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# THE ACID–CATALYSED REACTION OF THIOLS WITH ALKYL 2,3-DIDEOXY-GLYC-2-ENOPYRANOSIDES OR GLYCALS

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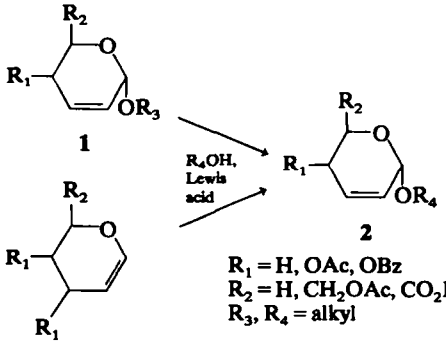
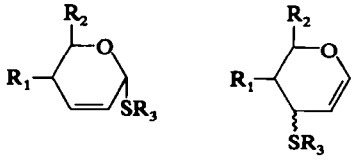
**Abstract**—The acid-catalysed (HCl or $SnCl_4$) reaction of alkyl 2,3-dideoxy-glyc-2-enopyranosides or 3,4,6-tri-O-acetyl-D-glycals with thiols leads to mixtures of alkyl 2,3-dideoxy-1-thio-glyc-2-enopyranosides and 3-S-alkyl-3-thioglycals. Under equilibrium conditions the latter are the preponderant products of the reaction. Cross experiments have confirmed the intermediacy of the allylic carbocation in the reaction. A rationalization of the substitution reactions of 1,2- and 2,3-unsaturated sugars based on HSAB principle has been proposed.

The C-1 alkoxy group in alkyl 2,3-dideoxy-glyc-2-enopyranosides (**1**) can be readily substituted for another OR group in an acid-catalysed reaction with alcohols.[1,2] This reaction enables a simple preparation of various glycosides belonging to 2,3-dideoxy-glyc-2-enopyranoside series (**2**). On the other hand, this class of sugar derivatives can be obtained in a well-known allylic displacement reaction of glycals (**3**) with alcohols.[3]




It was our intention to exploit both types of the approach for the preparation of 2,3-unsaturated thioglycosides, an unknown class of monosaccharides. The experiments have shown that acid-catalysed reaction of **1** and **3** with thiols gave thioglycosides (**4**) and also 3-S-alkyl-3-thio-glycals (**5**). The results allow more general conclusions to be drawn regarding the regioselectivity in substitution reactions of alkyl 2,3-dideoxy-glyc-2-enopyranosides (**1**) and glycals (**3**).




$R_1$ = H, OAc; $R_2$ = $CH_2OAc$, $CH_2NHAc$, etc.
$R_3$ = $CH_3$, $C_6H_{13}$

## RESULTS

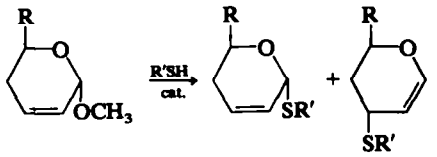
Methyl 2,3,4-trideoxy-glyc-2-enopyranosides (**6**–**11**) react slowly with an excess of thiols exchanging the methoxyl group for an SR group under mild conditions. The reaction in water-dioxane solution is catalysed by very diluted hydrochloric acid and takes about 5 days. By contrast, the displacement reaction in methylene chloride solution catalysed by stannic tetrachloride requires only 3 hr for completion. Only a slight excess of thiol is required in this case.

The yields of 2,3-unsaturated thioglycosides are moderate to good (20–65%); the formation of side-products can also be observed (tlc). In two cases, the side-products were isolated and identified as the isomeric 3-S-alkyl-3-thioglycals having the *erythro* configuration. The results are collected in Table 1.

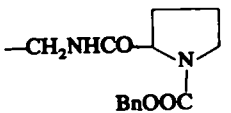
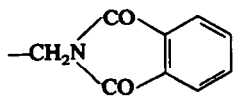
Stannic tetrachloride was next used as a catalyst in the reaction of thiols with typical glycals, e.g. 3,4,6-tri-O-acetyl-D-glucal (**21**)† and 3,4,6-tri-O-acetyl-D-galactal (**22**).† From the reaction of **21** with n-hexyl mercaptan five products could be isolated, they were identified as n-hexyl 2,3-dideoxy-1-thio-α- and β-D-*erythro*-hex-2-enopyranosides (**23** and **24**), 4,6-di-O-acetyl-3-S-n-hexyl-3-thio-D-allal and -D-glucal (**25** and **26**), and n-hexyl 4,6-di-O-acetyl-2-deoxy-3-S-n-hexyl-1,3-dithio-α-D-*arabino*-hexopyranoside (**27**). From the reaction of the same substrate with methyl mercaptan similar results were achieved although only three products, **29**, **30** and **31** were isolated and characterized. The analogous reaction of **22** with n-hexyl or methyl mercaptans afforded alkyl 4,6-di-O-acetyl-2,3-dideoxy-1-thio-α- and β-D-*threo*-hexopyranosides (**32**, **33** and **36**) and 4,6-di-O-acetyl-3-S-alkyl-3-

†Systematic names: 3,4,6-tri-O-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (**21**) and 3,4,6-tri-O-acetyl-1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol (**22**).

