Imidazole-promoted 1,4-migration of the *tert*-butyldiphenylsilyl group: influence on the selectivity control of the silylation reactions of carbohydrate OH groups †

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The regioselective protection of secondary hydroxy groups of gluco-, galacto-, manno-, rhamno- and fucopyranosides using TBDPSCl with imidazole in DMF has been studied. It was found that the relative spatial arrangement of the OH groups modulates the silylation selectivity which arises from the combination of kinetic factors and the intramolecular migrations of the secondary TBDPS groups. The rearrangement of the TBDPS groups has a much larger effect on the α-D-manno- and α-L-rhamnopyranosides, allowing the protection of the OH groups at positions 2, 3 or 2 and 4, in synthetically useful yields, by changing the reaction conditions. The relative reactivity of the secondary OH groups seems particularly likely to be governed by steric factors. This trend provides a valuable approach to the synthesis of 3-*O*-*tert*-butyldiphenylsilyl-1-thio-β-L-fucopyranoside.

Introduction

Carbohydrates are now well recognised to play a crucial role as recognition markers in fundamental biological processes and diseases.[1] Consequently, considerable research has been directed towards the synthesis of carbohydrate-based specific antigens, vaccines and therapeutic agents.[2] Much of this work has focussed on the development of versatile glycosidation strategies and efficient methods for the selective protection/deprotection of carbohydrate hydroxy groups.[3,4]

Silyl ethers, such as *tert*-butyldimethylsilyl (TBDMS), *tert*-butyldiphenylsilyl (TBDPS) and triisopropylsilyl (TIPS) ethers, are being widely applied as protecting groups.[3–16] It has been shown that their bulkiness is a key control element in the selective protection of hydroxy groups and it results in useful directing effects and stability in the presence of a wide variety of reagents under many conditions.[3a,4–6] These silyl protective groups have also proven applicable as building blocks employed in solid-phase glycopeptide and oligosaccharide synthesis.[3,4] The fact that they are removed during acid-catalysed cleavage of the target compound from the resin confers on them real advantages. On the other hand, silyl groups can migrate between different nucleophilic sites in a molecule under basic conditions.[5–8,10–12,15,16] These migrations not only have to be considered as possible side reactions, but also provide a valuable approach to interesting products that are not directly available. For instance, in the synthesis of chemically-modified cyclodextrins,[8] the migration of the TBDMS groups from the 2-O to the 3-O on all the D-glucopyranose residues was observed during alkylation with sodium hydride in THF. In a previous paper we have described a practical synthesis of the methyl and allyl 3,6-, 2,6- and 4,6-bis(*O*-*tert*-butyldiphenylsilyl)-α-D-mannopyranosides based on the differential migratory aptitudes of secondary TBDPS groups in several basic media.[12]

However, little systematic work has been reported on the selective protection of secondary hydroxy groups as TBDPS ethers in terms of monosaccharide structures.[10,12,13] We present in this paper a comparative study of the silylation reactions of methyl α-D-glucopyranoside (**1**), α-D-galactopyranoside (**2**), α-L-rhamnopyranoside[17] (**3**), and α-L-fucopyranoside[18] (**5**), as well as phenyl 1-thio-α-D-mannopyranoside[19] (**6**), and β-L-fucopyranoside[20] (**7**) (Scheme 1), using *tert*-butyldiphenylsilyl chloride (TBDPSCl) with imidazole in dry DMF. In order to gather more information, the influence of the stereochemical effects and the migrations of the TBDPS groups has been examined. To our knowledge, only the silylation of **1**[9a,c] and **2**[9b,d] has been employed for the regioselective protection of the primary hydroxy group, and the methyl 2-*O*-*tert*-butyldiphenylsilyl-α-L-fucopyranoside has been synthesised by a three-step procedure *via* the 3,4-*O*-isopropylidene acetal.[11]

