Carbohydrate Research, 144 (1985) 325-330
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

Selective silylation of 6-deoxyglycals*,†

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(Received February 12th, 1985; accepted for publication, April 17th, 1985)

This report shows that hindered silylating reagents react selectively with the allylic hydroxyl group of 6-deoxyglycals; in particular, *tert*-butylchlorodimethylsilane is very useful for the preparation of the 3-Bu^tMe_2Si ethers of L-rhamnal and L-fucal. Migration of the Bu^tMe_2Si group is observed in the monosilylated derivatives of L-fucal, resulting in a mixture of the 3- and 4-ethers. The 4-Bu^tMe_2Si ether of L-rhamnal was obtained by silylation of the readily accessible 3-*O*-acetyl-L-rhamnal and subsequent deacetylation.

Regioselective acylation of L-rhamnal (**1**) and L-fucal (**6**) with various reagents has been reported[2] in the accompanying paper. Such monosubstituted derivatives are valuable precursors for the preparation of disaccharides or specifically modified sugars required in connection with the synthesis of analogs of anthracycline antibiotics[3].

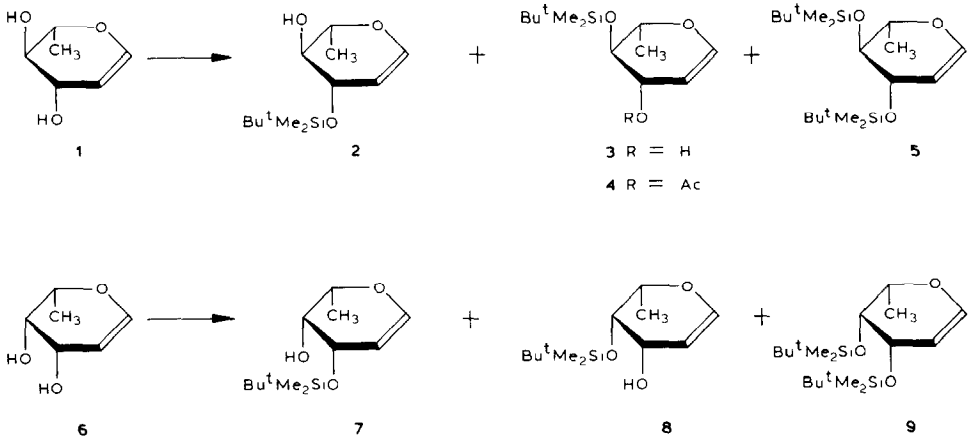
Selective acetylation reactions provided[2] preparative access to 3- or 4-monosubstituted derivatives of L-rhamnal (**1**), but the procedure was not effective for the preparation of selectively substituted L-fucal derivatives.

In the search for improved selectivity and a base-stable protecting group, the silylation of the 6-deoxyglycals **1** and **6** was investigated. Silyl ethers of various types have been widely used because of their ease of preparation and their facile cleavage with specific reagents[4]. *tert*-Butylchlorodimethylsilane[5] appeared to be a particularly suitable reagent because of its high selectivity and manipulative convenience; it has been successfully used for selective derivatization of such multifunctional polyols as nucleosides[6–8] and nucleotides[9,10].

From the wide variety of highly selective silylating reagents that are commercially available, *tert*-butylchlorodiphenylsilane, bromodimethyl(triphenylmethyl)silane, and *tert*-butylchlorodimethylsilane were selected for evaluation in

*For a preliminary report, see ref. 1.
†Supported, in part, by Grant No. GM-11976 from the National Institute of General Medical Sciences, U.S. Public Health Service.

0008-6215/85/$ 03.30



Bu^tMe_2Si = *tert*-butyldimethylsilyl

their reaction with L-rhamnal (**1**). All of them showed high selectivity towards the allylic hydroxyl group in **1** and also in L-fucal (**6**). However, difficulties were encountered with the first two reagents during isolation of the resultant 3-silyl ethers because of the presence of accompanying products (silanols) of similar polarity. In contrast, *tert*-butylchlorodimethylsilane converted L-rhamnal (**1**) into its 3-*tert*-butyldimethylsilyl ether **2** in good yield (70–95%, Table I), and the product was readily purified. A range of reaction conditions were evaluated (Table I). The nature of the solvent and the base employed had only a minor effect on the product distribution. The reaction appeared to be slower in pyridine, and the use of toluene as solvent, at higher temperatures (80°), led to increased formation of the disilylated derivative **5**. The most satisfactory results were obtained by using *N,N*-dimethylformamide–imidazole (2 h, 25°, Table I). Under these conditions, preparative-scale silylation of L-rhamnal (**1**) afforded the 3-Bu^tMe_2Si ether **2** in 89% yield. The high selectivity towards the (secondary) allylic hydroxyl group is similar