Table 1




**6–11** **12–18** **19, 20**

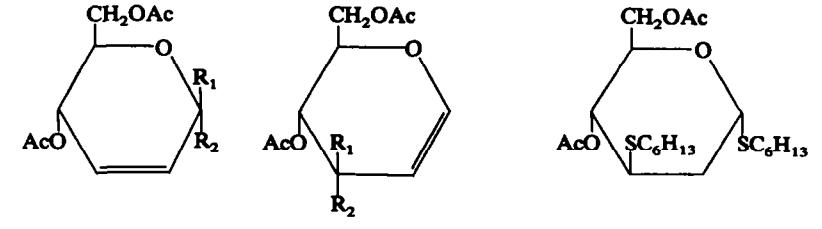
| R | Compd. no | Method | R' | Compd. no | Yield % | m.p. | Analysis Calcd. C | H | N | S | Found C | H | N | S |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $-CH_2NHAc$ | **6** | A[a] | $C_6H_{13}$ | **12** | 35.9 | 100.5° | 61.95 | 9.28 | 5.16 | 11.81 | 62.18 | 9.29 | 4.95 | 11.81 |
| $-CH_2NHAc$ | **6** | B[a] | $C_6H_{13}$ | **12** | 50.3 | 100.5° | | | | | | | | |
| $-CH_2NHAc$ | **6** | B | $CH_3$ | **13** | 41.2 | b | 53.70 | 7.51 | 6.96 | | 53.44 | 7.21 | 6.75 | |
| $-CH_2NHAc$ | **6** | c | $C_6H_{13}$ | **38** | 94.0 | b | 61.95 | 9.28 | 5.16 | 11.81 | 61.15 | 9.44 | 4.71 | |
|  | **7** | A | $C_6H_{13}$ | **14** | 65.7 | b | 65.18 | 7.87 | 6.08 | 6.96 | 65.25 | 7.95 | 6.00 | 6.99 |
| $-CHEtNHAc$ | **8** | A | $C_6H_{13}$ | **15** | 41.8 | b | | | | | | | | |
| $-CONH_2$ | **9** | B | $C_6H_{13}$ | **16** | 19.8 | 151–3° | 59.22 | 8.70 | 5.76 | 13.18 | 60.04 | 8.98 | 5.76 | 13.22 |
| $-CH_2NHCO_2Bn$ | **10** | B | $C_6H_{13}$ | **17** | 43.0 | b | 66.08 | 8.04 | 3.85 | 8.80 | 65.72 | 8.26 | 3.64 | 8.98 |
| | | | $C_6H_{13}$ | **19** | 13.8 | b | 66.08 | 8.04 | 3.85 | 8.80 | 65.62 | 8.24 | 3.64 | 9.43 |
|  | **11** | B | $CH_3$ | **18** | 56.0 | 137–40° | 62.26 | 5.23 | 4.84 | 11.08 | 62.28 | 5.11 | 4.61 | 10.92 |
| | | | $CH_3$ | **20** | 16.0 | b | 62.26 | 5.23 | 4.84 | 11.08 | 61.93 | 5.26 | 4.83 | 11.22 |

[a]See Experimental for details.
[b]Syrup, homogenous in TLC.
[c]Obtained by equilibration of **6** with $SnCl_4$.

le 2. Yields, physical and analytical data of alkyl 4,6-di-O-acetyl-2,3-dideoxy-1-thio-D-hex-2-enopyranosides and 4,6-di-O-acetyl-3-S-alkyl-3-thio-D-glycals

| No | Substrate no | Substr:$SnCl_4$ React. time (h) thiol | Product no | Yield % | $[\alpha]_D^t$ t° | Analysis Calcd. C | H | S | Found C | H | S |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **21**[b] | 43:1 (3) | **23**[c] | 41 | 210.1°(15) | 58.15 | 7.93 | 9.70 | 58.02 | 8.07 | 9.78 |
| | | | **25**[c] | | 201.4°(15) | 58.15 | 7.93 | 9.70 | 58.34 | 7.94 | 19.49 |
| | | $C_6H_{13}SH$ | **26**[c] | 3.8 | −98.3 (15) | 58.15 | 7.93 | 9.70 | 58.45 | 8.17 | 9.91 |
| 2 | **21**[d] | 12.5:1 (5), $C_6H_{13}SH$ | **27**[c] | 3.3 | 149.4 (15) | 58.89 | 8.99 | 14.29 | 58.94 | 9.20 | 14.52 |
| 3 | **28**[e] | 20:1 (3) $C_6H_{13}SH$ | **24**[c] | 9.1 | 75.0 (17) | | | | | | |
| 4 | **21** | 16.7:1 (2.5) | **29**[f] | 54.8 | 229.4 (21) | 50.77 | 6.20 | 12.30 | 50.89 | 6.32 | 12.34 |
| | | $CH_3SH$ | **30**[c] | | 309.0 (16) | 50.77 | 6.20 | 12.30 | 51.03 | 6.16 | 12.39 |
| | | | **31**[c] | 3.2 | −120.6 (16) | 50.77 | 6.20 | 12.30 | 50.83 | 6.17 | 12.32 |
| 5 | **22** | 14.6:1 (12) | **32**[c] | 43.0 | −51.8°(20) | 58.15 | 7.93 | 9.70 | 58.06 | 8.02 | 9.91 |
| | | $C_6H_{13}SH$ | **34**[c] | 10 | 109.8 (23) | 58.15 | 7.93 | 9.70 | 58.37 | 8.04 | 9.75 |
| 6 | **35**[g] | 46:1 (12) $C_6H_{13}SH$ | **33**[c] | 11.4 | −91.8 (20) | 58.15 | 7.93 | 9.70 | 58.11 | 8.32 | 9.71 |
| 7 | **22** | 30.5:1 (12) | **36**[h] | 41 | −109.8 (21) | 50.77 | 6.20 | 12.30 | 50.93 | 6.29 | 12.32 |
| | | $CH_3SH$ | **37**[i] | 17 | 164.1 (18) | 50.77 | 6.20 | 12.30 | 50.55 | 6.46 | 12.12 |

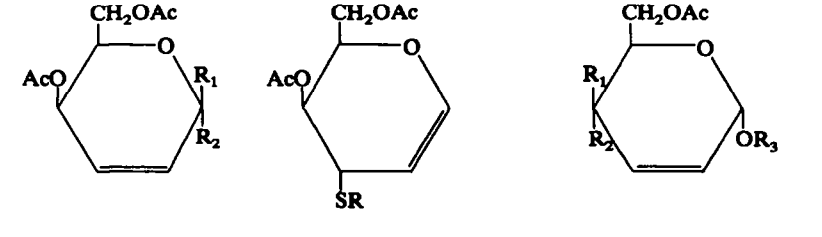
ethyl acetate soln.
ıe presence of **24** in the reaction mixture was detected by TLC.
rup.
eld of **23**:11% and of **25**+**26**:43%.
eld of **23**:36.9% and of **25**+**26**:3.1%.
st. at 130°/0.2 Torr.
eld of **32**:49.6% and of **34**:6%.
.p. 55–57°, b.p. 117–119°/0.2 Torr.
). 109–111°/0.2 Torr.




| | $R_1$ | $R_2$ |
|---|---|---|
| **23** | H | n-$C_6H_{13}S$ |
| **24** | n-$C_6H_{13}S$ | H |
| **29** | H | $CH_3S$ |

| | $R_1$ | $R_2$ |
|---|---|---|
| **25** | H | n-$C_6H_{13}S$ |
| **26** | n-$C_6H_{13}S$ | H |
| **30** | H | $CH_3S$ |
| **31** | $CH_3S$ | H |

**27**




| | $R_1$ | $R_2$ |
|---|---|---|
| **32** | H | n-$C_6H_{22}S$ |
| **33** | n-$C_6H_{13}S$ | H |
| **36** | H | $CH_3S$ |

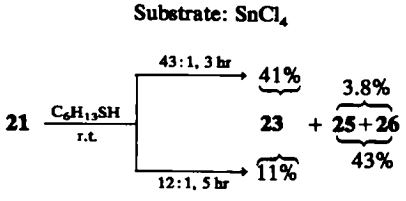
**34**: R = n-$C_6H_{13}$ **37**: R = $CH_3$

**28**: $R_1$ = H, $R_2$ = OAc, $R_3$ = $CH_3$
**35**: $R_1$ = OAc, $R_2$ = H, $R_3$ = $C_2H_5$

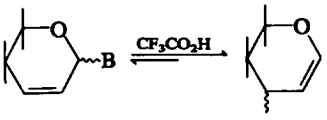
thio-D-gulal (**34** and **37**). The results are collected in Table 2.

