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Glycosulfoxides in carbohydrate chemistry

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Abbreviations: Ac, acetyl; AIBN, (*E*)-2,2′-azobis(2-methylpropionitrile), $NCCMe_2N{=}NCMe_2CN$; All, allyl; aq, aqueous; Bn, benzyl; BSNPO, 2-benzenesulfonyl-3-(*m*-nitrophenyl)oxaziridine; Bu, butyl; Bz, benzoyl; CD, cyclodextrin; Cy, cyclohexyl; DCM, dichloromethane; DFT, density functional theory; DMAP, 4-dimethylaminopyridine; DMF, *N*,*N*-dimethylformamide; DTBMP, 2,6-di-*tert*-butyl-4-methylpyridine; equiv, equivalent(s); Et, ethyl; h, hour(s); HFIP, 1,1,1,3,3,3-hexafluoro-2-propanol; HIV, human immunodeficiency virus; *i*, *iso*; LAH, lithium aluminium hydride; LB, Langmuir–Blodgett; LDA, lithium diisopropylamide; Lev, levulinoyl (3-acetylpropanoyl); lp, lone pair; *m*, *meta*; *m*-CPBA, *m*-chloroperbenzoic acid; Me, methyl; min, minutes; MMPP, magnesium monoperoxyphthalate; mol, molar or moles; MOM, methoxymethyl; MPAA, (*S*)-α-methoxyphenylacetic acid; MPM, 4-methoxyphenylmethyl; NBS, *N*-bromosuccinimide; NIS, *N*-iodosuccinimide; NMNO, *N*-methylmorpholine *N*-oxide; NMR, nuclear magnetic resonance; NPhth, *N*-phthalimido; NTCP, *N*-tetrachlorophthalimido; Nu, nucleophile; *o*, *ortho*; oxone, potassium peroxymonosulfate ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$); *p*, *para*; P, protecting group; Ph, phenyl; Piv, pivaloyl (2,2-dimethylpropanoyl); PMB, *p*-methoxybenzyl; PMP, *p*-methoxyphenyl; Py, pyridine; Ra, Raney; rt, room temperature; Selectfluor, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane (*N*-chloromethyl-*N*′-fluorotriethylenediammonium) bis(tetrafluoroborate), F–TEDA–$2BF_4$; SGLT2, sodium-dependent glucose transporter 2; *t*, tertiary (*tert*); TBDMS (TBS), *tert*-butyldimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; Tebbe reagent, bis(cyclopentadienyl)-μ-chloro(dimethylaluminum)-μ-methylenetitanium; TEMPO, 2,2,6,6-tetramethylpiperidyl-1-oxy radical; Tf_2O, trifluoromethanesulfonic (triflic) anhydride; TFA, trifluoroacetic acid; TFAA, trifluoroacetic anhydride; TfOH, trifluoromethanesulfonic (triflic) acid; THF, tetrahydrofuran; THP, tetrahydro-2*H*-pyran-2-yl; TMS, trimethylsilyl; TMSOTf, trimethylsilyl trifluoromethanesulfonate; Tol, *p*-tolyl; Triton B, benzyltrimethylammonium hydroxide; Troc, 2,2,2-trichloroethoxycarbonyl; Ts, tosyl (*p*-toluenesulfonyl); TTBP, 2,4,6-tri-*tert*-butylpyrimidine.

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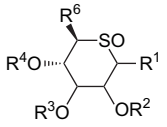
1. Introduction

Organic molecules including sulfur atoms are widespread in biological systems or in the pharmaceutical industry, and therefore play a significant role in synthetic organic chemistry. An analogy to oxygen-containing compounds is usually invoked when the structure, reactivity and nature of organosulfur compounds are described, even if sulfur is sufficiently different from oxygen in its oxidation states and bonding nature, so that remarkable diversities are observed.

We have introduced[1] the term 'glycosulfoxides' to group all sulfoxides having at least a sulfinyl moiety, which takes the place of an *endo*- or *exo*-cyclic oxygen in a sugar system. In glycosulfoxides, the intrinsic stereogenicity of the sugar backbone is close to the

Table 1
5-Thiopyranose monosaccharide *S*-oxides



D-Sugar series	R^1	R^2	R^3	R^4	R^6	(Sulfur config.)-comp. no.[a]	Ref.
Gluco	α-OMe	H	H	H	CH_2OH	(*R*)-**3**	4
Xylo	α-OMe	Ac	Ac	Ac	H	(*R*)-**5**	5
Xylo	β-OMe	Ac	Ac	Ac	H	**7**	5
Xylo	β-OMe	H	H	H	H	**8**	6
Ribo	α-OMe	Ac	Ac	Ac	H	(*R*)-**9**	6b
Ribo	α-OMe	H	H	H	H	(*R*)-**10**	6b
Ribo	β-OAc	Ac	Ac	Ac	H	(*R*)- and (*S*)-**13**	6b
Ribo	β-OMe	Ac	Ac	Ac	H	(*R*)- and (*S*)-**14**	6b,c
Gluco	α-OMe	Ac	Ac	Ac	CH_2OAc	(*R*)- and (*S*)-**18**	7,8
Gluco	α-OMe	Ac	Ac	Me	CH_2OAc	(*R*)-**19**	7a
Gluco	α-OMe	Me	Me	Me	CH_2OMe	(*R*)-**20**	7a
Gluco	α-OAc	Me	Me	Me	CH_2OMe	(*S*)-**21**	7a
Gluco	α-OAc	Me	Me	Ac	CH_2OMe	(*S*)-**22**	7a
Gluco-1,5-*S*	H	Ac	Ac	Ac	CH_2OAc	(*R*)- and (*S*)-**23**	7a
Galacto	α-OMe	Me	Me	Ac	CH_2OMe	(*R*)- and (*S*)-**24**	7b
Manno	α-OMe	Ac	Ac	Ac	CH_2OAc	(*S*)-**25**	7b
Manno	α-OMe	Ac	Ac	Ac	CH_2OAc	(*R*)-**26**	7b
Manno	α-OAc	Ac	Ac	Ac	CH_2OAc	(*S*)-**27**	7b
Gluco	α-OMe	Ac	Ac	Ac	CH_2OAc	(*S*)-**28**	7
Gluco	α-OBz	Ac	Ac	Ac	CH_2OAc	(*R*)- and (*S*)-**29**	7b
Gluco	α-OC(O)C_6H_4-4-CF_3	Ac	Ac	Ac	CH_2OAc	(*R*)- and (*S*)-**30**	7b
Gluco	α-OC(O)C_6H_4-4-Cl	Ac	Ac	Ac	CH_2OAc	(*R*)- and (*S*)-**31**	7b
Gluco	α-OC(O)C_6H_4-4-NO_2	Ac	Ac	Ac	CH_2OAc	(*R*)- and (*S*)-**32**	7b
Gluco	α-OC(O)PMP	Ac	Ac	Ac	CH_2OAc	(*R*)- and (*S*)-**33**	7b
Gluco-2,6-*S*	H	H	Bn	Bn	CH_2OH	(*R*)- and (*S*)-**35**	9
Gluco-2,6-*S*	H	H	H	H	CH_2OH	(*S*)-**36**	9
Gluco	β-*O*-2-[(4-Ethylphenyl)methyl]phenyl	H	H	H	CH_2OH	(*R*)-**37**	10
Gluco-1,5-*S*	H	Bz	Bz	Bz	CH_2OBz	(*R*)- and (*S*)-**38**	11
Gluco-1,5-*S*	H	Bz	CMe_2		CH_2OBz	(*R*)- and (*S*)-**39**	11
Gluco-1,5-*S*	H	CMe_2		Ac	CH_2OBz	(*R*)- and (*S*)-**40**	11
Gluco-1,5-*S*	H	MOM	CMe_2		CH_2OBz	(*R*)- and (*S*)-**41**	11
Gluco-1,5-*S*	β-D	Bz	CMe_2		(*R*)-CH(D)OBz	(*R*)- and (*S*)-**45**	11b
Gluco-1,5-*S*	H	MOM	CMe_2		CH_2OH	(*S*)-**46**	11b
Xylo	β-S-C_6H_4-4-CN	H	H	H	H	(*R*)-**50**	12
Xylo	β-*O*-(4-Ethyl-2-oxo-2*H*-1-benzopyran-7-yl)	H	H	H	H	(*R*)- and (*S*)-**52**	12
Arabino	β-SC_6H_4-4-NO_2	H	H	H	H	(*R*)- and (*S*)-**61**	13
Gluco	α-$(CH_2)_2CN$	Ac	Ac	Ac	CH_2OAc	(*R*) and (*S*)	7b
Gluco	α-F	Ac	Ac	Ac	CH_2OAc	(*R*) and (*S*)	7b
Gluco	α-OAc	Ac	Ac	Ac	CH_2OAc	(*R*)	7a,8
Gluco	α-OAc	Me	Me	Ac	CH_2OMe	(*R*)	7a
Gluco	α-OAc	Me	Me	Me	CH_2OMe	(*R*)	7a
Gluco	α-OC_6H_4-4-CF_3	Ac	Ac	Ac	CH_2OAc		14
Gluco	α-OC_6H_4-4-Cl	Ac	Ac	Ac	CH_2OAc		14
Gluco	α-OC_6H_4-4-F	Ac	Ac	Ac	CH_2OAc		14
Gluco	α-OC_6H_4-4-NO_2	Ac	Ac	Ac	CH_2OAc		14
Gluco	α-OPMP	Ac	Ac	Ac	CH_2OAc		14
Gluco	α-OMe	Ac	Ac	Me	CH_2OAc	(*S*)	7a
Gluco	α-OMe	Me	Me	Me	CH_2OMe	(*S*)	7a
Gluco	α-OPh	Ac	Ac	Ac	CH_2OAc		14
Gluco	β-OC_6H_4-4-CF_3	Ac	Ac	Ac	CH_2OAc		14
Gluco	β-OC_6H_4-4-Cl	Ac	Ac	Ac	CH_2OAc		14
Gluco	β-OC_6H_4-4-F	Ac	Ac	Ac	CH_2OAc		14
Gluco	β-OC_6H_4-4-NO_2	Ac	Ac	Ac	CH_2OAc		14
Gluco	β-OPMP	Ac	Ac	Ac	CH_2OAc		14
Gluco	β-OPh	Ac	Ac	Ac	CH_2OAc		14
Gluco-1,5-*S*	H	H	Bn	Bn	CH_2OH		9
Xylo	OH	H	H	H	H		15

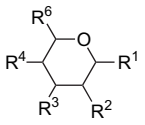
[a] Numbers are assigned only to the sulfoxides appearing in the schemes and/or text.

chirality of sulfoxide sulfur, creating a complex system that has been exploited as a chiral controller in stereoselective synthesis (see Section 4).[1a] Glycosulfoxides have, however, found a majority of applications as powerful glycosyl donors for O- and C-glycosylations. In particular, anomeric glycosyl sulfoxides have played the role of protagonists in one of the most practical approaches to oligosaccharide synthesis, the Kahne glycosylation (see Section 3), because of the mild conditions of this reaction, the good-to-excellent anomeric stereocontrol and the adaptability to both solution and solid-phase states.

Glycosulfoxides can also be regarded as systems that structurally mimic natural carbohydrates and thus represent potent probes in the mechanistic investigation of glycosidase biological behaviour. The replacement of an oxygen atom of oligosaccharides with a sulfur atom usually increases their resistance towards enzymatic hydrolysis, improves their availability and induces a higher affinity and selectivity for receptors (see Sections 2, 5 and 6). Moreover, some sulfinyl glycosides are known to be potential therapeutic compounds in the treatment of various pathologies, including cancer and infectious diseases (see Sections 2, 4, 5 and 7).

The rich and peculiar chemistry of glycosulfoxides motivates the choice of making them the subject of this report, where they are classified and distributed into seven sections, according to the position of one sulfinyl moiety in the carbohydrate skeleton. Selective

Table 2
Anomeric glycopyranose sulfoxides



Sugar series	R^1	R^2	R^3	R^4	R^6	(Sulfur config.)-comp. no.[a]	Ref.
D-Gluco	α-S(O)Et	OH	OH	OH	CH_2OH	**62**	5
L-Galacto	α-S(O)Ph	OBn	OBn	OBn	Me	**64**	20
D-Galacto	β-S(O)Ph	OPiv	OPiv	OPiv	CH_2OPiv	**65**	20,21
D-Gluco	β-S(O)Ph	OPiv	N_3	OPiv	CH_2OPiv	**68**	22
L-Xylo	α,β-S(O)Ph	H	OMe	$N(Et)C(O)CF_3$	H	**74**	23
L-Lyxo	α,β-S(O)PMP	H	OBn	OTMS	Me	**78**	24
L-Lyxo	α-S(O)C_6H_3–2,6-Cl_2	H	OPMB	OAc	Me	**81**	24c
D-Galacto	β-S(O)Ph	OPiv	OBn	OBn	CH_2OBn	**86**	20b
D-Manno	α-S(O)Ph	OH	OBn	OBn	CH_2OBn	**94**	25
D-Manno	α-S(O)Et	OAll	OBn	$OCH(Ph)OCH_2$		**101**	26
L-Galacto	β-S(O)Ph	OBn	OBn	OBn	Me	**128**	27
L-Galacto	β-S(O)Ph	OH	$OCMe_2O$		Me	**132**	25b,28
D-Gluco	β-S(O)$CMe_2CH(CO_2Et)_2$	OAc	OAc	OAc	CH_2OAc	(*R*)- and (*S*)-**138**	1b
D-Gluco	α-S(O)CH_2CH_2CN	OAc	OAc	OAc	CH_2OAc	(*R*)- and (*S*)-**142**	1a,29
D-Gluco	β-S(O)Tol	OH	OH	$OCH(Ph)OCH_2$		**147**	30
D-Manno	α-S(O)Et	OH	OH	$OCH(Ph)OCH_2$		(*R*)-**149**	26a,31
D-Manno	α-S(O)Et	OBn	OBn	$OCH(Ph)OCH_2$		(*R*)- and (*S*)-**150**	26a,31,32
D-Manno	α-S(O)All	OBn	OBn	$OCH(Ph)OCH_2$		(*R*)- and (*S*)-**151**	31
D-Manno	β-S(O)All	OBn	OBn	$OCH(Ph)OCH_2$		(*R*)- and (*S*)-**152**	31
D-Xylo	α-S(O)All	OBz	OBz	OBz	H	(*R*)-**153**	31
D-Xylo	β-S(O)All	OBz	OBz	OBz	H	(*R*)- and (*S*)-**154**	31
D-Gluco	β-S(O)Et	(*E*)-N=CHPMP	OBz	OBz	CH_2OBz	(*R*)- and (*S*)-**155**	33
D-Gluco	β-S(O)Et	(*E*)-N=CHPMP	OPiv	OPiv	CH_2OPiv	(*R*)- and (*S*)-**156**	33
D-Gluco	β-S(O)Et	NTCP	OBz	OBz	CH_2OBz	(*S*)-**159**	33
D-Gluco	β-S(O)Et	NH_2	OBz	OBz	CH_2OBz	(*S*)-**160**	33
D-Gluco	β-S(O)Et	NTCP	OPiv	OPiv	CH_2OPiv	(*S*)-**161**	33
D-Gluco	β-S(O)Et	NH_2	OPiv	OPiv	CH_2OPiv	(*S*)-**162**	33
D-Gluco	β-S(O)Et	NTCP	OAc	OAc	CH_2OAc	(*S*)-**164**	33
D-Gluco	β-S(O)Ph	NTCP	OAc	OAc	CH_2OAc	(*R*)- and (*S*)-**166**	33
D-Gluco	β-S(O)Ph	NPhth	OAc	OAc	CH_2OAc	(*R*)- and (*S*)-**168**	27b,33,34
D-Gluco	β-S(O)Ph	OBn	OBn	OBn	CH_2OBn	(*R*)- and (*S*)-**169**	32c,34a,35
D-Gluco	β-S(O)Ph	OAc	OAc	OAc	CH_2OAc	(*R*)- and (*S*)-**173**	27b,34a,36
D-Gluco	β-S(O)Ph	OH	OH	OH	CH_2OH	**179**	36b
D-Gluco	β-S(O)Tol	$NHCO_2Me$	OH	$OCH(Ph)OCH_2$		**179**	37
D-Gluco	β-S(O)Tol	NHTroc	OAc	$OCH(Ph)OCH_2$		**181**	37
D-Gluco	β-S(O)Tol	NPhth	OAc	OAc	CH_2OAc	**182**	38
D-Gluco	β-S(O)Tol	OAc	OAc	OAc	CH_2OAc	**183**	30a,37,39
D-Gluco	β-S(O)Tol	OBn	OBn	$OCH(Ph)OCH_2$		**184**	30a,37,39
D-Galacto	α-S(O)Et	OAc	OAc	OAc	CH_2OAc	(*R*) and (*S*)	40
D-Galacto	β-S(O)$C(CO_2t\text{-Bu})=CCO_2t\text{-Bu}$-(*E*)	OAc	OAc	OAc	CH_2OAc	(*R*) and (*S*)	1b
D-Galacto	β-S(O)$CMe_2CH(CO_2Et)_2$	OAc	OAc	OAc	CH_2OAc	(*R*) and (*S*)	1b
D-Galacto	β-S(O)Et	OAc	OAc	OAc	CH_2OAc	(*R*) and (*S*)	40
D-Galacto	β-S(O)Et	OBz	OBz	OBz	CH_2OBz	(*R*) and (*S*)	41
D-Galacto	β-S(O)Ph	NPhth	OAc	OAc	CH_2OAc		42
D-Galacto	β-S(O)Ph	OAc	OAc	OAc	CH_2OAc	(*R*) and (*S*)	21a,27b,36c
D-Galacto	β-S(O)Ph	OAc	OAc	$OCH(Ph)OCH_2$			27b
D-Galacto	β-S(O)Ph	OBn	OBn	OBn	CH_2OBn	(*R*) and (*S*)	21
D-Galacto	β-S(O)Ph	OBn	$OCMe_2O$		CH_2OBn		27b
D-Galacto	β-S(O)Ph	OBz	OBz	OBz	CH_2OBz		27b
D-Galacto	β-S(O)Ph	OBz	$OCMe_2O$		CH_2OBz		43
D-Galacto	β-S(O)Ph	OH	$OCMe_2O$		CH_2OAc	(*R*) and (*S*)	21a

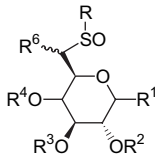
(*continued on next page*)

Table 2 (*continued*)