TABLE I

SILYLATION OF L-RHAMNAL (**1**) WITH *tert*-BUTYLCHLORODIMETHYLSILANE UNDER VARIOUS CONDITIONS[a]

Base[b]	*Solvent*	*Time (h)*	*Temp. (degrees)*	*Ratio of products (%)*		
				3-Ether (**2**)	*4-Ether* (**3**)	*3,4-Diether* (**5**)
$C_3H_4N_2$	$HCONMe_2$	2	25	95	3	2
$C_3H_4N_2$	$HCONMe_2$	20	25	89	4	7
$C_3H_4N_2$	$HCONMe_2$	1.5	80	93	3	3
$C_3H_4N_2$	PhMe	2.5	80	78	2	12
C_5H_5N	C_5H_5N	20	25	83	3	3
C_5H_5N	C_5H_5N	2 5	80	70	3	6

[a]See Experimental section. [b]$C_3H_4N_2$ = imidazole.

to that observed for the reactivity of *tert*-butylchlorodimethylsilane towards primary allylic hydroxyl groups in the presence of other primary alcohols[11,12].

Silylation of L-fucal (**6**) under the same conditions as described for L-rhamnal (**1**) gave the 3-Bu^{t}Me$_2$Si ether **7** in 70% yield. The reaction was highly selective; t.l.c. of the product-mixture showed only compound **7** and small quantities of unreacted substrate. Selectivity towards O-3 has been observed[2] in the acetylation of **6**, but the interconversion of the 3- and 4-monoacetates by acetyl migration impeded their preparative separation. In consequence, the ready access to the 3-ether **7** found here was considered very important.

Increasing the time of reaction in the etherification of **6** did not improve the yield of the 3-monoether **7**; on the contrary, the yield of **7** was lowered and the proportion of 4-ether **8** formed was increased. After 16 h, the 3-ether **7**, 4-ether **8**, and 3,4-diether **9** were isolated in 67, 16, and 10% yields, respectively. These observations suggest that O-3→O-4 migration of the *tert*-butyldimethylsilyl group was occurring. Such silyl-group migrations between vicinal, *cis*-[9,13] or *trans*-oriented[14] hydroxyl groups have been previously reported. The isomerization of the 3- and 4-monoethers **7** and **8** was confirmed by dissolving compound **7** in a solution of imidazole in *N,N*-dimethylformamide. T.l.c. examination after 20 h revealed the presence of both monosilylated derivatives **7** and **8** in 3:1 ratio (as established by ^{1}H-n.m.r. spectroscopy). The same experiment was performed with the 4-Bu^{t}Me$_2$Si ether **8** and formation of the 3-ether **7** was detected, indicating O-4→O-3 migration of the silyl group.

Although the 6-deoxyglycals react regioselectively to give the 3-*O*-silyl derivatives, the 4-silyl ethers may also be prepared. Thus, 3-*O*-acetyl-L-rhamnal[2] reacted with *tert*-butylchlorodimethylsilane to afford the 4-ether 3-ester **4**, which, after deacetylation with sodium methoxide in methanol, gave the 4-ether **3** in 84% yield. 4-*O*-*tert*-Butyldimethylsilyl-L-fucal (**8**) may be prepared from the 3-ether **7** by subjecting **7** to silyl group migration, and then separating **8** from the resultant mixture.

EXPERIMENTAL

General methods. — These were as in the accompanying paper[2]. The solvent used for t.l.c. was, in all instances, 5:1 hexane–ethyl acetate.

Structural identification of the silyl ethers. — Structures were determined from detailed analysis of their ^{1}H-n.m.r. spectra[15]; data will be published elsewhere. The ^{13}C-n.m.r. spectra (Table II) fully support the structural assignments.