The 2,3-unsaturated alkyl hexopyranosides **28** and **35** reacted with n-hexyl mercaptan in a $SnCl_4$-catalysed reaction in a similar fashion, affording the same products as in the appropriate reactions with glycals **21** and **22** described above (Table 2).

The relative proportions of products obtained from glycals and 2,3-unsaturated glycosides were strongly dependent on amount of the catalyst used and the time allowed for the reaction. Higher concentrations of the catalyst and prolongation of the reaction time markedly increased the yield of 3-thioglycals:




This led to the conclusion that 2,3-unsaturated thioglycosides **23, 24, 29, 32, 33,** and **36** were in fact the kinetic products of the reactions arising from allylic displacement or substitution reactions at C-1. It was interesting therefore to study the equilibration of 2,3-unsaturated thioglycosides in the presence of stannic chloride. The results collected in Table 3 proved that, in all cases, the equilibrium studied is strongly shifted towards the 3-S-alkyl-3-thio-glycals. It is worth noting that acid-catalysed equilibration of the products obtained from nucleoside–type bases and glycals led to similar results: 3-substituted glycal-type compounds prevailing in the equilibrium.[4]



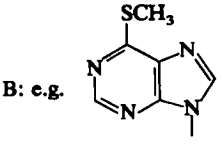
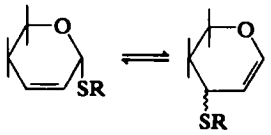
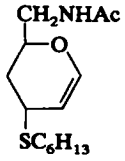




Table 3. The equilibrium ratios of 2,3-unsaturated thioglycosides and 3-S-alkyl-3-thioglycals ($CCl_4$ solution, 20°, $SnCl_4$ cat.)[a]



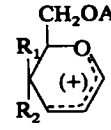

| | |
|---|---|
| **12** (6%) | **38** (94%) |
| **18** (5%) | **20** (95%) |
| **29** (9%) | **30** (33%) + **31** (58%) |
| **32** (5%) | **34** (95%) |
| **36** (5%) | **37** (95%) |

[a]The progress of equilibration was followed by $^1H$ NMR spectra. The ratios of products were determined by integration of the appropriate signals.




**38**

There is general agreement[2-4] that in acid-catalysed reactions of glycals and 2,3-unsaturated alkyl glyc-2-enopyranosides a carbocation, formed *via* elimination of the substituent at C-3 or C-1, is the main intermediate. The best proof for its existence would be a positive result of a cross experiment. We performed simultaneously the $SnCl_4$–catalysed isomerisation of n-hexyl 4,6-di-O-acetyl-2,3-dideoxy-1-thio-α-D-*erythro*-hex-2-enopyranoside (**23**) and methyl 4,6-di-O-acetyl-2,3-dideoxy-1-thio-α-D-*threo*-hex-2-enopyranoside (**36**), which gave all six possible glycals: **25, 26, 30, 31, 34** and **37**. This proves beyond any doubt the intermediacy of the carbocations **39** and **40** in the reaction.

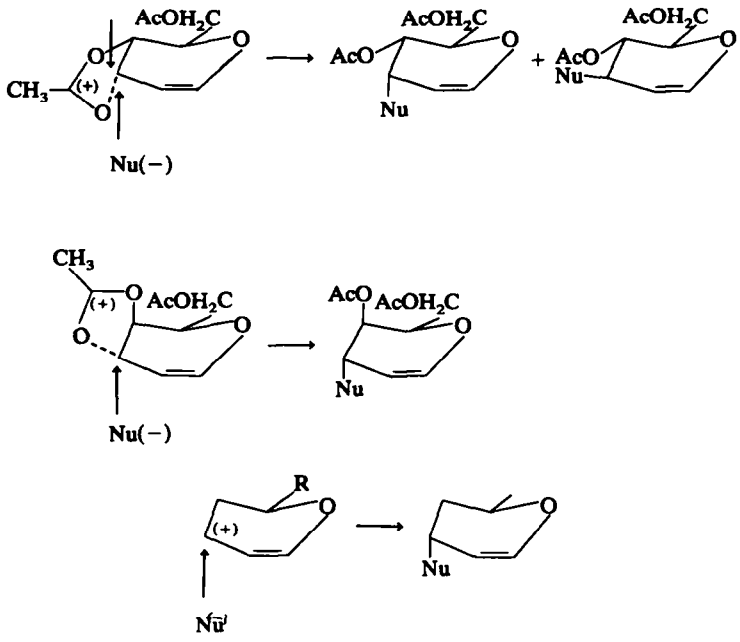



**39:** $R_1 = H$, $R_1 = OAc$
**40:** $R_1 = OAc$, $R_2 = H$

## DISCUSSION

The results described show that, under properly selected conditions, 2,3-unsaturated thioglycosides are available from either alkyl glyc-2-enopyranosides or glycals in acid-catalysed, kinetically-controlled reactions with thiols. It is important to note that α-anomers are the main products in these reactions, whereas in all reported syntheses of thioglycosides β-anomers usually prevail.[5] The application of unsaturated α-thioglycosides for synthetic purposes will be described in forthcoming papers.

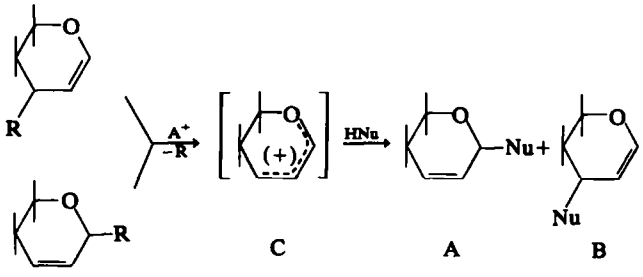
3-S-alkyl-3-thioglycals represent a new class of sugar derivatives which is of potential use in preparation of 3-thiohexoses. The stereochemistry of their formation merits some discussion. From 3,4,6-tri-O-acetyl-D-glucal (**21**), two stereoisomeric glycals were formed having the *ribo* (**25** and **30**, preponderant products) and the *arabino* (**26** and **31**) configurations. From 3,4,6-tri-O-acetyl-D-galactal (**22**) only the D-*xylo*-glycals (**34** and **37**) were obtained. In the case of 4-deoxy compounds only *erythro*-glycals (**16, 17,** and **38**) were formed. These stereochemical results can be rationalised if we assume that (i) the attacking nucleophile forms preferentially a pseudoaxial bond at position 3 of the pyranose ring, and (ii) the ester group at C-4 can—*via* the formation of a dioxolanium ion—assist or oppose the pseudoaxial attack, depending on the position occupied by the 5-membered ring. It is assumed that the bulky group at C-5 of the carbocation holds a conformation which enables differentiation between pseudoaxial or pseudoequatorial attack of the nucleophile (Scheme 1).



