in ether or ethanol has been generally used as a test for the reactivity of sugar isothiocyanates towards amino nucleophiles. Virtually quantitative transformations to the corresponding N-substituted thioureas are obtained either from glycosyl isothiocyanates[38,44] or deoxyisothiocyanato sugars.[59,145,146] No ammonolysis of acyl protecting groups has been observed under these conditions.

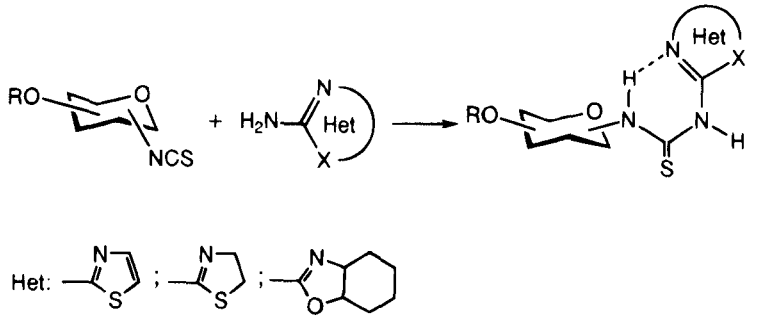
Analogously, primary and secondary amines add readily to the NCS functionality in sugar isothiocyanates to give di- or trisubstituted thioureas, respectively[14,45,46,146,147] (Scheme 32). The new examples reported include the preparation of antiviral,[148] antibacterial[149] and antitumor agents[20,149,150] by condensation of glycosyl isothiocyanates and biologically active amines such as triazole derivatives,[148] mitomycin,[149] isothiazolopyrimidines,[20] and platinum compounds.[150] Other *N*-nucleophiles such as hydrazine,[14] isothiourea,[151] and guanidine derivatives[152] have been similarly coupled to sugar isothiocyanates.

In connection with the interest in azole nucleosides as antineoplastic and antiviral compounds, several *N*-azolyl-*N'*-glycosylthioureas have been prepared by reaction of peracetylated glycosyl isothiocyanates or 2-deoxy-2-isothiocyanato-D-glucopyranose derivatives with heterocyclic amines.[153–155] The structures and conformational properties of these compounds have been the object of a complete spectroscopic (UV, IR, NMR and MS) study showing in many cases the existence of six-membered intramolecular hydrogen bonding in which the heterocyclic nitrogen atom

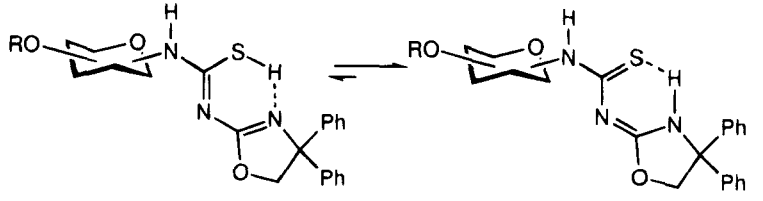


SCHEME 32

acted generally as acceptor and the sugar-NH as donor (Scheme 33). Notable exceptions are 4,4-diphenyloxazoline derivatives, which exist as tautomeric mixtures of thiourea and isothiourea derivatives with the thiocarbonyl and the thiol groups acting as hydrogen bond acceptor and donor, respectively[154] (Scheme 34).



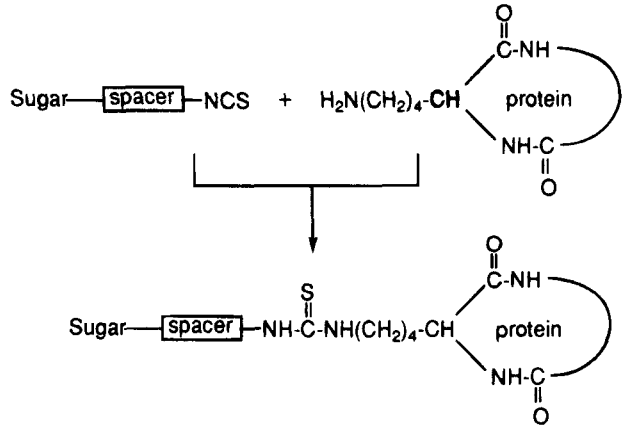
SCHEME 33



SCHEME 34

Proteins are by far the most important group of biologically active amino compounds. The growing awareness of the role that carbohydrate prosthetic groups of glycoproteins play in a wide array of recognition and binding phenomena has stimulated the preparation of non-natural conjugates among which thiourea-linked *neo*-glycoproteins have proved very convenient. Although some unprotected glycosyl isothiocyanates have been employed to label a glucose transport protein trough formation of the corresponding thiourea bridges,[29,30,32,33] sugar-isothiocyanate conjugates have been more generally used for this purpose (see Section 2.1.3.) because of their higher stability.[72,73,76,79] The major initial reaction that occurs under mild conditions at neutral or slightly alkaline pH is the formation of thiourea derivatives with terminal amino groups and with ε-amino groups of lysine residues (Scheme 35). Bovine serum albumin[79] (BSA), keyhole limpet hemocyanin[76] (KLH), immunoglobulin A[75] (IgA), human serum albumin[156] (HSA), R-phycoerythrin[78] and liposomal membrane fractions[77] have been used as the conjugated proteins, frequently labelled with fluorescein residues. This technique has allowed to raise antibodies against specific carbohydrate moieties and the investigation of biological phenomena related to the presence of oligosaccharide receptors in cell membranes.

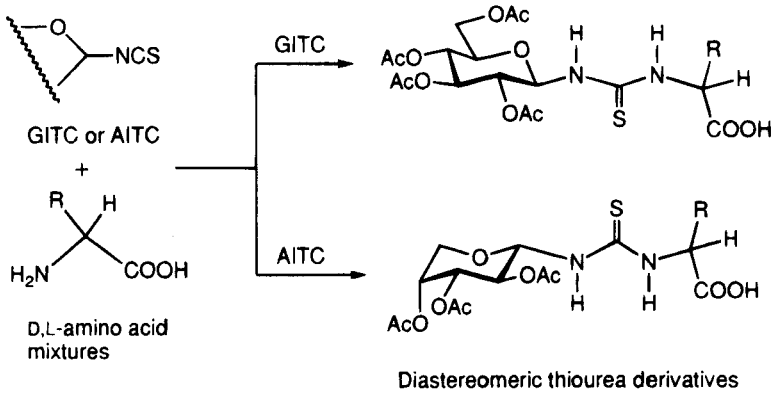
Gemeiner *et al.*[90,91] have used [^{14}C]glycine to check the binding capacity of cellulose isothiocyanates. Similarly, glycosyl isothiocyanates react



SCHEME 35

with amino acids and peptides to give *N*-(glycosylthiocarbamoyl)peptides which, in some cases, have shown immunoadjuvant and antitumor activities.[22]

The interest of this reaction for the chiral derivatization of amino acid enantiomers was already realized by Nimura *et al.*[157–159] in the early eighties. The preparation of diastereomeric derivatives using 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC) or 2,3,4-tri-*O*-acetyl -α-D-arabinopyranosyl isothiocyanate (AITC) as the chiral derivatization reagent (Scheme 36) allowed an excellent resolution of enantiomeric amino acid ethyl esters as well as of free amino acids using reversed-phase high-performance liquid chromatography (HPLC). The coupling reaction is complete in 20–30 min in mixtures of acetonitrile and water as the solvent and the reaction mixture can be injected directly into the chromatograph. Enantiomeric pairs were eluted in the order L before D when GITC was used and in the opposite order for AITC-amino acid thioureas. An alternative chromatographic analysis for GITC-derived D,L-amino acid diastereomers using a porous graphitic carbon (PGC) column has been recently proposed.[160]



SCHEME 36

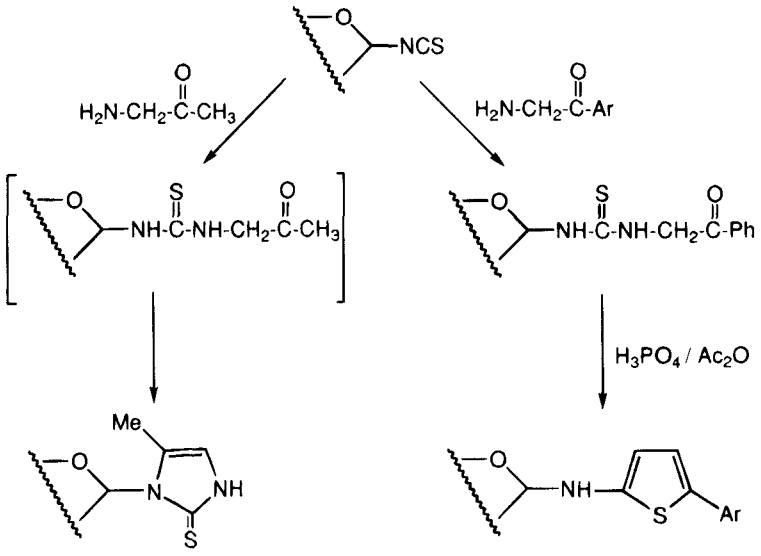
The same derivatization protocol has been applied to the optical resolution of other chiral physiologically active agents and pharmaceuticals containing amino groups such as catecholamines,[161] β-adrenergic antagonists,[162] adrenergic agents,[163–165] amphetamins,[166] and other amino alcohols,[167] thus illustrating the scope of GITC and AITC-diastereomeric

thioureas in HPLC analysis.[168] However, some analytical problems related with the presence of an unidentified reactive impurity in GITC, either commercial or home-made, have been pointed out.[169] Nevertheless, the side reaction could be completely eliminated by pretreatment of the reagent with another amine prior to the derivatization reaction.

The condensation of sugar isothiocyanates with suitable amino compounds carrying an electrophilic group results in sugar thioureas which, either spontaneously or after manipulation, yield heterocyclic compounds. The thiocarbonyl sulfur atom or one of the nitrogen atoms of the thiourea group may be involved in the heterocyclic ring closure, depending mainly on the nature of the electrophilic center. An interesting example is the reaction of acylated sugar isothiocyanates with α-amino carbonyl compounds. Condensation with α-aminoacetone[27,37,41,170–174] afforded directly 5-methyl-4-imidazoline-2-thione derivatives via transient β-oxo thioureas which, in some cases, could be isolated.[27] In contrast, the reaction with phenacylamines led to stable sugar thioureas[27,35–37,41,64,171–174] which were transformed into 2-amino-5-arylthiazole derivatives upon treatment with phosphoric acid in acetic anhydride[35,37,171–174] (Scheme 37). Obviously, in the first case the cyclodehydration step proceeds through nucleophilic addition of the sugar-bound nitrogen atom to the carbonyl group, whereas in the second case an enolic ester is probably displaced by sulfur in an S_N2 type reaction.

γ-Oxo thioureas have been similarly prepared by reaction of glycosyl isothiocyanates with β-amino carbonyl compounds and shown to exist as tautomeric mixtures of acyclic and cyclic compounds, i.e. 3-glycosyl-4-hydroxytetrahydropyrimidine-2-thione derivatives[175–177] (Scheme 38). Interestingly, these sugar thioureas acted as stimulants of non-specific resistance to infection, the stimulating action being independent of the carbohydrate component of the molecule and of the nature (aldehyde or ketone) of the aglycone.[177]

Although a rationalization of the ambident sulfur-versus-nitrogen nucleophilicity in thioureas is problematic, from the results available in the literature it appears that nitrogen is generally involved in nucleophilic addition to carbonyl groups, whereas cyclocondensations involving nucleophilic displacement generally proceed through sulfur. In agreement with that, the reaction of glycosyl isothiocyanates with 2-chloroethylamine yielded 2-glycosylamino-2-thiazolines[41,179–181] and not imidazoline-2-thiones as erroneously reported in a previous paper.[182] Eventually, the adduct may add to a second isothiocyanate to give *N,N,N'*-trisubstituted thioureas (Scheme 39).

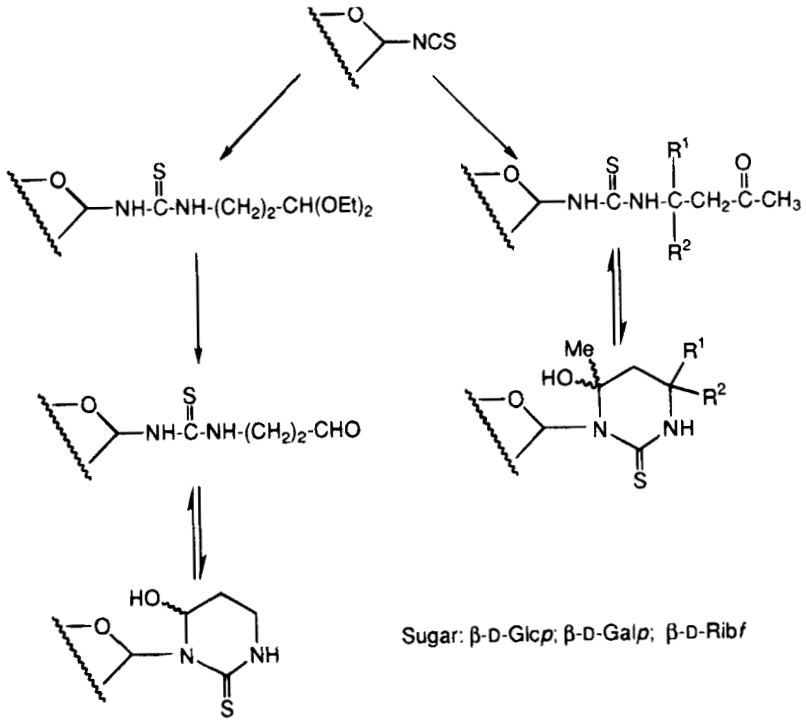


SCHEME 37

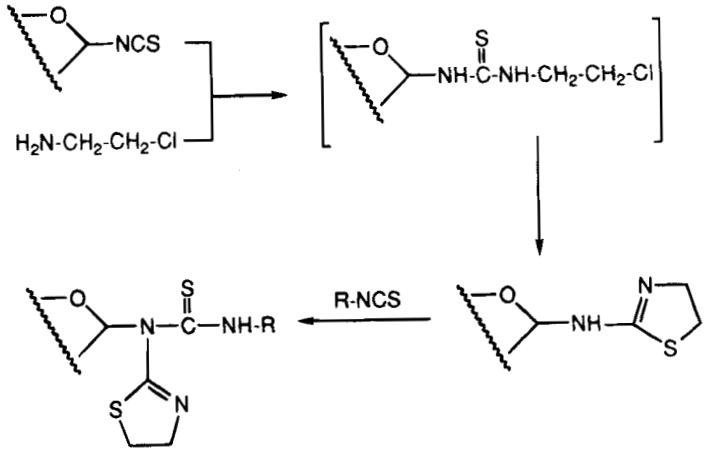
Glycosyl isothiocyanates have also been condensed with semioxamazide and the adducts cyclized by treatment with yellow mercury(II) oxide to the corresponding glycosylaminooxadiazole derivatives[183] (Scheme 40).

The attempted acid-catalysed cyclization of an *N*-(2-cyanoethyl)-*N'*-glycosylthiourea to the corresponding 5,6-dihydro-2-thiouracil *N*-nucleoside analog has been reported to be unsuccessful in contrast to what has been found for non-carbohydrate derivatives.[184] Instead, hydrolysis of the cyano group to the corresponding amide was observed.

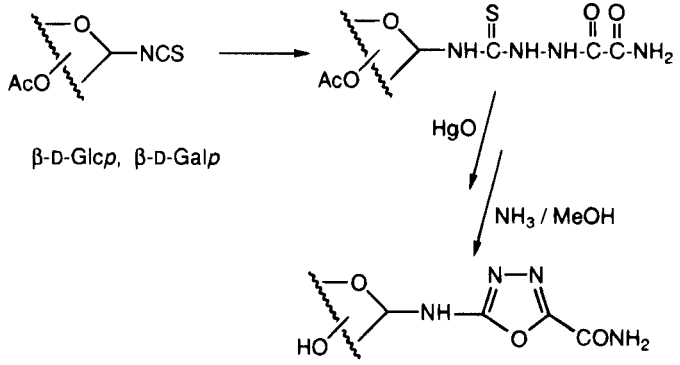
4.1.2. *Condensation of Amino Sugars with Isothiocyanates* Whereas fully unprotected glycosylamines react selectively with alkyl and aryl isothiocyanates in pyridine or *N*-methylpyrrolidine to give stable glycosylthioureas,[185,186] 2-amino-2-deoxy aldoses and the isomeric 1-amino-1-deoxy-2-ketoses undergo further cyclization entailing the acyclic carbohydrate form to give heterocyclic compounds (see Section 4.1.4.). After protection of the anomeric hydroxyl group, the corresponding thioureas were obtained.[147,187] Stable *N*-acyl thioureas have also been prepared from unprotected amino sugars and acyl isothiocyanates[187,188] (Scheme 41).



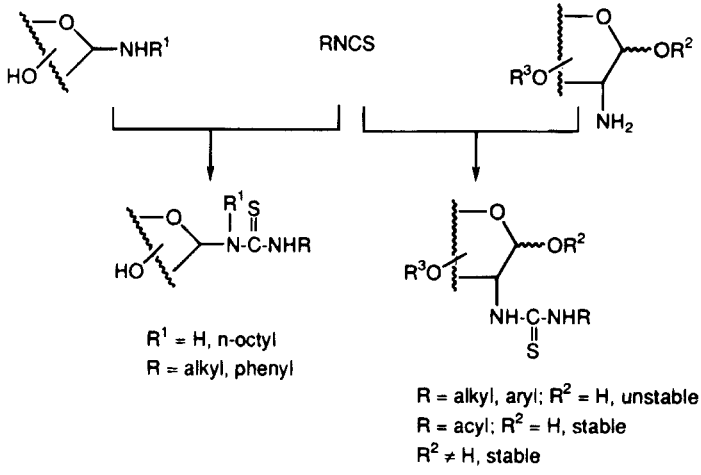
SCHEME 38



SCHEME 39



SCHEME 40



SCHEME 41

In spite of their above commented instability, the adducts resulting from condensation of 2-amino-2-deoxy-D-glucose and 2-amino-2-deoxy-D-galactose with phenyl isothiocyanate have been proposed for the quantitative determination of these amino sugars in glycoproteins.[189] The authors claim to have developed conditions to avoid further transformation, preserving the stability of the phenylthiocarbamoyl derivatives by quenching the reaction mixture with acetic acid-triethylamine buffer. Nevertheless, it must be

stressed that the structural characterization of the adducts was rather poor, and that the thiourea structure is improbable in view of the whole literature background on this and related condensations.[187,188] Alternatively, the amino sugars were reduced to the corresponding amino alcohols which after derivatization with phenyl isothiocyanate yielded stable thioureas.[189]

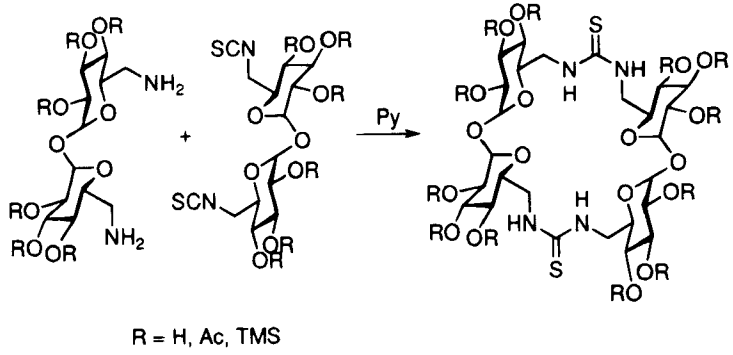
Fluorescein isothiocyanate has been used to introduce a fluorescent dye in carbohydrate derivatives bearing amino groups. The resulting fluorescein-labelled compounds were suitable for highly sensitive fluorometric assays allowing detection of lectins or saccharide-binding proteins. Several strategies have been proposed for the preparation of the amine precursors: reductive amination of reducing oligosaccharides,[190] copolymerization of allyl glycosides with allylamine and acrylamide,[191] incorporation of amine-containing spacers,[192] replacement of hydroxyl by amino,[193,194] or direct derivatization of amino sugars.[194] Particularly remarkable examples are the syntheses of thiourea-tethered fluorescein-tagged nucleotides[192] and sialic acid derivatives[193–198] which were enzymatically incorporated into DNA and oligosaccharide chains of glycoproteins, respectively.