Quantitative determination of the product distributions recorded in Table I. — Solutions of L-rhamnal (**1**, 0.2 mmol) in the appropriate solvent (0.5 mL) were treated with imidazole (0.5 mmol) and *tert*-butylchlorodimethylsilane (0.22 mmol) for the times and temperatures recorded in Table I. The mixtures were analyzed by g.l.c. on a 2-m column of 3% OV-101 operated isothermally at 120°, with a carrier gas (He) flow-rate of 30 mL/min. The ratio of products was determined from

TABLE II

^{13}C-N M R CHEMICAL SHIFTS (δ) FOR *tert*-BUTYLDIMETHYLSILYL ETHERS OF L-RHAMNAL AND L-FUCAL[a]

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*Bu^{t}Si*	*C-Si*	*SiMe$_2$*
2	143.7	103 5	70.6	75.0	74 4	17.1	25.8	18.1	−3.8, −4.0
3	144 7	103.2	71.1	76.7	75.3	17.8	25 9	18.2	−3.8, −4.6
4[b]	145.9	99.7	73.8	72 5	75.5	17.7	25.7	18.0	−3.7
5	143 1	102.7	69 2	74.8	75.2	17.1	26.0	18.1	−3.7
7	144.7	101.6	65.5	68 2	72.7	16.7	25.8	18.1	−4.6, −4.9
8	144.2	101.8	64 4	69.7	73 0	15 7	25.9	18 3	−4.3
9	142.8	102 4	66.4	70 3	73.7	15.6	25 9, 26.0	18.3	−3.9, −4.5, −4 6

[a]See Experimental section. [b]Acetyl-group signals appeared at δ 170.6 and 21 3

relative peak areas. The retention times for the products were: **1**, 1 min; **2**, 2.8 min; **3**, 3.5 min; and **5**, 9.6 min.

Preparative silylation of L-*rhamnal to give 3*-O-tert-*butyldimethylsilyl*-L-*rhamnal* (**2**), *and separation from 4*-O-tert-*butyldimethylsilyl*-L-*rhamnal* (**3**) *and 3,4-di*-O-tert-*butyldimethylsilyl*-L-*rhamnal* (**5**). — To a solution of L-rhamnal (**1**; 1.04 g, 8 mmol) and imidazole (1.36 g, 20 mmol) in *N,N*-dimethylformamide (3.0 mL) was added *tert*-butylchlorodimethylsilane (1.33 g, 8.8 mmol). The solution was stirred for 2 h at 25°, and then poured into water (30 mL) and extracted with hexane (60 mL × 3). The organic extract was washed with water (50 mL), dried ($MgSO_4$), and evaporated. The oily residue was purified by column chromatography with 10:1 hexane–ethyl acetate. The first fractions from the column (R_F 0.96) afforded syrupy **5**; yield 40 mg (1.5%); $[\alpha]_D^{25}$ +44° (*c* 1.0, chloroform).

Anal. Calc. for $C_{18}H_{38}O_3Si$: C, 60.28; H, 10.68. Found: C, 60.35; H, 10.70.

Subsequent fractions from the column gave the principal product **2**; yield 1.74 g (89%); $[\alpha]_D^{25}$ +75° (*c* 1.3, chloroform); R_F 0.52.

Anal. Calc. for $C_{12}H_{24}O_3Si$: C, 58.97; H, 9.90. Found: C, 59.05; H, 9.94.

The slowest-migrating component (R_F 0.44) was isolated and identified as the 4-ether **3**; yield 60 mg (3%); $[\alpha]_D^{25}$ −10° (*c* 1.0, chloroform).

Anal. Calc. for $C_{12}H_{24}O_3Si$: C, 58.97; H, 9.90. Found: C, 59.05; H, 9.93.

3-O-*Acetyl-4*-O-tert-*butyldimethylsilyl*-L-*rhamnal* (**4**). — 3-*O*-Acetyl-L-rhamnal[2] (0.34 g, 2 mmol) was dissolved in *N,N*-dimethylformamide (1 mL) and imidazole (0.34 g, 5 mmol) and *tert*-butylchlorodimethylsilane (0.36 g, 2.4 mmol) were added. The mixture was stirred for 4 h at 25°, poured into water (20 mL), and the mixture extracted with hexane (70 mL × 3). The extract was washed with water, dried ($MgSO_4$), and evaporated. The residue showed a single spot having R_F 0.63 in t.l.c.; yield 0.54 g (94%). Purification of a sample (50 mg) on a small column (20:1 hexane–ethyl acetate) afforded analytically pure, syrupy **4**; $[\alpha]_D^{25}$ +62° (*c* 1.0, chloroform).