Results and discussion

The silylation reactions were performed using molar ratios of substrate : TBDPSCl : imidazole of 1 : 2.2 : 5 for **1**, **2** and **6**, and 1 : 1 : 2.5 for **3**, **5** and **7**, at different temperatures and reaction times. The results obtained are collected in Table 1. For the α-series, the process exhibited the expected order of reactivity of the secondary hydroxy groups:[7,12,21] OH-2 > OH-3 ⩾ OH-4 for **1**, **2** and **5**; OH-3 > OH-2 ⩾ OH-4 for **3** and **6**. In all cases, the 4-OH group was found to be the least reactive, irrespective of its stereochemistry and the adjacent substituent at position 5. Moreover, the silylation of the methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside[22] (**4**) at 20 °C during 24 h afforded the 4-TBDPS ether **20** in 52% yield. A similar trend was reported for **1** and **2** using TBDMSCl under nearly identical conditions,[7] but with lower selectivity for the 2,6-isomer in the case of **1**. However, a critical change was observed for the phenyl 1-thio-β-L-fucopyranoside (**7**). The preponderant formation of the 3-TBDPS ether and the lower yield of the 2-isomer (<2%) is in sharp contrast to the results found in the preparation of the TBDMS ethers of methyl β-D-gluco- and β-D-galacto-pyranosides, where the ratio of the 2,6- and 3,6-isomers was *ca.* 1 : 1 and only traces of the 4,6-bis(TBDMS) ether were produced.[7] The lower reactivity of the 2-OH may be related to the presence of a sterically demanding substituent, β-SPh, at

† Electronic supplementary information (ESI) available: preparative details, physical and spectroscopic data of all the products, as well as structural assignments. See http://www.rsc.org/suppdata/p2/b2/b204396c/

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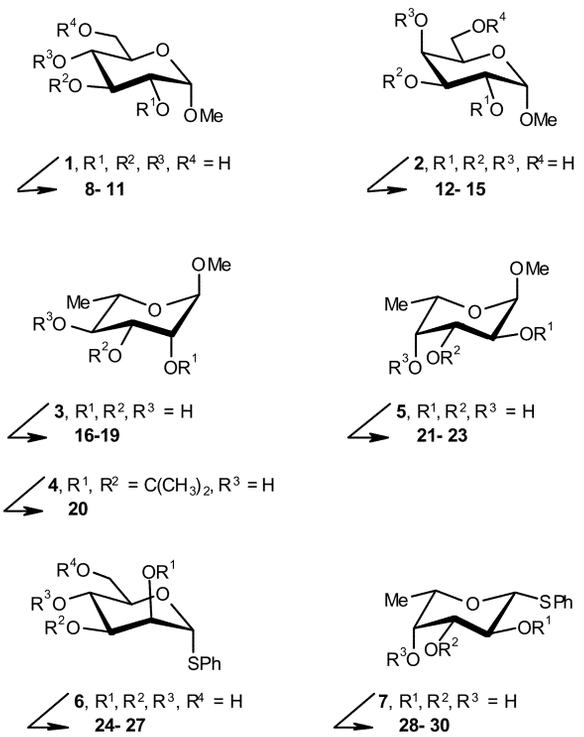

	R1	R2	R3	R4
8, 12, 24	H	H	H	TBDPS
9, 13, 25	TBDPS	H	H	TBDPS
10, 14, 26	H	TBDPS	H	TBDPS
11, 15, 27	H	H	TBDPS	TBDPS

	R1	R2	R3
16, 21, 28	TBDPS	H	H
17, 22, 29	H	TBDPS	H
18, 23, 30	H	H	TBDPS
19	TBDPS	H	TBDPS
20	$C(CH_3)_2$		TBDPS

Scheme 1 Silylation reactions with TBDPSCl–imidazole in DMF.

the anomeric position which makes the 3-OH and, to a lesser degree, the 4-OH more accessible. The same effect on the reactivity of the 2-OH was reported for the acylation of the phenyl 1-thio-β-D-gluco- and β-D-galactopyranosides with pivaloyl chloride.[23]

No appreciable dependence of the product distributions on the reaction conditions was detected for **1**, **2** and **5**, and it may be assumed that they are mainly determined by kinetic factors. The relative reactivities of the 2- and 3-OH groups appear to be modulated by the stereochemistry of the 4-OH group, probably due to a steric-approach control of the bulky reagent.[13,14,24] The methyl α-D-glucopyranoside (**1**), with the 2-, 3- and 4-OH groups in equatorial positions, exhibited the highest selectivity, affording the 2,6-bis(TBDPS) ether **9** in 92% yield. The axial 4-OH group in galacto- (**2**) and fucopyranosides (**5**) increases the reactivity of the 3-OH.