4.1.3. *Condensation of Sugar Isothiocyanates with Amino Sugars* The reaction of *O*-acylated monosaccharide isothiocyanates with *O*-acylated amino sugars led to pseudodisaccharide derivatives in which both monosaccharide subunits are joined through a thiourea spacer.[4,34,48] The new examples reported include pentose, hexose, and heptose moieties linked to the thiourea bridge at the anomeric or at the C-2 position. Similarly, disaccharide isothiocyanates and related amino sugars have been combined in the preparation of *O*-protected pseudooligosaccharides containing a thioureylene group.[64] Condensations of acylated glycosyl isothiocyanates with unprotected amino sugars[199] and of sugar-isothiocyanate conjugates with aminopolyols[200] have also been recorded.

The main interest in this type of compounds stems from the structural analogy of the thiourea group with other groups of atoms such as phosphate or urea which appear in nature linking monosaccharide frameworks in biologically important compounds. The synthesis of thiourea analogs suitable for biological assays requires the deprotection of the hydroxyl groups in the adducts, something which has been found either unsuccessful or low yielding in the case of *O*-acyl derivatives, probably because of instability of the thiourea group under basic conditions. Alternative strategies have been proposed using

acetal,[60] trimethylsilyl[60,62] or trityl *O*-protecting groups[201] which can be easily hydrolyzed under mildly acidic conditions. The successful deacetylation of a 3′-*N*-[(β-D-glucopyranosyl)thiocarbamoyl]daunorubicin derivative by using sodium carbonate in water-acetone has also been reported.[202]

Recently, the condensation of 6,6′-dideoxy-6,6′-diisothiocyanato-α,α′-trehalose derivatives with their parent diamines was effected[62] (Scheme 42). The reaction afforded macrocyclic pseudotetrasaccharides possessing the complexing abilities characteristic of cyclic oligosaccharides (typically cyclodextrins) and the conformational adaptability of cyclic polyamides (typically cyclopeptides). The conformational properties of these and other sugar thioureas are discussed in Section 4.1.7.



SCHEME 42

Glycosyl isothiocyanates have also been allowed to react with unprotected 2-amino-2-deoxy aldoses and 1-amino-1-deoxy-2-ketoses.[203] This reaction leads to the formation of heterocyclic derivatives resulting from cyclization involving the carbonyl group of the amino sugar moiety following the mechanistic pathway discussed below for similar condensation reactions with alkyl and aryl isothiocyanates.

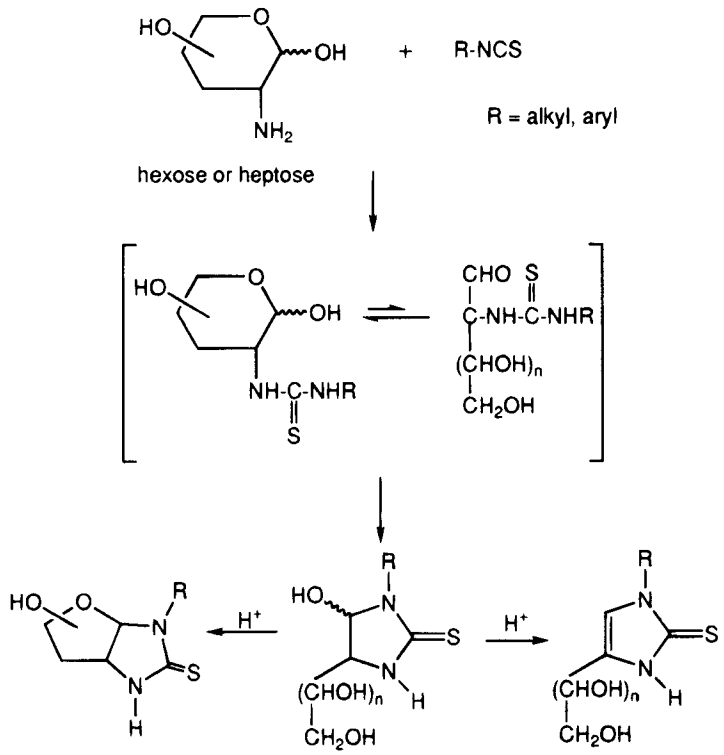
4.1.4. *Cyclization Reactions Involving the Carbohydrate Moiety* Reducing monosaccharides imply a masked carbonyl group which can actually act as the electrophilic target for counterattack reactions by thioureido substituents in a similar way to that discussed above for β- and γ-oxothioureas. As a matter of fact, the study of the reaction of unprotected amino

sugars with alkyl and aryl isothiocyanates started almost 100 years ago and has already been reviewed.[204]

The structures of the adducts resulting from the condensation of 2-amino-2-deoxy aldoses and 1-amino-1-deoxy-2-ketoses with isothiocyanates has been the subject of frequent controversy. The problem has been investigated by several Spanish groups in recent years with the aim to unequivocally establish the heterocyclic (mono- or bicyclic) nature of the reaction products by chemical and spectroscopic methods[205–212] as well as by X-ray diffraction.[213–215] Recently, the reaction mechanism has been positively identified by isolation of the early intermediates and their transformation into the final reaction products.[187,188] The reaction proceeds via transient thioureas which spontaneously undergo nucleophilic attack of a nitrogen atom at the sugar carbonyl group in the *aldehydo* or *keto* form. The resulting imidazolidine-2-thione derivatives, which in some cases were isolated,[187,188] can undergo either an acid-catalyzed intramolecular cyclization leading to bicyclic (aldoses) or spiro (2-ketoses) furanoid compounds or β-elimination to give imidazoline-2-thiones, the relative proportion of both isomers depending on the reaction conditions (Scheme 43). Remarkably, the kinetically unfavourable pyranoid bicyclic isomer has been obtained from 3,4,6-tri-*O*-acetyl-2-deoxy-2-(*N'*-phenylthioureido)-α-D-glucopyranose upon treatment with acetic acid.[187] It must be noticed that in this case formation of the furanoid bicycle is prevented by the acetyl group at O-4.

Similarly, 3-deoxy-3-thioureido aldoses, generated by trifluoroacetic acid-catalyzed deacetalation of isopropylidene derivatives, isomerized to the corresponding 4-hydroxytetrahydropyrimidine-2-thiones as the major tautomeric forms in aqueous solution[216] (Scheme 44). Further intramolecular glycosylation afforded bicyclic furanoid and pyranoid compounds, the outcome of the reaction depending on the reaction conditions and on the nature of the *N'*-substituent. In strong contrast, 6-deoxy-6-thioureido aldoses, obtained in a similar way, were stable compounds in the hemiacetal form of the sugar.[60]

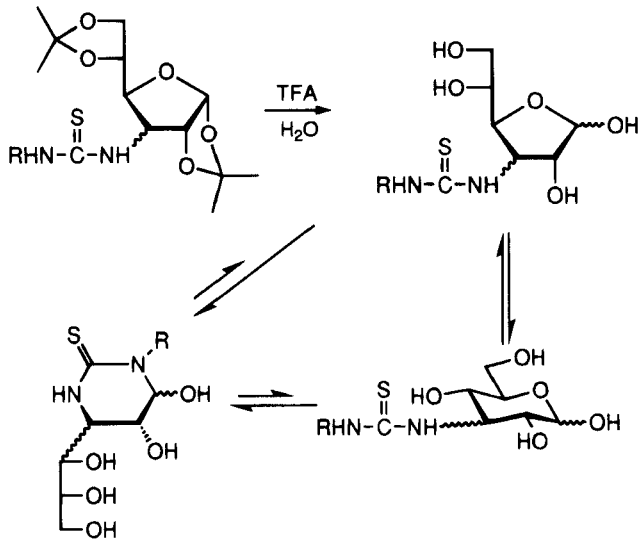
Per-*O*-acetyl-2-deoxy-2-thioureido aldopyranoses afforded *cis*-1,2-fused glycopyrano iminothiazolidinethiones upon treatment with tin(IV) chloride[187] or hydrogen bromide in acetic acid[45,147] (Scheme 45). The participation of the sulfur atom in the cyclization step likely involved nucleophilic displacement of the anomeric halide atom of glycosyl halide intermediates in an S_N2 type reaction, although an S_N1 mechanism via an



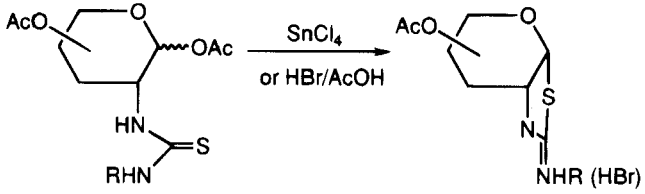
SCHEME 43

oxocarbenium cation is also possible. Analogously, 1,2-*trans*-2-deoxy-2-iodo glycopyranosylthioureas underwent nucleophilic displacement of iodine by the neighbouring thiocarbonyl sulfur atom to give bicyclic thiazolines.[44]

4.1.5. *Sugar Thioureas as Intermediates in the Preparation of Glycosidase inhibitors* The outburst of glycobiology in the carbohydrate field has stimulated the development of specific glycomimetics, i.e. analogs of sugars that mimic the structure and properties of carbohydrates, which could be used as glycoside hydrolase competitive inhibitors. All these compounds have in common a somehow flattened carbocyclic or heterocyclic structure that resembles the glycosyl cation. In this context, sugar thioureas have proved very convenient as synthetic intermediates allowing introduction of a planar amidine portion.



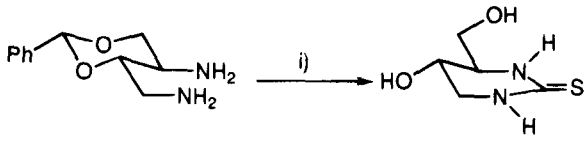
SCHEME 44



SCHEME 45

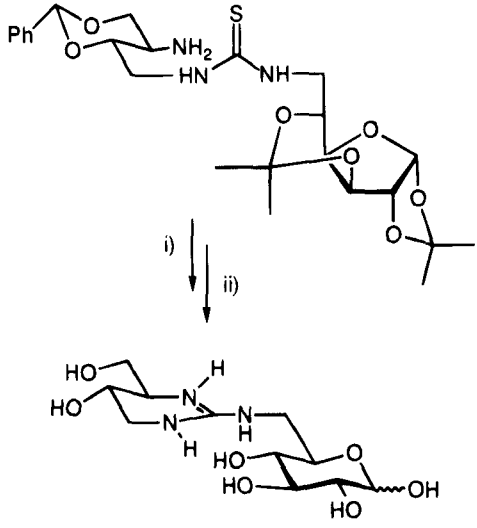
Lehmann *et al.*[217] reported the preparation of a glucomimetic containing a thiourea functionality by reaction of 1,3-diamino-2,4-*O*-benzylidene-1,3-dideoxy-D-erythritol with 1,1′-thiocarbonyldiimidazole and further deprotection (Scheme 46). This compound, although a very weak enzyme inhibitor, showed a high specificity for almond β-glucosidase. The transformation of the thiourea group into a guanidine group has recently been reported by other authors.[218]

Alternatively, cyclic guanidinium glycomimetics have been obtained from acyclic γ-amino thioureas upon treatment with lead(II) oxide.[219] This strategy has been extended to the synthesis of disaccharide analogs from mixed *N*-aminoalditol-*N*′-aldose thioureas[220] (Scheme 47).



i) 1,1'-thiocarbonyldiimidazole; 20% AcOH, 70°C

SCHEME 46

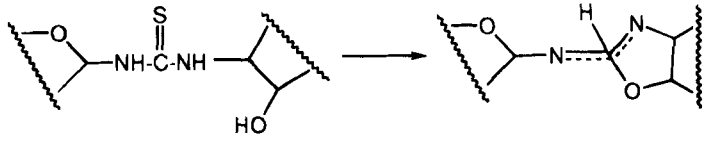


i) PbO, EtOH. ii) 50% TFA

SCHEME 47

An impressive number of papers has appeared in the last three years based on the use of sugar thioureas as intermediates in the synthesis of the naturally occurring potent trehalase inhibitor trehazolin and of several isomers.[26,42,56,221-226] The key reaction step involved the cyclization of the thiourea with participation of a β-located hydroxyl group to generate an aminooxazoline system (Scheme 48). Either mercury(II) oxide or 2-chloro-3-ethylbenzoxazolium tetrafluoroborate promoted the desired transformation.

4.1.6. *Miscellaneous Reactions of Sugar Thioureas* The thiourea group of linear or cyclic sugar thioureas can be transformed into other functional



SCHEME 48

groups including urea,[59,227,228] isourea,[207,211,212,229] carbodiimide,[56,224,225] and guanidine analogs[152,201,218–220] by classical standard procedures, thus opening a versatile route to a variety of other sugar derivatives.

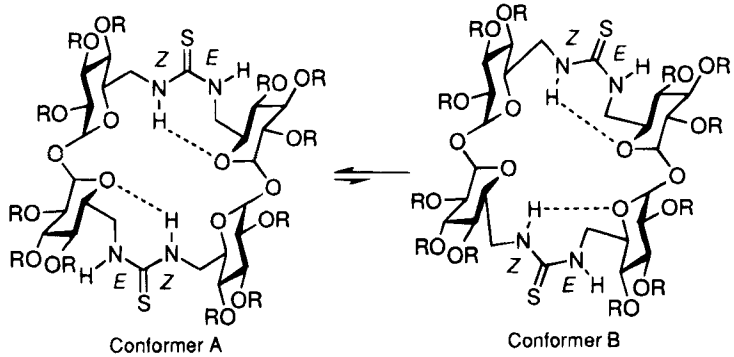
4.1.7. *Spectroscopic and Conformational Properties of Sugar Thioureas*
The more characteristic spectroscopic features of sugar thioureas are the well-known UV π-π^* absorption at 252–256 nm for monosubstituted derivatives[38,145] and at 242–247 nm for *N,N'*-disubstituted compounds[45,147,148] as well as the ^{13}C NMR chemical shift of the thiocarbonyl carbon atom at 180–185 ppm.[38,45,145,147]

The electron impact mass spectra of glycosylthioureas presented three basic groups of ions that were analytically significant: (a) rupture of the glycosidic sugar—NH bond, (b) cleavage of the sugar NH—C(=S) bond, and (c) cleavage of the C(=S)—NH aglycon bond.[154,155]

Similarly to thioamides (see Section 3.1), sugar thioureas may exhibit rotational isomerism about both NH—C(=S) bonds. Dynamic NMR studies have shown that derivatives bearing the thiourea group at a secondary carbon atom in a rigid pyranose framework exist exclusively in the sugar NH—C(=S) low energy, *Z*-configuration.[48,64,122] In strong contrast, both *Z* and *E* rotamers were found when the thioureido substituent was located at a methylene group, resulting in much more complex ^1H and ^{13}C NMR spectra.[145] These results have been rationalized on the basis of a stabilization of the *E* rotamers by seven-membered NH···O intramolecular hydrogen bonding. This hypothesis was supported by temperature coefficient measurements for the ^1H NMR chemical shifts of the NH protons as well as rotational barrier calculations.

Analogously, temperature variable NMR experiments showed the existence of a rotational equilibrium in macrocyclic derivatives containing two thiourea bridges, its position being dependent on the nature of the hydroxyl protecting groups[62] (Scheme 49). The involvement of the seven-membered ring hydrogen bond in the stabilization of the *E*-rotamers has been

further supported by designing rigid models allowing or disallowing its formation. In the first case, a *Z,E* rotameric equilibrium was observed, whereas exclusively sugar-NH—C(=S) *Z*-rotamers were present when this stabilizing interaction was prevented.[146]



R= H, Ac, TMS

SCHEME 49

4.2. *Sugar Thiocarbamates*

Originally prepared by reaction of sugar isothiocyanates with alcohols,[1] the chemistry of sugar derived thiocarbamic esters was initially much less developed than that of the above discussed thiocarbamides.[4] The reasons are mainly related with the low nucleophilicity of the hydroxyl group as compared to the amino group. Although isothiocyanates react with alkoxide anions, the reaction is reversible due to the instability of the resulting monothiourethanes in alkaline solutions.[7]

This situation significantly changed when Barton and McCombie conceived their radical deoxygenation of hydroxyl groups via thiocarbonyl esters.[131] Many examples of the application of this procedure in the carbohydrate field, involving thiocarbamate derivatives, can actually be found in more general reviews.[6,231–233]

It is remarkable that the only known examples of natural products embodying a thiocarbamate moiety are mustard oil glycosides derived from L-rhamnose.[234,235] These thiocarbamate glycosides, namely niazimin A

and B, niacimizin, and niaziminin A + B, isolated from fresh leaves of *Moringa oleifera*, are probably formed by addition of ethanol or methanol to sugar-isothiocyanate conjugates which occur in the plant, and possess a high hypotensive activity.

According to the position of the sugar residue with respect to the thiocarbamate segment, three types of thiocarbonyl-containing sugar thiocarbamates will be considered in the following discussion: *N*-sugar thiocarbamates, *O*-sugar thiocarbamates, and intramolecular cyclic thiocarbamates.

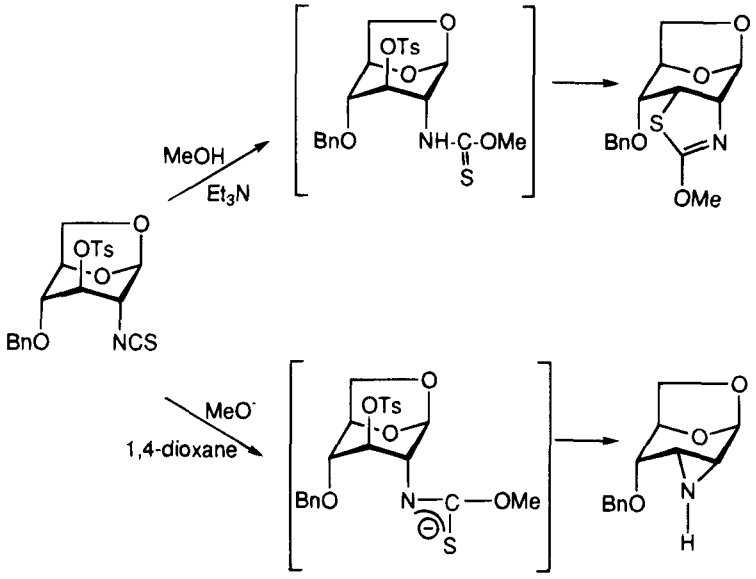
4.2.1. *N-Sugar Thiocarbamates* The reaction of sugar isothiocyanates with simple alcohols has been used as a tool for structure confirmation.[16] It requires the use of a large excess of the alcohol and reflux to shift the reaction to the desired thiourethane.