Scheme 1

The pseudoaxial attack of the nucleophile at position 3 of the carbocation has an apparent analogy in the similar attack of nucleophiles observed for Michael addition reactions in 6-membered, cyclic $\alpha\beta$-unsaturated systems.[6] This simple model explains not only the present results but also the majority of analogous reactions from the literature.[2,4,24,28,30]

The question of the regioselectivity in the acid-catalysed reactions of **1** and **3** with thiols and other nucleophiles will now be discussed. Essentially two types of products are formed in these reactions: 1-substituted 2,3-unsaturated pyranoses (A) or 3-substituted glycals (B) or both.†



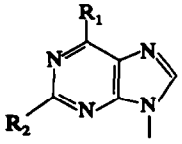
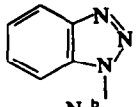
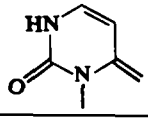
Scheme 2

It should be noted that the proportion of products A and B at equilibrium or thereabouts depends on the nature of the incoming nucleophile. In Table 4, these groups or molecules are ordered according to their preference for bonding to C-1 or C-3 of the unsaturated pyranose system.

It appears that a plausible explanation of the above results may be forwarded on the basis of Pearson's hard and soft acids and bases (HSAB) principle. The nucleophiles tabulated in the first column (Table 3) are the hard bases, whereas those in the second column are soft bases. Accordingly, the regioselectivity in the reactions can be rationalized by assuming that the *carbocationic site at* C-1 *is hard whereas that at* C-3 *is soft.* The selectivity in choosing the bonding site is especially striking with typical hard (e.g. $OR^-$, $F^-$) and soft (e.g. $SR^-$, $^-C(CN)_2CO_2Me$) bases. In these cases, the equilibrium $A \rightleftharpoons B$ is almost completely shifted towards 1- or 3-substituted products. Some nucleophiles give rise to both regioisomers A and B, and it is difficult in these cases to decide whether this is the consequence of the mixed character of the base, or whether the mixture obtained is not fully equilibrated. It is expected, therefore, that a

†In many reactions the formation of saturated products having Nu groups both at C-1 and C-3 was also observed. They undoubtedly resulted from secondary processes which will not be discussed here.

Table 4. List of atoms and groups which prefer bonding at C-1 or C-3 of the allylic C-1–C-3 system of carbohydrates[a]

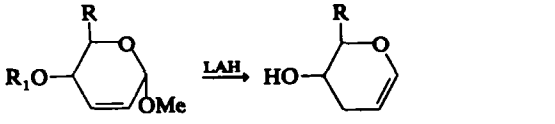
| C-1 | Ref. | C-3 | Ref. |
|---|---|---|---|
| —OH | 7, 8 | $—C(CN)_2CO_2CH_3$ | 2 |
| —OAr | 9 |  | 4, 22–25 |
| —OR | 10–15 | | |
| —OAc | 16–18 | $R_1$ = Cl, NHBz, $SCH_3$; $R_2$ = H, Cl, $SCH_3$, NHAC | |
| —F | 19 |  | 4, 26 |
| —Cl[b] | 20 | $—N_3$[b] | 27, 28 |
| | | $ClO_2S—N—CO_2Et$ | 29, 30 |
| $—P(OR)_2$ | 21 | —SR | this study |
| | |  | 31 |

[a]Taken from literature for acid-catalysed reactions of alkyl 2,3-dideoxy-glyc-2-enopyranosides, glycals, and 2-acyloxyglycals.

[b]Such anions are regarded as "borderline bases".[32] Therefore both possible products, *i.e.* substituted at C-1 and at C-3, should be considered for the equilibrium conditions.

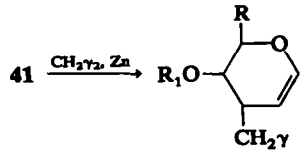
real classification of the reaction can be made only after careful equilibration of the products.

It seems that the HSAB principle may also be useful in the interpretation of other reactions, e.g. LAH—reduction of alkyl 2,3-dideoxy-hex-2-enopyranosides[33,34] (**41**) in which only 3-deoxy-glycals (**42**) are produced. The formation of **42** is



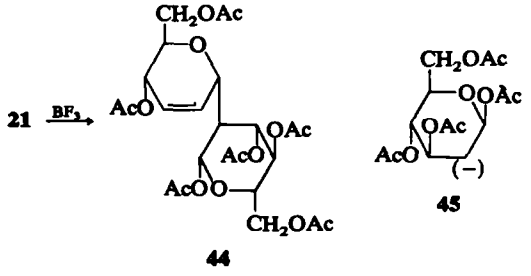
**41** **42** R = $CH_2OAc$, $CH_3$; $R_1$ = Ac

understandable because the hydride anion, as a soft base, binds preferentially to the soft center of the hexenopyranose skeleton (i.e. C-3). Also, the Simmons–Smith reaction of **41** leading to **43** as the primary product can be rationalised on the same basis.[35–37] On the other hand, the structure of the so-called dimer of 3,4,6-tri-O-acetyl-D-glucal,



**43**

namely 1,3,4,6-tetra-O-acetyl-2-C-(4,6-di-O-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-2-deoxy-β-D-glucopyranose (**44**),[38] contradicts the proposal outlined since a glucal-type structure would be predicted because the (—) $CHR_1R_2$ group (45 in this case) is usually regarded as a soft base. It may be **44** is the kinetic product or the carbanion **45** is a borderline base?

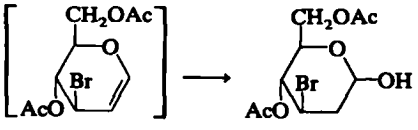


**44** **45**

The HSAB concept should show its usefulness in carbohydrate chemistry by providing the chance of predicting the reaction course in some transformations. It can be said e.g. that reaction of glycals with hydrogen bromide—due to the borderline character of $Br^-$—should lead to a mixture of both regioisomeric products i.e. 1-bromo-2,3-ene (A) and 3-bromo-1,2-ene (B).