Sugar series	R^1	R^2	R^3	R^4	R^6	(Sulfur config.)-comp. no.[a]	Ref.
D-Galacto	β-S(O)Ph	OH	OH	$OCMe_2OCH_2$		(*R*) and (*S*)	21a
D-Galacto	β-S(O)Ph	OH	OH	OH	CH_2OH	(*R*) and (*S*)	21a
D-Galacto	β-S(O)Ph	OTBDPS	$OCMe_2O$		CH_2OAc	(*R*) and (*S*)	21a
D-Galacto	β-S(O)Tol	OAc	OAc	OAc	CH_2OAc	(*R*) and (*S*)	38,44
D-Galacto	β-S(O)Tol	OBn	OBn	OBn	CH_2OBn		38,44
D-Galacto	β-S(O)Tol	OBn	OBn	$OCH(Ph)OCH_2$			30a,37
D-Galacto	β-S(O)Tol	OBz	OBz	OH	$CH_2OTBDPS$		30a
L-Galacto	α-S(O)PMP	OH	$OCMe_2O$		Me		25b
L-Galacto	α-S(O)C_6H_3–3-[*i*PrCH(OH)]–4-OMe	OH	$OCMe_2O$		Me		25b
L-Galacto	α-S(O)C_6H_4–4-NO_2	OH	$OCMe_2O$		Me		25b
L-Galacto	α-S(O)*t*-Bu	OH	$OCMe_2O$		Me		25b
L-Galacto	α,β-S(O)Et	OBn	OBn	OBn	Me	(*R*) and (*S*)	34a
D-Gluco	α-S(O)C(CO_2*t*-Bu)=CCO_2*t*-Bu-(*E*)	OAc	OAc	OAc	CH_2OAc	(*R*) and (*S*)	1
D-Gluco	α-S(O)C(CO_2Me)=CCO_2Me-(*E*)	OAc	OAc	OAc	CH_2OAc	(*R*) and (*S*)	1
D-Gluco	α-S(O)C(CO_2Me)=CH_2	OAc	OAc	OAc	CH_2OAc		1a
D-Gluco	α-S(O)CH=CCO_2Me-(*E*)	OAc	OAc	OAc	CH_2OAc		1a
D-Gluco	α-S(O)Ph	N_3	OH	$OCH(Ph)OCH_2$			34a
D-Gluco	α-S(O)Ph	OBn	OBn	OBn	CH_2OBn		45
D-Gluco	α-S(O)Ph	OBn	OBn	$OCH(Ph)OCH_2$		(*R*)	32c
D-Gluco	α-S(O)Ph	OH	OBn	OBn	CH_2OBn		25b
D-Gluco	β-S(O)C(CO_2*t*-Bu)=CCO_2*t*-Bu-(*E*)	OAc	OAc	OAc	CH_2OAc	(*R*) and (*S*)	1b
D-Gluco	β-S(O)C(CO_2Me)=CCO_2Me-(*E*)	OAc	OAc	OAc	CH_2OAc	(*R*) and (*S*)	1b
D-Gluco	β-S(O)C(CO_2Me)=CH_2	OAc	OAc	OAc	CH_2OAc		1a
D-Gluco	β-S(O)CH_2CH_2CN	OAc	OAc	OAc	CH_2OAc	(*R*) and (*S*)	1
D-Gluco	β-S(O)CH=CCO_2Me-(*E*)	OAc	OAc	OAc	CH_2OAc		1a
D-Gluco	β-S(O)Et	NPhth	OAc	OAc	CH_2OAc	(*R*) and (*S*)	40
D-Gluco	β-S(O)Et	OAc	OAc	OAc	CH_2OAc	(*R*) and (*S*)	40
D-Gluco	β-S(O)Et	OAc	OAc	$OCH(Ph)OCH_2$		(*R*) and (*S*)	40,46
D-Gluco	β-S(O)Et	OBz	OBz	OBz	CH_2OBz	(*R*) and (*S*)	41
D-Gluco	β-S(O)Et	OBz	OBz	OBz	$CH_2OTBDPS$		27b
D-Gluco	β-S(O)Et	OH	OH	$OCH(Ph)OCH_2$		(*R*) and (*S*)	40
D-Gluco	β-S(O)Ph	OBn	OBn	$OCH(Ph)OCH_2$			32c,43
D-Gluco	β-S(O)Ph	OBz	OBz	OBz	CH_2OBz		27b
D-Gluco	β-S(O)Ph	OBz	OBz	$OCH(Ph)OCH_2$			43
D-Gluco	β-S(O)Ph	OH	OBn	OBn	CH_2OBn		25b
D-Gluco	β-S(O)Ph	OH	OMe	OMe	CH_2OMe		25b
D-Gluco	β-S(O)Ph	OPiv	OPiv	OPiv	CH_2OPiv	(*R*) and (*S*)	32c,34a,47
D-Gluco	β-S(O)Tol	NHTroc	OAc	OAc	CH_2OAc		38
D-Gluco	β-S(O)Tol	OBn	OBn	OH	CH_2OH		38
D-Gluco	β-S(O)Tol	OBn	OBn	OH	$CH_2OTBDPS$		38
D-Gluco	β-S(O)Tol	OBz	OBz	OBz	CO_2Me	(*R*) and (*S*)	38
D-Gluco	β-S(O)Tol	OC(O)Tol	OC(O)Tol	OC(O)Tol	$CH_2OTBDPS$		38
D-Gluco	β-S(O)Tol	OC(O)Tol	OC(O)Tol	OH	CH_2OH	(*R*) and (*S*)	38
D-Gluco	β-S(O)Tol	OC(O)Tol	OC(O)Tol	OLev	$CH_2OTBDPS$	(*R*) and (*S*)	38
L-Gluco	β-S(O)Ph	OPiv	OPiv	OPiv	CH_2OPiv	(*R*) and (*S*)	48
D-Manno	α-S(O)C(CO_2*t*Bu)=CCO_2*t*Bu-(*E*)	OAc	OAc	OAc	CH_2OAc	(*R*) and (*S*)	1b
D-Manno	α-S(O)C(CO_2Me)=CCO_2Me-(*E*)	OAc	OAc	OAc	CH_2OAc	(*R*) and (*S*)	1b
D-Manno	α-S(O)CH_2CH_2CN	OAc	OAc	OAc	CH_2OAc	(*R*) and (*S*)	1b
D-Manno	α-S(O)$CMe_2CH(CO_2Et)_2$	OAc	OAc	OAc	CH_2OAc	(*R*) and (*S*)	1b
D-Manno	α-S(O)Et	OAc	OAc	OAc	CH_2OAc	(*R*) and (*S*)	25b,34a,40
D-Manno	α-S(O)Et	OAll	OAll	$OCH(Ph)OCH_2$		(*R*)	26a,32a,b
D-Manno	α-S(O)Et	OBn	OBn	OBn	CH_2OBn		26a,32,49
D-Manno	α-S(O)Et	OBn	$O(CHOMe)_2O$		CH_2OBn	(*R*)	50
D-Manno	α-S(O)Et	$OCMe_2O$		$OCH(Ph)OCH_2$		(*R*)	26a
D-Manno	α-S(O)Et	$OCMe_2O$		$OCMe_2OCH_2$			32b
D-Manno	α-S(O)Et	OTBDMS	OBn	$OCH(Ph)OCH_2$		(*R*)	26a,32a,b,51
D-Manno	α-S(O)Et	OTMS	OBn	$OCH(Ph)OCH_2$		(*R*)	26a,32a,b
D-Manno	α-S(O)Ph	OAc	OAc	OAc	CH_2OAc		36c
D-Manno	α-S(O)Ph	OBn	OBn	OBn	CH_2OBn		52
D-Manno	α-S(O)Ph	OBn	OBn	$OCH(Ph)OCH_2$		(*R*)	26a,32
D-Manno	α-S(O)Ph	OBn	$O(CHOMe)_2O$		CH_2OBn	(*R*)	50
D-Manno	α-S(O)Ph	$OCMe_2O$		OTs	Me		53
D-Manno	α-S(O)Ph	OMe	OMe	$OCH(Ph)OCH_2$		(*R*)	26a,32b
D-Manno	α-S(O)Ph	OMe	OMe	OMe	CH_2OMe	(*R*)	26a,32b
D-Manno	α-S(O)Ph	OPiv	OPiv	OPiv	CH_2OPiv	(*R*) and (*S*)	48,54
D-Manno	α-S(O)Ph	OTBDMS	OPMB	$OCH(Ph)OCH_2$			53
D-Manno	β-S(O)C(CO_2Me)=CCO_2Me-(*E*)	OAc	OAc	OAc	CH_2OAc	(*R*) and (*S*)	1b
D-Manno	β-S(O)CH_2CH_2CN	OAc	OAc	OAc	CH_2OAc	(*R*) and (*S*)	1b
D-Manno	β-S(O)Ph	OAc	OAc	OAc	CH_2OAc		36c
L-Manno	α-S(O)Ph	OAc	OAc	OAc	Me		27b
D-Xylo	α-S(O)All	OBz	OBz	OBz	H	(*S*)	31
D-Xylo	α-S(O)Ph	OBz	OBz	OBz	H		55
D-Xylo	β-S(O)Ph	OAc	OAc	OAc	H		27b
D-Xylo	β-S(O)Ph	OBz	OBz	OBz	H		26b,55

[a] Numbers are assigned only to the sulfoxides appearing in the schemes and/or text.

Table 3
6-Deoxy-6-sulfinyl D-monosaccharides



D-Sugar series	R^1	R^2	R^3	R^4	R	R^6	(Sulfur config.)-comp. no.[a]	Ref.
Galacto	α-$OCMe_2$		CMe_2		2-Benzothiazolyl	H	(*R*)- and (*S*)-**202**	79
Galacto	α-$OCMe_2$		CMe_2		2-Pyridyl	H	(*R*)- and (*S*)-**203**	79,81
Galacto	α-$OCMe_2$		CMe_2		Me	H	(*R*)- and (S)-**204**	79
Galacto	α-$OCMe_2$		CMe_2		Ph	Cl		82
Galacto	α-$OCMe_2$		CMe_2		Ph	H	(*R*)- and (*S*)-**205**	79
Galacto	β-OC_6H_4–4-NO_2	Ac	Ac	Ac	Me	H	(*R*)- and (*S*)-**206**	80
Galacto	β-OC_6H_4–4-NO_2	H	H	H	Me	H	(*R*)- and (*S*)-**207**	80
Gluco	α-OMe	Ac	Ac	Ac	1*H*-Purin-6-yl	H		83
Gluco	α-OMe	Ac	Ac	Ac	2-pyrimidinyl	H		83
Gluco	α-OMe	Ac	Ac	Ac	Me	H	(*S*)	84
Gluco	α-OMe	Ac	Ac	Ac	Ph	H	(*R*) and (*S*)	85
Gluco	α-OMe	H	H	H	1*H*-Purin-6-yl	H		83
Gluco	α-OMe	H	H	H	Me	H	(*S*)	86
Gluco	β-OMe	Ac	Ac	Ac	Me	H		87

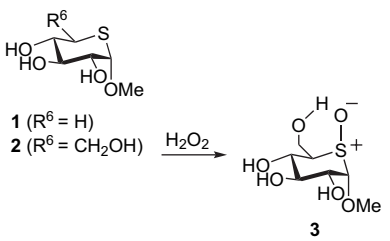
[a] Numbers are assigned only to the sulfoxides appearing in the schemes and/or text.

oxidation of ring thiosugar thioglycosides, known as orally active antithrombotic agents, has furnished both series of monosulfoxides having an *endo*- or *exo*-cyclic sulfinyl group (see Section 2.1).

In this report, Sections 2, 3 and 6 are accompanied by tables collecting not only the sulfinyl pyranose saccharides that appear in the schemes and/or text, but also further similar compounds and related references. The tables are not exhaustive, but useful, possibly, both in locating products of interest and realizing the high variety of available 5-thiopyranose monosaccharide *S*-oxides (Table 1), anomeric glycopyranose sulfoxides (Table 2) and 6-deoxy-6-sulfinyl D-monosaccharides (Table 3). On the contrary, to the best of our knowledge, only a very few examples are reported in the literature of sugars carrying a sulfinyl substituent on C-2 or C-3 of the pyranose ring, and we have found no examples of 4-deoxy-4-sulfinylglycopyranose derivatives.

2. Sulfoxide ring sugars

Sugar compounds with a sulfinyl function in place of oxygen in the sugar ring are frequently and directly indicated as sulfoxide ring sugars. In 1962, Whistler et al.[2] reported the first preparation of a sugar structure with a sulfur atom in place of oxygen in the sugar ring. Specifically, they prepared methyl 5-thio-α-D-xylopyranoside (**1**) (Scheme 1) as part of their programme to substitute sulfur and nitrogen for the ring oxygen in a number of sugars and sugar derivatives. They claimed that these "compounds are of both chemical and biochemical interest as sugar analogs and as antimetabolites of possible value in medical chemistry".



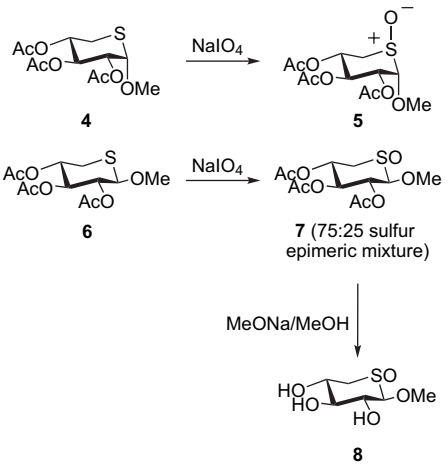
Scheme 1. Synthesis of methyl 5-thio-α-D-glucopyranoside S-(R_S)-oxide (**3**).

From the time of this discovery, the importance of these sulfur ring sugars in biochemical investigations has been widely recognized. 5-Thio-D-glucopyranose has some interesting biological activities, such as an inhibitory effect against D-glucose transport across membranes and against enzymes capable of metabolizing carbohydrates. Many pyranoses and furanoses with the ring oxygen replaced by an imino group are natural products and are useful as potent glycosidase inhibitors. This discovery stimulated interest in the development of effective procedures for the synthesis of various azasugars and analogues, such as thiopyran derivatives, for the investigation of glycosidase reactions and the development of specific glycosidase inhibitors to treat metabolic disorders such as diabetes, or as antiviral, antibacterial and anticancer agents. An evaluation of methyl 5-thio-α-D-glucopyranoside (**2**)[3] and its sulfoxide derivative **3** (Scheme 1) as glycosidase inhibitors was carried out. It was found that **2** was a strong inhibitor, but oxidation of the ring heteroatom weakened the inhibition.[4] Oxidation of the ring S with H_2O_2 to sulfoxide was carried out at room temperature. Protection of the anomeric centre as the methyl thioglucoside was required to prevent the ring opening. The sulfoxide **3** was obtained as a single diastereomer, and its stereochemistry was tentatively assigned as (R_S) with the oxygen occupying the axial position (Scheme 1). This assignment was consistent with the anomeric effect (see also Section 3.2) and the observation of a strong change in the ^{1}H NMR chemical shifts of the methylene protons at C-6 after oxidation.[4]

Initially, 5-thioglycopyranose *S*-oxides (Table 1) received great deal of attention, particularly in the chemical characterization of sugars with sulfur as the ring heteroatom. Oxidation of either the α or β anomer of methyl 2,3,4-tri-*O*-acetyl-D-xylothiopyranoside with $NaIO_4$ in MeOH and H_2O produced the sulfoxides, with the diastereoselection controlled by the anomeric configuration.[5] The α anomer **4** gave mainly one (R_S) sulfoxide **5**, while from the β anomer **6** two epimeric sulfoxides **7** were produced in a ratio of about 75:25 (Scheme 2).

Acid-catalyzed hydrolysis of methyl glycosides having sulfur as the ring heteroatom has been shown to be much faster than that of the ring-oxygen counterparts. This high rate of hydrolysis of the thiosugar derivatives has been explained in terms of the inductive effect of the herocyclic sulfur atom in releasing lp electrons for stabilization of the anomeric cation.

In the sulfoxide structures, there is a net loss of electrons from the sulfur to the sulfoxide oxygen atom, decreasing the electron flow from the heterocyclic sulfur to the anomeric carbon atom and, hence, greatly reducing the possibility of forming a carbonium–



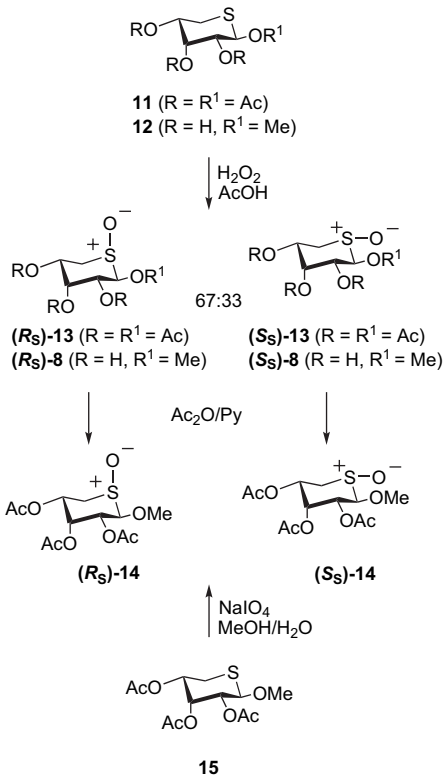
Scheme 2. Synthesis of 5-thio-α- and -β-D-xylopyranoside *S*-oxides.

sulfonium ion. The stability to acid of the methyl glycosides of the sugar sulfoxides is shown by their resistance to hydrolysis by dilute mineral acid. Methyl 5-thio-β-D-xylopyranoside *S*-oxides **8** (Scheme 2) are unaffected by treatment with 0.5 M HCl during 100 h at 75 °C. Under the same conditions, the time for complete hydrolysis of methyl β-D-xylopyranoside is approximately 24 h, whereas, for methyl 5-thio-β-D-xylopyranoside, the hydrolysis time is about 1 h. Compounds **8** were prepared by deacetylation with MeONa/MeOH of the corresponding 2,3,4-triacetates **7**, separated by column chromatography.[6a]

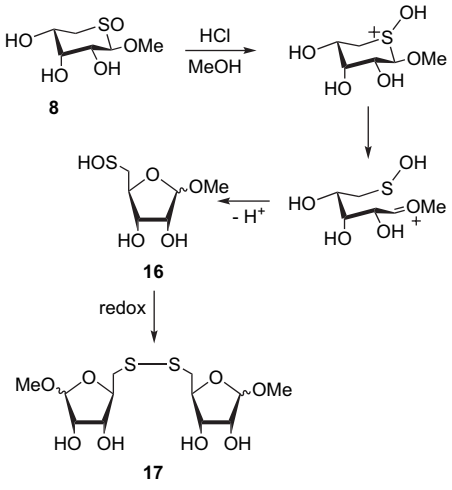
The stereochemical outcome of 5-thio-D-gluco- and -xylopyranoside oxidation (Schemes 1 and 2) has been confirmed in the 5-thio-D-ribopyranose series, and the sulfoxide configurations were assigned on the basis of ^{1}H NMR and conformational data.[6b] $NaIO_4$ oxidation of methyl 2,3,4-tri-*O*-acetyl-5-thio-α-D-ribopyranoside gave predominantly the (R_S) sulfoxide **9** (Table 1) and, again, an (R_S) sulfoxide **10** was the preponderant product of the oxidation of methyl 5-thio-α-D-ribopyranoside with cold H_2O_2 in AcOH. If the starting cyclic sulfides were the β-anomer derivatives **11**, **12** and **15** (Scheme 3), the corresponding epimeric mixtures of sulfoxides **13**, **8** and **14** were always obtained with an (R_S)/(S_S) ratio of about 67:33.