However, the product ratios are strongly influenced by the reaction conditions in the cases of **3**, **6** and **7**. Thus, the yield of the 3- or 3,6-isomers was reduced with increasing reaction times. These results suggest that the silylation selectivity arises from the combination of both kinetic factors and the migrations of the TBDPS group from the 3-O to the 2-O or 4-O.[12] For **3** and **6** the selectivity was inverted using a molar ratio of substrate : imidazole = 1 : 5 and long reaction times (48 h). Interestingly, the product distributions are closely similar to those reported for methyl and allyl α-D-mannopyranosides under the same conditions.[12] In addition, the disilylation of **3** at 48 °C during 72 h led to the formation of methyl 2,4-bis(*O*-*tert*-butyldiphenylsilyl)-α-L-rhamnopyranoside (**19**, 60%) and the 2-TBDPS ether (**16**, 20%) as the major products. The formation of **19** should take place by silylation of **16**, showing that the 4-OH may be more reactive than the 3-OH in the presence of an axial bulky substituent, such as a TBDPSO group,[24] at position 2.

The migratory preferences of the silyl groups were confirmed by treatment of the TBDPS ethers with imidazole in DMF under the silylation reaction conditions. As shown in Table 2 reversible *cis* and *trans* migrations of the secondary TBDPS groups to vicinal hydroxy groups may occur, while the primary TBDPS groups at position 6 remain unchanged. Increasing the temperature and the molar ratio of base : substrate markedly increased the rate of the rearrangement. Desilylated derivatives and/or other by-products were not detectable in yields higher than 2%.

The silyl derivatives of **3**, **6** and **7** readily undergo *cis* migrations leading to similar product ratios from each regioisomer (Table 2, entries 5–8, 13 and 14). Thus, isomerization of the 2,6- and 3,6-bis(TBDPS) ethers of **6** afforded a mixture of isomers, **25** and **26**, in a ratio of approximately 3 : 1. Likewise, the silyl shift from the 3-O to the 4-O proceeded to the extent of 21–24% for the TBDPS ethers **14** and **22**. As was expected, *trans* rearrangements occur very sluggishly.[7,12,16a] Such migrations were negligible for the silyl derivatives of gluco- (2-O⟶3-O), manno- and rhamnopyranosides (3-O⟶4-O). Nevertheless, the *trans* migration (2-O⇔3-O), proved to be more feasible for the silyl derivatives of galacto- and fucopyranosides, albeit to a low extent. Furthermore, small amounts of products involving two consecutive rearrangements were also found from the latter derivatives, according to the above considerations. Similar behaviour was observed when the TBDPS derivatives were treated with pyridine–H_2O (5%), while no isomerization was detected in dry DMF, pyridine or 2,6-di-*tert*-butylpyridine–CH_2Cl_2.

These results may be justified on the basis of a reversible intramolecular 1,4-O⟶O migration of the TBDPS group, which probably takes place by simultaneous acid and base catalysis, as has previously been proposed.[12] This pathway should explain the accelerative effect exerted by suitable proton donors,[7,12,15] such as the imidazole or the water, rather than the occurrence of a stepwise process involving anionic intermediates, as is generally accepted under strongly basic conditions.[8,12] Moreover, the fact that isomerization of 2′- and 3′-*O*-TBDMS ribonucleoside derivatives[15a] is much faster in methanol than in pyridine or pyridine–benzylamine also supports this assumption. On the other hand, the migration of the TBDPS groups promoted by imidazole and possibly by related moderate bases seems to be particularly likely to be governed by conformational factors.[7,12] The preferred migration involves the vicinal OH group that is in a *cis* orientation, in contrast to the course of the rearrangement in strongly basic media, where both *cis* and *trans* migrations may occur readily.[8,10,12,16] As *cis* migrations lead to thermodynamically equilibrated mixtures of the TBDPS ethers, the extent of the process is also a function of their relative stability.

All the silyl derivatives afforded ^{1}H and ^{13}C spectral data in accordance with their structures.[3a,12,25] The experimental values of the coupling constants between neighbouring protons on the pyranoside ring indicate a chair conformation, $^4C_1$, for the gluco-, galacto- and mannopyranosides and $^1C_4$ for the rhamno- and fucopyranosides.[3a,12,14,25] Because of constraints imposed by the 2,3-acetonide function in **20**, the pyranoside ring exists as distorted $^1C_4$ chair.[3a] The product distributions resulting from *cis* migrations give additional information about the relative thermodynamic stability of the TBDPS ethers (Table 2). Thus, the phenyl 2,6-bis(*O*-*tert*-butyldiphenylsilyl)-1-thio-α-D-mannopyranoside (**25**) is more stable than the 3,6-isomer **26**, in agreement with the unusually small *A*-value

Table 1 Silylation reactions using *tert*-butylchlorodiphenylsilane with imidazole in DMF[a]