It has been reported[20] that only A-type products were found when 3,4-di-O-acetyl-D-xylal and -D-arabinal reacted with hydrogen bromide. On the

other hand, it has been found[39] that 3,4,6-tri-O-acetyl-D-glucal reacts with hydrogen bromide in acetic acid to afford 4,6-di-O-acetyl-3-bromo-2,3-dideoxy-D-*arabino*-hexose (**46**). It is obvious that a B-type bromo compound (**47**) preceded **46**. Both




**47** **46**

results confirm—at least to some extent—the expectation based on Pearson's concept. Certainly further studies on the regioselectivity in reactions of **1** and **3** with a variety of nucleophiles would be profitable for acceptance or rejection of the concept.

Finally, it must be born in mind that the HSAB principle does not provide an interpretation of the results, but rationalization.[32] It is hoped this concept may prove to be useful in planning syntheses from unsaturated sugar derivatives.

## EXPERIMENTAL

$^1$H NMR spectra were recorded for solns in $CDCl_3$ with a Jeol JNM-4H-100 spectrometer. Optical rotations were measured with a Perkin–Elmer 141 automatic polarimeter. For column chromatography silica gel Merck (230–400 mesh) was used. For catalysis stannic chloride soln in ethylene chloride (100 mg/ml) was employed.

Substrates **6**, **7** and **10** were obtained by LAH reduction of 6-methoxy-3,6-dihydro-2H-pyran-2-carboxamide (**9**)[40] to the amine, which was then acylated with appropriate acylating reagents.[41] Compounds **8**,[42] **11**,[43] **21**,[44] **22**,[44] **28**[11] and **35**[15] were prepared according to literature methods.

*n-Hexyl 6-acetamido-2,3,4,6-tetradeoxy-1-thio-α-DL-hex-2-enopyranoside* (**12**)

*Method A.* To a soln of **6** (19 g) in dioxane-water 1:1 (200 ml) containing 0.036% HCl, 26 ml of n-hexyl mercaptan were added. The mixture was vigorously stirred at room temp.

After 5 days the soln was neutralized with $NaHCO_3$ and extracted with EtOAc. The extract was dried ($MgSO_4$) and evaporated to dryness. The residue was chromatographed over a silica gel column (with benzene–ether–methanol (20:20:1) as eluent) affording **12** (10 g, 35.9%), m.p. 100.5° from ether.

*Method B.* To a soln of **6** (1.86 g) and n-hexyl mercaptan (1.5 ml) in methylene chloride (60 ml), stannic chloride catalyst (1.15 ml) was added. After 3 hr at room temp, the mixture was shaken with sat $NaHCO_3$ aq, washed twice with water, and dried ($MgSO_4$). The solvent was evaporated under diminished pressure and the residue was purified by column chromatography over silica gel (using light petroleum–acetone–methanol (100:10:1) for elution); 1.37 g (50.3%) of **12** were obtained.

Thioglycosides **13–18** were obtained according to methods A or B; in some cases the proportion of benzene, ether and MeOH used for elution of products from chromatographic columns differed slightly from that given above. The preparations were performed on 10 mmole-scale. The yields and analytical data of products **12–20** are recorded in Table 1, $^1$H NMR data of products **12–18**—in Table 5. The IR spectra of thioglycosides **12–18** are fully compatible with the structures assigned.

The constitution and configuration of both 3-S-alkyl-3-thio-DL-glycals **19** and **20** was deduced from their $^1$H NMR spectra (see below).

*Reaction of 3,4,6-tri-O-acetyl-D-glucal* (**21**) *with mercaptans*

(*A*) *With n-hexyl mercaptan* (Table 2, entry 2). A soln of **21** (1.105 g) and n-hexyl mercaptan (0.6 ml) in 25 ml of ethylene chloride was treated with stannic chloride catalyst (0.85 ml). After 5 hr at room temp, the reaction was interrupted by shaking the soln with $NaHCO_3$ aq. The organic layer was washed twice with water and dried ($MgSO_4$). Evaporation of the solvent under diminished pressure left a residue which was separated over a silica gel column using light petroleum—EtOAc (30:1) as

Table 5. $^1$H NMR data of alkyl 2,3,4-trideoxy-1-thio-α-DL-hex-2-enopyranosides **12–18**[a] (100 MHz, $CDCl_3$)

