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Note

Allylic rearrangement of 6-deoxyglycals having practical utility*

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3,4-Di-*O*-acetyl-L-rhamnal (**1**) in dichloromethane reacted with methanol in the presence of a catalytic amount of tin(IV) chloride to give in 90% yield an equilibrated mixture of methyl 4-*O*-acetyl-2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside (**2**) and its β-L anomer **7**, from which the α-L anomer could be readily isolated. Re-equilibration of the remaining material may be effected without competing reactions, so that the procedure provides a practical, high-yielding preparation of **2** and other α glycosides. Lewis acid-catalyzed rearrangement of glycals in the presence of alcohols, leading to the formation of 2,3-unsaturated alkyl glycosides, has been extensively studied by Ferrier and coworkers[2–5]. This transformation, the Ferrier reaction, has been widely used and provides a very convenient route to 2,3-unsaturated glycosides. Boron trifluoride is the Lewis acid that has been most commonly employed. However, the reported[6–8] yields (41–55%) of alkyl 2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranosides, as prepared by Ferrier's conditions (boron trifluoride) from L-rhamnal diacetate (**1**), are only moderate. Thus, development of a high-yielding method for the preparation of α-glycosides of 2,3-unsaturated 6-deoxy-L-sugars, for instance compounds **2**, **3**, and **4**, would be worthwhile, especially in view of the high cost of the starting material, 3,4-di-*O*-acetyl-L-rhamnal (**1**).

It has been reported[9] that the tin(IV) chloride-catalyzed Ferrier reaction of 3,4,6-tri-*O*-acetyl-D-glucal and -D-galactal, conducted in dichloromethane or 1,2-dichloroethane, affords the corresponding 2,3-unsaturated derivatives in excellent yields. Under the same conditions, glycal **1** afforded an anomeric mixture of glycosides **2** and **7** in 90% yield (see Experimental). The anomeric ratio was estimated, by integration of the ^{1}H-n.m.r. signals of the anomeric mixture and by gas–liquid chromatography, to be 5.6:1 in favor of the α-L anomer. Column

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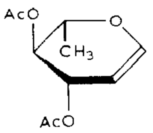

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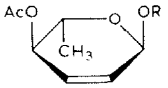
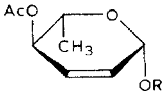
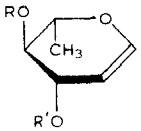


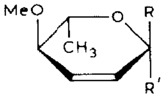
2 R = Me
3 R = Et
4 R = Bzl
5 R = $CHMe_2$
6 R = CMe_3



7 R = Me
8 R = Et
9 R = Bzl
10 R = $CHMe_2$



11 R = R' = Me
12 R = Me, R' = Ac
13 R = Ac, R' = Me



14 R = OMe, R' = H
15 R = H, R' = OMe

chromatography on silica gel afforded the α-L anomer **2** (70%) and an anomeric mixture now enriched with the β-L anomer **7**.

In order to determine whether the anomeric ratio measured corresponds to a true anomeric equilibrium, compounds **2** and **7** were separately treated with methanol in the presence of tin(IV) chloride in dichloromethane. In both cases, an anomeric mixture was isolated that had the same anomeric ratio (g.l.c.), within experimental error, as that obtained from **1**. These results demonstrate that anomeric equilibrium is indeed attained during the tin(IV) chloride-catalyzed Ferrier reaction of glycal **1** with alcohols.

Thus, the anomeric mixture of **2** and **7**, enriched with the β-L anomer **7**, as obtained after chromatographic separation may, in principle, be re-equilibrated to give an anomeric mixture now enriched in the α-L anomer **2**. A multi-gram preparation that gives compound **2** in 90% yield, based on the aforementioned re-equilibration, is described in the experimental section.

Table I gives the anomeric ratio of the 2,3-unsaturated derivatives obtained by the tin(IV) chloride-catalyzed Ferrier reaction of glycal **1** with various alcohols. When primary alcohols (methanol, ethanol, and benzyl alcohol) were used, the anomeric ratio obtained was approximately the same, within experimental error. Use of a secondary alcohol (2-propanol) shifted the anomeric equilibrium more towards the α-L anomer **5** (α:β, 11:1), and only traces of the β-L anomer were formed when *tert*-butyl alcohol was used. As depicted in Scheme 1, in addition to the Lewis acid-catalyzed anomeric equilibrium I $\rightleftharpoons$ II, conformational equilibria exist between the half-chair conformers I $\rightleftharpoons$ Ia and II $\rightleftharpoons$ IIa. The anomeric effect[10,11] favors conformer I $[^5H_O(\text{L})]$ for the α-L anomers ($J_{4,5}$ 9.2–9.3 Hz for