Entry	Substrate	*T*/°C	Reaction time/h	Disilylation[b,c] yield (%)	TBDPS ether ratio[b] 6-	2,6-	3,6-
1	**1**	4	24	67 (63)	**8**, 33	**9**, 67	**10**, traces
2		20	24	97 (95)	—	92	2
3			48	90	—	88	2
4		48	8	95	—	91	4
5			24	91	—	84	7
6	**2**	4	24	88	**12**, 12	**13**, 70	**14**, 18
7		20	24/48	96 (80)	2	74	20
8	**6**	20	8	84 (72)	**24**, 16	**25**, 22	**26**, 60
9			24	95	3	52	41
10			48	98	—	63	33
				Monosilylation[b,c] yield (%)	TBDPS ether ratio[b] 2-	3-	4-
11	**3**	20	24	98	**16**, 19	**17**, 76	**18**, 3
12			48	97	27	68	2
13			24	98 (75)	45	51	2
14			48	98	63	33	2
15	**5**	20	24	100	**21**, 76	**22**, 22	**23**, 2
16			48	98 (82)	76	18	4
17	**7**	20	24	100	**28**, —	**29**, 86	**30**, 14
18			48	98 (80)	2	72	24

[a] Molar ratio of substrate : TBDPSCl : imidazole = 1 : 2.2 : 5 for entries 1–10; 1 : 1 : 2.5 for entries 11, 12 and 15–18; 1 : 1 : 5 for entries 13 and 14. [substrate] = 0.25 M. [b] Determined by ^{1}H NMR spectroscopy (±1%). [c] For entries 1–10 this value also includes the small amount of the 4,6-bis(TBDPS) ethers (**11**, **15** and **27**, respectively) detected (≤3%). Difference from 100% corresponds to the 6-TBDPS ethers and/or trisilylated derivatives for entries 1–10 and bis(TBDPS) ethers in other cases. Yields of isolated products are given in parenthesis.

Table 2 Imidazole-induced migrations of the secondary TBDPS groups in DMF[a] at 20 °C

Entry	Substrate TBDPS ether	TBDPS ether ratio[b] 2,6- (2-)	3,6- (3-)	4,6- (4-)
1	**9** (2,6-α-D-Glcp)	97	3	—
2	**13** (2,6-α-D-Galp)	84	12	4
3		82	13	5
4	**14** (3,6-α-D-Galp)	14	65	21
5	**25** (2,6-α-D-Manp)	73	27	—
6	**26** (3,6-α-D-Manp)	71	29	—
7	**16** (2-α-L-Rhap)	61	36	3
8	**17** (2-α-L-Rhap)	62	36	3
9	**21** (2-α-L-Fucp)	93	5	2
10		85	11	4
11	**22** (3-α-L-Fucp)	9	67	24
12	**29** (3-β-L-Fucp)	11	57	32
13	**30** (4-β-L-Fucp)	12	55	33
14	**29** (3-β-L-Fucp)	—	94	6
15		—	91	9

[a] Molar ratio of substrate : imidazole = 1 : 5 for entries 1–13; 1 : 2.5 for entries 14 and 15; [substrate] = 0.09 M; 8 h except for entries 3, 10 and 15 (24 h). [b] Deduced by ^{1}H NMR spectroscopy (±1%).

reported by Eliel and Satici[26] for a *tert*-butyldiphenylsilyloxy group.

In summary, the rearrangements of the TBDPS groups promoted by imidazole will play a key role in the silylation selectivity when kinetic control does not lead to the most stable isomer and the equilibration involves a *cis* 1,4-O⟶O migration. This can be exploited especially in the case of α-D-manno- and α-L-rhamnopyranosides to achieve the protection of the hydroxy groups at positions 2, 3 or 2 and 4 in synthetically useful yields (60–75%). On the other hand, in the silylation reactions of gluco-, galacto- and fucopyranosides, the product ratios are mainly determined by the relative reactivities of the secondary hydroxy groups. Interestingly, while the methyl α-L-fucopyranoside allowed access to the 2-TBDPS ether, the phenyl 1-thio-β-L-fucopyranoside allowed entry to the 3-TBDPS derivative. The easy access to these partially protected carbohydrates makes them versatile and useful intermediates for further derivatization processes and for the synthesis of oligosaccharides and glycoconjugates.

Experimental

Silylation and isomerization reactions were performed following the method previously described.[12] Procedures were readily amenable to large-scale preparations, as outlined for methyl α-D-glucopyranoside and methyl α-D-galactopyranoside. Preparative details, physical and spectroscopic data of all the products, as well as structural assignments, are available as electronic supplementary information (ESI).

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