Elbert and Cerny[59] have reported the condensation of 1,6-anhydro-4-*O*-benzyl-2-deoxy-2-isothiocyanato-3-*O*-*p*-toluenesulfonyl-β-D-glucopyranose with methanol. The presence of a good leaving group vicinal to the thiocarbamate functionality resulted in spontaneous cyclization, the outcome of the reaction being strongly dependent on the reaction conditions. Thus, with sodium methoxide in 1,4-dioxane, the reaction involved the nitrogen atom to give an epimine as the sole product. In contrast, with methanolic triethylamine, a bicyclic thiazoline was obtained (Scheme 50).

Conformational properties of sugar thiocarbamates have never been reported. Nevertheless, comparison of the NMR spectral parameters for ethyl *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiocarbamate with those for *E* and *Z* thioformamides suggested that this compound exists in the exclusive *Z* configuration at the sugar NH—C(S) bond.[122]

4.2.2. *O-Sugar Thiocarbamates* The kinetics of the reaction of hydroxyl groups of monosaccharides, oligosaccharides, and polyols with benzyl isothiocyanate has been checked by Augustín and Baláz using UV spectroscopy.[236] However, due to the reversibility of the reaction, this procedure is not of synthetic utility. O-Sugar thiocarbamates have been more conveniently obtained by aminolysis of thiocarbonate derivatives[237,238] or by thiocarbamoylation of free hydroxyl groups with 1,1′-thiocarbonyldiimidazole.[6,231–233]

The main synthetic utility of *O*-sugar thiocarbamates is the aforementioned radical deoxygenation of secondary hydroxyl groups (see also Section 3.2), the driving force of the reaction being the formation of a ther-

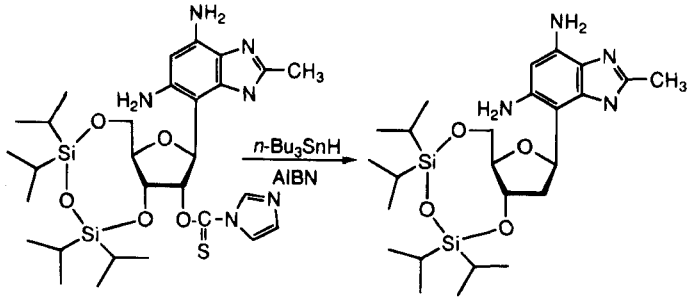


SCHEME 50

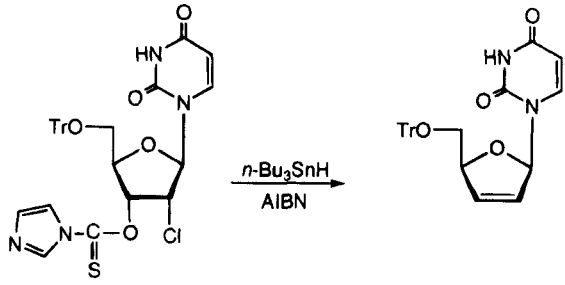
modynamically more stable *S*-thiocarbamate. Several reports on the use of this methodology for the synthesis of deoxynucleosides[245–247] as well as their carbocyclic analogs[248,249] are on record. It is worth mentioning that, unlike other procedures which involve an ionic mechanism, this radical process is not subject to steric hindrance or electrostatic repulsions. Although *N,N*-diethylaminothiocarbonyl derivatives were originally employed,[239,240] the *O*-(imidazolylthiocarbonyl) analogs have proved more efficient.[6,231–233,241–244] A particularly interesting application which shows the compatibility of the methodology with the presence of other functional groups is the synthesis of 2′-deoxyadenosine derivatives[250] as depicted in Scheme 51.

Thioacylimidazole esters have been found, however, less effective than thionocarbonates and xanthates in promoting radical *C*-allylation, even in the presence of α,α′-azobis(isobutyronitrile) (AIBN) as initiator.[139]

In the case of vicinally disubstituted sugars with a pair of radical leaving groups, e.g. thiocarbamate and halogen, treatment with tri-*n*-butyltin hydride and AIBN led to the corresponding unsaturated derivatives in high yield without observed side products[251] (Scheme 52).



SCHEME 51

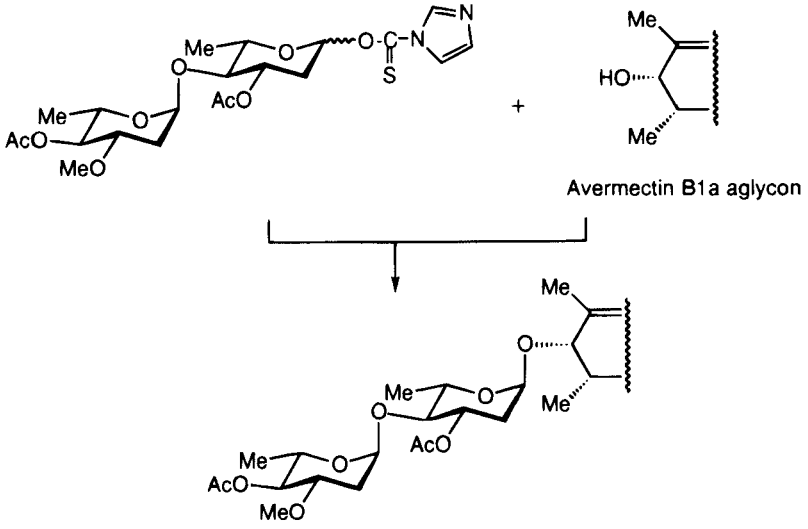


SCHEME 52

Ley *et al.*[252,253] have investigated the use of glycosyl imidazolethiocarbamates as glycosyl donors using silver perchlorate as promotor. The method was successfully applied to the total synthesis of avermectin B1a (Scheme 53).

4.2.3. *Intramolecular Cyclic Thiocarbamates* The long-known[254] condensation of reducing sugars with thiocyanic acid to give oxazolidine-2-thione derivatives has been re-examined by Grouiller *et al.*[255] for D-fructose. Reaction of D-fructose with KSCN and 10 M HCl afforded a mixture of the β-D-pyranose 2,3-bicyclic thiocarbamate (major) and the β-D-furanose isomer (Scheme 54). The latter was further desulfurized with Raney nickel and transformed to an N-nucleoside analog.

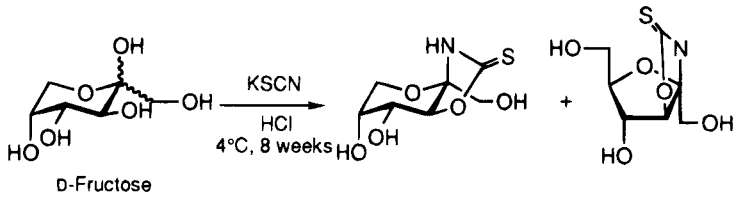
This reaction probably involves the corresponding fructosyl isothiocyanates which undergo nucleophilic attack by the neighbouring OH-3



Acetyl Avermectin B1a (62%) + β-anomer (11%)

i) $AgClO_4$, K_2CO_3, THF/ toluene

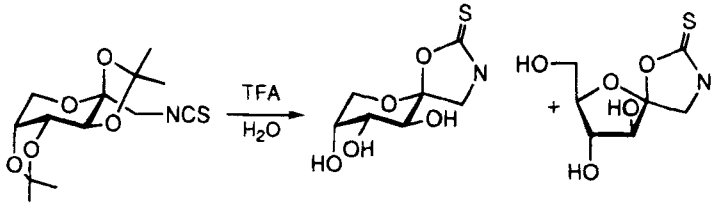
SCHEME 53



D-Fructose

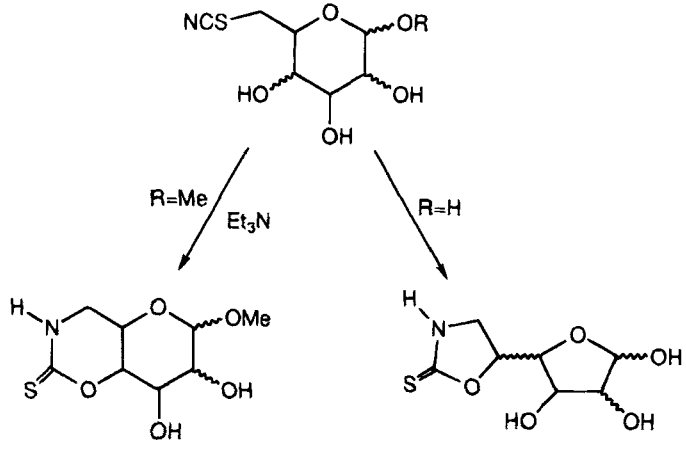
SCHEME 54

group. A similar mechanism was set forth for the formation of spiro five-membered cyclic thiocarbamates upon reaction of 1-amino-1-deoxy-D-fructose with carbon disulfide at 75 °C.[256] Indeed, the same spiro compounds were obtained when 1-deoxy-1-isothiocyanato-D-fructose was unequivocally generated from the 2,3:4,5-di-*O*-isopropylidene derivative[53] (Scheme 55). A further isomerization to an open-chain *S*-thiocarbamate was observed when longer reaction times or higher temperatures were used.



SCHEME 55

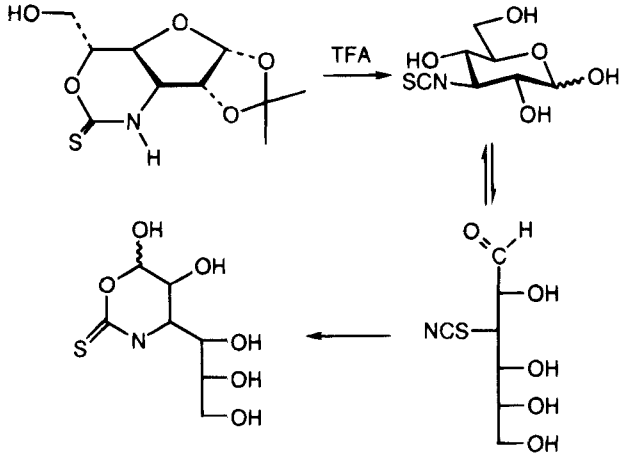
The spontaneous cyclization reaction of sugar isothiocyanates possessing a β-located free hydroxyl group in *cis* relative disposition has been found to be a general method to prepare enantiopure five-membered cyclic thiocarbamates.[51,52,54] Analogously, γ-hydroxy isothiocyanates have been transformed into the corresponding six-membered analogs (tetrahydro-1,3-oxazine-2-thione heterocycles) in the presence of a catalytic amount of base. In the case of reducing compounds, the reaction always proceeded through the tautomeric form leading to the oxazolidine-2-thione heterocyclic system (Scheme 56). Similar results were obtained when the fully unprotected amino sugar precursors were directly treated with thiophosgene, although kinetic studies suggested the involvement of a more reactive chloroformate intermediate in this case.[52,54]



D-*gluco*, D-*galacto*, D-*manno*

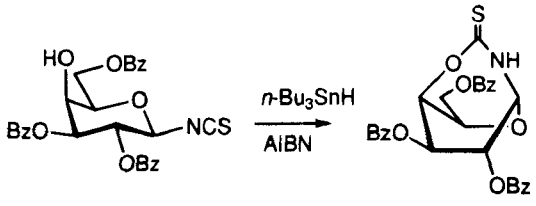
SCHEME 56

The unexpected reversion of 3-amino-3-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose 3,5-(cyclic thiocarbamate) to 3-deoxy-3-isothiocyanato-D-glucose on deacetalation has been noticed,[54] probably due to the sterically unfavourable six-membered—five-membered fused bicyclic arrangement. In the absence of a *cis* hydroxyl group either in the pyranose or in the furanose forms, the isothiocyanate underwent intramolecular condensation with the carbonyl group through the open-chain tautomer (Scheme 57) to give a 6-hydroxytetrahydro-1,3-oxazine-2-thione derivative.



SCHEME 57

The formation of a seven-membered thiocarbamate ring system has also been observed, although in low yield, during the attempted reduction of a selectively protected β-D-galactopyranosyl isothiocyanato derivative having a free hydroxyl group at C-4 (Scheme 58).



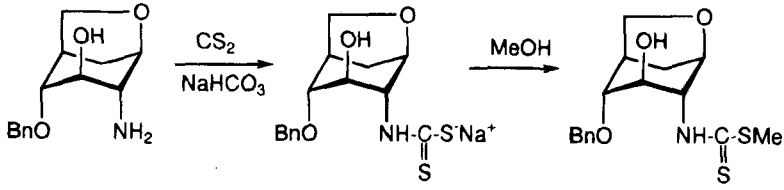
SCHEME 58

Recently, Pintér *et al.*[257] have reported the use of the known 1,2-(cyclic thiocarbamate) derived from α-D-glucofuranosylamine as starting material in the synthesis of cyclic isoureas by *S*-*p*-chlorobenzylation and subsequent nucleophilic displacement of the *p*-chlorobenzylthio group with morpholine.

4.3. *Sugar Dithiocarbamates*

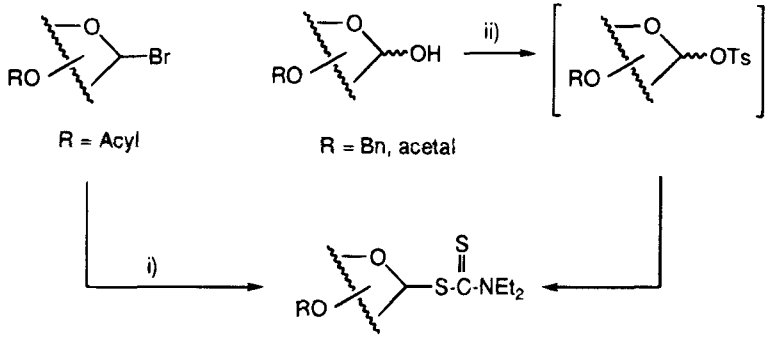
4.3.1. *N-Sugar Dithiocarbamates* The reaction of isothiocyanates with thiols is, in general, impractical for the preparation of dithiocarbamates since *N*-monosubstituted derivatives readily decompose into the starting materials. Nevertheless, the method is synthetically useful in the case of aryl isothiocyanates. Thus, cellulose-isothiocyanate conjugates containing an aromatic NCS group exhibited a substantial thiol-binding capacity which was absent for isohiocyanates with non-aromatic spacers.[93,94]

A valuable alternative for the preparation of *N*-sugar dithiocarbamates is the reaction of a sodium dithiocarbamate salt, obtained from the condensation of an amino sugar with carbon disulfide, with excess alcohol[59] (Scheme 59).



SCHEME 59

4.3.2. *S-Sugar Dithiocarbamates* *S*-Glycosyl *N,N*-dialkyldithiocarbamates have attracted attention because of the known fungicidal, insecticidal, and anticarcinogenic properties of related dialkyldithiocarbamates. The classical synthetic methodology for their preparation involves the reaction of an *O*-acyl protected glycosyl bromide with the sodium salt of a dialkyl dithiocarbamate[258] (Scheme 60). An original approach developed by Szeja and Bogusiak,[259] specially suited for acetal and benzyl protecting groups, involves *in situ* generated glycosyl tosylates under phase transfer conditions (Scheme 60).



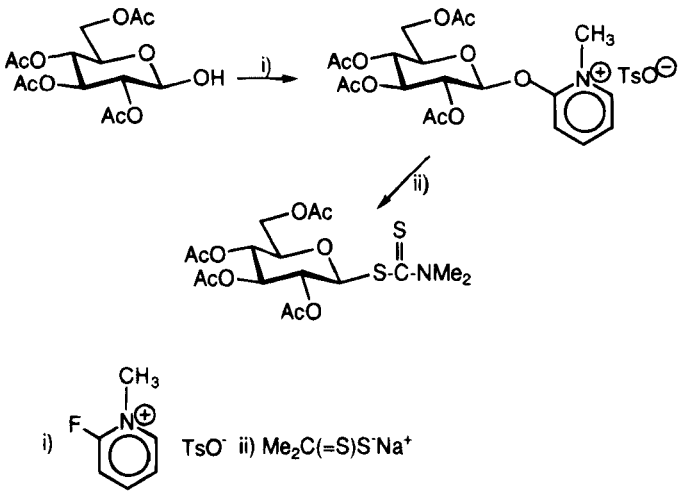
i) $Et_2C(=S)S^-Na^+$; ii) i, TsCl, n-$Bu_4N^+Cl^-$, C_6H_6, 50% NaOH

SCHEME 60

Mention should also be made of the application of Mukaiyama's methodology to the synthesis of *S*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl) *N,N*-dimethyldithiocarbamate.[260] The reaction of 2,3,4,6-tetra-*O*-acetyl-D-glucose with 1-methyl-2-fluoropyridinium tosylate afforded the corresponding glucosylpyridinium salt which underwent further nucleophilic displacement with sodium *N,N*-dimethyl-dithiocarbamate. Only the β-anomer was obtained as expected from the participating character of the neighbouring acetoxy group (Scheme 61).

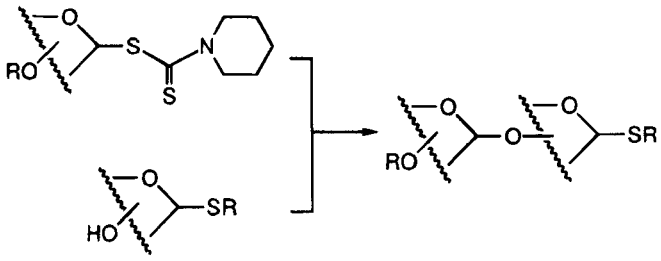
Lee *et al.*[261,262] have achieved the deprotection of peracetyl *S*-glycosyl *N,N*-diethyl- and *N,N*-diallyldithiocarbamates using methanolic ammonia and checked the biological, biochemical, and pharmacokinetic properties of the fully unprotected adducts. Derivatives of D-glucose, cellobiose and lactose showed inhibition of nitrosamine-induced DNA damage, which led the authors to assume that this class of compounds possesses anticarcinogenic activity, thus representing an important concept for chemoprevention.