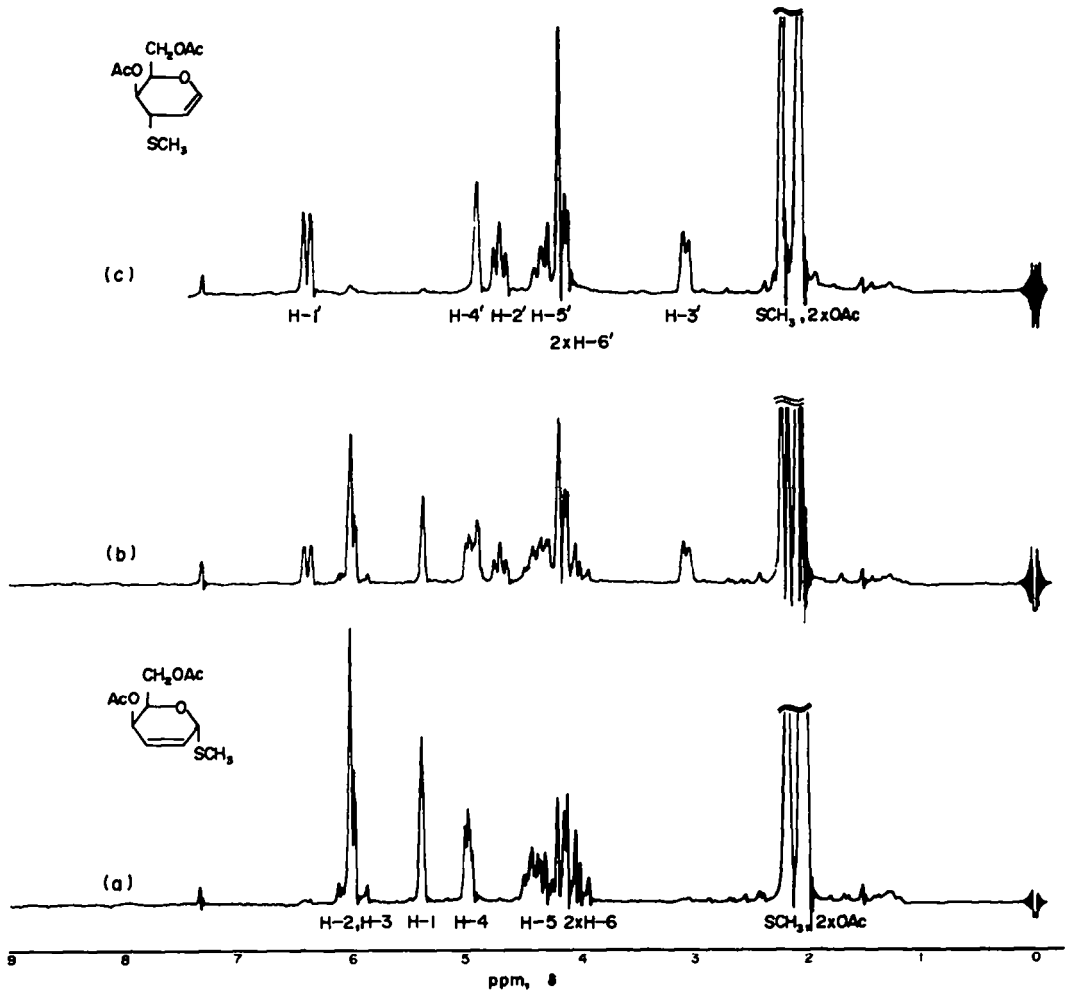
| Compd. no | |
|---|---|
| **12** | 5.63–6.20 (m, 3H, NH, H-2, H-3), 5.48 (bs, 1H, H-1), 4.19 (m, 1H, H-5), 3.50 (m, 1H, $J_{6,NH}$ = 6 Hz, $J_{6,5}$ = 3.8 Hz, $J_{6,6'}$ = 14 Hz, H-6'), 3.30 (pt, 1H, $J_{6,NH}$ = 6 Hz, $J_{6,5}$ = 6 Hz, H-6), 2.63 (m, 2H, $CH_2S$), 1.94–2.20 (m, 2H, H-4, H-4'), 2.00 (s, 3H, NAc), 1.12–1.90 (m, 8H, 4×$CH_2$), 0.92 (t, 3H, $CH_3$). |
| **13** | 6.24 (bs, 1H, NH), 5.84 (m, 2H, H-2, H-3), 5.40 (s, 1H, H-1), 4.19 (m, 1H, H-5), 3.15–3.70 (m, 2H, H-6, H-6'), 2.20 (s, 3H, $SCH_3$), 2.03 (s, 3H, Ac). |
| **14** | 7.32 (s, 5H, aromatic H), 5.77 (s, 2H, H-2, H-3), 5.44 (bs, 1H, H-1), 5.12 (s, 2H, $PhCH_2$), 4.30 (m, 1H, H-2'), 4.10 (m, 1H, H-5), 3.23–3.70 (m, 4H, 2×H-5' and 2×H-6), 2.61 (m, 2H, $SCH_2$), 1.82–2.40 (m, 6H, 2×H-3', 2×H-4' and 2×H-4), 1.15–1.72 (m, 8H, 4×$CH_2$), 0.91 (t, 3H, $CH_3$). (Primed numbers refer to protons of L-proline moiety). |
| **15** | 5.70 (m, 3H, NH, H-2, H-3), 5.39 (s, 1H, H-1), 3.70–4.25 (m, 2H, H-5, H-6), 2.56 (m, 2H, $SCH_2$), 1.10–2.30 (m, 12H, 2×H-4, 4×$CH_2$, 2×H-7), 1.97 (s, 3H, Ac), 0.90 (m, 6H, 2×$CH_3$). |
| **16** | 6.60 (bd, 2H, $CONH_2$), 5.85 (m, 2H, H-2, H-3), 5.55 (bs, 1H, H-1), 4.60 (dd, 1H, $J_{4a,5}$ = 4.5 Hz, $J_{4a,5}$ = 10.2 Hz, H-5), 2.70–2.87 (m, 4H, $CH_2S$, 2×H-4), 1.05–1.84 (m, 8H, 4×$CH_2$), 0.92 (t, 3H, $CH_3$). |
| **17** | 7.32 (s, 5H, aromatic H), 5.80 (m, 2H, H-2, H-3), 5.47 (bs, 1H, H-1), 5.10 (s, 3H, NH, $CH_2Ph$), 4.22 (m, 1H, H-5), 3.05–3.68 (m, 2H, 2×H-6), 2.62 (m, 2H, $CH_2S$), 2.10 (m, 2H, 2×H-4), 1.13–1.82 (m, 8H, 4×$CH_2$), 0.90 (t, 3H, $CH_3$). |
| **18** | 7.84 (m, 4H aromatic H), 5.83 (m, 2H, H-2, H-3), 5.38 (bs, 1H, H-1), 4.47 (m, 1H, H-5), 3.60–4.17 (m, 2H, 2×H-6), 2.17 (m, 2H, 2×H-4), 1.94 (s, 3H, $CH_3S$). |

Table 6. $^1$H NMR data of alkyl 4,6-di-O-acetyl-2,3-dideoxy-1-thio-D-hex-2-enopyranosides (**23**, **24**, **29**, **32**, **33**, **36**) and 3-S-alkyl-3-thio-glycals (**19**, **20**, **25**, **26**, **30**, **31**, **34**, **37**, **38**) (100 MHz, $CDCl_3$ soln, $\delta$ scale)