The sulfoxides **8** were stable to base, but were converted by methanolic HCl into the αα, αβ, and ββ forms of 5,5′-dithiobis[methyl 5-deoxy-D-ribofuranoside] **17** (Scheme 4). These products presumably arise via the transient sulfenic acids **16** (formed by protonation of the sulfinyl moiety in both epimers **8**), which then disproportionate into the disulfides **17** and thiosulfonates. The sulfoxides **8** were unaffected in the cold, but, with hot, dilute HCl (0.2 M), they gave a reducing sugar chromatographically identified as 5,5′-dithiobis[5-deoxy-D-ribofuranose] and which was assumed to have arisen via the glycosides **17**.[6b]

A remarkable difference was observed in stereoselectivity between 1-*O*-methyl and 1-*O*-acetyl derivatives of 5-thio-α-D-glucopyranose in the *m*-CPBA oxidation, and this was discussed with regard to the substituent effects.[7a] At first, methyl tetra-*O*-acetyl-5-thio-α-D-glucopyranose and 5-thio-α-D-glucopyranose pentaacetate were oxidized with *m*-CPBA at −20 °C in DCM. It was found that the axial sulfoxide (R_S)-**18** (Table 1) was preferentially obtained [(R_S)/(S_S)∼83:17] from the 1-*O*-methyl derivative, while the equatorial sulfoxide (S_S)-**18** was preferentially obtained [(R_S)/(S_S)∼30:70] from the 1-*O*-acetyl derivative. The finding of this distinct reverse stereoselectivity prompted Hashimoto et al.[7a] to investigate in detail the substituent effect at other than the anomeric position and the effects of different factors such as solvent and temperature on the stereoselectivity. Thus, various kinds of both 1-*O*-methyl and 1-*O*-acetyl derivatives of 5-thio-α-D-glucopyranose and a 1-deoxy analogue (1,5-dideoxy-1,5-epithio-D-glucitol



Scheme 3. Synthesis of 5-thio-β-D-ribopyranose pentaacetate and methyl 5-thio-β-D-ribopyranoside *S*-oxides.



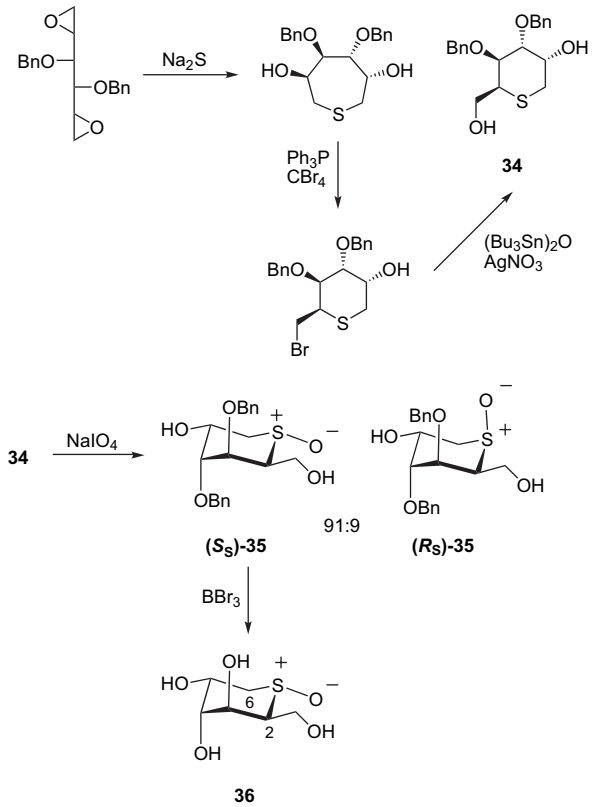
Scheme 4. Conversion of methyl 5-thio-β-D-ribopyranoside *S*-oxides into 5,5′-dithiobis[methyl 5-deoxy-D-ribofuranosides].

tetraacetate) were subjected to oxidation in different conditions. The following tendencies were observed, i.e., (i) preferential formation of axial (R_S)-**18**, **19**, **20** and equatorial (S_S)-**18**, **21**, **22** sulfoxides (Table 1) when the anomeric substituent is a methoxy and an acetoxy group, respectively (except for 5-thio-α-D-glucopyranose pentaacetate in acetonitrile) and (ii) ineffectiveness of substituents other than at the anomeric position on the stereoselectivity. On the other hand, less stereoselectivity was observed in the oxidation of the 1-deoxy derivative (1,5-dideoxy-1,5-epithio-D-glucitol tetraacetate) to **23** (Table 1). Several considerations suggested that the sulfoxide formation was kinetically controlled.

Next, various 5-thio-α-D-glycopyranose derivatives, including 5-thio-α-D-galacto- and -mannopyranose derivatives, were oxidized to the sulfoxides (R_S)-**18**, **24**–**28** (Table 1) with *m*-CPBA or BSNPO[7b]

in order to probe the origin of the reversal of stereoselectivity observed in the *m*-CPBA oxidation of the 1-*O*-methyl and 1-*O*-acetyl derivatives of 5-thio-α-D-glucopyranose.[7a] Analyses of the stereoselectivity in the oxidation of 1-*O*-(*p*-substituted-benzoyl)-5-thio-α-D-glucose derivatives suggested that the electron-donating and -withdrawing substituents, respectively, tend to afford more and less of the axial/equatorial ratios of the sulfoxides **29**–**33** (Table 1).

A series of enantiomerically pure sulfur ring sugars, and their corresponding sulfoxides or sulfones, were synthesized via thiocyclization of C_2 symmetric bis-epoxides (Scheme 5).[9] These compounds have been evaluated as inhibitors of several glycosidases (α- and β-D-glucosidases, α-D-mannosidase and α-L-fucosidase). The results of the inhibition studies show again[4] that thiosugars are inhibitors of glycosidases, and that their oxidation into sulfoxide and sulfone, respectively, reduces or abolishes the inhibition. The authors claim[9] that "if these compounds exhibit only moderate inhibition against glycosidases, they can serve as conformationally constrained scaffolds for the rational drug design of potent HIV inhibitors". Mild oxidation of **34** (Scheme 5) leads to a 91:9 mixture of sulfur epimers **35** (82%), easily separated by flash chromatography. It was found that the equatorial sulfoxide (S_S)-**35** was the major product, deprotected to the sulfoxide **36** using a solution of BBr_3 in DCM at −60 °C. Two seven-membered sulfoxide ring sugars were also reported, i.e., 1,6-dideoxy-1,6-episulfinyl-3,4-bis-*O*-(phenylmethyl)-D-mannitol and -L-iditol.[9]



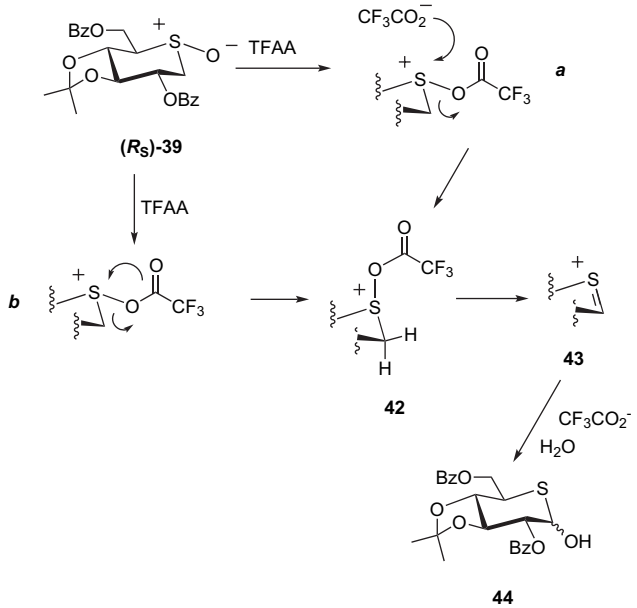
Scheme 5. Synthesis of 2,6-dideoxy-2,6-episulfinyl-D-glucitols.

2-[(4-Ethylphenyl)methyl]phenyl 5-thio-β-D-glucopyranoside *S*-(R_S)-oxide (**37**) (Table 1) has been recently described in a Japanese patent[10] among 5-thio-β-D-glucopyranoside compounds contained in antidiabetic medicines as an active component for the inhibition of SGLT2 in the kidney. The applications of these compounds in the treatment of diabetes mellitus, its complications and its related diseases have been discussed. 4-Thio-D-xylofuranose and 2,3-*O*-(1-methylethylidene)-4-thio-D-ribofuranose 1-acetate 5-benzoate *S*-oxides were also reported in the patent literature.[15,16]

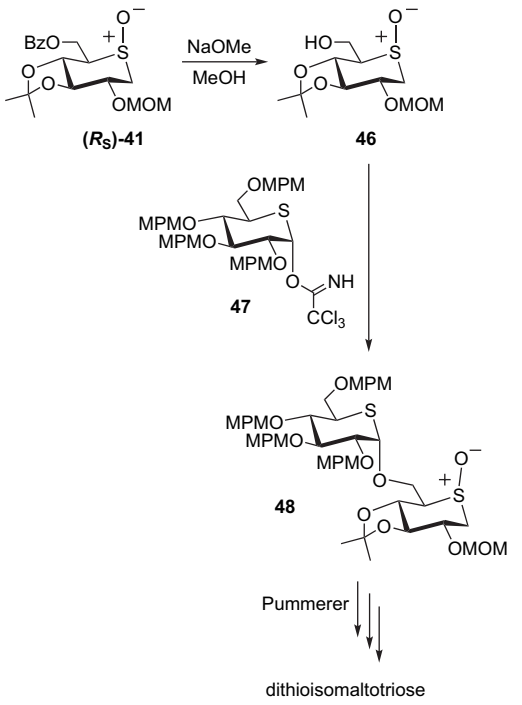
2.1. Pummerer rearrangement and orally active antithrombotic thioglycosides

1-Deoxy-5-thio-D-glucopyranose *S*-oxides **38**–**41** (Table 1) carrying various protective groups were prepared[11a] as substrates for studying the reactivity and regioselectivity in the Pummerer rearrangement. The best results were obtained starting from 3,4-*O*-isopropylidene derivatives **39** and **41**, which underwent regioselectively the rearrangement at the C-1 position in the presence of TFAA/Py to give the corresponding 5-thiopyranoses. The mechanistic proposal is shown in Scheme 6: the isomerization of (R_S)-**39** to **44** (Scheme 6) may occur through intermolecular path ***a*** or intramolecular path ***b***; a sulfonium cation **42** is formed that liberates the carbenium ion **43**. A trifluoroacetate anion attacks the cation **43** to terminate the reaction. Subsequent hydrolysis of the ester moiety during the workup affords the 5-thioglucopyranose **44**. The sulfur configuration seems to be unimportant for the observed regioselectivity. Studies employing deuterium-labelled derivatives **45** (Table 1) confirmed that the reaction was induced by E2 1,2-elimination of TFA from the trifluoroacetoxy sulfonium intermediate **42** (Scheme 6).[11b] The Pummerer rearrangement of 1-deoxy-5-thio-D-glucopyranose *S*-oxides was applied to the synthesis of an isomaltotriose derivative having two 5-thio-D-glucopyranoside units. The starting product was the sulfoxide (R_S)-**41** (Scheme 7), the Bz group of which was removed by NaOMe in MeOH. The resulting primary alcohol **46** was coupled with thioglucopyranosyl trichloroacetimidate **47** in the presence of a catalytic amount of TMSOTf in DCM, giving stereoselectively the α-glucoside **48** in 93% yield, to be involved in the Pummerer rearrangement.

Some aromatic thioglycosides of thiosugars in which the ring oxygen is substituted by sulfur are known orally active antithrombotic agents.[17] As sulfides can easily undergo in vivo oxidation, the behaviour of ring thiosugar thioglycosides towards different oxidants was investigated. The obtained results showed that general rules for the oxidation site cannot be proposed. Pérez et al. reported in 1997 the characterization of molecular and crystalline structures of 1,5-dithio- and 5-thio-β-D-xylopyranoside *S*-oxides **50** and (R_S)-**52** (Scheme 8) by X-ray diffraction.[12] The molecular geometries and conformations that resulted were very similar to those of their homologues non-oxidized at the ring sulfur. The same

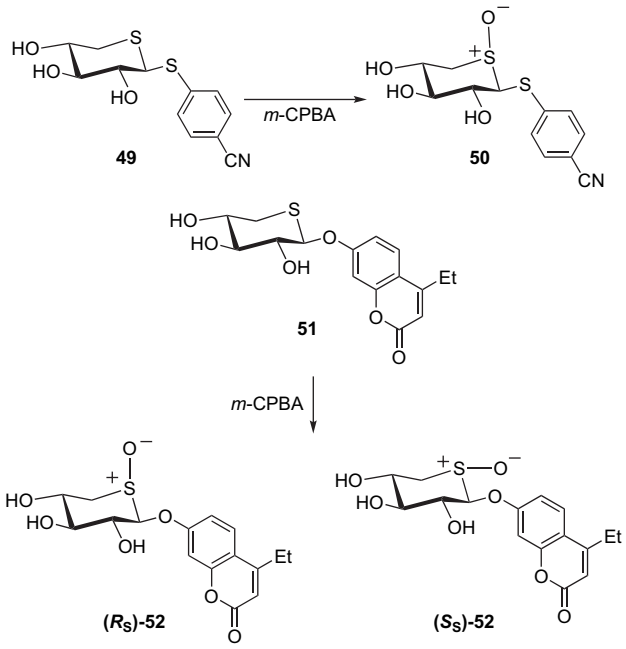


Scheme 6. Pummerer rearrangement of (R_S)-1,5-dideoxy-1,5-episulfinyl-3,4-*O*-(1-methylethylidene)-D-glucitol dibenzoate [(R_S)-**39**].



Scheme 7. Synthesis of a dithioisomaltotriose via Pummerer rearrangement.

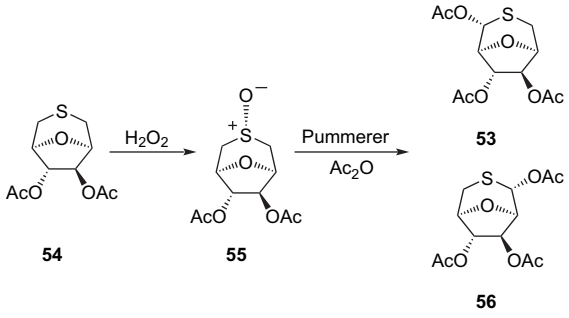
preparation method was used for the two xylosides **50** and **52**. The oxidation was performed with *m*-CPBA rather than $NaIO_4$, which was less favourable. From compound **49**, the axial isomer **50** was only obtained in poor yield (27%) due, in part, to crystallization problems. The xyloside **51**, in contrast, gave in high yield a 50:50 mixture of the sulfoxide epimers **52**, easily separable by column chromatography. The xyloside **49** (beciparcil) (Scheme 8) has frequently been used as a reference compound in the evaluation of biological activity.[17]



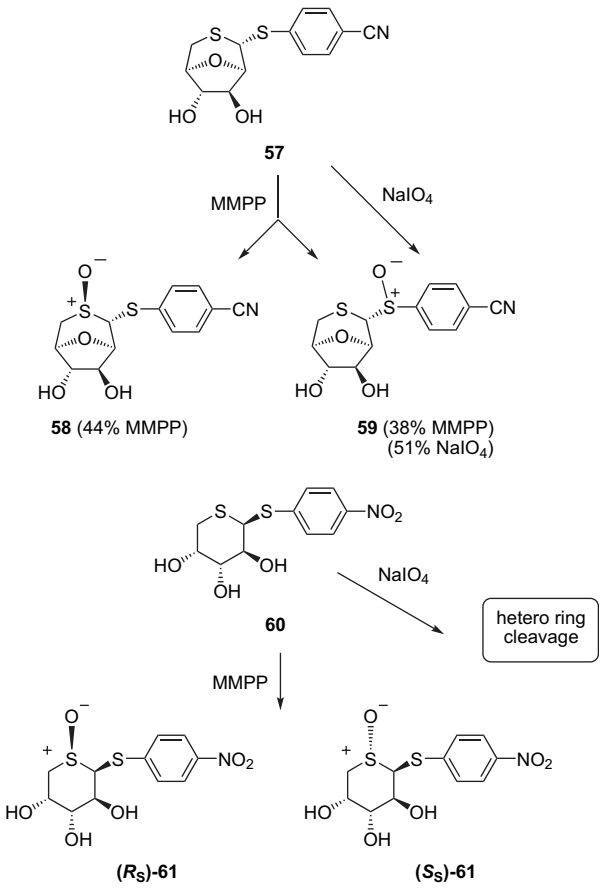
Scheme 8. Synthesis of 1,5-dithio- and 5-thio-β-D-xylopyranoside ring oxides.

Within the study of orally active antithrombotic thioglycosides,[12,17] (S_S)-2,5-anhydro-1,6-dideoxy-1,6-episulfinyl-D-glucitol diacetate (**55**) was obtained by H_2O_2 oxidation of **54** (Scheme 9).[18]

Pummerer rearrangement of **55** gave a 10:90 mixture of 1,3,4-tri-*O*-acetyl-2,5-anhydro-6-thio-α-L-gulo- (**53**) and D-glucoseptanose (**56**). Both **53** and **56** were used as donors, together with 4-cyanobenzenethiol as acceptor and TMSOTf as promoter, in glycosidation reactions suitable to afford eptanosides, which showed relevant antithrombotic activity after removal of the Ac protection (see thiosugar thioglycoside **57** in Scheme 10). The treatment of glucoseptanoside **57** with 1 equiv of MMPP (Scheme 10) resulted in a mixture of six compounds, including bis-sulfoxides.[13] The *endo*-cyclic **58** and *exo*-cyclic **59** (R_S) sulfoxides were formed as the main products in almost equal amounts, while all other derivatives were only minor by-products in the oxidation reaction of **57** with MMPP. If 1 equiv of $NaIO_4$ was used for the oxidation of **57**, the *exo*-cyclic (R_S) sulfoxide **59** was the main product, and all other derivatives were formed as by-products only. Under the same conditions, however, the behaviour of the arabinopyranoside **60** (Scheme 10)



Scheme 9. Pummerer rearrangement of 1,6-episulfinyl-D-glucitol **55**.



Scheme 10. Synthesis of 4-[(2,5-anhydro-6-thio-α-D-glucoseptanosyl)thio]benzonitrile *endo*- and *exo*-*S*-oxides, and 4-nitrophenyl-1,5-dithio-β-D-arabinopyranoside S5-oxides.

was quite different. On treatment with MMPP, only the two epimeric *endo*-cyclic sulfoxides **61** could be detected and isolated from the reaction mixture in yields of 30 and 33%, respectively (Scheme 10). On the other hand, when $NaIO_4$ was used as the oxidant, both sulfur atoms in **60** remained intact and the carbohydrate ring was oxidatively cleaved. The oral antithrombotic activity of **59**–**61** was determined on rats. From the collected data, the biological activity of the oxidation products was found to depend upon both the location (*endo*-/*exo*-cyclic) as well as the configuration of the sulfoxide groups, but no generally valid structure–activity relationship could be established. Oxidation cleavage of the sugar ring was accompanied by a decrease in activity.