Fügedi *et al.*[263] have examined the potential of glycosyl 1-piperidinecarbodithioates as glycosyl donors in oligosaccharide synthesis. Thiophilic promotors such as methyl or silver triflate were efficient activators for the glycosylation reaction, although other less expensive salts such as tin(IV) chloride or iron(III) chloride also gave good yields. Interestingly, under the conditions used by the authors, thioglycoside acceptors, which are them-



SCHEME 61

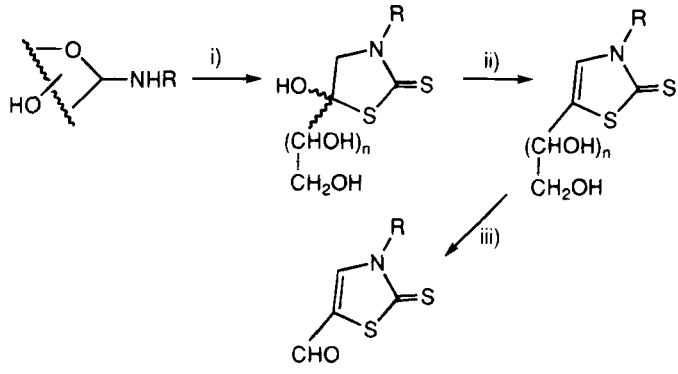
selves potential glycosyl donors, remained stable (Scheme 62). *S*-Glycosyl-*N,N*-dimethyldithiocarbamate derivatives have been analogously used as glycosyl donors in the 2-amino-2-deoxyhexose series.[264]



SCHEME 62

4.3.3. *Intramolecular Cyclic Dithiocarbamates* The reaction of fully unprotected 2-amino-2-deoxy sugars or glycosylamines with carbon disulfide leads to five-membered cyclic dithiocarbamates entailing the open-chain tautomeric form, i.e. 5-hydroxy-4 or 5-(polyhydroxyalkyl)thiazoline-2-thiones, respectively.[265] By using *N*-alkylglycopyranosylamines as starting materials, Fernández-Bolaños *et al.*[266] obtained the

corresponding *N*-alkyl heterocycles which, after sequential acetylation and deacetylation, afforded thiazoline derivatives. Further oxidation of the polyhydroxyalkyl chain provided access to the 5-carbaldehyde structures (Scheme 63).



i) CS_2, MeOH; ii) Ac_2O-pyridine, then Na^+MeO^-/MeOH; iii) $NaIO_4$

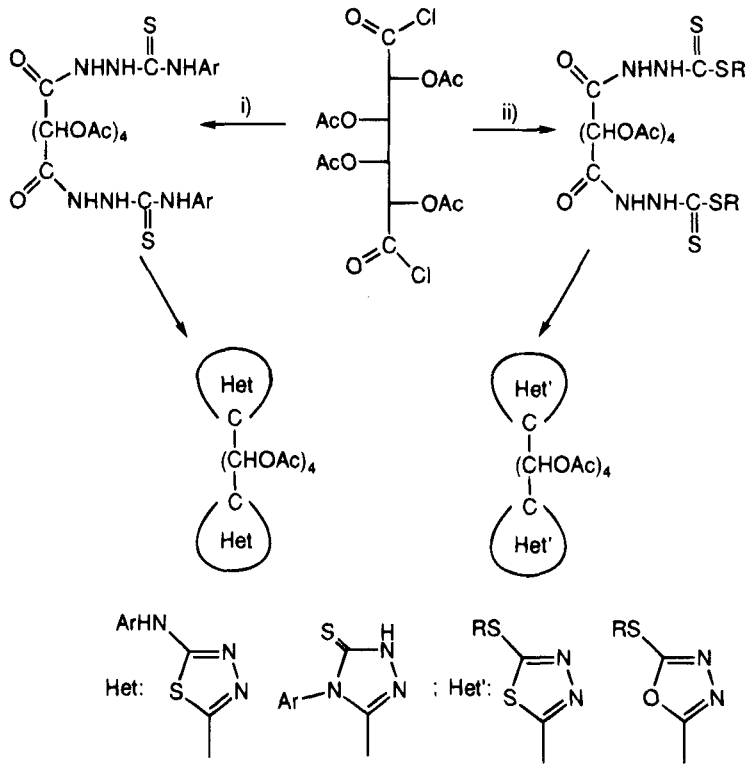
SCHEME 63

4.4. *Miscellaneous Thiocarbamic Acid Derivatives*

Egyptian authors have reported on the synthesis of several bis(thiocarbonyl)hydrazide derivatives of galactaric acid by reaction of 2,3,4,5-tetra-*O*-acetylgalactaroyl dichloride with 4-arylthiosemicarbazides or *S*-methyl(benzyl) hydrazinecarbodithioates.[267,268] The adducts were subsequently converted into a variety of heterocyclic compounds including thiadiazole, triazole, and oxadiazole derivatives (Scheme 64). The reaction of bis-2-[thioalkyl(thiocarbonyl)]hydrazide derivatives with diamines afforded monomeric or polymeric bis-hydrazide salts depending on the reagent ratio.[269]

5. THIOCARBONIC ACID DERIVATIVES

Investigation of carbohydrate esters of thiocarbonic acid goes back to more than one century ago. As early as in 1892, a crucial discovery in the history of carbohydrate thiocarbonates was reported: cellulose was con-



i) H_2NNH-C(=S)-NHAr; ii) H_2NNH-C(=S)-SR

SCHEME 64

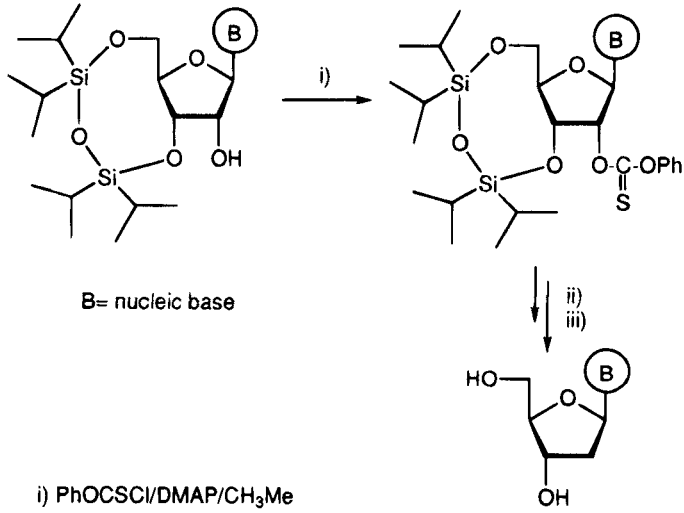
verted into a soluble xanthate derivative from which cellulose could be regenerated, an observation which is the basis of the industrial viscose process. Further development of the chemistry of these compounds was related with the variety of transformations undergone by the thiocarbonic ester functional group, including thermal rearrangements, CS→CO transformation, and desulfurization reactions. A revision of the literature up to 1960 is available.[3]

The usefulness of sugar thiocarbonates as synthetic intermediates in modern carbohydrate chemistry is mainly related with processes involving radical reactions. As above commented for thioesters (Section 3.2) and thiocarbamates (Section 4.2.2), the thiocarbonyl group is a very convenient pre-

cursor for carbon centered radicals. Many applications of this basic concept, conceived and developed by Barton,[131] to the synthesis of biologically important carbohydrate derivatives can be found in more general reviews dealing with radical reactions in organic chemistry.[232,233]

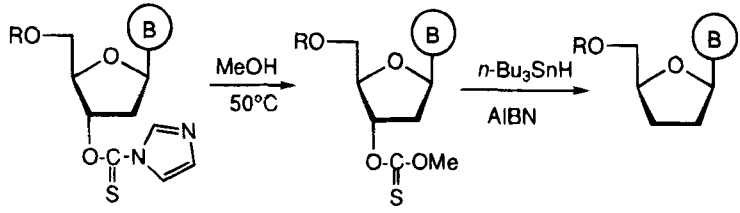
5.1. *Thiono-di-O-carbonates*

5.1.1. *Linear Thionocarbonates* The use of *O*-phenoxythiocarbonyl derivatives as precursors for Barton-McCombie radical deoxygenations has proved particularly convenient in the nucleoside field. Phenoxythiocarbonyl chloride reacts with secondary hydroxyl groups in dichloromethane or acetonitrile, in the presence of 4-(dimethylamino)pyridine (DMAP), to give the corresponding phenylthiocarbonate esters which, on reaction with tri-*n*-butyltin hydride and AIBN as initiator undergo clean homolytic deoxygenation. This procedure is compatible with the presence of the 3′,5′-*O*-(1,1,3,3-tetraisopropyldisilox-1,3-diyl) protecting group and avoids the use of basic conditions, used e.g. for the preparation of xanthate esters, that may cause nucleic base elimination[270,271] (Scheme 65).



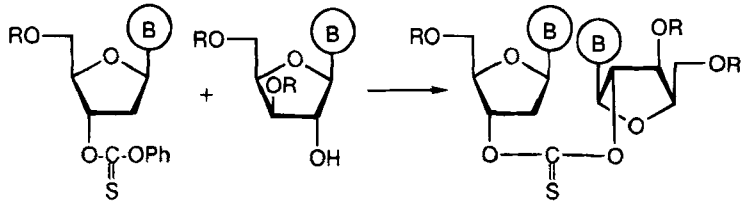
SCHEME 65

This general protocol has been widely used for the preparation of biologically important 2′- and 3′-deoxynucleosides[272–276] as well as of carbocyclic analogs.[277] Treatment with tri-*n*-butyl deuteride instead of the hydride afforded deuterionucleosides.[271,278] Alternatively, methyl thionocarbonate esters, prepared from the corresponding imidazolides and methanol, have been used[279] (Scheme 66).



SCHEME 66

Attempts of deoxygenation at C-2 in xylofuranosyl nucleosides by the phenoxythiocarbonyl method resulted, however, in concomitant reversion to the parent nucleoside.[280] Isolation of a dimeric nucleosid-2′-yl thionocarbonate ester indicated that transesterification of the less hindered O-2′ of the xylofuranosyl moiety relative to ribofuranosyl nucleosides is responsible for this side reaction (Scheme 67).

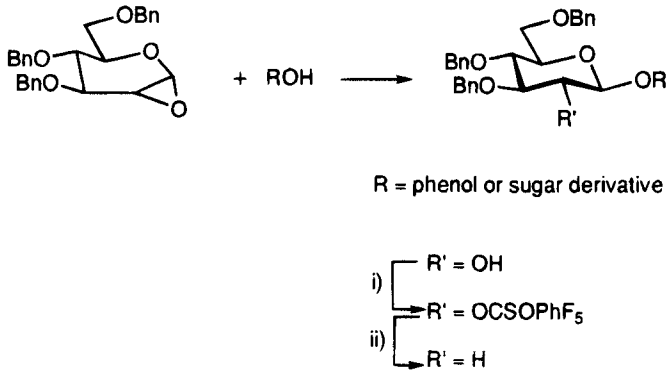


SCHEME 67

Apart from nucleosides, linear thionocarbonates have also found application for the preparation of deoxysugars in both the furanose[281,282] and pyranose series.[283] In addition, *O*-phenoxythiocarbonyl and *O*-(*p*-tolylthiocarbonyl)esters of sialic acid derivatives provided access to a variety of deoxy analogs.[284,285] The latter were prepared by reaction of

suitably protected compounds with thiophosgene and then with *p*-cresol. Using DMAP as base catalyst, even the strongly hindered OH group at C-7 was transformed into the corresponding *p*-tolyl thiocarbonate and further deoxygenated.[285]

The Barton-McCombie methodology has been further extended to phenoxythiocarbonyl derivatives incorporating electron withdrawing groups at the aromatic ring, thus improving the radicophilicity of the thiocarbonyl group.[286] 2,4,6-Trifluorophenoxythiocarbonyl,[287] pentafluorophenoxythiocarbonyl,[287] and 4-fluorophenoxythiocarbonyl derivatives[288] have been used for this purpose, resulting in faster and cleaner transformations. 3-*O*-Thionocarbonate esters of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose have been generally used as model compounds for comparative reactivity studies. Some elegant applications of pentafluorophenylthiocarbonate esters to the synthesis of 2-deoxy-β-glycosides have been reported by Gervay and Danishefsky[289] (Scheme 68). Moreover, fluorophenylthionocarbonates have proved very efficient for the radical deoxygenation of the less reactive primary hydroxyl groups.[290]



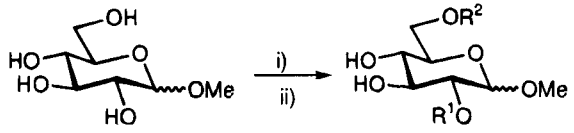
i) *N*-hydroxysuccinimide/ $F_5PhOCSCl$/ pyridine
ii) Ph_3SnH/ AIBN

SCHEME 68

Although the use of tributyltin hydride both as the hydrogen donor and the chain carrier source is still the most popular method for thiocarbonyl-based radical chain deoxygenation, the problems associated with the price

and toxicity of tin residues has stimulated a search for alternative systems.[286] Diphenylsilane-triethylborane-air,[288] triethylsilane-benzoyl peroxide,[291] hypophosphorous acid and its salts,[292] and phenylsilane-AIBN or benzoyl peroxide[293] have been successfully used for this purpose starting from 4-fluorophenylthiocarbonates.

Application of the Barton-McCombie methodology or its modifications to carbohydrate templates requires selective protection of the hydroxyl groups which need not be involved in the reaction prior to the thioacylation step. The regioselective thioacylation of non-protected sugars appears then as an attractive alternative approach. Haque *et al.*[294,295] have found that combination of dibutyltin oxide treatment of methyl glucopyranosides whose hydroxyl groups are all trans oriented and subsequent phenoxythiocarbonylation affords monoesters in high yield and with good selectivity (Scheme 69). The secondary phenylthiocarbonates were acetylated and deoxygenated, whereas the primary derivatives gave the corresponding deoxysugars in poor yield, obviously due to the lower stability of the primary relative to the secondary carbon radicals.



Me α-Glc 2-ester (93.5%) + 6-ester (6.5%)
Me β-Glc 6-ester (100%)

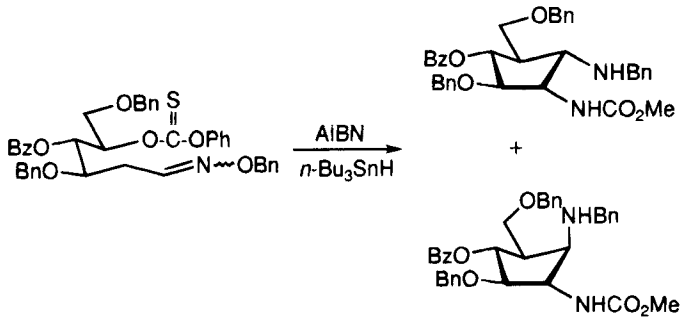
i) Bu_2SnO (1.5 mol eq)/ MeOH; ii) PhOCSCl/ dioxane

SCHEME 69

Recently, some promising results on the direct radical reductive deoxygenation of partially protected and fully unprotected monosaccharides via phenylthiocarbonate esters have been reported.[296]

Linear thionocarbonates have also been used for the preparation of unsaturated carbohydrates from vicinal radical-leaving-group derivatives,[251] and have been found to be the best precursors for the radical *C*-allylation of sugars via reaction of allyltri-*n*-butylstannane with the corresponding carbon centered radicals.[139,297] Intramolecular carbon-carbon bond formation

has also been reported.[298] The reaction involves the addition of a carbon radical, generated from a phenylthiocarbonate functionality, to an oxime double bond, and has been used for the preparation of aminocyclitols structurally related to the allosamizoline portion of the potent chitinase inhibitor allosamidin (Scheme 70).

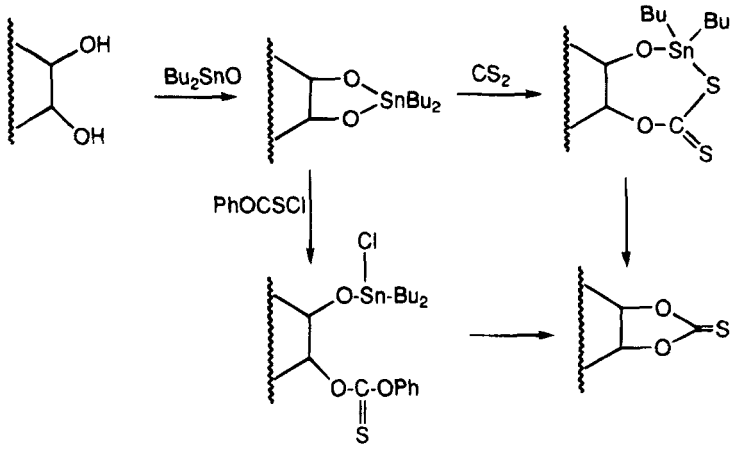


SCHEME 70

5.1.2. *Intramolecular Cyclic Thionocarbonates* Sugar cyclic thionocarbonates of 1,2- and 1,3-diol systems are classically obtained from suitably protected derivatives by treatment with 1,1′-thiocarbonyldiimidazole[299] or by reaction with thiophosgene in the presence of various bases.[300] The use of carbon disulfide and methyl iodide in a solid-liquid two-phase system ($KOH\text{-}CH_2Cl_2$) with tetra-*n*-butylammonium hydrogen sulfate as phase-transfer catalyst has recently been proposed.[301] The method is, however, limited to *cis* vicinal hydroxyl groups.

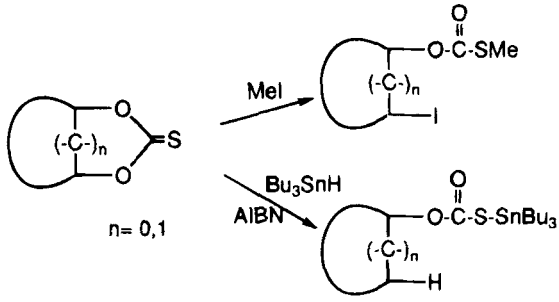
Five-membered cyclic thionocarbonates *cis*-fused to a pyranose ring have also been prepared by regioselective thioacylation of fully unprotected glycopyranosides by the dibutyltin oxide method[294,295] using phenoxythiocarbonyl chloride or carbon disulfide[302] as the thiocarbonylating reagent (Scheme 71). The procedure has been further extended to the preparation of six-membered *trans*-fused systems.[303]

Similarly to their acyclic counterparts, carbohydrate cyclic thionocarbonates have been widely used as intermediates in the preparation of deoxy sugars. Two complementary routes, originally developed by Barton,[299,304] may be followed for this purpose: (a) ring opening of the cyclic thiocarbonate with methyl iodide or (b) radical reduction with tri-

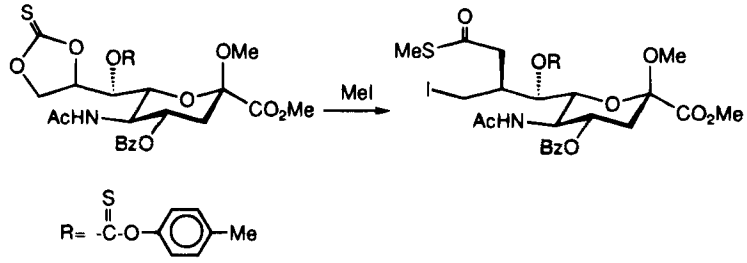


SCHEME 71

n-butyltin hydride with AIBN as initiator (Scheme 72). The first reaction is ionic in mechanism, its outcome being, therefore, strongly determined by stereochemical considerations and dipolar interactions in the transition state, as discussed by Patroni *et al.*[305] As a general rule, deoxygenation proceeds exclusively at the primary positions for thiocarbonates involving primary-secondary diols, whereas the formation of *trans*-diaxial deoxyiodo sugars is favoured from cyclic derivatives involving two secondary positions. A notable example is the preparation of 9-deoxy-9-iodo derivatives of sialic acids from the corresponding 8,9-cyclic thionocarbonates[285] (Scheme 73).