Anal. Calc. for $C_{14}H_{26}O_4Si$: C, 58.70; H, 9.15. Found: C, 58.81; H, 9.19.

4-O-tert-*Butyldimethylsilyl*-L-*rhamnal* (**3**). — Compound **4** (0.49 g, 1.7 mmol)

dissolved in methanol (10 mL) was treated with M sodium methoxide in methanol (2.5 mL) for 1 h at 25°. The solution was made neutral with Dry Ice, diluted with water, and extracted with hexane. The residue obtained after evaporation of the extract was purified through a short column (10:1 hexane–ethyl acetate), affording pure **3** (0.37 g, 89%).

3-O-tert-*Butyldimethylsilyl*-L-*fucal* (**7**). — To a solution of L-fucal[2] (**6**, 0.65 g, 5 mmol) in *N,N*-dimethylformamide (2.5 mL) was aded imidazole (0.85 g, 12.5 mmol) and *tert*-butylchlorodimethylsilane (0.83 g, 5.5 mmol). The solution was stirred at room temperature for 2 h, whereupon t.l.c. showed a main product having R_F 0.56, and some unreacted L-fucal (**6**). The mixture was poured into water (30 mL) and the product extracted with hexane (80 mL × 3). The extract was washed with water (50 mL), dried ($MgSO_4$), and evaporated, affording **7** as a syrup; yield 0.86 g (70%); $[\alpha]_D^{25}$ +46° (*c* 1.4, chloroform).

Anal. Calc. for $C_{12}H_{24}O_3Si$: C, 58.97; H, 9.90. Found: C, 58.97; H, 9.95.

4-O-tert-*Butyldimethylsilyl*-L-*fucal* (**8**) *and 3,4-di*-O-tert-*butyldimethylsilyl*-L-*fucal* (**9**). — L-Fucal[2] (0.33 g, 2.5 mmol), imidazole (0.43 g, 6.3 mmol), and *tert*-butylchlorodimethylsilane (0.45 g, 3.0 mmol) were dissolved in *N,N*-dimethylformamide (1 mL) and the mixture was stirred for 16 h at 25°. T.l.c. examination of the mixture revealed the presence of three components (R_F 0.94, 0.56, and 0.46), which were separated by column chromatography with 10:1 hexane–ethyl acetate as eluant. The faster-migrating component was the 3,4-diether **9**; yield 90 mg (10%); $[\alpha]_D^{25}$ +53° (*c* 1.0, chloroform).

Anal. Calc. for $C_{18}H_{38}O_3Si_2$: C, 60.28; H, 10.68. Found: C, 60.23; H, 10.75.

Subsequent fractions afforded the 3-ether **7** (0.41 g, 67%). Finally, the compound having R_F 0.46 was isolated and identified as 4-*O*-*tert*-butyldimethylsilyl-L-fucal (**8**; 0.1 g, 16%); $[\alpha]_D^{25}$ +5.4° (*c* 1.3, chloroform).

Anal. Calc. for $C_{12}H_{24}O_3Si$: C, 58.97; H, 9.90. Found: C, 58.86; H, 9.92.

Migration of the tert-*butyldimethylsilyl group in the monosilylated fucal derivatives* **7** *and* **8**. — A solution of the 3-ether **7** (0.24 g, 1 mmol) and imidazole (0.17 g, 2.5 mmol) in *N,N*-dimethylformamide (1 mL) was stirred for 20 h at 25°. T.l.c. examination of the mixture showed two spots having R_F 0.56 and 0.46. The mixture was purified by conventional extraction with hexane. ^{1}H-N.m.r. spectroscopic examination of the product showed the exclusive presence of the 3- and 4-monosilyl ethers **7** and **8**, in 73:27 ratio.

Treatment of the 4-ether **8**, under the conditions used with compound **7**, afforded a mixture of **7** and **8**, and the proportion of **7** increased with time. After 40 h, the ratio of **7** to **8** was ~1:1.

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