3. Anomeric sulfoxide sugars

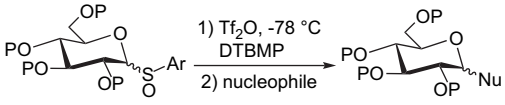
In 1939, Micheel and Schmitz described the first anomeric sulfinyl sugar, ethyl α-D-glucopyranosyl sulfoxide **62** (Table 2), obtained by the oxidation of ethyl 1-thio-α-D-glucopyranoside with dilute aq H_2O_2.[5]

Since then, the effectiveness and versatility of these compounds in organic synthesis have attracted an unstoppable growth of interest and this class of glycosulfoxides can now be regarded as the most outstanding among sulfinyl sugars.

3.1. Glycosylation reactions

3.1.1. Kahne glycosylation: main features and practical relevance

The use of anomeric glycosulfoxides has rapidly occupied a position of predominance in organic synthesis and, in particular, in the field of oligosaccharide preparation, after the paper published by Kahne in 1989,[19] where the author illustrated "a new method for glycosylation of unreactive substrates in high yield under mild conditions". Kahne glycosylation, based essentially on the reaction of a nucleophilic acceptor with an anomeric glycosulfinyl donor, activated usually by Tf_2O in the presence of an acid scavenger such as DTBMP, is still regarded as an efficient procedure for the preparation of oligosaccharides (Scheme 11).



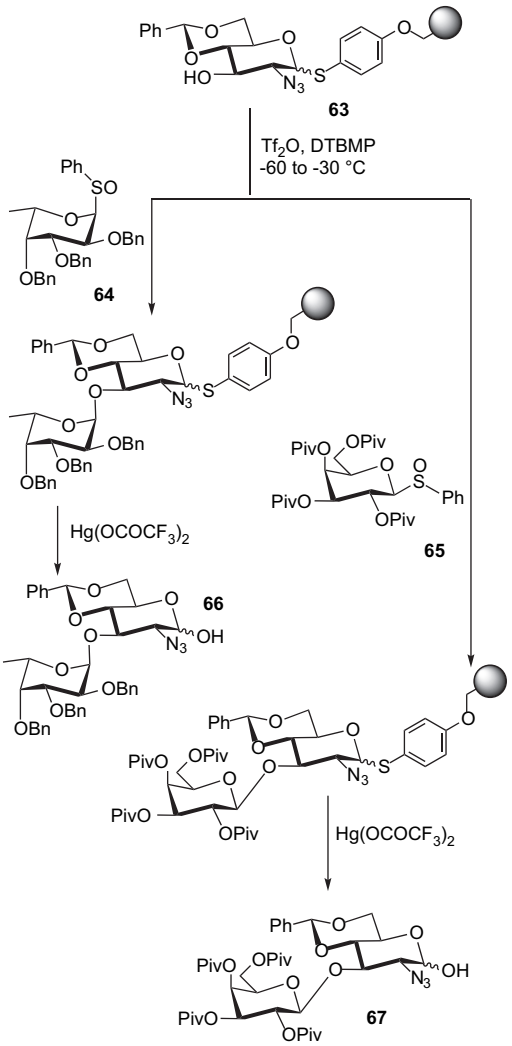
Scheme 11. General procedure of Kahne glycosylation.

The significant features described in Kahne's paper[19] were:

(i) The high reactivity of the sulfinylglycosyl donor. The most striking example of the effectiveness of the reaction involved the direct glycosylation of an acetamide on the nitrogen atom, a reaction previously accomplished by means of enzymatic catalysis.
(ii) The stereochemical outcome of the reaction. In many cases, the α or β isomer could be obtained selectively by varying the solvent or protecting groups.
(iii) The effectiveness of the reaction, regardless of the electron-releasing or -withdrawing properties of the sugar protecting groups. This finding overcame the 'armed/disarmed' concept previously used in the coupling of saccharides.

Since then, several very elegant papers have appeared on the synthesis of structurally complex glycosylated natural products, in which the Kahne glycosylation methodology has been improved and extended to a number of monosaccharides. The method has been successfully applied to an impressive variety of glycosyl acceptors including acetamides,[19] phenols,[19] hydroxylamines,[56] hydroxylated amino acids[57] and tertiary alcohols.[58] A number of activators of the glycosyl sulfoxides have been adopted,[49,59] some of which display easier handling than Tf_2O, are non-volatile, and are thus environmentally benign.[52,60]

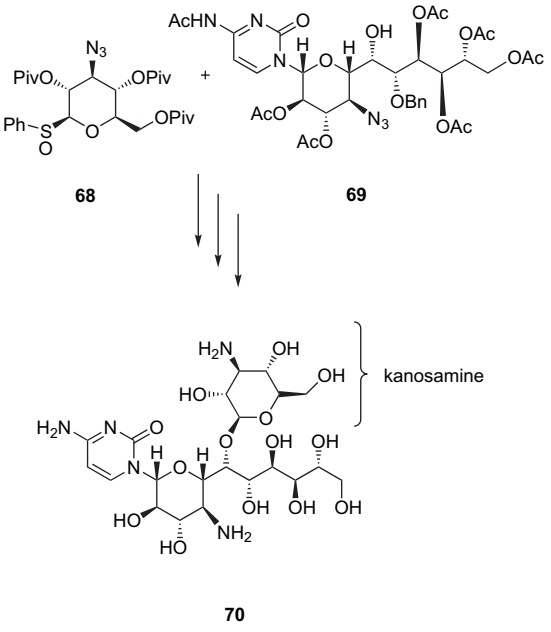
The remarkable reactivity of anomeric sulfoxides as glycosyl donors encouraged Kahne to apply the sulfoxide glycosylation to the solid-phase synthesis of oligosaccharides.[20a] Merrifield resin was used as the solid support for the stereoselective construction of both α and β linkages to secondary alcohols of the type found in the Lewis blood group antigens (Scheme 12). The thiophenyl ether linkage to the resin was chosen because it was stable to the reaction conditions used, but could be easily hydrolyzed at the end of the synthetic pathway. A solution of the sulfoxide **64** and DTBMP was added to the resin **63**, together with Tf_2O as the activating reagent. Glycosylation was repeated twice and the resin was then treated with $Hg(OCOCF_3)_2$ to give the desired α-linked disaccharide **66** in very good yield.



Scheme 12. Kahne glycosylation on Merrifield resin.

Treatment of the resin **63** with the perpivaloylated D-galactose sulfoxide **65**, using the conditions already described, allowed the β-linked disaccharide **67** to be obtained. According to the authors, the stereochemical outcome in this case was controlled by neighbouring group participation of the pivaloyl group at C-2.

Schreiber and Ikemoto described the total synthesis of the anthelmintic agent, hikizimycin (**70**) (Scheme 13), isolated from the fermentation broth of *Streptomyces A-5*.[22] The introduction of the



Scheme 13. Kahne glycosylation in total synthesis of hikizimycin (**70**).

3-amino-3-deoxy-D-glucose sugar (kanosamine) was achieved by the reaction of sulfoxide **68** with alcohol **69**, applying the Kahne methodology for the sulfoxide activation.

An important structural aspect of antibiotics such as esperamicin or calicheamicin is the presence of an unusual oligosaccharide moiety common to both series. The approach to the construction of this A–B–E trisaccharide moiety **71** (Fig. 1) was taken at almost the same time by the Kahne[61] and Beau[47] groups, applying the glycosulfoxide glycosylation. Although the most remarkable result of these two investigations is the construction of the crucial N–O interglycosidic bond between rings A and B, mild conditions of Kahne glycosylation were fundamental in the development of the overall synthesis of **71**. A few years later, Kahne again tackled the synthetic problem of the unusual structural skeleton of calicheamicin γ_1 oligosaccharide **75** (Scheme 14).[23] All three glycosidic linkages were formed stereoselectively using the sulfoxide glycosylation reaction. The E ring sulfoxide **74** was activated with Tf_2O at −78 °C and then coupled to the stannyl alkoxide **72** of a readily available fucose derivative, that represented the A ring. The desired α-linked disaccharide **73** was isolated in 65% yield. The high α selectivity (α/β92:8) resulted from the equilibration of the initially formed mixture of anomers as the temperature was increased to 0 °C. The glycosylation was carried out in the absence of base. The fact that the acid-labile isopropylidene ketal remained intact during the reaction underscores the mildness of the sulfoxide method.

In a positive effort to develop the glycosylation method that involves the use of anomeric phenyl sulfoxides, Kahne described the construction of two glycosidic linkages sequentially in a single reaction for obtaining the cyclamycin 0 trisaccharide.[24a] Cyclamycin is a complex of anthracyclin antibiotics that was isolated from

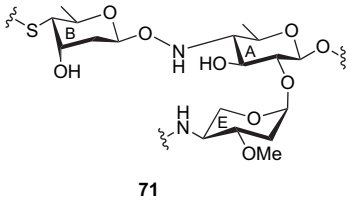
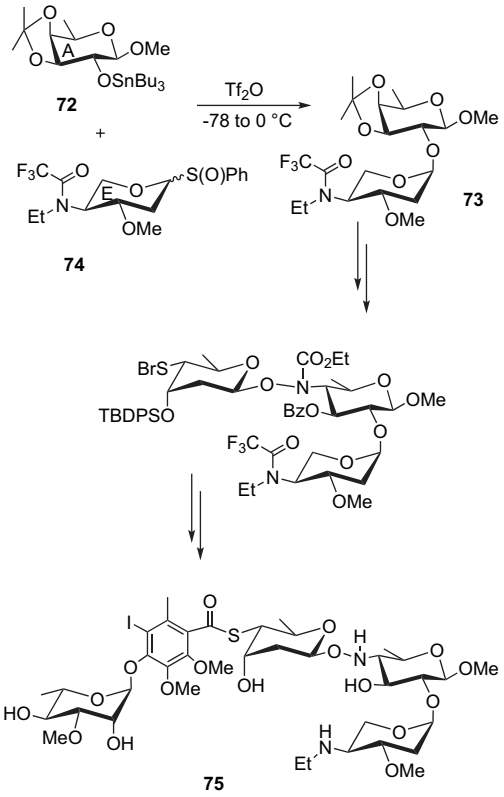


Figure 1. Trisaccharide moiety of esperamicin and calicheamicin.



Scheme 14. Synthesis of calicheamicin γ_1 oligosaccharide.

Streptomyces capoamus and possesses good activity against tumours both in vitro and in vivo. Most anthracyclines in the cyclamycin complex contain the same aglycon and the differences in activity and toxicity are due to differences in the oligosaccharides.

In particular, the stereoselective synthesis of the trisaccharide of cyclamycin 0 (**76**) (Fig. 2) was performed starting from the component monosaccharides in one step (Scheme 15). This novel strategy[24a] was based on the ability to manipulate the reactivity of both the glycosyl donors and acceptors. The reactivity of the glycosyl donor was influenced by the substituent in the *p*-position of the phenyl ring. For benzylated glycosulfoxides, the difference in reactivity is large enough for the *p*-methoxyphenyl sulfoxide **78** to be able to react faster than the corresponding unsubstituted phenyl sulfoxide **77**, as long as only 0.5 equiv of the activating agent was present. In addition, silyl ethers are good glycosyl acceptors when a catalytic acid is the activating agent, but they react more slowly than unprotected alcohols, because they must be unmasked to couple. The reaction was conducted at −78 °C for 45 min by

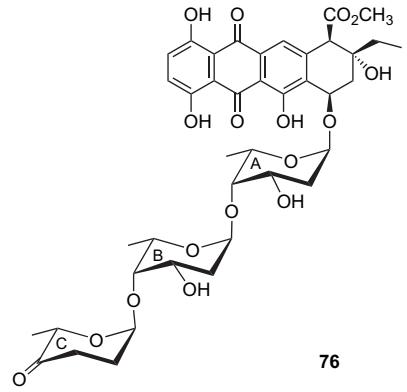
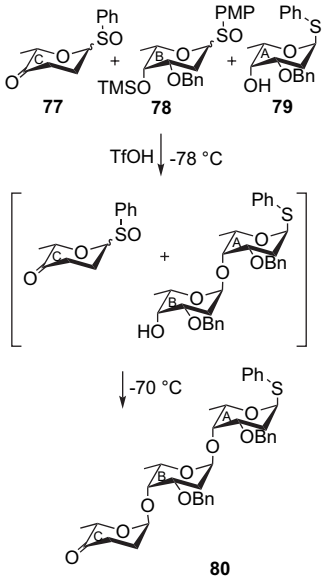


Figure 2. Cyclamycin 0 (**76**).



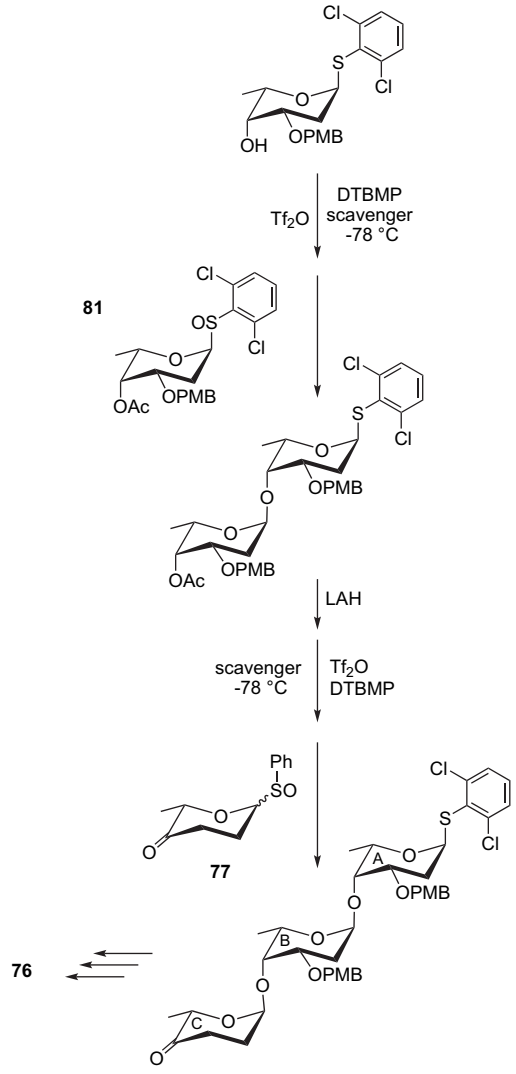
Scheme 15. One-step synthesis of trisaccharide residue of cyclamycin 0.

premixing glycosulfoxides **77** and **78** and phenyl sulfide **79**, and then adding the required amount of TfOH. The glycosylation took place in a sequential manner with *p*-methoxyphenyl sulfoxide **78** activating faster than phenyl sulfoxide **77** and the C-4 alcohol in **79** reacting faster as a glycosyl acceptor than the C-4 silyl ether of **78**. The trisaccharide **80**, produced in the one-step reaction, has an anomeric phenyl sulfide residue on the A ring that could be readily oxidized and coupled to the cyclamycin aglycone.

The synthesis of cyclamycin 0 (**76**) was optimized by the same research group after mechanistic studies that will be discussed later.[24c] By simply modifying the protecting groups, including an alkene (4-allyl-1,2-dimethoxybenzene) as the phenylsulfenyl triflate scavenger and using the methodology of inverse addition in order to avoid sulfenate formation (see Section 3.1.2), the yield of the glycosylation reactions was dramatically improved (Scheme 16): this new synthesis required six steps from the starting monomers, compared to the two-step procedure employed previously, and proceeded with an overall yield of 17%.

An impressive example of the efficiency and α/β stereoselectivity of the Kahne glycosylation is the synthesis of the blood group antigens Le^a, Le^b, Le^x, in which a wide range of α- and β-glycosidic linkages have been constructed under a single set of reaction conditions.[20b] The syntheses of Le^a (**85**), Le^b (**88**), and Le^x (**93**) are reported in Schemes 17–19, respectively.

The coupling of phenyl 2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-glucopyranoside (**82**) with the perpivaloyl galactosyl sulfoxide **65** produced stereoselectively the β-1,3-linked disaccharide **83** (Scheme 17) in the synthesis of Le^a (**85**). The stereocontrol was a result of neighbouring group participation from the C-2 pivaloyl ester. Kahne glycosylation was repeated to obtain the trisaccharide **84** with the α-1,4 glycosidic link in 95% yield, corroborating the observation that the sulfoxide glycosylation method occurs with good-to-excellent α stereoselectivity for glycosylations to secondary alcohols. Le^b (**88**) was constructed following a route similar to that used for Le^a (**85**), except that the galactosyl sulfoxide **86** was synthesized with a protecting group pattern that would permit the selective unmasking of the C-2 alcohol of the galactose ring in the disaccharide **87** at a later stage in the synthesis (Scheme 18). In Le^x (**93**), the positions of the galactose and fucose sugars are reversed with respect to Le^a (**85**) (compare Scheme 17 to Scheme 19). Therefore, the synthesis (Scheme 19) required the skill to build both an α and a β linkage to both secondary alcohols at C-3 and C-4



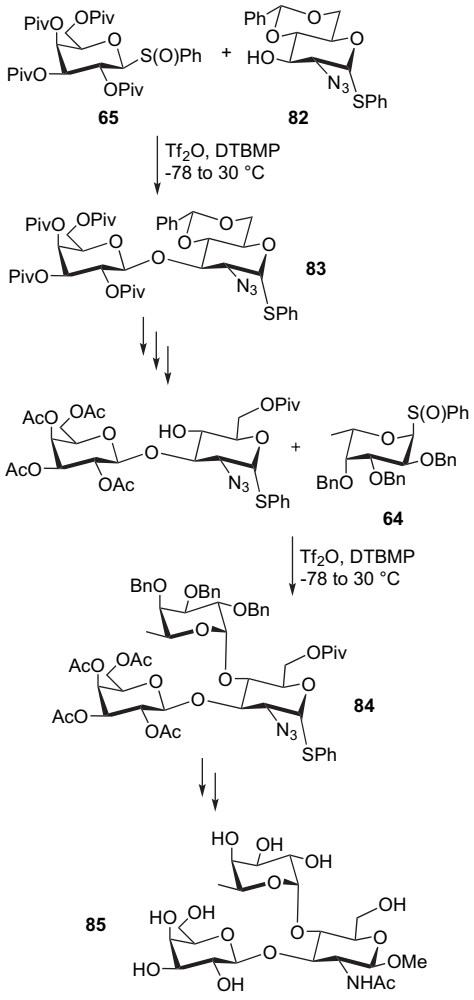
Scheme 16. Improved synthesis of cyclamycin 0 (**76**).

of glucosamine. Formation of the β linkage to the C-4 position of phenyl 2-azido-1-thioglucopyranoside **89** proceeded in 65% yield to produce the disaccharide **90**. The disaccharide nucleophile **91** was fucosylated with the sulfoxide **64** to introduce stereoselectively the α-1,3 linkage in **92** in 83% yield. The results pointed to the conclusion that the sulfoxide reaction is quite reliable for forming α linkages to secondary alcohols, and for forming β linkages whenever neighbouring group participation is used.

Very recently, Kahne and co-workers have published the total synthesis of moenomycin A (Fig. 3),[62] a potent antibiotic consisting of a highly functionalized pentasaccharide attached via a unique phosphoglycerate linkage to a polyprenyl chain. Each glycosidic linkage was constructed stereoselectively by means of the sulfoxide glycosylation reaction, further emphasizing that this reaction has a wide spectrum of applications.