SCHEME 72



SCHEME 73

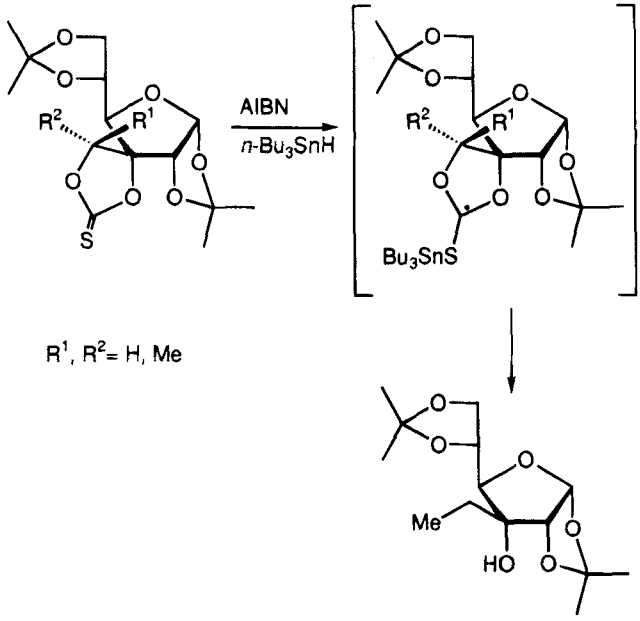
In the case of the radical reduction, the reaction proceeds through the more stable, i.e. higher degree of substitution, carbon radical. In this way, 5-deoxy and 4-deoxy sugars have been prepared from the corresponding 5,6- or 4,6-cyclic thionocarbonates. No selectivity is generally observed when two secondary positions are involved.[246,248,299]

However, diol thiocarbonates involving the tertiary hydroxyl group of branched chain sugars underwent preferential deoxygenation at the secondary oxygen, in spite of the expected higher stability of a tertiary radical as compared to a secondary one.[306] An explanation has been provided on the basis of hydrogen transfer to a cyclic radical intermediate prior to C-O bond cleavage. The steric demand of tri-*n*-butyltin hydride would then favour the more accessible secondary position (Scheme 74).

Attempts to prepare deoxy derivatives of 3-acetamido-3-deoxy glucopyranosides by these procedures have been reported to be infeasible, the corresponding 4,6-cyclic thiocarbonates being obtained only in low yield.[307]

Cyclic *vic*-thionocarbonates are good precursors for the synthesis of alkenes by treatment with trimethyl phosphite acording to the Corey-Winter method.[308,309] This protocol has been successfully applied to the preparation of several unsaturated carbohydrate derivatives which, eventually, were hydrogenated to the corresponding dideoxy sugars[294,295,299,310] (Scheme 75). Other useful transformations include CS→CO exchange with dibutyltin oxide[302] and radical rearrangement to *S*-carbonates from which thiosugars have been obtained after alkaline hydrolysis[311,312] (Scheme 75).

Finally, 3,5-di-*O*-benzyl-1,2-*O*-thiocarbonyl-α-D-xylofuranose has been used as glycosyl donor using cesium fluoride and methyl fluorosulfonate as promotors. Excellent yields and β-selectivities were obtained for primary hydroxyl groups, including monosaccharide acceptors.[313,314]

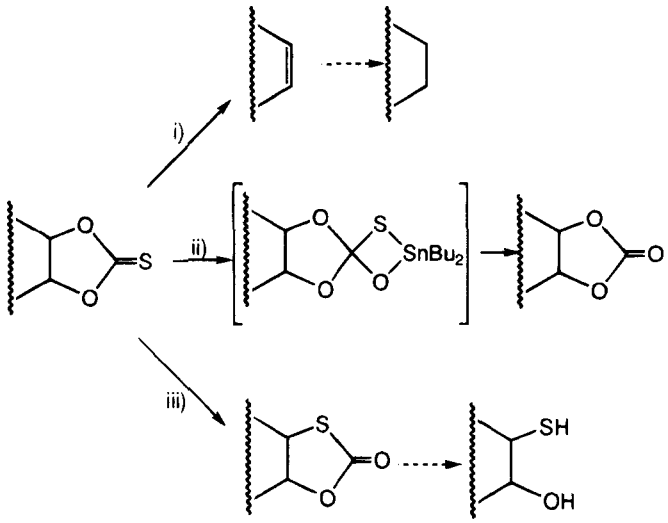


SCHEME 74

5.2. *Dithio-O-carbonates (Xanthates)*

5.2.1. *O-Sugar Xanthates* The hydroxyl groups of carbohydrates react readily with carbon disulfide in the presence of sodium hydroxide or sodium hydride to form *O*-(sodium thiolthiocarbonyl) derivatives known as xanthates.[3,315] This simple reaction is of high industrial value for the preparation of carbohydrate biopolymer derived materials. Thus, the viscous orange-red aqueous solution of sodium cellulose xanthate, known as "viscose", is an intermediate for the manufacture of rayon and cellophane.[316] Recent reports deal with the preparation of cellulose xanthate-based ion exchange resins[317] and of chitin xanthate,[318] a key intermediate for the preparation of novel composites or materials blended with other organic and inorganic compounds.

Reaction of sodium xanthates with alkyl halides affords the corresponding xanthic esters.[3,315] This reaction is generally carried out *in situ* without isolation of the intermediate salt.[130,319] The simplicity of their preparation makes *O*-(alkylthio)thiocarbonyl sugars very convenient pre-



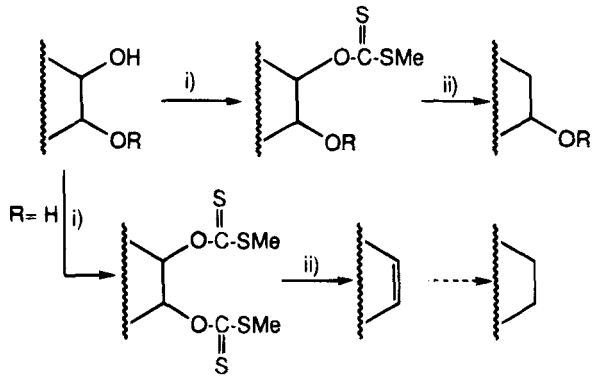
i) $P(OMe)_3$, 150 °C; ii) *n*-Bu_2SnO; iii) *n*-Bu_3SnH/ AIBN

SCHEME 75

cursors for deoxysugars and unsaturated carbohydrate derivatives via radical chain deoxygenation[286,291–293,307,320–328] and olefination reactions[292,293,310,329–332] according to the Barton methodology[131,132] (Scheme 76). *S*-Methyl *O*-sugar xanthates have been most often used for these purposes, although *O*-(cyanoethylthio)thiocarbonyl derivatives have been recommended for the deoxygenation of 2′- and 3′-hydroxyl groups in nucleosides.[333]

The standard conditions for xanthate formation (NaH in refluxing THF, followed by introduction of CS_2) have been reported to be unsuccessful for the esterification of OH-4 in a 6-*O*-silyl protected hexopyranoside derivative, probably because of silyl migration. This side reaction could be avoided by use of carbon disulfide as solvent.[334]

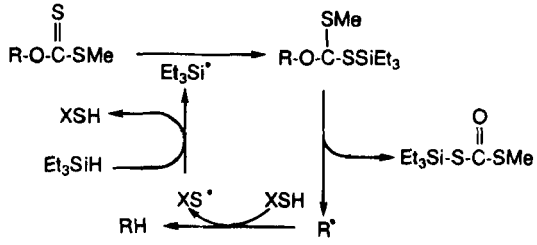
All hydrogen donor-radical chain carrier source systems already commented for their thionocarbonate congeners are equally effective in the case of xanthates. Tributyltin deuteride has similarly been used for the preparation of deuterium labelled carbohydrates via xanthic ester derivatives.[278,335]



i) NaH/ THF reflux/ CS_2, then MeI
ii) *n*-Bu_3SnH/AIBN

SCHEME 76

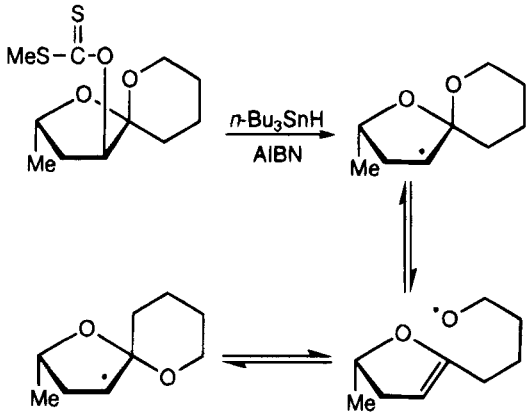
A further modification of the Barton deoxygenation protocol, reported by Roberts *et al.*,[336,337] involves the reaction of the corresponding *O*-sugar methylxanthate with triethylsilane in non-aromatic solvents. The reaction is promoted by thiols which act as polarity reversal catalysts accelerating the radical chain propagation (Scheme 77). Di-*tert*-butyl peroxide was used as initiator.



SCHEME 77

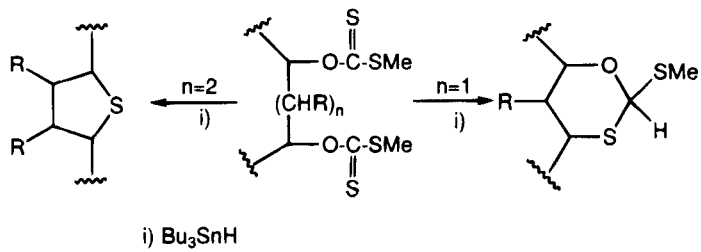
Some cases of epimerization have been noticed during the radical deoxygenation of sugar xanthates. This side reaction can be attributed either to hydrogen atom abstraction in the case of tertiary positions, e.g. C-5 in

1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose,[335] or to isomerization of the transient carbon-centered radical into an oxygen radical in the case of quaternary positions[328] (Scheme 78). Formation of a mixture of the deoxy sugar (20%) and the elimination product (67%) has also been observed during tributyltin hydride treatment of a vicinal azido xanthate.[338]



SCHEME 78

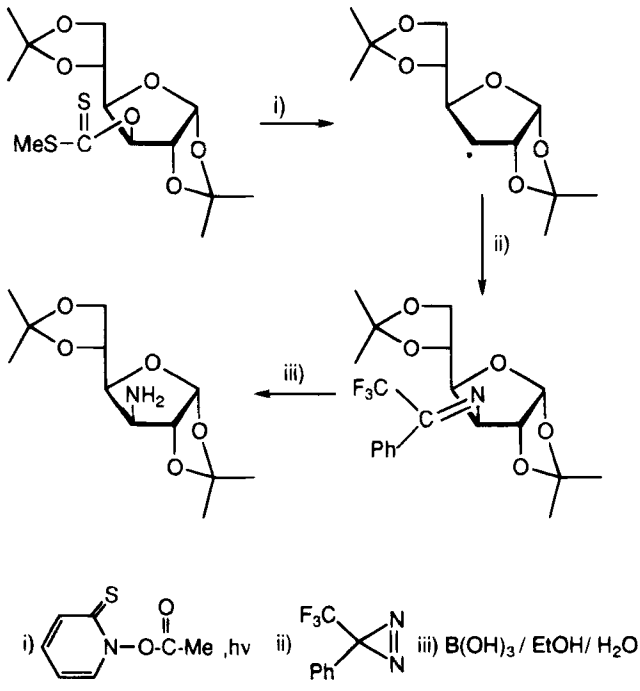
Some sugar derived 1,3- and 1,4-*bis*(dithiocarbonates) have been reported to undergo cyclization reactions under radical deoxygenation reaction conditions. In the first case, a secondary carbon-centered radical underwent attack by the thiocarbonyl sulfur atom of the second, primary xanthate group to give a 1,3-oxathiane ring.[339] The 1,4-diesters afforded thiolane derivatives by annelation reaction involving a thiol group after xanthate→ di-*S*-thiocarbonate isomerization[340] (Scheme 79).



SCHEME 79

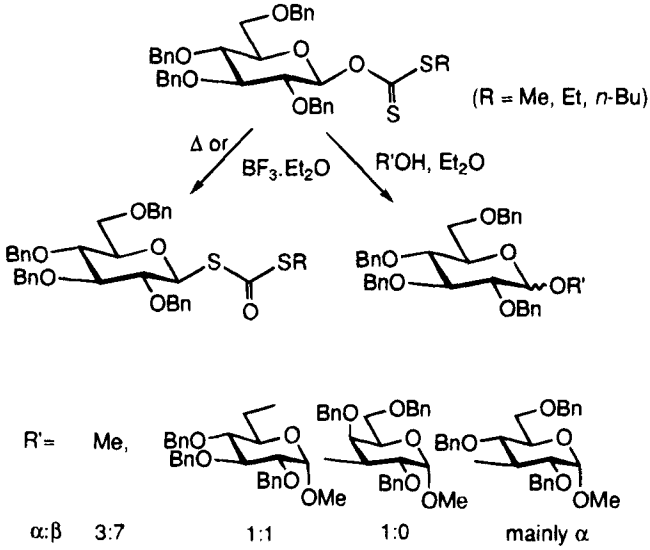
O-(Methylthio)thiocarbonyl derivatives have been additionally used as precursors for radical C—C bond formation, although in rather moderate yield. Literature reports deal with *C*-allylation,[139,297] synthesis of *C*-glycosides by addition of glycosyl radicals generated from xanthates to olefins,[341,342] and intramolecular cyclization of unsaturated sugar derivatives.[343] The formation of isomeric di-*S*-thiocarbonates was a frequent side reaction during these transformations.

A further application of xanthates in sugar chemistry is the conversion of secondary hydroxyl groups into amino groups by trapping of the generated radical with 3-phenyl-3-(trifluoromethyl)diaziridine and subsequent hydrolysis of the resulting imine. Starting from 1,2:5,6-di-*O*-isopropylidene-3-*O*-(methylthio)thiocarbonyl-α-D-glucofuranose, exclusively the 3-amino-3-deoxy sugar with the D-*gluco* configuration was obtained, probably due to the steric bulk of the 1,2-acetonide group[344] (Scheme 80).



SCHEME 80

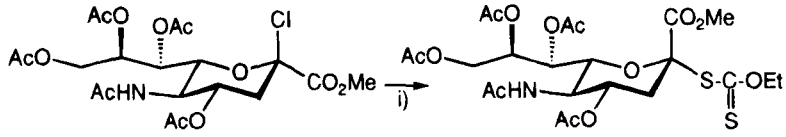
Anomeric *O*-sugar xanthates undergo thermal or acid-catalysed rearrangement to the thermodynamically more stable di-*S*-thiocarbonates (Scheme 81). Interestingly, the reaction with boron trifluoride etherate in the presence of an alcohol affords the corresponding glycosides. Through this new glycosylation scheme, Pougny[345] prepared a series of disaccharides using 2,3,4,6-tetra-*O*-benzyl-1-*O*-(alkylthio)-thiocarbonyl-β-D-glucopyranoses as glycosyl donors and several selectively protected monosaccharides as acceptors (Scheme 81). A preference for the α-anomeric linkage was observed for secondary hydroxyl groups.



SCHEME 81

5.2.2. *S-Sugar Xanthates* The reaction of glycosyl halides with simple alcohol xanthates provides the corresponding *S*-glycosyl xanthates which have been classically used as precursors for 1-thio sugars.[115–315] Alternatively, *O*-alkyl *S*-glycosyl dithiocarbonates have been prepared under phase-transfer conditions either from reducing sugar derivatives[346,347] or from glycosyl halides.[348] In the first case, the stereoselectivity of the reaction was dependent on the substrate. Thus, 2,3,4,6-tetra-*O*-benzyl-D-gluco- and -D-galacto-pyranose formed only β-products, whereas the analogous

mannose and xylose derivatives gave α,β-mixtures. In contrast, the substitution of glycosyl halides proceeded with complete inversion of configuration at the anomeric center according to a S_N2 mechanism. Noteworthy is the high yield (> 91%) obtained in the synthesis of a peracetyl sialic acid *S*-glycosyl xanthate derivative by this procedure[348] (Scheme 82).



i) K^+ EtOC(=S)S^-, *n*-Bu_4N^+ HSO_4^-, EtOAc/ 2M Na_2CO_3

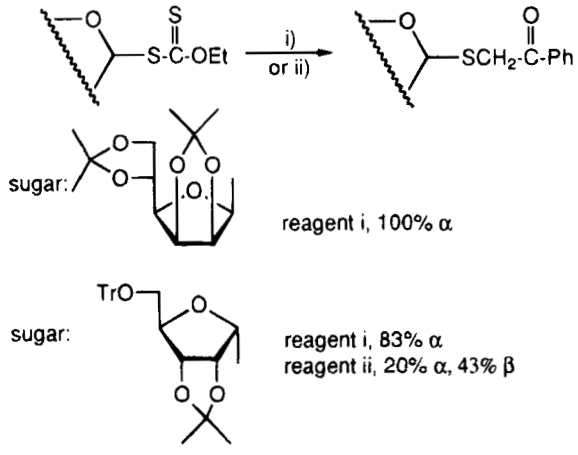
SCHEME 82

Paulsen *et al.*[349] prepared *O*-ethyl *S*-(2-azido-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-galactopyranosyl) xanthate by S_N2 displacement on the corresponding galactopyranosyl nitrate. Further reaction with sodium iodide in acetone afforded the related ethyl thioglycoside. This protocol has also been applied to the synthesis of an *S*-ethyl sialic acid derivative from an *O*-ethyl *S*-glycosyl xanthate precursor.[350]

Vasella *et al.*[141] obtained phenacyl thioglycosides from *S*-glycosyl xanthates upon treatment with sodium ethoxide and phenacyl chloride. The anomeric configuration of the reaction products was dependent on the nature of the monosaccharide template and on the solvent, as indicated in Scheme 83. The transformation of *S*-glycosyl xanthates into glycosyl disulfides has also been recorded.[351]

In the last five years *S*-glycosyl xanthates have acquired much relevance as stable and efficient glycosylation agents, especially in the 2-azido-2-deoxy-D-galactose and sialic acid series.[313,352,353] Sinay *et al.*[354–356] used copper(II) triflate and dimethyl(methylthio)sulfonium triflate as glycosylation promotors. It is noteworthy that the dithiocarbonate functionality was stable under the reaction conditions employed in other glycosylation methodologies, thus allowing the preparation of elaborated disaccharide building blocks for complex oligosaccharide synthesis.[355]

Lönn *et al.*[357] have regarded the influence of temperature and solvent in the α-selectivity as well as side-product formation during glycosylation



i) NaOEt, EtOH, phenacyl chloride
ii) NaOEt, THF, phenacyl chloride

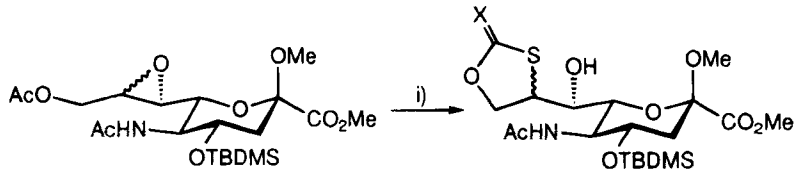
SCHEME 83

reactions involving sialic acid glycosyl xanthates with methanesulfenyl bromide (MSB) as promotor. Both the α:β ratio and the proportion of disaccharide versus elimination products increases at lower temperatures (–70 °C) and was optimal in acetonitrile-dichloromethane mixtures. These most favourable reaction conditions were further applied to the preparation of biologically active sialic acid-containing oligosaccharides.[358,359]

5.2.3. *Intramolecular Cyclic Xanthates* Formation of a sialic acid derived cyclic *O,S*-dithiocarbonate has been noticed during the reaction of methyl [5-acetamido-7,8-anhydro-4-*O*-tert-butyldimethylsilyl-3,5-dideoxy-D-*glycero*- and -L-*glycero*-β-D-galacto-2-nonulopyranosid]onate with 1,1′-thiocarbonyldiimidazole.[360] A mixture of cyclic *O,S*-thiocarbonates was simultaneously formed under these conditions (Scheme 84).