| Compound no | H-1 | H-2 | H-3 | H-4 | H-5 | H-6, 6' | Other signals | Coupling constants Hz |
|---|---|---|---|---|---|---|---|---|
| **23** | 5.52 (bs) | 5.72 (d) | 5.93 (pq) | 5.33 (bd) | 4.0–4.42 (m) | | 2.09 (s, 6H, 2×Ac), 0.9 (t, 3H, $CH_3$), 2.65 (m, 2H, $CH_2S$), 1.1–1.93 (m, 8H, 4×$CH_2$) | $J_{2,3}$ 10.0<br>$J_{4,5}$ 8.8 |
| **24** | 5.35 (s) | 5.87 (m) | | 5.25 (m) | 3.83 (m) | 4.23 (d) | 1.16–1.8 (m, 8H, 4×$CH_2$), 0.9 (t, 3H, $CH_3$), 2.11 (s, 6H, 2×Ac), 2.65 (m, 2H, $CH_2S$) | $J_{4,5}$ 8.0<br>$J_{5,6}$ 4.5 |
| **29** | 5.46 (s) | 5.79 (m) | 5.97 (m) | 5.38 (m) | 4.27 (m) | | 2.21 (s, 3H, $CH_3S$), 2.09 (s, 6H, 2×Ac) | $J_{2,3}$ 10.7<br>$J_{3,4}$ 1.9<br>$J_{4,5}$ 8.6 |
| **32** | 5.61 (d) | 5.89–6.20 (m) | | 5.07 (dd) | 4.54 (m) | 4.02–4.30 (m) | 2.66 (m, 2H, $CH_2S$), 2.05, 2.07 (2s, 6H, 2×Ac), 1.1–1.86 (m, 8H, 4×$CH_2$), 0.91(t, 3H, $CH_3$) | $J_{1,2}$ 2.0<br>$J_{3,4}$ 4.2<br>$J_{4,5}$ 2.5 |
| **33** | 5.28 (bs) | 6.05 (m) | | 5.04 (m) | 3.98 (m) | 4.23 (d) | 2.65 (m, 2H, $CH_2S$), 2.09 (s, 6H, 2×Ac), 1.1–1.82 (m, 8H, 4×$CH_2$), 0.91 (t, 3H, $CH_3$) | $J_{5,6}$ 7.9 |
| **36** | 5.51 (d) | 6.07 (m) | | 5.06 (dd) | 4.50 (m) | 4.18–4.30 (m) | 2.21 (s, 3H, $CH_3S$), 2.08 (s, 6H, 2×Ac) | $J_{1,2}$ 2.2<br>$J_{3,4}$ 4.2<br>$J_{4,5}$ 2.5 |
| **19** | 6.35 (d) | 4.79 (t) | 3.20–3.70 (m) | 1.8–2.05 (m) | 4.18 (m) | 3.20–3.70 (m) | 7.31 (s, 5H, arom. H), 5.06 (s, 2H, Ph-$CH_2$), 2.50 (t, 2H, $CH_2S$), 1.18–1.75 (m, 8H, 4×$CH_2$), 0.9(t, 3H, $CH_3$) | $J_{1,2}$ 6.0 |
| **20** | 6.37 (d) | 4.79 (dd) | 3.31 (m) | 1.82–2.10 (m) | 4.41 (m) | 3.68–4.18 (m) | 7.76 (m, 4H, arom. H), 2.11 (s, 3H, $CH_3S$) | $J_{1,2}$ 6.0<br>$J_{1,3}$ < 1.0<br>$J_{2,3}$ 5.5<br>$J_{5,6}$ 5.0 |
| **25** | 6.33 (dd) | 4.82 (dd) | 3.72 (t) | 5.17 (m) | 4.14–4.54 (*m*) | | 2.54 (m, 2H, $CH_2S$), | $J_{1,2}$ 6.0 |

Table 6 (*Contd.*)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | 2.09, 2.12 (2s, 6H, 2×Ac), 1.12–1.82 (m, 8H, 4×$CH_2$), 0.9 (t, 3H, $CH_3$) | $J_{1,3}$ 1.1<br>$J_{2,3}$ 5.6<br>$J_{3,4}$ 4.5<br>$J_{4,5}$ 9.6 |
| **26** | 6.42 (dd) | 4.8 (dd) | 3.36 (m) | 5.14 (t) | 3.99–4.51 (*m*) | | 2.55 (m, 2H, $CH_2S$), 2.11 (s, 6H, 2×Ac), 1.15–1.75 (m, 8H, 4×$CH_2$), 0.92 (t, 3H, $CH_3$) | $J_{1,2}$ 6.1<br>$J_{1,3}$ 2.3<br>$J_{2,3}$ 2.8<br>$J_{2,4}$ ~0.7<br>$J_{3,4}$ 7.3<br>$J_{4,5}$ 6.5 |
| **30** | 6.36 (dd) | 4.83 (dd) | 3.67 (t) | 5.22 (m) | 4.37 (*m*) | | 2.14 (s, 3H, $CH_3S$), 2.08, 2.12 (2s, 6H, 2×Ac) | $J_{1,2}$ 6.0<br>$J_{1,3}$ ~1.0<br>$J_{2,3}$ 5.9<br>$J_{3,4}$ 3.6<br>$J_{4,5}$ 10.4 |
| **31** | 6.47 (dd) | 4.75 (ddd) | 3.35 (pt) | 5.12 (t) | 3.97–4.52 (*m*) | | 2.17 (s, 3H, CH, $CH_3S$), 2.04, 2.09 (2s, 6H, 2×Ac) | $J_{1,2}$ 6.2<br>$J_{1,3}$ 2.3<br>$J_{2,3}$ 2.6<br>$J_{2,4}$ ~0.7<br>$J_{3,4}$ 8.7<br>$J_{4,5}$ 8.6 |
| **34** | 6.46 (d) | 4.78 (ddd) | 3.21(bd) | 4.97 (s) | 4.43 (m) | 4.25 (d) | 2.70 (m, 2H, $CH_2S$), 2.10 (s, 6H, 2×Ac), 1.14–1.83 (m, 8H, 4×$CH_2$), 0.91 (t, 3H, $CH_3$) | $J_{1,2}$ 6.1<br>$J_{1,3}$ <1.0<br>$J_{2,3}$ 5.1<br>$J_{2,4}$ 1.6 |
| **37** | 6.50 (d) | 4.80 (ddd) | 3.15 (bd) | 5.03 (bs) | 4.18–4.55 (m) | | 2.22 (s, 3H, $CH_3S$), 2.09 (s, 6H, 2×Ac) | $J_{1,2}$ 6.2<br>$J_{1,3}$ <1.0<br>$J_{2,3}$ 5.1<br>$J_{2,4}$ 1.5 |
| **38** | 6.39 (d) | 4.82 (dd) | 3.25–3.80 (m) | 1.85–2.04 (m) | 4.19 (ddd) | 3.25–3.80 (m) | 6.07 (bd, 1H, NH), 2.53 (m, 2H, $CH_2S$), 2.03 (s, 3H, NAc), 1.2–1.77 (m, 8H, 4×$CH_2$), 0.92 (t, 3H, $CH_3$) | $J_{1,2}$ 6.0<br>$J_{1,3}$ <1.0<br>$J_{2,3}$ 5.6<br>$J_{3,4}$ 3.4<br>$J_{4,5}$ 3.5<br>$J_{4,5}$ 10.0<br>$J_{5,6}$ 6.8 |




eluent. The following fractions were obtained:

1. 570 mg (43%) of a mixture of both **25** and **26**; 2. 60 mg (3.3%) of **27**; the configuration of **27** was deduced from its $^1$H NMR data:

$^1$H NMR: δ 5.33 (t, 1H, $\sum J = 6.3$ Hz, H-1), 4.82 (dd, 1H, $J_{3,4} = 10.1$ Hz, $J_{4,5} = 8.9$ Hz, H-4), 3.76–4.41 (m, 3H, H-5, 2×H-6), 3.01 (bd, 1H, $J_{2a,3} = 8.2$ Hz, H-3), 2.50 (m, 4H, 2×$CH_2$S), 2.20 (m, 2H, 2×H-2), 2.08, 2.10 (2s, 6H, 2×Ac), 1.15–1.90 (m, 16H, 8×$CH_2$), 0.91 (bt, 6H, 2×$CH_3$).