The effectiveness and generality of the Kahne glycosylation have been widely recognized by a number of synthetic chemists, who have employed the reaction starting from monosaccharides of various structural skeletons and have always emphasized the high reactivity of the sulfinylglycosyl donors.

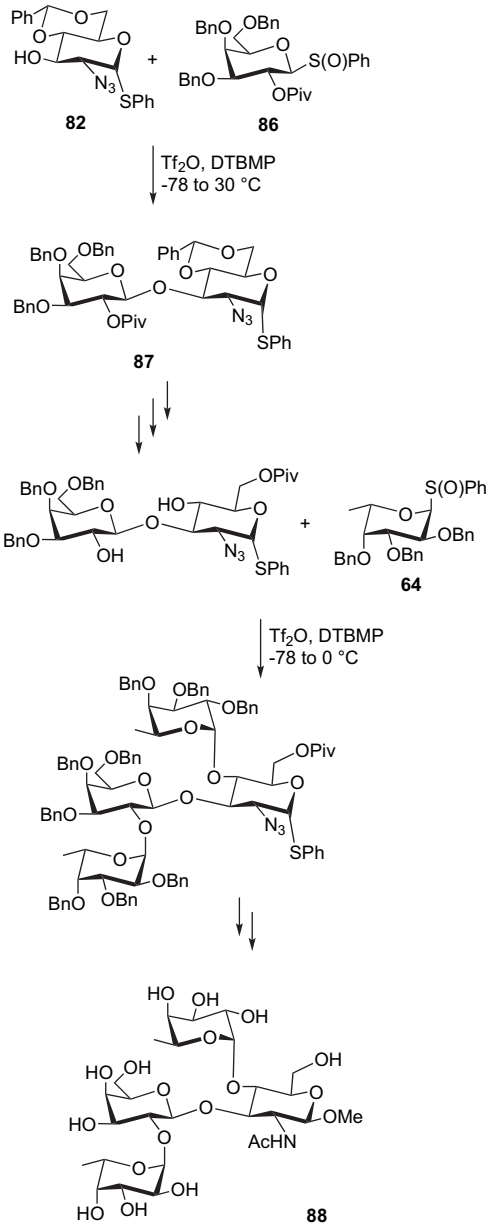
Stork[25a] used the sulfoxide glycosylation methodology of Kahne to develop the formation of a variety of β-linked mannopyranosides. The stereoselective formation of β-mannopyranosides has proved to be particularly difficult to achieve, owing to a combination of steric and stereoelectronic factors that play against the



Scheme 17. Synthesis of antigen Le[a] (**85**).

formation of the β-mannoside in classical glycosidation protocols. Stork, in particular, exploited the formation of a temporary silyl ether connection between the glycosyl donor and glycosyl acceptor for controlling the stereochemistry at the anomeric carbon.[25a] An exemplified procedure is reported in Scheme 20, where the β-mannoside **97** was produced simply by the reaction of an equimolecular mixture of the mannose sulfoxide **94** and the sugar to be tethered **95** with 1 equiv of Me_2SiCl_2, followed by activation of the tethered species **96** with Tf_2O in the presence of DTBMP, at −100 °C, to obtain the 1,6-β linkage in the disaccharide **97**. Starting from suitably protected mannose sulfoxides, the authors[25a,63] could form 1,6-, 1,3- and 1,2-β glycosidic bonds in reasonable yields, even if the temporary silicon connection method does not appear a straightforward methodology.

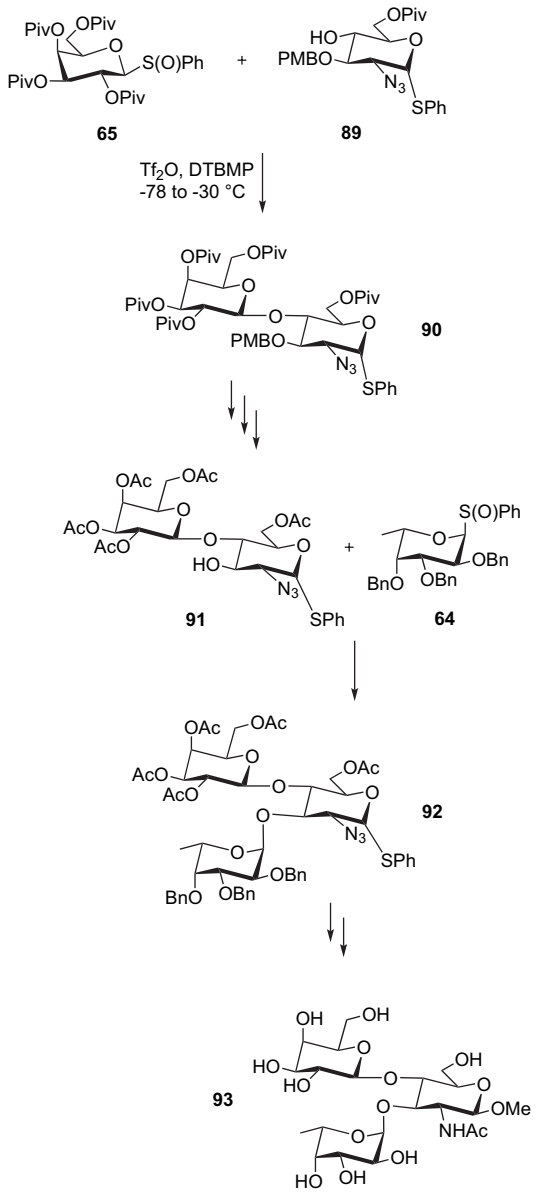
A direct strategy for the formation of β-mannopyranosides was developed by Crich and co-workers,[32a,64] who conducted very impressive studies on the mechanism of the Kahne glycosylation (see Section 3.1.2) and opportunely modified the methodology (Scheme 21). The protocol consisted of activation of a sulfoxide donor such as **98** with Tf_2O in the presence of a hindered non-nucleophilic base such as TTBP, at −78 °C, to give the highly reactive glycosyl donor **99**. Subsequent addition of the glycosyl acceptor provided high yields of the β-mannoside **100**. In the course of his work directed towards the comprehension of the α/β selectivity in the sulfoxide glycosylation, Crich also discussed the importance of the protecting groups and solvent, giving a significant contribution to Kahne's initial work.



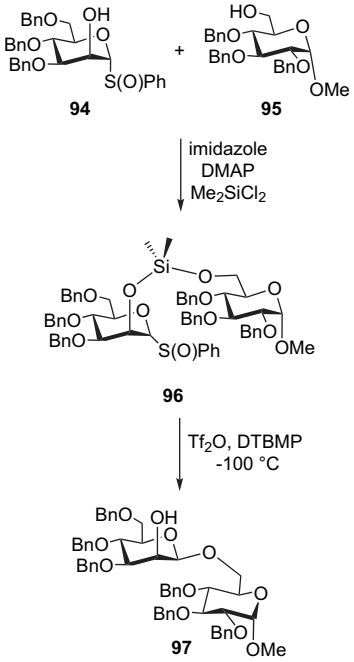
Scheme 18. Synthesis of antigen Le[b] (**88**).

A concise synthesis of the trisaccharide component of the *Hyriopsis schlegelii* glycosphingolipid **105** is shown in Scheme 22,[26b] in which the key β-mannosylation reaction is achieved directly, with high yield (87%) and α/β selectivity (80%), by Tf_2O-mediated coupling of sulfoxide **101** with methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**102**). After deallylation of the resulting disaccharide **103**, β-xylopyranosylation was conducted with tri-*O*-benzoyl-α-D-xylopyranosyl bromide **104** activated with AgOTf.

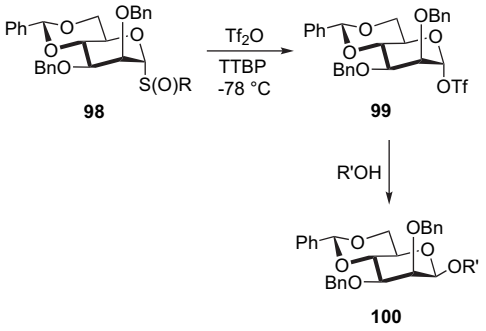
The problem of the β stereoselectivity already discussed for the mannopyranosides is equivalent for the arabinofuranosides. This problem was tackled, nearly simultaneously, by the research groups of Crich[65] and Lowary.[66] Arabinose is a very common component of natural oligosaccharides and, together with galactose, it is one of the most common sugars found in the furanose form in nature. β-L-Arabinofuranosides are less common than their α-L-versions, but they are still the key building blocks in glycoproteins. As part of an investigation of efficient glycosylation methods for the synthesis of arabinofuranosyl oligosaccharides that are fragments of two mycobacterial cell wall polysaccharides, Lowary proposed the use of



Scheme 19. Synthesis of antigen Le^x (**93**).



Scheme 20. Temporary silicon connection methodology in sulfoxide glycosidation methodology.



Scheme 21. Formation of β-mannopyranosides by sulfoxide glycosylation.

the 2,3-anhydro-α-D-lyxofuranosyl sulfoxide **106** as precursor of the β-D-arabinofuranosyl residues, adopting the protocol developed by Crich and co-workers that consists of the preventive donor activation, followed by the acceptor addition. The trisaccharide **107**, obtained with complete β selectivity in 83% yield (Scheme 23), could be straightforwardly converted into the corresponding L-arabinofuranoside by regioselective epoxide opening. After a mechanistic study, conducted by the combined use of computational chemistry and low-temperature NMR spectroscopy on this highly stereoselective glycosylation employing 2,3-anhydrofuranosylglycosyl sulfoxides, Lowary postulated that the reaction involves a two-step process. In the first step, the sulfoxide **106** is reacted with Tf_2O, leading to the formation of the ion pair **110** that would be in equilibrium with the glycosyl triflates **109** and **111** (Scheme 24). It is expected that the α-triflate **109** would be the more stable and would predominate at equilibrium. In the second step, the acceptor alcohol is added to the reaction mixture and an S_N2-like displacement of the triflate leaving group in **109** can be envisaged that leads to the highly stereocontrolled formation of the β-glycoside product **108**. These investigations into the reaction pathways allowed the identification of better glycosylation conditions with respect to those that were previously adopted.

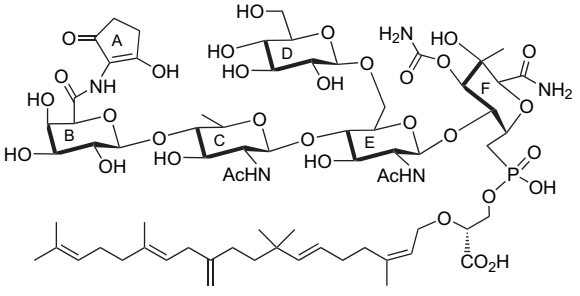
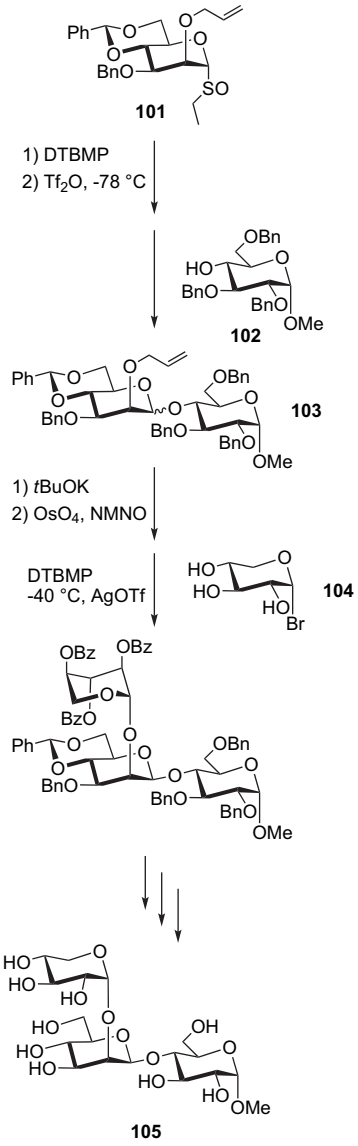


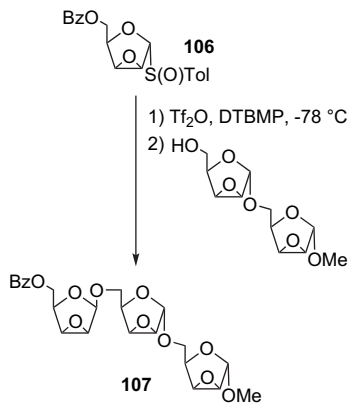
Figure 3. Moenomycin A.

Following his work with β-mannopyranosides, Crich then directed his attention to the use of arabinofuranosyl sulfoxides to accomplish the synthesis of β-arabinofuranosides. A 2-*O*-benzyl-3,5-*O*-(bis-*tert*-butylsilylene)-1-deoxy-1-phenylsulfinyl-α-L-arabinofuranose donor **112**, proposed by Crich and co-workers, was activated with Tf_2O at −70 °C, giving a relatively complex mixture that, on warming to −50 °C, was converted into a product, the low-temperature ^1H NMR spectrum of which was consistent with that

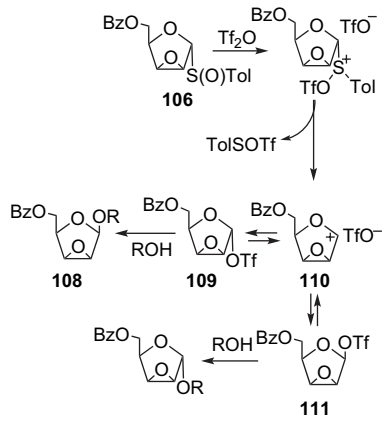


Scheme 22. Synthesis of trisaccharide component of *Hyriopsis schlegelii* glycosphingolipid.

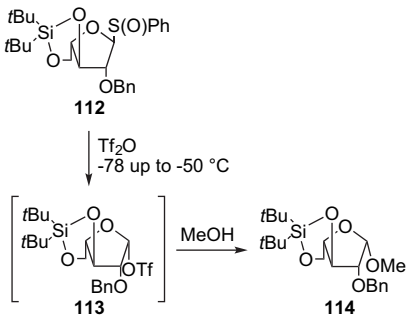
of the corresponding β-glycosyl triflate **113** (Scheme 25). Quenching of this intermediate at −40 °C with MeOH as a model acceptor provided the methyl glycoside **114** with excellent β selectivity. The relatively high temperature required for the activation of the



Scheme 23. Stereocontrolled synthesis of 2,3-anhydro-β-D-lyxofuranosyl glycoside **107**.



Scheme 24. Proposed mechanistic pathway for glycosylation employing 2,3-anhydro-1-deoxy-1-[(*p*-tolyl)sulfinyl]-α-D-lyxofuranose benzoate (**106**).



Scheme 25. Glycosylation with silylene-protected α-L-arabinofuranosyl sulfoxide donor.

sulfoxide **112** suggested that the triflate **113** acts as a reservoir of a glycosyl oxacarbenium ion (see Section 3.1.2).[65]

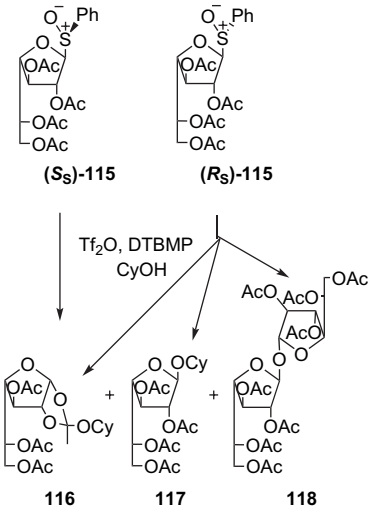
Recently, Lowary has extended the 2,3-anhydrosugar methodology adopted for the stereocontrolled synthesis of oligosaccharides containing arabinofuranosyl residues to the preparation of α-D-galactofuranosides.[67] In this work, the author demonstrated that the nature of the protecting groups at O-5 and O-6 influences the stereoselectivity and yield of the glycosylation reactions, with the best results being obtained when benzoate esters are present at these positions.

Ferrières and co-workers[68] directed their attention towards the reactivity of each sulfur epimer of the anomeric sulfoxide donor in the Kahne glycosylation methodology. Mixtures of (R_S) and (S_S) sulfinyl glycosides are generally used in the glycosylation without previous separation, since it is acknowledged that both isomers are similarly activated. Ferrières synthesized and chromatographically separated the epimeric sulfoxides **115** (Scheme 26) and investigated their reactivity with cyclohexanol as the model acceptor under Kahne reaction conditions. A mixture of **116**, **117** and **118** was obtained when (R_S)-**115** underwent this reaction, with a predominance of the β-galactofuranoside **117** and the disaccharide **118**. In contrast, the ortho ester **116** was nearly exclusively obtained from the major, less-polar sulfoxide (S_S)-**115**. The authors[68] reached the conclusion that the marked differences in reactivity between the furanosyl sulfoxides **115** are related to the formation of different intermediates for the two epimers in the reaction pathways.

3.1.2. Mechanistic studies on Kahne glycosylation

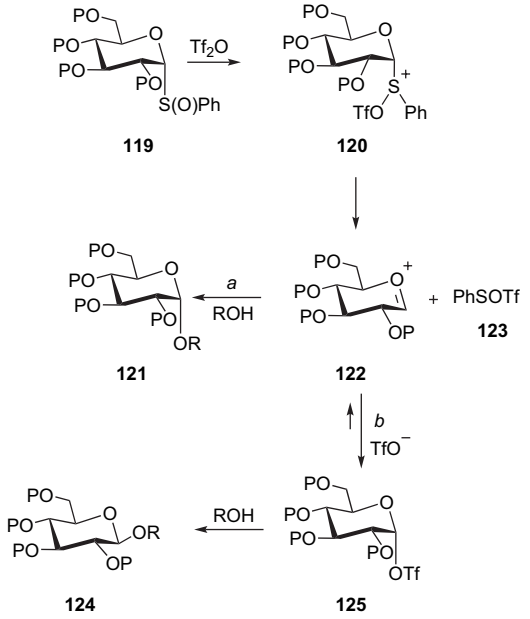
"Are glycosyl triflates intermediates in the sulfoxide glycosylation method?"

This question is the title of a Crich work[69] in which the author confronted this problem by a chemical and spectroscopic investigation. He answered the question with a long series of



Scheme 26. Glycosylation of two sulfur epimeric galactofuranosyl sulfoxides.

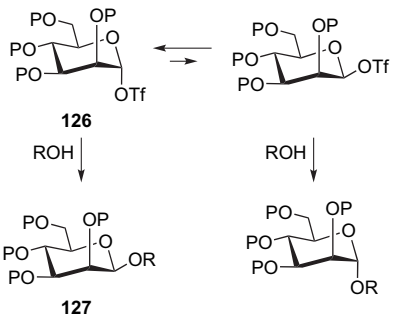
thoughtful experiments, which led to the evidence that glycosyl triflates, such as **125** in Scheme 27, are intermediates in the sulfoxide glycosylation method when the sulfoxide is activated with Tf_2O prior to the addition of the glycosyl acceptor. Going into more detail, the glycosyl donor **119** is activated by Tf_2O in the form of the sulfonium ion **120** that collapses to the oxacarbenium ion **122** and the sulfenyl triflate **123**. Crich did not detect the triflate **123**, but demonstrated that it reacts with, and activates in competition with Tf_2O, the sulfoxide **119**. This would explain the ability, noted by Kahne[24a] for sulfoxide glycosylations, to be carried out in high yield with only 0.5 mol equiv of Tf_2O. When the activation is performed in the presence of a glycosyl acceptor, which is more nucleophilic than the triflate anion, **122** is trapped directly, giving the α-glycoside **121** (pathway ***a*** in Scheme 27). When the activation is conducted prior to the addition of the glycosyl acceptor, **122** is trapped by the triflate anion to give the α-glycosyl triflate **125** (pathway ***b***). The stability of the anomeric triflate formed is a function of the protecting groups and the solvent, or, in other words, it is substrate dependent.