5.3. *Sugar Trithiocarbonates*

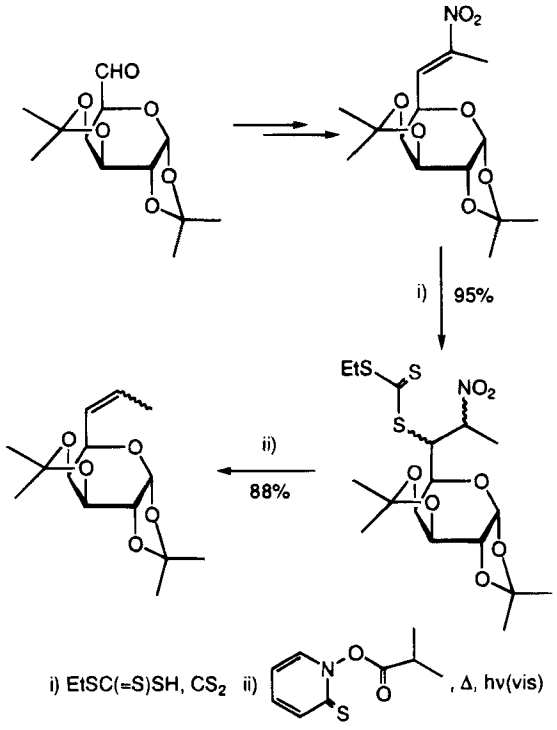
Barton *et al.*[361] prepared a D-galactose derived *vic*-nitro trithiocarbonate by addition of ethyl trithiocarbonate to a nitroolefin precursor in the presence of carbon disulfide. The crude mixture of diastereomeric products underwent radical induced elimination of the nitro group upon treatment with carbon



i) 1,1'-thiocarbonyldiimidazole X = S, O

SCHEME 84

radicals generated by visible light photolysis from the corresponding Barton ester. Taking into consideration that the starting nitroolefins can be prepared via nitroaldol condensation (Henry reaction), this methodology allows access to carbohydrate olefins from the readily available aldehydes (Scheme 85).



SCHEME 85

Acknowledgments

We wish to acknowledge our co-workers and the research group of Prof. J. Fuentes for their help. We especially thank Dr. J. Defaye for discussions and for reading this manuscript. Finally, we are also indebted to the Dirección General de Investigación Científica y Técnica (Grant no. PB94-1040-C02-01) and the CNRS for financial support of our work in this field.

References

[1] Fischer, E. (1914). *Ber.*, **47**, 1377.
[2] Goodman, I. (1958). *Adv. Carbohydr. Chem.*, **13**, 215.
[3] Hough, L., Priddle, J. E. and Theobald, R. S. (1960). *Adv. Carbohydr. Chem.*, **15**, 91.
[4] Witczak, Z. J. (1986). *Adv. Carbohydr. Chem. Biochem.*, **44**, 91.
[5] Duus, F. (1979). In *Comprehensive Organic Chemistry, Vol. 3*, Eds. D. Barton and W. D. Ollis, Pergamon Press, London, Chapter 11.22.
[6] Crich, D. and Quintero, L. (1989). *Chem. Rev.*, **89**, 1413.
[7] Drobnica, L., Kristian, P. and Augustín, J. (1977). In *The Chemistry of Cyanates and Their Thio Derivatives, Part 2*, Ed. S. Patai, John Wiley & Sons, New York, Chapter 22.
[8] Walter, W. and Voss, J. (1970). In *The Chemistry of Amides*, Ed. J. Zabicky, John Wiley & Sons, London, Chapter 8.
[9] Griffin, T. S., Woods, T. S. and Klayman, D. L. (1975). *Adv. Heterocycl. Chem.*, **18**, 99.
[10] Sharma, S. (1989). *Sulfur Rep.*, **8**, 327.
[11] Mukerjee, A. K. and Ashare, R. (1991). *Chem. Rev.*, **91**, 1.
[12] Scheithauer, S. and Mayer, R. (1979). In *Topics in Sulfur Chemistry*, Vol. 4, Ed. A. Senning, Thieme-Verlag, Stuttgart, pp. 295–306.
[13] Zurabyan, S. E., Tesler, I. D., Macharadze, R. G. and Khorlin, A. Ya. (1989 & 1990). *Farmatsiya*, **38**, 71; *Chem. Abstr.*, **113**, 6716m.
[14] Tashpulatov, A. A., Rakhmatullaev, I., Afanas'ev, V. A. and Ismailov, N. (1988). *Zh. Org. Khim.*, **24**, 1893.
[15] Rakhmatullaev, I., Tashpulatov, O. A. and Afanas'ev, V. A. (1987). *Zh. Org. Khim.*, **23**, 454.
[16] Camarasa, M. J., Fernández-Resa, P., García-López, M. T., de las Heras, F. G., Méndez-Castrillón, P. P. and San Félix, A. (1984). *Synthesis*, 509.
[17] Camarasa, M. J., Fernández-Resa, P., García-López, M. T., de las Heras Martín Maestro, F. G., Méndez-Castrillón, P. P. and San Félix, A. (C.S.I.C.) (1985 & 1988). **Spanish Patent ES 527,758**; *Chem. Abstr.*, **108**, 6345m.
[18] Hassel, T. and Müller, H. P. (Bayer A.-G.) (1985 & 1986). **Ger. Offen. DE 3,341,018**; *Chem. Abstr.*, **104**, 51081a.
[19] Witczak, Z. J. (1986). *Tetrahedron Lett.*, **27**, 155.
[20] Machón, Z., Mielczarek, I., Wieczorek, J. and Mordarski, M. (1987). *Arch. Immunol. Ther. Exp.*, **35**, 609.
[21] Camarasa, M. J., García-López, M. T. and de las Heras, F. G. (1991). *Nucleic Acid Chem.*, **4**, 54.
[22] Abashev, Yu. P., Andronova, T. M., Zurabyan, S. E., Mal'kova, V. P., Sorokina, I. B. and Khorlin, A. Ya. (1984). *Bioorg. Khim.*, **10**, 18.
[23] Lee, H. H., Baptista, J. A. B. and Krepinsky, J. J. (1980). *Can. J. Chem.*, **68**, 953.
[24] Günther, W. and Kunz, H. (1990). *Angew. Chem., Int. Ed. Engl.*, **29**, 1050.
[25] Stöckl, W. P. and Weidmann, H. (1989). *J. Carbohydr. Chem.*, **8**, 169.

[26] Uchida, C., Kitahashi, H., Watanabe, S. and Ogawa, S. (1995). *J. Chem. Soc., Perkin Trans. 1*, 1707.
[27] Fuentes, J., Pradera, M. A. and Robina, I. (1991). *Tetrahedron*, **47**, 5797.
[28] Klimov, E. M., Demchenko, A. V. and Malysheva, N. N. (1993). *Dokl. Akad. Nauk*, **331**, 53.
[29] Taverna, R. D. and Langdon, R. G. (1973). *Biochem. Biophys. Res. Commun.*, **54**, 593.
[30] Langdon, R. G. (1976). *Methods Enzymol.*, **46**, 164.
[31] Shulman, M. L., Lakhtina, O. E., and Khorlin, A. Ya. (1977). *Biochem. Biophys. Res. Commun.*, **74**, 455.
[32] Mullins, R. E. and Langdon, R. G. (1980). *Biochemistry*, **19**, 1199.
[33] Rees, W. D., Gliemann, J. and Holman, G. D. (1987). *Biochem. J.*, **241**, 857.
[34] Babiano Caballero, R., Fuentes Mota, J. and Galbis Pérez, J. A. (1986). *Carbohydr. Res.*, **154**, 280.
[35] Fuentes Mota, J., García Fernández, J. M., Pradera Adrián, M. A., Ortiz Mellet, C. and García Gómez, M. (1990). *An. Quim.*, **86**, 655.
[36] Fuentes Mota, J., López-Barba, E., Robina, I., Molina Molina, J. and Portal Olea, D. (1993). *Carbohydr. Res.*, **247**, 165.
[37] Fuentes Mota, J., Pradera Adrián, M. A., Ortiz Mellet, C., García Fernández, J. M., Babiano Caballero, R. and Galbis Pérez, J. A. (1988). *Carbohydr. Res.*, **173**, 1.
[38] Ortiz Mellet, C., Jiménez Blanco, J. L., García Fernández, J. M. and Fuentes, J. (1993). *J. Carbohydr. Chem.*, **12**, 487.
[39] Pradera, M. A., Molina, J. L. and Fuentes, J. (1995). *Tetrahedron*, **51**, 923.
[40] Fuentes Mota, J., García Fernández, J. M., Ortiz Mellet, C., Pradera Adrián, M. A. and Babiano Caballero, R. (1989). *Carbohydr. Res.*, **188**, 35.
[41] Fuentes, J., Moreda, W., Ortiz, C., Robina, I. and Welsh, C. (1992). *Tetrahedron*, **48**, 6413.
[42] Uchida, C. and Ogawa, S. (1994). *Carbohydr. Lett.*, **1**, 77.
[43] Igarashi, K. and Honma, T. (1967). *J. Org. Chem.*, **32**, 2521.
[44] Santoyo-González, F., García-Calvo-Flores, F., Isac-García, J., Hernández-Mateo, F., García-Mendoza, P. and Robles-Díaz, R. (1994). *Tetrahedron*, **50**, 2877.
[45] Avalos González, M., Fuentes Mota, J., Gómez Monterrey, I. M., Jiménez Requejo, J. L., Palacios Albarrán, J. C. and Ortiz Mellet, M. C. (1986). *Carbohydr. Res.*, **154**, 49.
[46] Fuentes Mota, J., Avalos González, M., Jiménez Requejo, J. L., Palacios Albarrán, J. C. and Gómez Monterrey, I. M. (1985). *An. Quim.*, **81C**, 239.
[47] Jochims, J. C. and Seeliger, A. (1965). *Tetrahedron*, **21**, 2611.
[48] Avalos, M., Babiano, R., Cintas, P., Jiménez, J. L., Palacios, J. C. and Fuentes, J. (1990). *J. Chem. Soc., Perkin Trans. 1*, 495.
[49] Ortiz Mellet, C., Jiménez Blanco, J. L., García Fernández, J. M. and Fuentes, J. (1995). *J. Carbohydr. Chem.*, **14**, 1133.
[50] Ramjeesingh, M. and Kahlenberg, A. (1977). *Can. J. Chem.*, **55**, 3717.
[51] García Fernández, J. M., Ortiz Mellet, C. and Fuentes, J. (1992). *Tetrahedron Lett.*, **33**, 3931.
[52] García Fernández, J. M., Ortiz Mellet, C. and Fuentes, J. (1993). *J. Org. Chem.*, **58**, 5192.
[53] Fuentes Mota, J., Jiménez Blanco, J. L., Ortiz Mellet, C. and García Fernández, J. M. (1994). *Carbohydr. Res.*, **257**, 127.
[54] García Fernández, J. M., Ortiz Mellet, C., Jiménez Blanco, J. L. and Fuentes, J. (1994). *J. Org. Chem.*, **59**, 5565.
[55] Knapp, S., Naughton, A. B. J. and Dhar, T. G. M. (1992). *Tetrahedron Lett.*, **33**, 1025.
[56] Kobayashi, Y., Shiozaki, M. and Ando, O. (1995). *J. Org. Chem.*, **60**, 2570.
[57] Shibanuma, T., Shiono, M. and Mukaiyama, T. (1977). *Chem. Lett.*, **573**.
[58] Olejniczak, B. and Zwierzak, A. (1989). *Synthesis*, 300.
[59] Elbert, T. and Cerny, M. (1985). *Collect. Czech. Chem. Commun.*, **50**, 2000.
[60] Fuentes, J., Díaz Pérez, V. M., Jiménez Blanco, J. L., Ortiz Mellet, C. and García Fernández, J. M. *8th Eur. Carbohydr. Symp.*, Sevilla (Spain), 2–7 July, 1995, Abstr. A-6.

[61] García Fernández, J. M., Ortiz Mellet, C., Jiménez Blanco, J. L., Fuentes Mota, J., Gadelle, A., Coste-Sarguet, A. and Defaye, J. (1995). *Carbohydr. Res.*, **268**, 57.
[62] García Fernández, J. M., Jiménez Blanco, J. L., Ortiz Mellet, C. and Fuentes, J. (1995). *J. Chem. Soc., Chem. Commun.*, 57.
[63] García Fernández, J. M., Maciejewski, S. and Defaye, J. *8th Eur. Carbohydr. Symp.*, Sevilla (Spain), 2–7 July, 1995, Abstr. A O-13.
[64] Fuentes Mota, J., Cuevas, T. and Pradera, M. A. (1994). *Carbohydr. Res.*, **260**, 137.
[65] Buss, D. H. and Goldstein, I. J. (1968). *J. Chem. Soc., C*, 1457.
[66] McBroom, C. R., Samanen, C. H. and Goldstein, I. J. (1972). *Methods Enzymol.*, **28B**, 212.
[67] Duke, J., Little, N. and Goldstein, I. J. (1973). *Carbohydr. Res.*, **27**, 193.
[68] Lindberg, A. A., Rosenberg, L. T., Ljunggren, A., Garegg, P. J., Svensson, S. and Wallin, N.-H. (1974). *Infect. Immun.*, **10**, 541.
[69] Ebisu, S., Garegg, P. J., Iversen, T. and Goldstein, I. J. (1978). *J. Immunol.*, **121**, 2137.
[70] Reichert, C. M. and Goldstein, I. J. (1979). *J. Immunol.*, **122**, 1138.
[71] Svenson, S. B. and Lindberg, A. A. (1979). *J. Immunol. Methods*, **25**, 323.
[72] Stowell, C. P. and Lee, Y. C. (1980). *Adv. Carbohydr. Chem. Biochem.*, **37**, 225.
[73] Aplin, J. D. and Wriston, Jr., J. C. (1981). *CRC Crit. Rev. Biochem.*, **10**, 1259.
[74] Roche, A.-C., Barzilay, M., Midoux, P., Junqua, S., Sharon, N. and Monsigny, M. (1983). *J. Cell. Biochem.*, **22**, 131.
[75] Ekborg, G., Vranesic, B., Bhattacharjee, A. K., Kovác, P. and Glaudemans, C. P. J. (1985). *Carbohydr. Res.*, **142**, 203.
[76] Garegg, P. J. and Lindberg, A. A. (1988). *The Synthesis of Oligosaccharides for Biological and Medical Applications*, in *Carbohydrate Chemistry*, Ed. J. F. Kennedy, Oxford University Press, Oxford, Chapter 12.
[77] Jonas, A. J. and Jobe, H. (1990). *Biochem. J.*, **268**, 41.
[78] Hilditch, C. M., Balding, P., Jenkins, R., Smith, A. J. and Rogers, L. J. (1991). *J. Appl. Phycol.*, **3**, 345.
[79] Reichert, C. M., Hayes, C. E. and Goldstein, I. J. (1994). *Methods Enzymol.*, **242**, 108.
[80] Ekborg, G., Garegg, P. J. and Gotthammar, B. (1975). *Acta Chem. Scand. B*, **29**, 765.
[81] Eklind, K., Garegg, P. J. and Gotthammar, B. (1976). *Acta Chem. Scand. B*, **30**, 305.
[82] Garegg, P. J. and Gotthammar, B. (1977). *Carbohydr. Res.*, **58**, 345.
[83] Lindberg, A. A., Wollin, R., Bruse, G., Ekwall, E. and Svenson, S. B. (1983). *ACS Symp. Ser.*, **231**, 83.
[84] Monsigny, M., Roche, A.-C. and Midoux, P. (1984). *Biol. Cell*, **51**, 187.
[85] Eby, R. and Schuerch, C. (1979). *Carbohydr. Res.*, **77**, 61.
[86] Eby, R. and Schuerch, C. (1980). *Carbohydr. Res.*, **79**, 53.
[87] Dahmén, J., Frejd, T., Magnusson, G. and Noori, G. (1982). *Carbohydr. Res.*, **111**, C1.
[88] Smith, D. F., Zopf, D. A. and Gingsburg, V. (1978). *Methods Enzymol.*, **50**, 169.
[89] Kallin, E., Lönn, H. and Norberg, T. (1986). *Glycoconjugate J.*, **3**, 311.
[90] Kallin, E. (1994). *Methods Enzymol.*, **242**, 119.
[91] Banoub, J. H., Shaw, D. H., Nakhla, N. A. and Hodder, H. J. (1989). *Eur. J. Biochem.*, **179**, 651.
[92] Augustín, J., Drobnica, L. and Gemeiner, P. (1976). *Chem. Zvesti*, **30**, 246.
[93] Gemeiner, P., Augustín, J. and Drobnica, L. (1976). *Chem. Zvesti*, **30**, 254.
[94] Gemeiner, P., Augustín, J. and Drobnica, L. (1977). *Carbohydr. Res.*, **53**, 217.
[95] Ogura, H. and Takahashi, H. (1982). *Heterocycles*, **17**, 87.
[96] Parrot-Lopez, H., Leray, E. and Coleman, A. W. (1993). *Supramol. Chem.*, **3**, 37.
[97] Takahashi, H., Takeda, K., Nimura, N. and Ogura, H. (1979). *Chem. Pharm. Bull.*, **27**, 1137.
[98] Fischer, E., Helferich, B. and Ostmann, P. (1920). *Ber.*, **53**, 873.
[99] Khorlin, A. Ya., Shiyan, S. D., Lakthina, O. E. and Shulman, M. L. (1975). *Bioorg. Khim.*, **1**, 393.
[100] Naito, T. and Sano, M. (1961). *Chem. Pharm. Bull.*, **9**, 709.