The presence of **24** in the post-reaction mixture was detected by tlc on comparison with an authentic sample of **24** obtained from another experiment (*cf* Table 2, entry 3). The amount of **24** was too small for isolation and characterisation.

The mixture of **25** and **26** was separated into pure components by HPLC on a Siemens H-100 apparatus using four interconnected 30 cm-columns packed with sedimented silica gel; a mixture of heptane and EtOAc (85:15) was used for elution.

The reaction of **21** (1.084 g) with n-hexyl mercaptan (0.58 ml) catalysed by stannic chloride (0.24 ml; substrate: catalyst ratio 43:1, Table 2, entry 1) was performed similarly. For chromatographic separation of products a mixture of light petroleum and EtOAc (10:1) was used. The reaction of (**28** 305 mg, Table 2, entry 3) with n-hexyl mercaptan (0.21 ml) and stannic chloride soln (0.16 ml) was performed in a similar manner. The mixture of products (275 mg) obtained was separated by HPLC on a 30 cm-column packed with Lichrosorb SI 60 (10 μ). For elution a mixture of hexane and EtOAc (8:1) was taken. Along with **23**, **25** and **24**, the unchanged substrate **28** was also isolated in 16.3% yield.

(B) *With methyl mercaptan* (Table 2, entry 4). To a cooled (−20°) soln of **21** (8.2 g) and methyl mercaptan (1.53 g) in ethylene chloride (100 ml) stannic chloride soln (1.68 ml) was added. The mixture was kept in a closed vessel at room temp for 2.5 hr. The work-up of the post-reaction mixture was performed as described under (A). For elution of products from the chromatographic column a mixture of benzene and ether (50:1) was used.

The $^1$H NMR data of thioglycosides **23**, **24** and **29** and 3-thioglycals **25**, **26**, **30** and **31** are recorded in Table 6.

*Reaction of* 3,4,6-*tri*-*O*-*acetyl*-D-*galactal* (**22**) *with mercaptans*

(A) *With n-hexyl mercaptan* (Table 2, entry 5). To a soln of **22** (450 mg) and n-hexyl mercaptan (0.282 ml) in ethylene chloride (25 ml), 0.03 ml of the $SnCl_4$–catalyst was added at 0°. The mixture was kept overnight at 5° and then worked-up as described above. Elution was carried out with benzene–ether (50:1).

The reaction of **35** (1.544 g) with n-hexyl mercaptan (0.9 ml) in methylene chloride soln (40 ml) in the presence of $SnCl_4$ (35 mg) took ca 12 hr for completion. Work-up of the mixture was performed as described above (Table 2, entry 6).

(B) *With methyl mercaptan* (Table 2, entry 7). The reaction of **22** (2.84 g) with methyl mercaptan (0.657 g) in

ethylene chloride (25 ml) soln catalysed by $SnCl_4$ (89 mg) was performed as described for the analogous reaction with **21**. The products of the reaction were separated by column chromatography using benzene–ether (50:1) for elution.

The structures of alkyl 4,6-di-O-acetyl-2,3-dideoxy-1-thio-D-hex-2-enopyranosides and 4,6-di-O-acetyl-3-S-alkyl-3-thio-D-glycals were deduced from $^1$H NMR data (Table 6).

The spectra of thioglycosides **23**, **24**, **29**, **32**, **33** and **36** are similar to these of their oxygen precursors **28** and **35**. The glycal structure of compounds **25**, **26**, **30**, **31**, **34** and **37** could be easily derived from the H-1, H-2, and H-3 signals and the appropriate coupling constants $J_{1,2} \sim 6.0$–6.2 Hz, $J_{1,3} \leq 1$ Hz for *ribo*-(**25**, **30**), *xylo*-**34**, **37**) and *erythro*-(**19**, **20**) glycals, and $J_{1,3} \sim 2.3$ Hz for *arabino*-(**26**, **31**) glycals. Equilibration of thioglycosides **12**, **18**, **29**, **32** and **36**. A soln of the appropriate thioglycoside (*ca* 50–100 mg) in $CCl_4$ (*ca* 1 ml) was placed in a NMR test-tube and a $SnCl_4$ soln in the same solvent was added to make the substrate: catalyst ratio equal to 10:1. In case of thioglycosides **29**, **32** and **36**, equilibrium was attained after 2–2.5 hr. The soln of **18** was heated to boiling point to speed-up equilibration. As the equilibration of **12** was very slow, more catalyst was added (ratio 3.8:1), and the soln was refluxed and left at room temp for 2 days. The proportions of thioglycoside **12** and 3-thioglycal **38** did not change after this time.

The results of equilibration are collected in Table 3. Fig. 1 shows three $^1$H NMR spectra recorded during equilibration of **36**:

(a) after mixing the substrate with $SnCl_4$;

(b) 5 minutes after the addition of a fresh portion of $SnCl_4$; and

(c) after a further 25 min.

*Simultaneous rearrangement of n-hexyl 4,6-di-O-acetyl-2,3-dideoxy-1-thio-α-D-erythro-hex-2-enopyranoside* (**23**) *and methyl 4,6-di-O-acetyl-2,3-dideoxy-1-thio-α-D-threo-hex-2-enopyranoside* (**36**)

Thioglycosides **23** (123 mg) and **36** (132 mg) were dissolved in 2 ml of ethylene chloride and $SnCl_4$ (13.1 mg) was added. The mixture was left at room temp for 40 min, whereafter it was diluted with methylene chloride (5 ml) and shaken with $NaHCO_3$ aq. After washing with water and drying ($MgSO_4$) the solvents were evaporated to dryness. The oily residue was distilled at 170°/0.2 Torr and the distillate was separated into components by HPLC a 30 cm-column packed with Lichrosorb SI 60 (10μ); elution with hexane–EtOAc (11:1). The following compounds were obtained: **31** (18.4%), a mixture of **30** (11.6%) and **37** (20.7%), and a mixture containing **25**, **26** and **34** (total yield 49.3%). This last mixture was rechromatographed with hexane-ethyl acetate (15:1) and afforded two fractions: **25**+**34** and pure **36**. All compounds were identified by comparison of their $^1$H NMR spectra and HPLC retention times with those of authentic samples.

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