Scheme 27. Mechanistic pathways of sulfoxide glycosylation proposed by Crich.

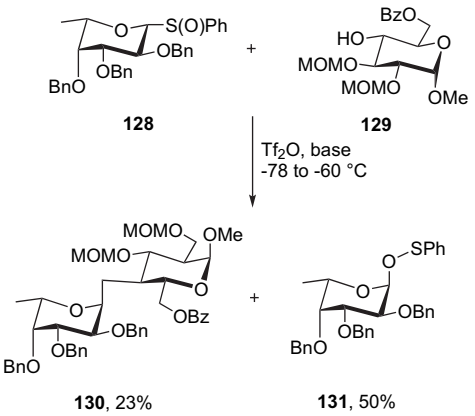
Moreover, glycosylation can occur in some instances via the intermediacy of transient ion pairs such as **122**/TfO^- in an S_N1-like manner, leading to the α-glycoside **121**. In other cases, when the protecting groups are 'disarming' either by virtue of their electronegativity or for torsional reasons, the glycosylation reaction will follow an S_N2-like pathway with the formation of the β-glycoside **124**. The authors stated that it is very likely that, in the 4,6-benzylidene-protected series, the α-mannosyl triflates are displaced in an S_N2-like manner in DCM at low temperatures, to give the corresponding β-glycosides.

In one of his papers,[32c] Crich discussed the question of the contrasting behaviour between the gluco and manno series: activation of the glucosyl sulfoxide with Tf_2O in DCM, at −78 °C in the presence of DTBMP, provides α-glucosides **121** with high selectivity, whereas the analogous activation conditions applied to the mannopyranoside series afford the β-mannosides, again with excellent selectivity. The author suggests that the difference between the two series lies in the magnitude of the anomeric effect. Mechanistic considerations support the hypothesis that the intermediate of the glycosylation method involves a dynamic system in which the α-triflate is in equilibrium with β-triflate. In the mannose series (Scheme 28), the importance of the anomeric effect, that is larger than in the glucose series, justifies the significant preference for the α-triflate intermediate **126**, leading to the β-mannopyranosides **127**, whereas, in the glucose series, the equilibrium is shifted towards the β-triflate, giving mainly the α-glucopyranosides **121**.



Scheme 28. α/β-Triflate equilibrium in mechanistic proposal concerning sulfoxide mannosylation.

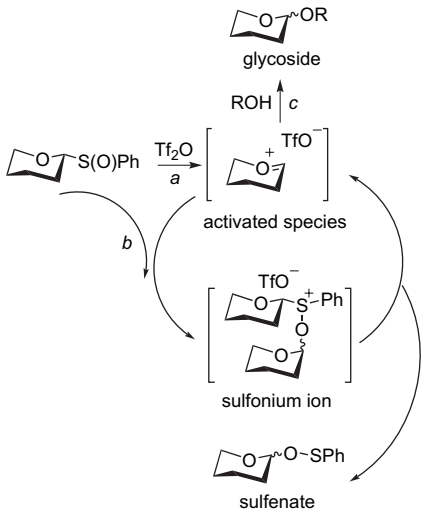
Kahne also published his contribution on the mechanism of the sulfoxide glycosylation reaction,[27a] and his, and Crich's, studies demonstrate that this reaction is much more complex than it appeared in the first publication[19] on this subject. The observations from which Kahne progressed were: (i) in some glycosylation reactions, the product starts to form at low temperature (−78 °C), then stops forming, then starts again after the temperature has been raised, and (ii) in the reaction of sulfoxide **128** with alcohol **129** (Scheme 29), the desired disaccharide **130** was isolated in 23%



Scheme 29. Identification of sulfenate **131** in mechanistic studies of Kahne glycosylation.

yield together with a 50% yield of the unexpected anomeric sulfenate **131**. The formation of the glycosyl sulfenate impedes glycosylation at low temperatures and, unfortunately, it is difficult to control its formation, because it appears to be dependent upon the structure of the starting sulfoxide and alcohol.

The potential pathways, proposed by Kahne for the glycosylation reaction, are shown in Scheme 30. The starting sulfoxide can either be triflated to form the activated species (path ***a***) or glycosylated to produce a sulfonium ion (path ***b***). As the activated species is produced, it can react with either the alcohol, giving the glycosylation product (path ***c***), or the sulfoxide, giving the sulfenate. Although sulfoxides are usually thermodynamically favoured over sulfenates, Kahne demonstrated that the presence of an oxygen on the α carbon of the sulfoxide moiety dramatically increases the energetic preference towards the sulfenate, and predicted that all anomeric sulfoxides can be converted into the corresponding anomeric sulfenates under suitable conditions. Nevertheless, sulfenates are not observed in every sulfoxide glycosylation reaction, suggesting that there can be significant differences in the kinetic accessibility of different anomeric sulfenates. A strategy to control sulfenate formation was proposed, based on the order of addition of the starting materials: slow addition of the sulfoxide to a solution containing the acceptor alcohol, Tf_2O and base gives the best results in terms of disaccharide formation. Finally, Kahne demonstrated that, if sulfenates impede glycosylation at low temperatures, they can act as glycosyl donors at sufficiently high temperatures, and this provides a simple explanation for the observation that raising the temperature of the reaction often results in additional product formation.

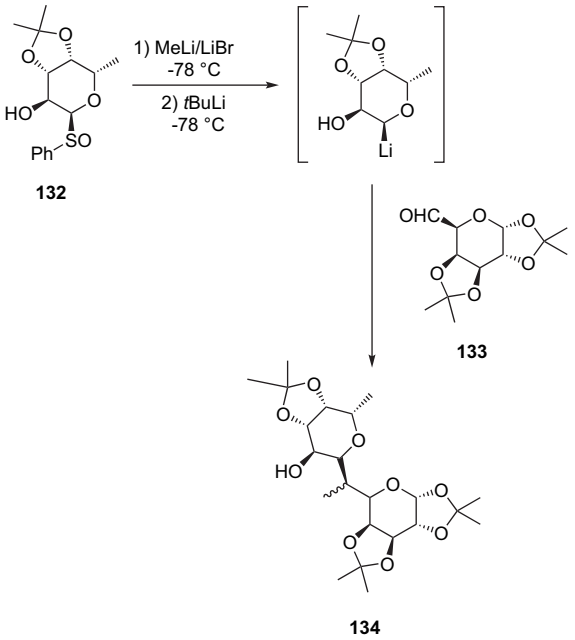


Scheme 30. Mechanistic pathways of sulfoxide glycosylation proposed by Kahne.

In concluding this mechanistic treatment, at least three different intermediates can be produced: the initially formed reactive species, an anomeric triflate and an anomeric sulfenate. The relative proportion of each intermediate formed depends upon the structures of the glycosyl donors and acceptors, as well as upon the order of addition of the reagents and the nature of the solvent. These intermediates affect the quantitative and stereochemical outcome of the glycosylation reaction in different ways, and operators should understand the nature of the potential intermediate, in order to steer the reaction towards the desired product.

3.1.3. Further glycosylation methodologies involving anomeric sulfoxide monosaccharides

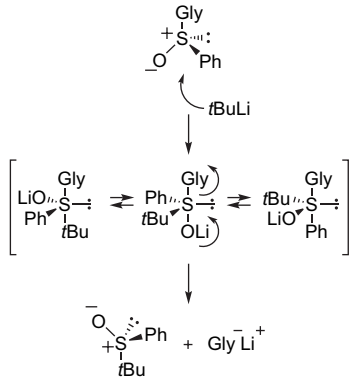
The *C*-disaccharide **134** (Scheme 31) was the product of a significant process of glycosylation, starting from the fucopyranosyl



Scheme 31. Stereospecific synthesis of C-glycosides from glycosyl sulfoxides.

sulfoxide **132**.[28] This methodology represents a significant mean of synthesizing *C*-glycosides, important products as structural subunits of natural compounds and mimics of biologically relevant O-glycosides. C-glycosides are resistant to acid and enzymatic hydrolysis, providing structures of great value for studies concerning conformation around the glycosidic linkage. The glycosylation is based on the generation of a glycosyl carbanion, through a phenylsulfinyl/lithium exchange, and was extended to the synthesis of a number of C-glycosides derived from α-L-fuco-, α-D-gluco-, β-D-gluco- and α-D-mannopyranose, starting from the corresponding glycosyl phenyl sulfoxides. The best results were obtained when *t*-BuLi was first added dropwise to THF at −78 °C, in order to remove the trace moisture in THF. To this solution was then added the glycosyl sulfoxide **132**, previously treated with MeLi/LiBr dissolved in a minimum amount of THF. When the anomeric carbanion so generated was trapped by the aldehyde **133** derived from D-galactose, compound **134** was obtained in 44% yield (Scheme 31).[25b] This reaction and all of the others tested were stereospecific at the anomeric centre and proceeded with retention of the configuration. With regard to the diastereomeric ratio at the newly generated chiral centre in **134**, the authors observed a slight excess of one diastereoisomer (55:45). *tert*-Butyl phenyl sulfoxide was always present in the mixtures analyzed at the end of the reactions, indicating that the process takes place through ligand exchange. The proposed mechanism involves the attack of *t*-BuLi on the sulfur atom of the glycosulfoxide, and the generation of a σ-sulfurane (Scheme 32), with the sulfur in the centre of a trigonal bipyramid. Different complexes are formed by a pseudorotational process. The complex that has the more electronegative group in the apical position is the more stable and the one which results in bond rupture: the anomeric carbanion, which is configurationally stable at −78 °C, is so formed.

An example of a straightforward access to multivalent thiosaccharides, based on the generation of a transient glycosulfenic acid and its addition onto the unsaturation of an alkyne carbohydrate, has been described by the Aversa group.[1b] Thioglycosides are valuable glycoside analogues and potential therapeutic compounds in the treatment of various pathologies. Sulfenic acids are implicated in a wide variety of relevant chemical and biochemical reactions and, although the vast majority of known sulfenic acids are

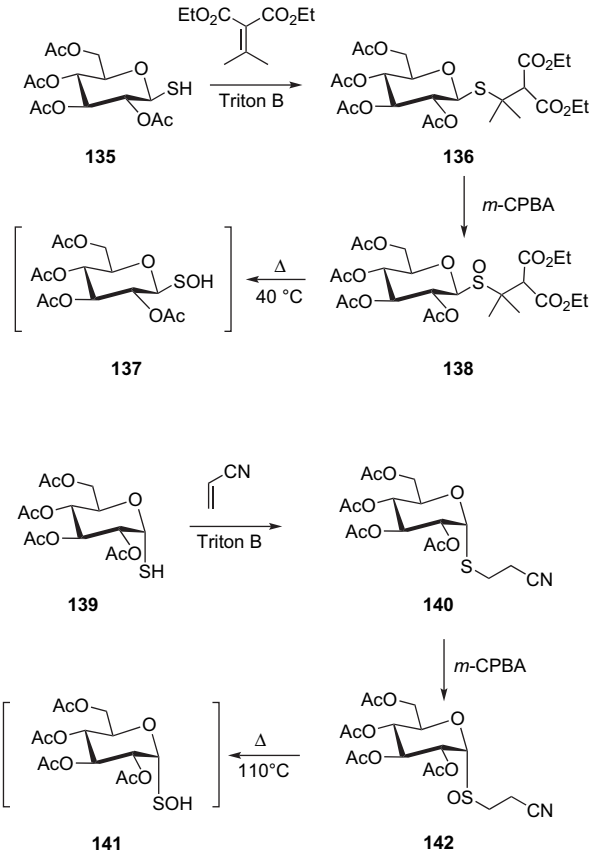


Scheme 32. Proposed mechanism for generation of glycosyl carbanion in stereospecific synthesis of C-glycosides depicted in Scheme 31.

too unstable to be isolated, they cannot be considered just to be casual intermediates in organic and biological processes. For instance, the *syn*-addition of sulfenic acids onto carbon–carbon triple bonds gives a reliable, easy method to obtain vinyl sulfoxides in mild conditions, without the need for acidic or basic catalysis and with some stereoselectivity in the formation of the *S*-epimeric mixtures of sulfoxides, exerted by the structural features of the sulfenic acid and the electronic properties of its unsaturated acceptor. This reaction and its applications in organic synthesis have been widely studied by Aversa and co-workers, who showed that (i) it is possible to generate sulfenic acids in three steps, starting from suitable thiols: in the thermolysis that represents the last step, the sulfenic acid is generated in the presence of the unsaturated acceptor, leading to the formation of the sulfoxides;[70] (ii) it is possible to generate enantiopure sulfenic acids by synthesizing their precursors with an enantiopure alkyl or aryl residue;[71] and (iii) the generation of sulfenic acids with an amino acidic or a glycosidic residue corresponds to a direct strategy for the preparation of molecules possessing biologically active residues.[72]

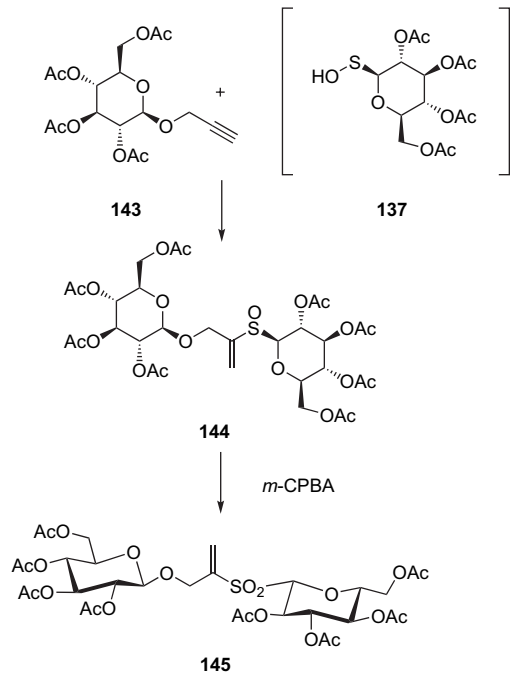
Scheme 33 shows the synthetic procedure adopted for preparing glucosyl sulfoxides **138** and **142**, and the conditions applied for the in situ generation of the corresponding sulfenic acids **137** and **141**.[1] The glucosyl sulfoxides **138** and **142** were prepared through a base-catalyzed Michael-like addition of the corresponding 1-thio-D-glucopyranoses **135** and **139** to either diethyl isopropylidenemalonate or acrylonitrile, followed by *m*-CPBA oxidation of the resulting thioglucosides **136** and **140**, respectively. The thermolysis of the glucosyl sulfoxide **138** was performed in DCM at reflux, while **142** was thermolyzed to the sulfenic acid **141** in toluene at 110 °C. This synthetic pathway has also been applied in the D-galacto and D-manno series, leading to the generation of several transient glycosulfenic acids. The glucosulfenic acid **137**, generated in situ from the glucosyl sulfoxide **138**, was reacted with 2-propynyl β-D-glucopyranoside tetraacetate (**143**) (Scheme 34), used as an acceptor of **137**.[1b] The 50:50 sulfur epimeric mixture of pseudodisaccharide sulfoxides **144** was obtained in 45% yield and quantitatively oxidized to the unique sulfone **145**.

The generation of glycosulfenic acids by simple thermolysis, at temperatures depending upon the chosen sulfoxide precursors, and their in situ *syn*-addition to propynyl glycosides do not imply acidic or basic conditions, and thus allow the use of any protecting group or the presence of any reactive functional residue in the sugar rings. The addition of enantiopure sulfenic acids to alkynes allows an easy and stereocontrolled introduction of a glycosyl sulfoxide moiety into a suitable framework and the retention of configuration at the anomeric centre. The sulfoxide function, characterizing sugars such as **144**, can be easily reduced to a sulfide or oxidized to a sulfone, or even transformed into other functional



Scheme 33. Synthesis of glucosyl sulfoxides and generation of corresponding sulfenic acids.

groups. Various carbohydrate-derived sulfenic acids, differing in their glycosyl moiety and SOH localization, and various alkynyl carbohydrates can be adopted as combining units in the synthesis of alkene-linked multivalent thiosaccharides.



Scheme 34. Synthesis of pseudothiodisaccharide **145**.

3.2. Selective oxidations of glycosyl sulfides to glycosyl sulfoxides

Glycosulfides are generally oxidized to glycosulfoxides by means of common suitable reagents such as H_2O_2, *m*-CPBA, or $NaIO_4$ in the usual conditions. In particular, the oxidation of glycosyl sulfides to sulfoxides, very important as glycosyl donors, has most successfully been achieved using *m*-CPBA. This method, however, suffers from a number of shortcomings, including the requirement of low temperature to prevent overoxidation to sulfone and the consequent low solubility of *m*-CPBA in the reaction medium. Accordingly, new methods, sufficiently selective to terminate oxidation at the sulfoxide stage and prevent overoxidation to sulfones with mild reaction conditions and simple workup, have been performed. At the same time, factors controlling stereoselectivity in the formation of glycosyl sulfoxides have been widely investigated.

The oxidation method involving $H_2O_2/Ac_2O/SiO_2$ in DCM[34a] has represented a simple, inexpensive, and highly efficient approach for both the small- and large-scale preparation of glycosyl sulfoxides. In a typical experiment, the reagents have been used in the following amounts: 1 mmol sulfide/1.1 mmol Ac_2O/200 mg silica gel/5 ml DCM/1.2 mmol 30% H_2O_2 solution.

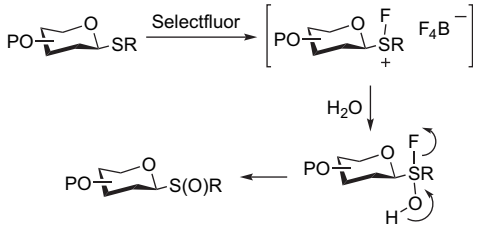
In 1998, a French group exploited a new and selective oxidation reaction of sulfides to sulfoxides with H_2O_2 in HFIP under neutral conditions and at rt.[43] This method can be applied to the oxidation of many sulfides without sulfone formation, even with excess aq 30% H_2O_2. No strict conditions are required for this selectivity, in that the formation of a strong hydrogen bond between the HFIP solvent and the sulfoxide oxygen atom greatly decreases the sulfur nucleophilicity, preventing further oxidation. Following this protocol, the oxidation of glycosyl sulfides to the corresponding sulfoxides was achieved in high yield without affecting the *O*-protecting groups. The reaction was fast, the experimental procedure simple, and the HFIP was recovered and could be re-used as such without any further purification.