[101] Heyns, K. and Hohlweg, R. (1978). *Chem. Ber.*, **111**, 1632.
[102] Ferrier, R. J. and Vethaviyasar, N. (1970). *Chem. Commun.*, 1385.
[103] Ferrier, R. J. and Vethaviyaser, N. (1971). *J. Chem. Soc., C*, 1907.
[104] Zurabyan, S. E., Macharadze, R. G. and Khorlin, A. Ya. (1978). *Bioorg. Khim.*, **4**, 1135.
[105] Zurabyan, S. E., Macharadze, R. G. and Khorlin, A. Ya. (1979). *Izv. Akad. Nauk SSSR, Ser. Khim.*, 877.
[106] Khorlin, A. Ya., Zurabyan, S. E. and Macharadze, R. G. (1980). *Carbohydr. Res.*, **85**, 201.
[107] Garg, H. G. and Jeanloz, R. W. (1985). *Adv. Carbohydr. Chem. Biochem.*, **43**, 135.
[108] Kunz, H. (1987). *Angew. Chem., Int. Ed. Engl.*, **26**, 294.
[109] Parrot-Lopez, H., Galons, H., Coleman, A. W., Mahuteau, J. and Miocque, M. (1992). *Tetrahedron Lett.*, **33**, 209.
[110] Avalos, M., Babiano, R., García-Verdugo, C., Jiménez, J. L. and Palacios, J. C. (1990). *Tetrahedron Lett.*, **31**, 2467.
[111] Hassel, T., Müller, H. P. and Boeshagen, H. (Bayer A.-G.) (1986). **Ger. Offen. DE 3,429,432** (1986); *Chem Abstr.*, **105**, 91567j.
[112] Hassel, T. and Müller, H. P. (1987). *Angew. Chem., Int. Ed. Engl.*, **26**, 359.
[113] Shulman, M. L., Shiyan, S. D. and Khorlin, A. Ya. (1976). *Biochim. Biophys. Acta*, **445**, 169.
[114] Mullins, R. E. and Langdon, R. G. (1980). *Biochemistry*, **19**, 1205.
[115] Horton, D. and Wander, J. D. (1980). In *The Carbohydrates, Chemistry and Biochemistry*, Vol. 1B, Eds. W. Pigman, D. Horton and J. D. Wander, Academic Press, New York, Chapter 18.
[116] Defaye, J. and Gelas, J. (1991). In *Studies in Natural Products Chemistry, Vol. 8: Stereoselective Synthesis (Part E)*, Ed. Atta-ur-Rahman, Elsevier, Amsterdam, pp. 315–357.
[117] Watanabe, K. A., Beránek, J., Friedman, H. A. and Fox, J. J. (1965). *J. Org. Chem.*, **30**, 2735.
[118] Wolfrom, M. L. and Winkley, M. W. (1968). *J. Org. Chem.*, **33**, 4227.
[119] Kuzuhara, H., Mori, O. and Emoto, S. (1976). *Tetrahedron Lett.*, 379.
[120] Bedi, G. S., Shah, R. H. and Bahl, O. P. (1978). *Carbohydr. Res.*, **62**, 253.
[121] Bovin, N. V., Zurabyan, S. E. and Khorlin, A. Ya. (1981). *Izv. Akad. Nauk SSSR, Ser. Khim.*, 441.
[122] Avalos, M., Babiano, R., Durán, C. J., Jiménez, J. L. and Palacios, J. C. (1992). *J. Chem. Soc., Perkin Trans. 2*, 2205.
[123] Ortiz Mellet, C., Moreno Marín, A., García Fernández, J. M. and Fuentes, J. (1994). *Tetrahedron: Asymmetry*, **5**, 2313.
[124] Herczegh, P. and Bognár, R. (1978). *Acta Chim. Acad. Sci. Hung.*, **98**, 321.
[125] Avalos, M., Babiano, R., Durán, C. J., Jiménez, J. L. and Palacios, J. C. (1994). *Tetrahedron Lett.*, **35**, 477.
[126] Isecke, R. and Brossmer, R. (1993). *Tetrahedron*, **49**, 10009.
[127] Brossmer, R. and Gross, H. J. (1994). *Methods Enzymol.*, **247**, 153.
[128] Brossmer, R., Isecke, R. and Herrler, G. (1993). *FEBS Lett.*, **323**, 96.
[129] Machytka, D., Kharitonenkov, I., Isecke, R., Hetterich, P., Brossmer, R., Klein, R. A., Klenk, H.-D. and Egge, H. (1993). *FEBS Lett.*, **334**, 117.
[130] Stewart, W. E. and Siddall, III, T. H., (1970). *Chem. Rev.*, **70**, 517.
[131] Barton, D. H. R. and McCombie, S. W. (1975). *J. Chem. Soc., Perkin Trans. I*, 1574.
[132] Hassner, A. and Stumer, C. (1995). in *Organic Syntheses Based on Name Reactions and Unnamed Reactions. Tetrahedron Org. Chem. Ser.*, Vol. 11, Elsevier, Oxford, p. 26.
[133] Herczegh, P., Zsély, M., Bognár, R. and Szilágyi, L. (1986). *Tetrahedron Lett.*, **27**, 1509.
[134] Herczegh, P., Zsély, M., Szilágyi, L. and Bognár, R. (1989). *Heterocycles*, **28**, 887.
[135] Barrett, A. G. M., Bezuidenhoudt, B. C. B., Howell, A. R., Lee, A. C. and Russell, M. A. (1989). *J. Org. Chem.*, **54**, 2275.
[136] Barrett, A. G. M. and Lee, A. C. (1992). *J. Org. Chem.*, **57**, 2818.

[137] Pedersen, B. S., Scheibye, S., Clausen, K. and Lawesson, S.-O. (1978). *Bull. Soc. Chim. Belg.*, **87**, 293 (1978); *Chem. Abstr.*, **89**, 109786z.
[138] Lajoie, G., Lépine, F., Maziak, L. and Belleau, B. (1983). *Tetrahedron Lett.*, **24**, 3815.
[139] Keck, G. E., Enholm, E. J., Yates, J. B. and Wiley, M. R. (1985). *Tetrahedron*, **41**, 4079.
[140] Kahne, D., Yang, D., Lim, J. J., Miller, R. and Paguaga, E. (1988). *J. Am. Chem. Soc.*, **110**, 8716.
[141] Hürzeler, M., Bernet, B. and Vasella, A. (1993). *Helv. Chim. Acta*, **76**, 995.
[142] Hürzeler, M., Bernet, B., Mäder, T. and Vasella, A. (1993). *Helv. Chim. Acta*, **76**, 1779.
[143] Nicolaou, K. C., Mitsunobu, S., Theodorakis, E. A. and Miller, N. D. (1995). *J. Chem. Soc., Chem. Commun.*, 1583.
[144] Hwu, J. R. and Gilbert, B. A. (1989). *Tetrahedron*, **45**, 1233.
[145] Ortiz Mellet, C., Moreno Marín, A., Jiménez Blanco, J. L., García Fernández, J. M. and Fuentes, J. (1994). *Tetrahedron: Asymmetry*, **5**, 2325.
[146] García Fernández, J. M., Ortiz Mellet, C., Jiménez Blanco, J. L., Fuentes, J., Diánez, M. J., Estrada, M. D., López-Castro, A. and Pérez-Garrido, S. *Carbohydr. Res.*, in press.
[147] Avalos, González, M., Cintas Moreno, P., Gómez Monterrey, I. M., Jiménez Requejo, J. L., Palacios Albarrán, J. C. and Fuentes Mota, J. (1988). *An. Quim.*, **84C**, 5.
[148] Todoulou, O. G., Papadaki-Valiraki, A. E., Filippatos, E. C., Ikeda, S. and De Clercq, E. (1994). *Eur. J. Med. Chem.*, **29**, 127.
[149] McPherson, E. and Schein, P. S. (1986 & 1988). (Georgetown University), **PCT Int. Appl. WO 86 07,260**; *Chem. Abstr.*, **108**, 22205w.
[150] Talebian, A., Green, D. C., Hammer, C. F. and Schein, P. S. (1989 & 1990). (Georgetown University), **PCT Int. Appl. WO 89 00,574**; *Chem. Abstr.*, **112**, 90426b.
[151] Desmukh, S. P., Berad, B. N. and Paranjpe, M. G. (1986). *J. Indian Chem. Soc.*, **63**, 315.
[152] Reitz, A. B., Tuman, R. W., Marchione, C. S., Jordan, Jr., A. D., Bowden, C. R. and Maryanoff, B. E. (1989). *J. Med. Chem.*, **32**, 2110.
[153] Rashkes, Ya. V., Mil'grom, Yu. M. and Ambartsumova, R. F. (1989 & 1990). *Khim. Geterotsikl. Soedin.*, 1539; *Chem. Abstr.*, **112**, 235728p.
[154] Fuentes Mota, J., García Fernández, J. M., Ortiz Mellet, C., Pradera Adrián, M. A. and Cuevas Lorite, T. (1990). *J. Carbohydr. Chem.*, **9**, 837.
[155] Pleshkova, A. P., Uspenskaya, M. N. and Volkovich, S. V. (1993). *Zh. Anal. Khim.*, **48**, 731.
[156] Lindenberg, S., Kimberg, S. J. and Kallin, E. (1990). *J. Reprod. Fert.*, **89**, 431.
[157] Nimura, N., Ogura, H. and Kinoshita, T. (1980). *J. Chromatogr.*, **202**, 375.
[158] Kinoshita, T., Kasahara, Y. and Nimura, N. (1981). *J. Chromatogr.*, **210**, 77.
[159] Nimura, N., Toyama, A. and Kinoshita, T. (1984). *J. Chromatogr.*, **316**, 547.
[160] Chang, W. C., Micklewright, R. and Barrett, D. A. (1995). *J. Chromatogr. A*, **697**, 213.
[161] Nimura, N., Kasahara, Y. and Kinoshita, T. (1981). *J. Chromatogr.*, **213**, 327.
[162] Sedman, A. J. and Gal, J. (1983). *J. Chromatogr.*, **278**, 199.
[163] Gal, J. (1984). *J. Chromatogr.*, **307**, 220.
[164] Walle, T., Christ, D. D., Walle, U. K. and Wilson, M. J. (1985). *J. Chromatogr.*, **341**, 213.
[165] Christ, D. D. and Walle, T. (1985). *Drug Metab. Dispos.*, **13**, 380.
[166] Miller, K. J., Gal, J. and Ames, M. M. (1984). *J. Chromatogr.*, **307**, 335.
[167] Gal, J. (1986). *J. Liq. Chromatogr.*, **9**, 673.
[168] Gal, J. and Murphy, R. C. (1984). *J. Liq. Chromatogr.*, **7**, 2307.
[169] Ahnoff, M., Balmér, K. and Lindman, Y. (1992). *J. Chromatogr.*, **592**, 323.
[170] Fuentes Mota, J., Ortiz Mellet, C. and Pradera Adrián, M. A. (1984). *An. Quim.*, **80C**, 48.
[171] Fuentes Mota, J., Pradera Adrián, M. A., Ortiz Mellet, C. and García Fernández, J. M. (1986). *Carbohydr. Res.*, **153**, 318.
[172] Fuentes Mota, J., García Fernández, J. M., Ortiz Mellet, M. C., Pradera Adrián, M. A. and Babiano Caballero, R. (1989). *Carbohydr. Res.*, **193**, 314.
[173] Fuentes Mota, J., Ortiz Mellet, M. C., García Fernández, J. M., Pradera Adrián, M. A. and Gómez Monterrey, I. M. (1987). *Carbohydr. Res.*, **162**, 307.

[174] Fuentes Mota, J., Pradera Adrián, M. A., Ortiz Mellet, C. and García Fernández, J. M. (1987). *An. Quim.*, **83C**, 124.
[175] Shutalev, A. D., Ignatova, L. A. and Unkovskii, B. V. (1982). *Khim. Geterotsikl. Soedin.*, 825; *Chem. Abstr.*, **97**, 163356n.
[176] Shutalev, A. D., Ignatova, L. A. and Unkovskii, B. V. (1984). *Khim. Geterotsikl. Soedin.*, 548; *Chem. Abstr.*, **101**, 55448m.
[177] Ignatova, L. A., Shutalev, A. D., Unkovskii, B. V., Sinilova, N. G. and Duplishcheva, A. P. (1985 & 1986). *Khim.-Farm. Zh.*, **19**, 1447; *Chem. Abstr.*, **104**, 101954k.
[178] Avalos González, M., Babiano Caballero, R., Cintas Moreno, P., Fuentes Mota, J., Jiménez Requejo, J. L. and Palacios Albarrán, J. C. (1989). *Heterocyles*, **29**, 1.
[179] Ogura, H., Takeda, K. and Takaynagi, H. (1989). *Heterocyles*, **29**, 1171.
[180] Avalos, M., Babiano, R., Cintas, P., Fuentes, J., Jiménez, J. L. and Palacios, J. C. (1990). *Nucleosides Nucleotides*, **9**, 137.
[181] Avalos, M., Babiano, R., Cintas, P., Jiménez, J. L. and Palacios, J. C. (1990). *Carbohydr. Res.*, **198**, 247.
[182] Ogura, H., Takahashi, H. and Sato, O. (1981). *J. Carbohydr.Nucleosides,Nucleotides*, **8**,437.
[183] Wojtowicz, M. (1985). *Acta Pol. Pharm.*, **42**, 521.
[184] Yamamoto, I., Fukui, K., Yamamoto, S., Ohta, K. and Matsuzaki, K. (1985). *Synthesis*, 686.
[185] Plusquellec, D., Roulleau, F. and Brown, E. (1984). *Tetrahedron Lett.*, **25**, 1901.
[186] Plusquellec, D., Roulleau, F., Lefeuvre, M. and Brown, E. (1990). *Tetrahedron*, **46**, 465.
[187] Avalos, M., Babiano, R., Cintas, P., Jiménez, J. L., Palacios, J. C. and Valencia, C. (1994). *Tetrahedron*, **50**, 3273.
[188] Fernández-Bolaños Guzmán, J., García Rodríguez, S., Fernández-Bolaños, J., Diánez, M. J. and López-Castro, A. (1991). *Carbohydr. Res.*, **210**, 125.
[189] Anumula, K. R. and Taylor, P. B. (1991). *Anal. Biochem.*, **197**, 113.
[190] Hase, S. (1992). *J. Biochem.*, **112**, 266.
[191] Tichá, M. and Kocourek, J. (1991). *Carbohydr. Res.*, **213**, 339.
[192] Sarfati, R. S., Berthod, T., Guerreiro, C. and Canard, B. (1995). *J. Chem. Soc., Perkin Trans. 1*, 1163.
[193] Brossmer, R. and Gross, H. J. (1991 & 1992). **Ger. Offen. DE 4,009,630**; *Chem. Abstr.*, **116**, 21417v.
[194] Brossmer, R. and Gross, H. J. (1994). *Methods Enzymol.*, **247**, 177.
[195] Gross, H. J. and Brossmer, R. (1988). *Eur. J. Biochem.*, **177**, 583.
[196] Gross, H. J., Sticher, U. and Brossmer, R. (1990). *Anal. Biochem.*, **186**, 127.
[197] Gross, H. J. and Brossmer, R. (1991). *Clin. Chim. Acta*, **197**, 237.
[198] Gross, H. J. (1992). *Eur. J. Biochem.*, **203**, 269.
[199] Ogura, H., Furuhata, K., Ito, M. and Shidori, Y. (Mekuto K. K.) (1986 & 1987). **Jpn. Kokai Tokkyo Koho JP 61,243,094**; *Chem. Abstr.*, **106**, 84995w.
[200] Uppugunduri, S., Dakour, J., Kallin, E., Norberg, T., Zopf, D. and Lundblad, A. (1991). *Glycoconjugate J.*, **8**, 102.
[201] Dempcy, R. O., Browne, K. A. and Bruice, T. C. (1995). *J. Am. Chem. Soc.*, **117**, 6140.
[202] Povarov, L. S., Potapova, N. P., Bakina, E. V., Preobrazhenskaya, M. N. and Rozynov, B. V. (1992). *Bioorg. Khim.*, **18**, 1117.
[203] Pradera, M. A., Molina, J. L., Olano, D. and Fuentes, J. *8th Eur. Carbohydr. Symp.*, Sevilla (Spain), 2–7 July, 1995; Abstr. A-8.
[204] García González, F., Fernández-Bolaños, J. and López Aparicio, F. J. (1976). *ACS Symp. Ser.*, **39**, 207.
[205] Fernández-Bolaños, J., Trujillo Pérez-Lanzac, M., Fuentes Mota, J. and Cert Ventulá, A. (1985). *Carbohydr. Res.*, **143**, 260.
[206] Fernández-Bolaños, J., Galbis Pérez, A. and Zamora Mata, F. (1985). *An. Quim.*, **81C**, 205.
[207] Fernández-Bolaños, J., Trujillo Pérez-Lanzac, M., Fuentes Mota, J., Viguera Rubio, F. J. and Cert Ventulá, A. (1985). *An. Quim.*, **81C**, 147.

[208] Galbis Pérez, J. A., Jiménez Requejo, J. L., Palacios Albarrán, J. C., Avalos González, M. and Fernández-Bolaños, J. (1986). *An. Quim.*, **82C**, 11.
[209] Fernández-Bolaños, J., Robina Ramírez, I., Zamora Mata, F., Benárquez Fonseca, F. and Fuentes Mota, J. (1986). *An. Quim.*, **82C**, 211.
[210] Fernández-Bolaños, J., Trujillo Pérez-Lanzac, M., Fuentes Mota, J. and Cert Ventulá, A. (1986). *An. Quim.*, **82C**, 260.
[211] Avalos González, M., Jiménez Requejo, J. L., Palacios Albarrán, J. C. Ramos Montero, M. D. and Galbis Pérez, J. A. (1987). *Carbohydr. Res.*, **161**, 49.
[212] Fuentes Mota, J., Fernández García-Hierro, J. I., Areces Bravo, P., Rebolledo Vicente, F. and Galbis Pérez, J. A. (1988). *Nucleosides Nucleotides*, **7**, 457.
[213] Conde, C. F., Millan, M., Conde, A. and Márquez, R. (1985). *Acta Cryst., Ser. C*, **41**, 277.
[214] Conde, C. F., Millan, M., Conde, A. and Márquez, R. (1985). *Acta Cryst., Ser. C*, **41**, 1658.
[215] Estrada, M. D., Conde, A. and Márquez, R. *Acta Cryst., Ser. C.* (1986). **42**, 1659.
[216] Jiménez Blanco, J. L., Ortiz Mellet, C., García Fernádez, J. M. and Fuentes, J. 2-7 July, (1995). *8th Eur. Carbohydr. Symp.*, Sevilla (Spain), Abstr. A-7.
[217] Jiricek, R., Lehmann, J. Rob, B., and Scheuring, M. (1993). *Carbohydr. Res.*, **250**, 31.
[218] Chan, A. W.-Y. and Ganem, B. (1995). *Tetrahedron Lett.*, **36**, 811.
[219] Lehmann, J. and Rob, B. (1994). *Liebigs Ann. Chem.*, 805.
[220] Lehmann, J. and Rob, B. (1994). *Tetrahedron: Asymmetry*, **5**, 2255.
[221] Kobayashi, Y., Miyazaki, H. and Shiozaki, M. (1992). *J. Am. Chem. Soc.*, **114**, 10065.
[222] Ogawa, S. and Uchida, C. (1993). *Chem. Lett.*, 173.
[223] Uchida, C., Yamagishi, T. and Ogawa, S. (1993). *Chem. Lett.*, 971.
[224] Kobayashi, Y. and Shiozaki, M. (1994). *J. Antibiot.*, **47**, 243.
[225] Uchida, C., Yamagishi, T. and Ogawa, S. (1994). *J. Chem. Soc., Perkin Trans. 1*, 589.
[226] Kobayashi, Y., Miyazaki, H. and Shiozaki, M. (1994). *J. Org. Chem.*, **59**, 813.
[227] Avalos González, M., Cintas Moreno, P., Gómez Monterrey, I. M., Jiménez Requejo, J. L., Palacios Albarrán J. C., Rebolledo Vicente, F. and Fuentes Mota, J. (1989). *Carbohydr. Res.*, **187**, 1.
[228] Avalos, M., Babiano, R., Cintas, P., Jiménez, J. L., Palacios, J. C. and Valencia, C. (1993). *Tetrahedron*, **49**, 2676.
[229] Galbis Pérez, J. A., Areces Bravo, P., Rebolledo Vicente, F., Fernández Garcia-Hierro, J. I. and Fuentes, J. (1988). *Carbohydr. Res.*, **176**, 97.
[230] Areces, P., Avalos, M., Babiano, R., González, L., Jiménez, J. L., Palacios, J. C. and Pilo M. D. (1991). *Carbohydr. Res.*, **222**, 99.
[231] Barton, D. H. R. and Motherwell, W. B. (1981). *Pure Appl. Chem.*, **53**, 15.
[232] Hartwig, W. (1983). *Tetrahedron*, **39**, 2609.
[233] Ramaiah, M. (1987). *Tetrahedron*, **43**, 3541.
[234] Faizi, S., Siddiqui, B. S., Saleem, R., Siddiqui, S., Aftab, K. and Gilani, A. H. (1992). *J. Chem. Soc., Perkin Trans. 1*, 3237.
[235] Faizi, S., Siddiqui, B. S., Saleem, R., Siddiqui, S., Aftab, K. and Gilani, A. H. (1994). *J. Chem. Soc. Perkin Trans. 1*, 3035.
[236] Augustin, J. Baláz, S., *5th Eur. Carbohydr. Symp.*, Prague (Czechoslovakia), 21–25 August, 1989, Abstr. A-114
[237] Doane, W. M., Shasha, B. S., Stout, E. I., Russell, C. R. and Rist, C. E. (1969). *Carbohydr. Res.*, **11**, 321.
[238] Shasha, B. S. and Doane, W. M. (1971). *Carbohydr. Res.*, **16**, 145.
[239] Barrett, A. G. M., Prokopious, P. A. and Barton, D. H. R. (1979). *J. Chem. Soc., Chem. Commun.*, 1175.
[240] Barrett A. G. M., Prokopious, P. A. and Barton, D. H. R. (1981). *J. Chem. Soc., Perkin Trans. 1*, 1510.
[241] De Bernardo, S., Tengi, J. P., Sasso, G. J. and Weigele, M. (1985). *J. Org. Chem.*, **50**, 3457.