Oxidation of various 1-thioglycopyrano- and -furanosides with $H_2O_2/Ac_2O/SiO_2$ was performed in DCM/aprotic perfluorinated solvent mixtures (100:0 to 5:95, v/v).[41] Unlike HFIP,[43] perfluorodecalin, -hexane and -toluene cannot act as participating solvents in the sulfoxidation. The best results were achieved using perfluorodecalin as the co-solvent. The reactions appeared to be much faster at a solvent ratio of 50:50 without significant overoxidation to sulfones and modification of diastereoselectivity. Nevertheless, the nature of both the glycosyl moiety and the protecting groups influenced the $(R_S)/(S_S)$ product ratio. In particular, shorter reaction times were required when the less-electron-withdrawing Ac (vs Bz) and Bn groups were introduced to protect the hydroxy functions.

Chen et al. reported in 2003 an alternative method based on the use of oxone/SiO_2 as an oxidant[38] for preparing glycosyl sulfoxides from the corresponding sulfides. The selective oxidation occurred with excellent yields. The combination of silica gel/oxidant was found to be compatible with various protecting groups on glycosides. Especially, the Lev group, which has the potential to undergo Baeyer–Villiger oxidation with *m*-CPBA, survived under these mild reaction conditions. The following year,[30a] the same group reported another selective and mild method that involves MMPP as an oxidant under microwave irradiation.

New TEMPO-linked metalloporphyrins were synthesized, and these compounds exhibited efficient catalytic activity for the selective oxidation of sulfides to the corresponding sulfoxides using NaClO as the oxidant.[30b] In the field of glycosyl sulfoxides, compounds **146** and **147** (Table 2) were obtained from their sulfide precursors in the presence of Bu_4NBr and KBr, in DCM/satd aq $NaHCO_3$ solution at 0 °C. No overoxidation to sulfone was observed, even on using an excess of NaClO. The yields were excellent (88–91%) and the protective and hydroxy groups remained intact during the reactions.

The electrophilic nature of Selectfluor was used to fluorinate thioglycosides[73] for use as activated glycosylation reagents or to convert them into sulfoxides (Scheme 35). These authors[73] have found that Selectfluor in MeCN–H_2O (95:5) can quantitatively oxidize thioglycosides to the corresponding sulfinyl glycosides in a few minutes, and no purification is needed. The reaction may proceed through the fluoro-sulfonium cation, which reacts with water to give the sulfoxide (Scheme 35). This procedure has been applied to the synthesis of several monosaccharide sulfoxides and 4-methylphenyl 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-1-sulfinyl-β-D-glucopyranoside (sulfur epimeric mixtures).

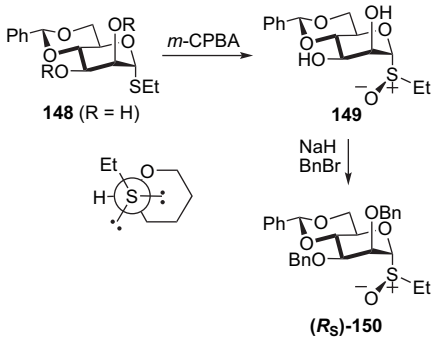


Scheme 35. Conversion of glycosyl sulfides into glycosyl sulfoxides by Selectfluor.

On the same theme, Agnihotri and Misra[27b] have recently described the excellent results of their reasoning that KF/*m*-CPBA in MeCN–H_2O could produce KOF·MeCN, which could selectively oxidize glycosyl sulfides to the corresponding sulfoxides utilizing the electrophilic nature of the oxygen atom of KOF·MeCN. The KF/*m*-CPBA combination was employed to synthesize a series of glycosyl sulfoxides having a wide range of protecting groups. In every case, the reaction was exceptionally fast and the exclusive formation of the sulfoxide was observed in excellent yield, without any trace of sulfone, in a few minutes. Acid-labile functional groups such as benzylidene acetal, isopropylidene, or TBDPS groups remained intact under the reaction conditions. The oxidation rate depends upon the nature of the protecting group linked to C-2. 'Armed sugars' having an electron-donating group at C-2 such as a Bn group, were oxidized at a higher rate than 'disarmed sugars' having an electron-withdrawing group such as Ac or Bz at C-2. In most of these cases, a diastereomeric mixture of sulfoxides was formed from β-thioglycosides. Since the reaction was carried out in MeCN–H_2O, there was no need to use anhydrous conditions and *m*-CPBA was completely soluble in the reaction mixture.

The use of thioglycosides as glycosidase-resistant analogues of glycosides is well documented.[74] Such analogues, which should markedly affect the biological activity, make sulfinyl glycosides interesting in their own sight, and a reliable revision of their stereochemistry as a result of the sulfide oxidation remains highly desirable. In 1998, Crich et al. demonstrated that, as a consequence of the *exo*-anomeric effect, and in contrast to their β-anomers, α-thioglycosides undergo stereoselective oxidation by *m*-CPBA to give very predominantly the (R_S) sulfoxides, as revealed by X-ray crystallography.[26a] For example, thioglycoside **148** (Scheme 36) was submitted to oxidation with *m*-CPBA and one major sulfoxide **149** (>91:9) was isolated.

Crystals suitable for X-ray analysis were obtained and the structure was consequently revealed to be (R_S). A diverse range of oxidants provided the same major sulfoxide **149**. Treatment of **149** with NaH and then BnBr in THF provided the sulfoxide (R_S)-**150**, albeit in only 35% yield, fixing its configuration at sulfur. In view of the range of different oxidants and solvents employed, each giving the same result, Crich concluded that the stereoselectivity of the oxidation is dictated predominantly by steric effects and that the

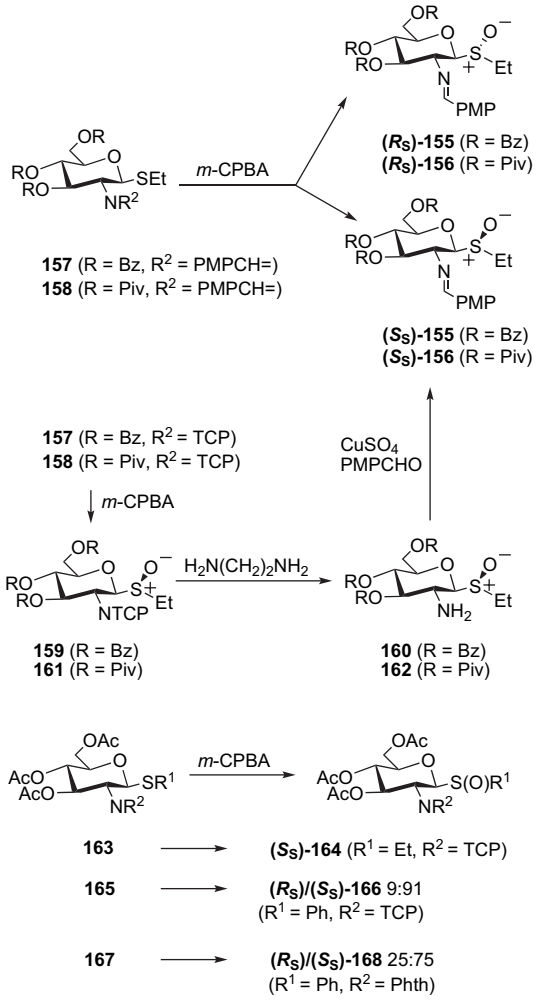


Scheme 36. Stereoselective sulfoxidation of α-mannopyranosyl thioglycoside **148**.

conformation is imposed on the thioglycosides by the *exo*-anomeric effect. Thus, as seen from the Newman projection in Scheme 36, in the conformation imposed by the *exo*-anomeric effect the *pro-R* lp of the α-thioglycosides is exposed to attack. On the other hand, oxidation of the *pro-S* lp would be substantially hindered by the pyranose ring, and especially by the axial H-4 and H-5. In the case of equatorial β-thioglycosides, the two lps are less sterically differentiated and mixtures of sulfoxides result.

A series of four *S*-allyl D-thiopyranosides, the α- and β-manno and xylo derivatives, were oxidized with *m*-CPBA at low temperature to given seven (**151**–**154** in Table 2)[31] of the eight possible sulfoxides, the configuration of which at sulfur was determined either directly by X-ray crystallography or by correlation with closely related structures. For the axial thioglycosides, oxidation leads very predominantly to the (R_S) diastereomer in the xylo series and exclusively in the manno series; the configuration at C-2 is of little importance in determining the stereoselectivity of oxidation of the axial thioglycopyranosides. In the equatorial series, the configuration at C-2 has a significant effect on the outcome of the reaction as, although both series favoured the (S_S) sulfoxide, the selectivity was significantly higher in the case of the β-mannoside than that of the β-xyloside. The two α-xylo sulfoxides have different conformations of the pyranoside ring, with the (R_S) isomer adopting the $^1C_4$ chair and the (S_S) diastereomer the $^4C_1$. The authors[31] found, besides, that oxidation with *t*-BuClO$_4$ in MeOH/DCM at −40 °C was significantly less stereoselective, providing a 67:33 ratio of (R_S)/(S_S) isomers **150** from the α-sulfide **148** (R=Bn) (Scheme 36, and Table 2). This change in selectivity was attributed to the different mechanism, which does not involve direct oxygen transfer to the sulfide but, rather, chlorination followed by nucleophilic displacement.

In 2003, Khiar et al.[33] reported a detailed study on the diastereoselective oxidation of 2-amino-2-deoxy-1-thio-β-D-glucopyranosides (Scheme 37). Oxidation of the iminothioglycoside **157** (R^2=PMPCH=) with *m*-CPBA, in DCM as usual, leads to the corresponding epimeric sulfoxides **155** in a 65:35 mixture. Surprisingly, the major isomer was shown unambigously to have the (R_S) absolute configuration, at variance with the recent assumption that the oxidation of β-thioglycosides in the galacto, gluco and manno series always give the (S_S) sulfoxides predominantly.[31] These results, as well as those recently reported by Ferrières and Plusquellec,[41] could indicate that the oxidation of β-thioglycosides depends not only upon the C-2 configuration, but also on the nature of the protective group. In order to get a better insight into the stereochemical outcome of the oxidation, iminothioglycosides with bulky Piv protective groups were studied, but the usual oxidation of **158** (R^2=PMPCH=), using *m*-CPBA at −78 °C, afforded a 55:45 mixture of epimeric sulfoxides **156**. Here again, the slightly major isomer was shown to have the (R_S) absolute configuration. Khiar et al. were therefore delighted to find that the oxidation of the TCP-protected derivative **163** gave the corresponding sulfoxide **164** in high yield as a single (S_S) isomer. Due to the diastereocontrolling bias exerted by



Scheme 37. Diastereoselective oxidation of 2-amino-2-deoxy-1-thio-β-D-glucopyranosides.

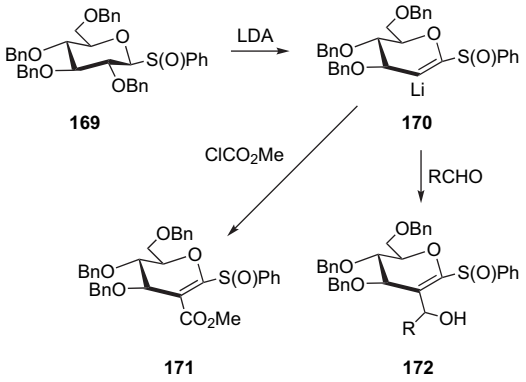
the TCP group, the access to enantiopure imino sulfoxides is thus possible, as long as the oxidation of the thioglycosides is conducted at the TCP stage. Accordingly, oxidation of either **157** (R^2=TCP) or **158** (R^2=TCP) with *m*-CPBA in DCM led to the corresponding (S_S) sulfoxides **159** and **161** almost as a single isomer in good yields. Aminolysis with $H_2N(CH_2)_2NH_2$ gave the (S_S) amino sulfoxides **160** and **162** in acceptable yields. Imination with PMPCHO using $CuSO_4$ afforded the desired (S_S) imino sulfoxides in good yields (Scheme 37). Khiar et al.[33] concluded that the diastereoselectivity of β-D-thioglycoside oxidation is a fine balance of steric and stereoelectronic effects. In the *exo*-anomeric stabilized conformations of the starting thioglycosides of the galacto and gluco series, the approximation of the peracid to the *pro-S* lp is favoured by hydrogen bonding and π–π stacking, as in the case of the compounds **157** (R^2=TCP), **158** (R^2=TCP), **163** and **165**, this last furnishing the epimeric mixture **166**. In the absence of these stabilizing factors, as in the case of the imine-protected compounds **157** (R^2=PMPCH=) and **158** (R^2=PMPCH=), the approximation to the *pro-R* lp is slightly favoured. In the case of the NPhth derivative **167**, the modest diastereoselection, observed in the oxidation to **168**, was justified as a consequence of its dependence on the substituent of the sulfinyl sulfur.[33]

Recently, we have presented the X-ray crystallographic analysis of 3-[(R_S)-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)sulfinyl]propanenitrile [(R_S)-**142**] (Table 2 and Scheme 33), which corroborates the role of the *exo*-anomeric effect in highly favouring the formation of the (R_S) sulfoxide by oxidation of the axial sulfide precursor.

The results of ab initio and DFT calculations for model compounds have been discussed to support the relevance of the sulfur anomeric interactions in determining the structural characteristics of aldohexosyl sulfoxides.[29]

3.3. Miscellaneous

Schmidt and Kast[35a] described the synthesis of C-2 branched sugars by the direct β lithiation of 1-phenylsulfinyl-substituted glucals. Typical examples of the synthetic protocol are shown in Scheme 38.



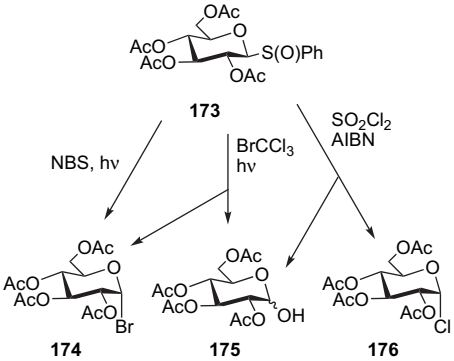
Scheme 38. Synthesis of C-2 branched sugars from anomeric sulfoxides.

Treatment of sulfur epimeric mixture **169** with LDA as a base provided the lithiated 1-phenylsulfinyl glucal **170**. Reaction with methyl chloroformate or aldehydes afforded the sulfinyl glucals **171** and **172**, respectively, as epimeric mixtures. Removal of the sulfoxide function (Ra-Ni in THF) gave enantiopure products.

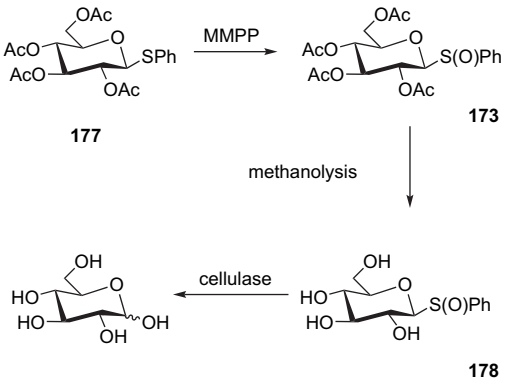
The photohalogenation of suitable glycosides allows their original and various functionalizations to occur with excellent regio- and stereoselectivities. Following this research line, Descotes and Praly[36a] studied the reactivity of the sulfur epimeric mixture **173**, as obtained by *m*-CPBA oxidation of the β-sulfide **177** (Schemes 39 and 40). The α-bromide **174** was obtained (78%) by NBS treatment of **173** under irradiation.

Irradiation of the same epimeric mixture in CCl_4 and in the presence of $BrCCl_3$ afforded the same bromide **174** (65%) and the hydrolysis product **175** (30%). Analogously, the photochlorination [SO_2Cl_2, CCl_4, 77 °C, AIBN] afforded the α-chloride **176** (36%) and tetraacetyl glucose **175** (23%).

During a study of cellulase-catalyzed glycosylation reactions, Kobayashi et al.[36b] observed that both sulfur epimers of **178** (Scheme 40) decreased the enzyme activity, but, interestingly, diastereoselective hydrolysis of the glucosidic bond took place.



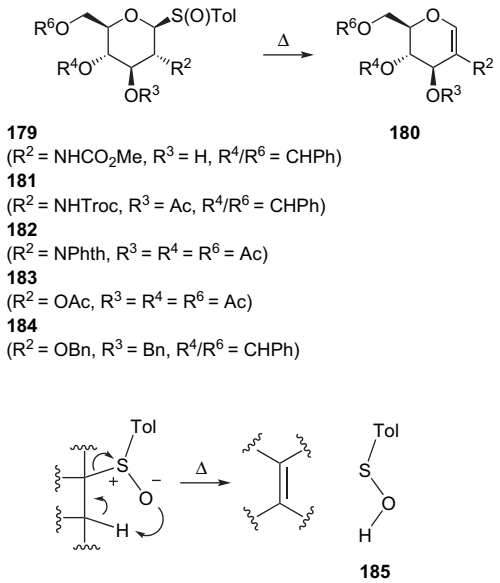
Scheme 39. Photohalogenation of phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside *S*-oxide (**173**).



Scheme 40. Cellulase hydrolysis of thioglucosidic bond.

After 8 h, one diastereoisomer of substrate **178** was completely hydrolyzed, whereas the other remained unchanged. This was attributed to the β-glucosidase present in the crude cellulase mixture. The authors[36b] claimed that, to the best of their knowledge, this was the first evidence of chiral discrimination using β-glucosidases.

A new and efficient route[37] to 2-amino- and 2-hydroxyglycals from glycosyl sulfoxides was developed, taking advantage of the well-documented β elimination of suitable sulfoxides. After refluxing in toluene overnight, both protected 2-amino- **179**, **181** and **182** and 2-hydroxy- **183** and **184** glucosyl sulfoxides afforded the respective glucals **180** in high yields via the intramolecular *syn*-elimination of *p*-toluenesulfenic acid (**185**) under thermal conditions (Scheme 41). 2-Amino- and 2-hydroxy-glycals are useful synthons for a variety of chemical reactions.

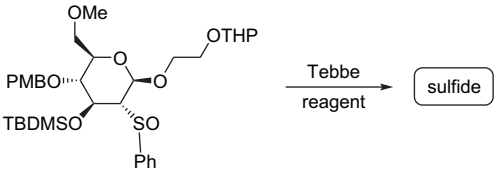


Scheme 41. Preparation of 2-amino- and 2-hydroxyglycals from glycosyl sulfoxides.

4. 2-Deoxy-2-sulfinyl-D-glucopyranosides

Over the course of the past several years, sulfoxide moieties have become increasingly important functional groups in organic chemistry, particularly as chirons in stereoselective synthesis. As such, there has been an enduring interest among chemists in developing novel methods to effect the deoxygenation of sulfoxides to sulfides, so that this functionality can be cleanly extruded from the molecule of interest once its presence is no longer required. During the course of recent synthetic investigations, Nicolaou et al.[53] uncovered a novel method to effect such a conversion with

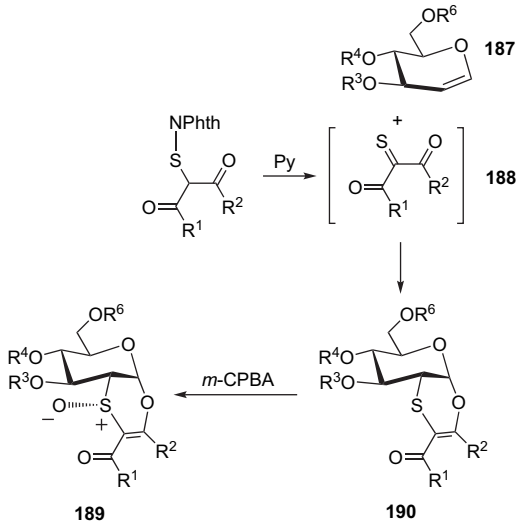
a titanocene methylidene complex generated from the Tebbe reagent. In particular, the authors[53] attempted to chemoselectively reduce the sulfoxide group in several sugars, due to their widespread use in carbohydrate chemistry. Gratifyingly, sugars containing a sulfoxide moiety in both the anomeric and the 2-position were smoothly reduced in high yield in the presence of various acetal, silyl, Bn, THP and Ts protecting groups. Scheme 42 shows the fully, variously protected 2-deoxy-2-phenylsulfinyl-β-D-glucopyranoside **186**, which was reduced to the corresponding sulfide by the Tebbe reagent (0.5 M in toluene) in mild conditions (THF, −40 to 0 °C, 3 h, 79% yield).



186

Scheme 42. Reduction to sulfide of 2-deoxy-2-phenylsulfinyl-β-D-glucopyranoside.

Enantiopure cycloadducts between glycals and alkyl or aryl heterodienes were selected as small, rigid, non-peptide molecules able to mimic the structure of cyclopeptide tachykinin NK-2 antagonists.[75] The presence of three aromatic groups in the pyranose ring was essential for NK-2 affinity, while an increase in activity was shown by the corresponding sulfoxides. The synthesis of the cycloadducts **190** (Scheme 43) was performed by means of the chemo-, regio- and stereoselective inverse electron-demand [4+2] cycloaddition between glycals **187** and in situ generated α,α′-dioxothiones **188**. Fused 2-deoxy-2-sulfinyl-α-D-glucopyranosides **189** were synthesized by treating the parent cycloadducts **190** in DCM with equimolar amounts of *m*-CPBA. As expected, the sulfoxides **189** were obtained as diastereomerically pure compounds (R_S). No trace of the other epimer at sulfoxide sulfur was ever detected (^{1}H NMR analysis of the crude products).

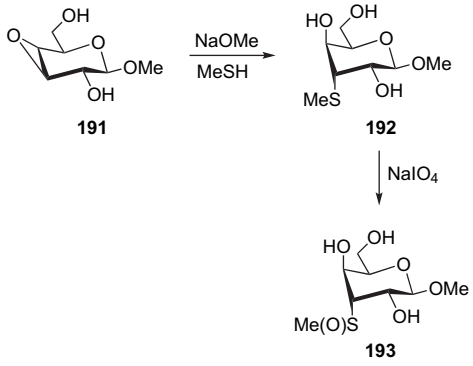


R^1	OEt	OEt	OEt	OEt	OEt	OPh	Ph
R^2	Me	Me	Me	Me	Me	Me	Ph
R^3	Bn	Bn	Bn	H	H	Bn	Bn
R^4	Bn	Bn	H	Bn	Bn	Bn	Bn
R^6	Bn	H	Bn	Bn	H	Bn	Bn

Scheme 43. Synthesis of hetero ring-fused 2-deoxy-2-alkylsulfinyl-α-D-glucopyranosides.

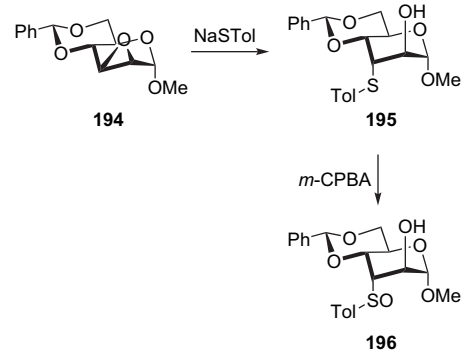
5. 3-Deoxy-3-sulfinylglycopyranosides

In 1962, Chastain, Dahlgard, and Han described[76] the formation of methyl 3-deoxy-3-(methylsulfinyl)-β-D-gulopyranoside **193** (Scheme 44) within a search for possible antimetabolites of the pentose phosphate pathway of carbohydrate metabolism to test as potential anticancer agents. The author's interest[76] was really directed towards preparing hexose analogues containing sulfur in place of oxygen. When methyl 3,4-anhydro-β-D-galactopyranoside (**191**) was treated with MeSH and NaOMe, a theoretical yield of crude methyl 3-deoxy-3-methylthio-β-D-gulopyranoside (**192**) was obtained as an oil. The guloside **192** was reacted with an equimolar amount of $NaIO_4$, and the sulfoxide **193** was isolated as a white crystalline compound.



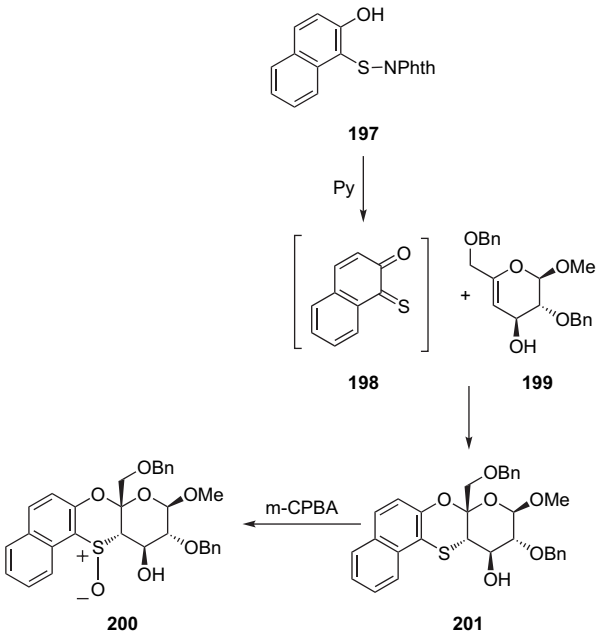
Scheme 44. Synthesis of 3-deoxy-3-sulfinylgulopyranoside.

In 1987, a Japanese group obtained the fused 3-deoxy-3-sulfinyl-α-D-altropyranoside **196** by *m*-CPBA oxidation of the sulfide **195** (Scheme 45).[77] This latter product was prepared in turn by adding NaSTol to the 2,3-anhydrosugar **194**.

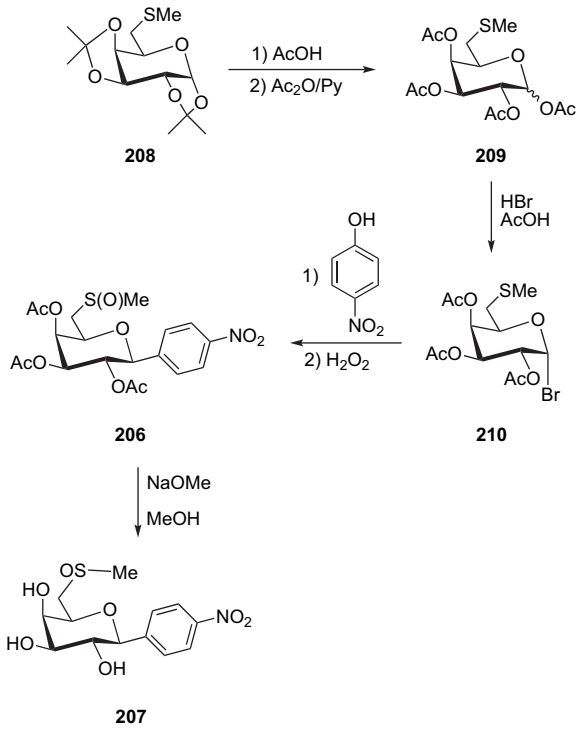


Scheme 45. Synthesis of methyl 3-deoxy-3-[(4-methylphenyl)sulfinyl]-4,6-*O*-(phenylmethylene)-α-D-altropyranoside.

The authors[76,77] faced the problem of sulfur configuration neither in **194** nor in **196** (Schemes 44 and 45). In contrast to this work, 3-deoxy-3-sulfinyl-α-L-sorbopyranoside **200** was obtained in the enantiopure form[78] shown in Scheme 46 within a new series of thio-substituted sugars synthesized by taking advantage of the totally regio- and stereoselective cycloaddition of suitable unsaturated pyranose derivatives to in situ-generated oxothiones. In particular, the sulfide **201** was the only product of the inverse electron-demand Diels–Alder reaction of **199** and *o*-thioquinone **198**, which, in turn, was generated in situ by the base treatment of 2-[(2-hydroxy-1-naphthalenyl)thio]-1*H*-isoindole-1,3(2*H*)-dione (**197**), as depicted in Scheme 46 (see Scheme 43 for an analogy). Under oxidation conditions (*m*-CPBA, DCM, rt), the sulfide **201** gave the corresponding sulfoxide **200** with complete diastereoselectivity.



Scheme 46. Synthesis of (S_S)-3-deoxy-3-sulfinyl-α-L-sorbopyranoside.



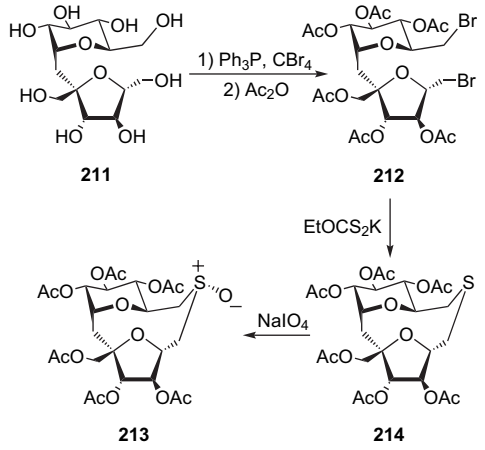
Scheme 47. Synthesis of 4-nitrophenyl 6-deoxy-6-methylsulfinyl-β-D-galactopyranosides.

6. 6-Deoxy-6-sulfinyl sugars

Several examples of 6-deoxy-6-sulfinyl D-monosaccharides are shown in Table 3. In particular, MPAA was used as an NMR shift reagent to predict the sulfur absolute configuration of some 6-deoxy-1,2:3,4-bis-*O*-(1-methylethylidene)-6-sulfinyl-α-D-galactopyranoses **202**–**207** (Table 3).[79] The correctness of the assignments was confirmed by X-ray crystallography.

During an investigation directed towards the incorporation of modified galactosides into biologically active oligosaccharides, Vulfson et al.[80] obtained a range of diastereomeric 6-substituted derivatives, which required separation. Although this could be achieved by chromatography, it was evident that the development of a facile, enzyme-based 'resolution' method would be of considerable interest. The diastereoselectivity of the enzymatic hydrolyses of 4-nitrophenyl (R_S)- and (S_S)-6-deoxy-6-(methylsulfinyl)-β-D-galactopyranosides **207** (Scheme 47 and Table 3) was investigated using a range of crude glycosidase preparations. It was shown that the enzymes display a high degree of discrimination between diastereomers, thereby demonstrating the utility of glycosidases for the diastereomeric resolution (hydrolysis) of unnatural 6-substituted monosaccharide derivatives. The sulfoxides **207** were prepared as shown in Scheme 47. Deketalization of sulfide **208** followed by acetylation afforded the fully protected derivative **209** as a 40:60 mixture of α/β anomers. After conversion into the α-bromide **210**, the 4-nitrophenyl group was introduced under phase-transfer conditions. Controlled oxidation then yielded the diastereomeric sulfoxides **206**, which were separated by column chromatography and finally deprotected to give **207** (Scheme 47 and Table 3). The absolute stereochemistry of the more polar diastereomer **207** was unequivocally established by a single-crystal X-ray analysis and was shown to be (*S*) at the sulfoxide stereocentre.

The family of known 6-deoxy-6-sulfinyl sugars of the D series also includes 6,6′-epithiosucrose hexaacetate *S*-(R_S)-oxide (**213**) (Scheme 48), which was prepared in 1988 by a research group engaged in the synthesis of sucrose analogues containing various functionalities,[88] owing to the enormous enhancement of the sweetness of sucrose (**211**) by the introduction of suitable substituents into the molecule. The reaction of sucrose (**211**) with Ph_3P and CBr_4 in Py gave 91% of a syrupy dibromide, which could be converted into a crystalline hexaacetate **212**. When compound **212** was treated with $EtOCS_2K$ in DMF, it gave a mixture of products, from which the major compound **214** was isolated in 46% yield. Oxidation of the episulfide **214** with $NaIO_4$ afforded 86% of a single (R_S) sulfoxide **213** showing the *S*-oxygen in a pseudo-equatorial position.



Scheme 48. Synthesis of 6,6′-epithiosucrose hexaacetate S-(R_S)-oxide (**213**).

Stimulating results were obtained in the field of supramolecular chemistry involving 6-deoxy-6-sulfinyl β-CDs. It is well known that *m*-substituted phenyl acetates are hydrolyzed more rapidly than the corresponding *p*-isomers by α- or β-CDs, a phenomenon termed '*m*-selectivity'. Fujita et al. described,[89] firstly, that a substitution in the β-CD of a primary hydroxy group with a *tert*-butylthio or hexylthio group caused a clear reversion of the *m*- to the *p*-selectivity and, secondly, that such a *p*-selectivity was reversed again to a *m*-selectivity by a simple and small structural change, an H_2O_2 oxidation of the alkylthio group to its sulfoxide. These results suggest that the capping of the CD cavity by the sulfoxide substituents is not as effective as that of the sulfide substituents. This might be explained by assuming that the intramolecular hydrogen bonding between the

sulfoxide oxygen and the primary hydroxy group of the neighbouring glucose unit locates the *tert*-butyl or hexyl group at a different (less effective) position from that in the corresponding sulfides. On the whole, the selectivity of the CD catalysis is very sensitive to the modification of the primary hydroxy side, a non-catalytic moiety.

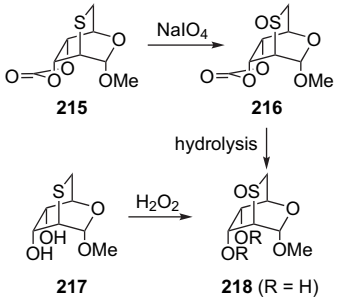
A Japanese group[90] reported in 1987 the X-ray analysis of 6-deoxy-6-[(R_S)-phenylsulfinyl]-β-cyclodextrin as an example of a macrocycle showing dual host (CD moiety) and guest (phenylsulfinyl group) character. These authors[90] demonstrated that this host–guest compound forms a helical polymer by intermolecular inclusion in the crystalline state. In aqueous solution, it forms dimers or higher complexes again by intermolecular interactions.

Finally, LB films are interesting molecular assembly systems characterized by the ultra-thin nature and high degree of alignment of the molecules. Developments of new classes of monolayer-forming materials are indispensable in order to utilize this unique system for practical purposes. With this object in view, Kawabata et al. synthesized[91] some heptakis(6-alkylsulfinyl-6-deoxy)-β-cyclodextrins and examined their capabilities for the formation of stable monolayers and their deposition as LB films. The monolayers of CDs were spread from $CHCl_3$ solutions on pure water. The LB films were obtained for heptakis(6-deoxy-6-dodecylsulfinyl)-β-cyclodextrin and its Ac-protected derivative.

7. Sulfur-bridged glycosulfoxides

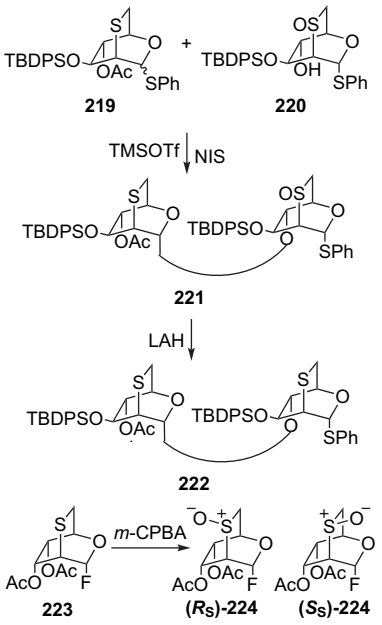
Some monosaccharides carrying a sulfinyl bridge have been reported in the literature.[13,18,92]

In the context of a study concerning the assignment of sulfoxide configuration by ^{1}H NMR, Foster et al. reported[92a] the reaction of methyl 2,6-dideoxy-2,6-epithio-α-D-altropyranoside cyclic carbonate (**215**) with boiling aq ethanolic $NaIO_4$ (Scheme 49) to give the separable sulfoxide epimers **216**. The saponification of their mixture gave the diol sulfoxides **218** (R=H), also obtainable by the action of H_2O_2 on **217**. The corresponding (R_S) and (S_S) diacetates **218** (R=Ac) have additionally been described.



Scheme 49. Synthesis of methyl 2,6-dideoxy-2,6-epithio-α-D-altropyranoside *S*-oxides.

A methodology for the controlled synthesis of 2,6-dideoxy oligosaccharides by combinational use of an activated 2,6-anhydro-2-thio sugar and a deactivated 2,6-anydro-2-sulfinyl sugar, both having the same leaving group at the anomeric position, was reported in 1993.[92d,e] The glycosidation of the 2,6-anhydro-2-thio sugar **219**, possessing a thiophenyl group at the anomeric centre, with the corresponding 2,6-anhydro-2-sulfinyl sugar **220**, having the same leaving group, proceeded nicely by NIS–TMSOTf to give the oligosaccharide **221** in 89% yield (Scheme 50). Notably, this glycosidation and related couplings were highly α-selective. Further, the obtained oligosaccharide **221** was easily converted into the oligosaccharide **222** by simple reduction of the sulfoxide moiety using LAH in THF. The 2,6-anhydro-2-sulfinyl fluorides **224** were prepared from the 2,6-anhydro-2-thio fluoride **223** by *m*-CPBA oxidation in DCM. The stereochemistry of the sulfoxides **224** was clearly determined by their ^{1}H NMR analyses, mainly on the basis of the chemical shifts of H-1 and H-3.[92e]



Scheme 50. Synthesis of 2,6-dideoxy oligosaccharides.

(S_S)-2,5-Anhydro-1,6-dideoxy-1,6-episulfinyl-D-glucitol diacetate (**55**) (Scheme 9) and 4-[(2,5-anydro-6-thio-α-D-glucoseptanosyl)-thio]benzonitrile *S*-(R_S)-oxide (**58**) (Scheme 10) could have been included in this section,[13,18,92b,c] but we have chosen to discuss them among the sulfoxide ring sugars in Section 2 for safeguarding the consistency of exposition.

8. Conclusions

We are conscious that this report cannot be exhaustive with regard to all of the extensive and varied scientific work performed on glycosulfoxides, but we hope that we have given here a highlight of the chemistry developed around these compounds that could stimulate the intellectual curiosity of the readers.

Glycosulfoxides have provided an opportunity for synthetic chemists to exploit new strategic methodologies, to design and realize challenging molecular architectures and to develop the synthesis of intriguing products for biological investigations, as well as for medicinal applications. We are sure that, in future, this subject will continue to offer opportunities for new relevant discoveries and inventions.

Acknowledgements

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