[242] Fiandor, J. and de las Heras, F. G. (1986). *Carbohydr. Res.*, **153**, 325.
[243] Meuwly, R. and Vasella, A. (1986). *Helv. Chim. Acta*, **69**, 751.
[244] Ogawa, S., Kimura, H., Uchida, C. and Ohashi, T. (1995). *J. Chem. Soc., Perkin Trans. 1*, 1695.
[245] Marquez, V. E., Tseng, C. K. H., Kelley, J. A., Mitsuya, H., Broder, S., Roth J. S., and Driscoll, J. S. (1987). *Biochem. Pharmacol.*, **36**, 2719.
[246] Kim, C.-H., Marquez, V. E., Broder, S., Mitsuya, H. and Driscoll, J. S. (1987). *J. Med. Chem.*, **30**, 862.
[247] Mitchell, W. L., Ravenscroft, P., Hill, M. L., Knutsen, L. J. S., Judkins, B. D., Newton, R. F. and Scopes, D. I. C. (1986). *J. Med. Chem.*, **29**, 809.
[248] Marquez, V. E., Tseng, C. K. H., Treanor, S. P. and Driscoll, J. S. (1987). *Nucleosides Nucleotides*, **6**, 239.
[249] Madhavan, G. V. B. and Martin, J. C. (1986). *J. Org. Chem.*, **51**, 1287.
[250] Kanaya, E. N., Howard, F. B., Frazier, J. and Miles, H. T. (1987). *Biochemistry*, **26**, 7159.
[251] Lin, T.-S., Yang, J.-H., Liu, M.-C. and Zhu, J.-L. (1990). *Tetrahedron Lett.*, **31**, 3829.
[252] Ford, M. J., Knight, J. G., Ley, S. V. and Vile, S. (1990). *Synlett*, 331.
[253] Ley, S. V., Armstrong, A., Díez-Martin, D., Ford, M. J., Grice, P., Knight, J. G., Kolb, H. C., Madin, A., Marby, C. A., Mukherjee, S., Shaw, A. N., Slawing, A. M. Z., Vile, S., White, A. D., Williams, D. J. and Woods, M. (1991). *J. Chem. Soc., Perkin Trans. 1*, 667.
[254] Jochims, J. C., Seeliger, A. and Taigel, G. (1967). *Chem. Ber.*, **100**, 845.
[255] Grouiller, A., Mackenzie, G., Najib, B., Shaw, G. and Ewing, D. (1988). *J. Chem. Soc., Chem. Commun.*, 671.
[256] Fernández-Bolaños, J., Blasco López, A. and Fuentes Mota, J. (1990). *Carbohydr. Res.*, **199**, 239.
[257] Mészáros, P., Pintér, I., Kovács, J. and Tóth, G. (1994). *Carbohydr. Res.*, **258**, 287.
[258] Tejima, S. and Ishiguro, S. (1967). *Chem. Pharm. Bull.*, **15**, 255.
[259] Szeja, W. and Bogusiak, J. (1988). *Synthesis*, 224.
[260] Hojo, K., Yoshino, H. and Mukaiyama, T. (1977). *Chem. Lett.*, 437.
[261] Lee, B.-H., Bertram, B., Schmezer, P., Frank, N. and Wiessler, M. (1994). *J. Med. Chem.*, **37**, 3154.
[262] Lee, B.-H., Bertram, B., Schmezer, P. and Wiessler, M. (1993). *Food and Cancer Prevention: Chemical and Biological Aspects, Spec. Publi.-R. Soc. Chem.*, **123**, 53.
[263] Fügedi, P., Garegg, P. J., Oscarson, S., Rosén, G. and Silwanis, B. A. (1991). *Carbohydr. Res.*, **211**, 157.
[264] Ogawa, Y., Ito, H., Chiba, H., Sato, S. and Morita, S. (1991 & 1992). **Jpn. Kokai Tokkio Koho JP 03,215,492**; *Chem Abstr.*, **116**, 59897q.
[265] Jochims, J. C. (1975). *Chem. Ber.*, **108**, 2320.
[266] Fernández-Bolaños, J., Blasco López, A. and Fuentes Mota, J. (1990). *An. Quim.*, **86**, 675.
[267] Shaban, M. A. E., Nasr, A. Z. and Taha, M. A. M. (1995). *J. Carbohydr. Chem.*, **14**, 985.
[268] Mansour, E.-S. M. E., Kassem, A. A., Abass, T. M., El-Toukhy, A. A. and Nassr, M. A. M. (1991). *J. Carbohydr. Chem.*, **10**, 429.
[269] Kassem, A. A., Mansour, E.-S M. E., Abass, T. M., El-Toukhy, A. A. and Nassr, M. A. M. (1992). *J. Carbohydr. Chem.*, **11**, 305.
[270] Robins, M. J. and Wilson, J. S. (1981). *J. Am. Chem. Soc.*, **103**, 932.
[271] Robins, M. J., Wilson, J. S. and Hansske, F. (1983). *J. Am. Chem. Soc.*, **105**, 4059.
[272] Knotz, H. and Zbiral, E. (1986). *Monatsh. Chem.*, **117**, 1437.
[273] Papageorgiou, C. and Tamm, C. (1987). *Helv. Chim. Acta*, **70**, 138.
[274] Seela, F. and Muth, H.-P. (1988). *Liebigs Ann. Chem.*, 215.
[275] Calvo-Mateo, A., Camarasa, M.-J., Díaz-Ortiz, A. and de las Heras, F. G. (1988). *Tetrahedron Lett.*, **29**, 941.
[276] Cocuzza, A. J. (1988). *Tetrahedron Lett.*, **29**, 4061.
[277] Biggadike, K., Borthwick, A. D., Exall, A. M., Kirk, B. E., Roberts, S. M. and Youds, P. (1987). *J. Chem. Soc., Chem. Commun.*, 1083.

[278] Wu, J.-C., Bazin, H. and Chattopadhyaya, J. (1987). *Tetrahedron*, **43**, 2355.
[279] Prisbe, E. J. and Martin, J. C. (1985). *Synth. Commun.*, **15**, 401.
[280] Robins, M. J., Madej, D., Hansske, F., Wilson, J. S., Gosselin, G., Bergogne, M.-C., Imbach, J.-L., Balzarini, J. and De Clercq, E. (1988). *Can. J. Chem.*, **66**, 1258.
[281] Nicolaou, K. C., Daines, R. A., Uenishi, J., Li, W. S., Papahatjis, D. P. and Chakraborty, T. K. (1987). *J. Am. Chem. Soc.*, **109**, 2205.
[282] Hiebl, J. and Zbiral, E. (1990). *Tetrahedron Lett.*, **31**, 4007.
[283] Khare, D. P., Hindsgaul, O. and Lemieux, R. (1985). *Carbohydr. Res.*, **136**, 285.
[284] Okamoto, K., Kondo, T. and Goto, T. (1988). *Tetrahedron*, **44**, 1291.
[285] Schreiner, E., Christian, R. and Zbiral E. (1990). *Liebigs Ann. Chem.*, 93.
[286] Barton, D. H. R. (1992). *Tetrahedron*, **48**, 2529.
[287] Barton, D. H. R. and Jaszberenyi, J. Cs. (1989). *Tetrahdron Lett.*, **30**, 2619.
[288] Barton, D. H. R., Jang, D. O. and Jaszberenyi, J. Cs. (1990). *Tetrahedron Lett.*, **31**, 4681.
[289] Gervay, J. and Danishefsky, S. (1991). *J. Org. Chem.*, **56**, 5448.
[290] Barton, D. H. R., Blundell, P., Dorchak, J., Jang, D. O. and Jaszberenyi, J. Cs. (1991). *Tetrahedron*, **47**, 8969.
[291] Barton, D. H. R., Jang, D. O. and Jaszberenyi, J. Cs. (1990). *Synlett*, **6**, 435.
[292] Barton, D. H. R., Jang, D. O. and Jaszberenyi, J. Cs. (1991). *Tetrahedron Lett.*, **32**, 7187.
[293] Barton, D. H. R., Jang, D. O. and Jaszberenyi, J. Cs. (1992). *Tetrahedron Lett.*, **33**, 5709.
[294] Haque, M. E., Kikuchi, T., Kanemitsu, K. and Tsuda, Y. (1986). *Chem. Pharm. Bull.*, **34**, 430.
[295] Haque, M. E., Kikuchi, T., Kanemitsu, K. and Tsuda, Y. (1987). *Chem. Pharm. Bull.*, **35**, 1016.
[296] Misbahi, K., Raphalen, D. and Plusquellec, D. 30 May-3 June, (1994). *XVèmes Jour. Chim. Biochim. Glucides*, Le Croisic (France), Abstr. P-50.
[297] Keck, G. E., Kachensky, D. F. and Enholm, E. J. (1985). *J. Org. Chem.*, **50**, 4317.
[298] Takahashi, S., Inoue, H. and Kuzuhara, H. (1995). *J. Carbohydr. Chem.*, **14**, 273.
[299] Barton, D. H. R. and Stick, R. V. (1975). *J. Chem. Soc., Perkin Trans. 1*, 1773.
[300] Trimnell, D., Shasha, B. S. and Doane, W. M. (1980). In *Methods Carbohydr. Chem.*, Vol. VIII, Eds. R. L. Whistler and J. N. BeMiller, Academic Press, New York, 277.
[301] Neumann, K. (1992). *Acta Chem. Scand.*, **46**, 913.
[302] Tsuda, Y., Sato, Y., Kakimoto, K. and Kanemitsu, K. (1992). *Chem. Pharm. Bull.*, **40**, 1033.
[303] Bredenkamp, M. W., Holzapfel, C. W. and Toerien, F. (1991 & 1992). *S. Afr. J. Chem.*, **44**, 97; *Chem. Abstr.*, **116**, 59766w.
[304] Barton, D. H. R. and Subramaniam, (1977). *J. Chem. Soc., Perkin Trans. 1*, 1718.
[305] Patroni, J. J., Stick, R. V., Engelhardt, L. M. and White, A. H. (1986). *Aust. J. Chem.*, **39**, 699.
[306] Redlich, H., Sudau, W. and Paulsen, H. (1985). *Tetrahedron*, **41**, 4253.
[307] Patroni, J. J. and Stick, R. V. (1985). *Aust. J. Chem.*, **38**, 947.
[308] Corey, E. J. and Winter, R. A. E. (1963). *J. Am. Chem. Soc.*, **85**, 2677.
[309] Hassner, A. and Stumer C. (1995). In *Organic Syntheses Based on Name Reactions and Unnamed Reactions. Tetrahedron Org. Chem. Ser.* Vol. 11, Elsevier, Oxford, p. 80.
[310] Chu, C. K., Bhadti, V. S., Doboszewski, B., Gu, Z. P., Kosugi, Y., Pullaiah, K. C. and Van Roey, P. (1989). *J. Org. Chem.* **54**, 2217.
[311] Tsuda, Y., Kanemitsu, K., Kakimoto, K. and Kikuchi, T. (1987). *Chem Pharm. Bull.*, **35**, 2148.
[312] Van Laak, K. and Scharf, H.-D. (1989). *Tetrahedron Lett.*, **30**, 4505.
[313] Toshima, K. and Tatsuta, K. (1993). *Chem. Rev.*, **93**, 1503.
[314] Murakami, M. and Mukaiyama, T. (1983). *Chem. Lett.*, 1733.
[315] Doane, W. M. (1972). In *Methods Carbohydr. Chem.*, Vol. VI, Eds. R. L. Whistler and J. N. BeMiller, Academic Press, New York, 413.
[316] Muller, T. E. and Purves, C. B. (1963). In *Methods Carbohydr. Chem.*, Vol. III, Ed. R. L. Whistler, Academic Press, New York, 238.

[317] Wong, T. C., Chan, W. H. and Cheng, V. K. W. (1994). *J. Chem. Ed.*, **71**, 803.
[318] Hirano, S., Usutani, A. and Zhang, M. (1994). *Carbohydr. Res.*, **256**, 331.
[319] Just, G. and Luthe, C. (1980). *Can J. Chem.*, **58**, 1799.
[320] Klein, L. L. (1985). *J. Am. Chem. Soc.*, **107**, 2573.
[321] Kochetkov, N. K., Sviridov, A. F., Yashunskii, D. V., Ermolenko, M. S. and Borodkin, V. S. (1986 & 1987). *Izv. Akad. Nauk SSSR, Ser. Khim.*, 441; *Chem. Abstr.*, **106**, 120150c.
[322] Binder, T. P. and Robyt, J. F. (1986). *Carbohydr. Res.*, **147**, 149.
[323] Yadav, J. S., Joshi, B. V. and Gurjar, M. K. (1987). *Carbohydr. Res.*, **165**, 116.
[324] Zbiral, E., Brandstetter, H. H. and Schreiner, E. P. (1988). *Monatsh. Chem.*, **119**, 127.
[325] Florent, J.-C., Uguetto-Monfrin, J. and Monneret, C. (1988). *Carbohydr. Res.*, **181**, 253.
[326] Lowary, T. L., Swiedler, S. J. and Hindsgaul, O. (1994). *Carbohydr. Res.*, **256**, 257.
[327] Izquierdo Cubero, I., Plaza López-Espinosa, M. T. and Kari, N. (1994). *Carbohydr. Res.*, **261**, 231.
[328] Izquierdo Cubero, I., Plaza López-Espinosa, M. T. and Kari, N. (1995). *Carbohydr. Res.*, **268**, 187.
[329] Barrett, A. G. M., Barton, D. H. R., Bielski, R. and McCombie, S. W. (1977). *J. Chem. Soc., Chem. Commun.*, 866.
[330] Barrett, A. G. M., Barton, D. H. R. and Bielski, R. (1979). *J. Chem. Soc., Perkin Trans. 1*, 2378.
[331] Schultz, M., Waldmann, H., Kunz, H. and Vogt, W. (1990). *Liebigs Ann. Chem.*, 1019.
[332] Barton, D. H. R., Jang, D. O. and Jaszberenyi, J. Cs. (1991). *Tetrahedron Lett.*, **32**, 2569.
[333] Chu, C. K. and Chen, Y. (1995). (The University of Georgia Research Foundation), **U.S. US 5,384,396**; Chem Abstr., **122**, 265937e.
[334] Paquette, L. A. and Oplinger, J. A. (1988). *J. Org. Chem.*, **53**, 2953.
[335] Conway, R. J., Nagel, J. P., Stick, R. V. and Tilbrook, D. M. G. (1985). *Aust. J. Chem.*, **38**, 939.
[336] Kirwan, J. N., Roberts, B. P. and Willis, C. R. (1990). *Tetrahedron Lett.*, **31**, 5093.
[337] Cole, S. J., Kirwan, J. N., Roberts, B. P. and Willis, C. R. (1991). *J. Chem. Soc., Perkin Trans. 1*, 103.
[338] Santoyo-González, F., Calvo-Flores, F. G., Hernández-Mateo, F., García-Mendoza, P., Isac-García, J. and Pérez-Alvarez M. D. (1994). *Synlett*, 454.
[339] Herdewijn, P. A. M., Van Aerschot, A., Jie, L., Esmans, E., Feneau-Dupont, J. and Declercq, J.-P. (1991). *J. Chem. Soc., Perkin Trans. 1*, 1729.
[340] Rama Rao, A. V., Ashok Reddy, K., Gurjar, M. K. and Kunwar, A. C. (1988). *J. Chem. Soc., Chem. Commun.*, 1273.
[341] Araki, Y., Endo, T., Tanji, M., Nagasawa, J. and Ishido, Y. (1987). *Tetrahedron Lett.*, **28**, 5853.
[342] Araki, Y., Endo, T., Tanji, M., Nagasawa, J. and Ishido, Y. (1988). *Tetrahedron Lett.*, **29**, 351.
[343] Marco-Contelles, J., Ruiz-Fernández, P. and Sánchez, B. (1993). *J. Org. Chem.*, **58**, 2894.
[344] Barton, D. H. R., Jaszberenyi J. Cs. and Theodorakis, E. A. (1992). *J. Am. Chem. Soc.* **114**, 5904.
[345] Pougny, J.-R. (1986). *J. Carbohydr. Chem.*, **5**, 529.
[346] Bogusiak, J. and Szeja, W. (1988 & 1989). (Politechnika Slaska), **Pol. PL 146,104**; *Chem. Abstr.*, **111**, 174582s.
[347] Szeja, W. and Bogusiak, J. (1987). *Carbohydr. Res.*, **170**, 235.
[348] Tropper, F. D., Andersson, F. O., Cao, S. and Roy, R. (1992). *J. Carbohydr. Chem.* **11**, 741.
[349] Paulsen, H., Rauwald, W. and Weichert, U. (1988). *Liebigs Ann. Chem.*, 75.
[350] Marra, A. and Sinaÿ, P. (1989). *Carbohydr. Res.*, **187**, 35.
[351] Hürzeler, M., Bernet, B. and Vasella, A. (1992). *Helv. Chim. Acta*, **75**, 557.
[352] Sinaÿ, P. (1991). *Pure Appl. Chem.*, **63**, 519.

[353] Sinaÿ, P. (1994). *Phosphorus, Sulfur, Silicon, Relat. Elem.*, **95 & 96**, 89.
[354] Marra, A., Shun, L. K. S., Gauffeny, F. and Sinaÿ, P. (1990). *Synlett*, 445.
[355] Marra, A. and Sinaÿ, P. (1990). *Carbohydr. Res.*, **195**, 303.
[356] Marra, A., Gauffeny, F. and Sinaÿ, P. (1991). *Tetrahedron*, **47**, 5149.
[357] Birberg, W. and Lönn, H. (1991). *Tetrahedron Lett.*, **32**, 7453.
[358] Birberg, W. and Lönn, H. (1991). *Tetrahedron Lett.*, **32**, 7457.
[359] Lönn, H. and Stenvall, K. (1992). *Tetrahedron Lett.*, **33**, 115.
[360] Zbiral E. and Brandstetter, H. H. (1991 & 1992). *J. Prakt. Chem.*, **333**, 759; *Chem. Abstr.*, **116**, 129468b.
[361] Barton, D. H. R., Dorchak, J. and Jaszberenyi, J. Cs. (1993). *Tetrahedron Lett.*, **34**, 8051.