TABLE I

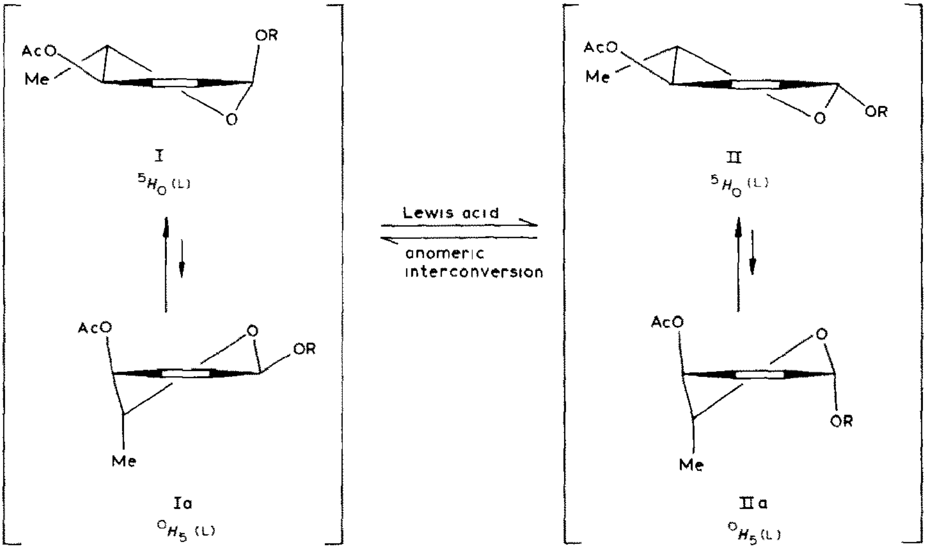
EXPERIMENTAL DATA FOR THE TIN(IV) CHLORIDE-CATALYZED FERRIER REACTION OF GLYCAL **1** WITH VARIOUS ALCOHOLS

Alcohol	*Time (min)*	α-L *anomer*	β-L *anomer*	*Yield (%)* (α-L + β-L)	*Anomeric ratio*[a] α-L:β-L
Methanol	30	**2**	**7**	90	5.6:1
Ethanol	20	**3**	**8**	82	5.9:1
Benzyl alcohol	5	**4**	**9**	85	5.3:1
2-Propanol	15	**5**	**10**	75	11:1
tert-Butyl alcohol	5	**6**		50	Traces of β-L

[a] Determined by g.l.c.

compounds **2, 3, 4, 5**, and **6**) and conformer IIa [$^{\mathrm{O}}H_5$(L)] for the β-L anomers, which have the electronegative substituents at the anomeric carbon atom quasi-axially disposed in these conformations. However, the axial orientation of the C-5 substituents in conformer IIa generates 1,3-diaxial interaction with the C-1 substituent and leads to a $^5H_{\mathrm{O}} \rightleftharpoons {}^{\mathrm{O}}H_5$ conformational equilibrium that is reflected in averaged coupling constant $J_{4,5}$ of 6.4–6.5 Hz. Such interactions should increase with increasing steric bulk of the C-1 substituent and could be responsible for the higher α:β anomeric ratios observed for isopropyl and *tert*-butyl glycosides.

In order to study the effect of the leaving group at C-3 on the tin(IV) chloride-catalyzed Ferrier reaction of glycals, differently substituted derivatives (**11, 12**, and **13**) of L-rhamnal, were prepared. Treatment of **12**, bearing a good



Schema 1

leaving group (OAc) at C-3, with methanol in the presence of tin(IV) chloride gave the corresponding rearranged anomers **14** and **15** in 75% yield. Their anomeric ratio, as estimated by gas–liquid chromatography, was 4.6:1 in favor of the α-L anomer. When compounds **11** and **13**, both of which bear a poor leaving group (OMe) at C-3, were each subjected to the same conditions, an anomeric mixture of the corresponding rearranged products was obtained, but only in low yields. In addition to these products, three to four additional, polar products were formed that were not characterized. The results indicate that a suitable leaving-group at C-3 is essential for the reaction to proceed to completion in good yield.

EXPERIMENTAL

General methods. — Solvent evaporation was performed under diminished pressure at a bath temperature <50°. A Perkin–Elmer Model 141 polarimeter and 1-dm tubes were used for measurement of specific rotations. Unless otherwise noted, solutions were in chloroform. T.l.c. was performed on precoated glass plates (0.25 mm) of Silica gel 60F-254 (E. Merck); zones were detected by spraying the plates with 10% (v/v) aqueous H_2SO_4 solution, with subsequent heating. Silica gel 60 (E. Merck) was used for column chromatography. Microanalysis were performed by Atlantic Microlab Inc., Atlanta, Georgia. ^{1}H-N.m.r. spectra were recorded at 200 MHz with a Bruker WP-200 spectrometer operating in the F.t. mode at ~25°. The assignments were confirmed by decoupling experiments. ^{13}C-N.m.r. spectra were recorded at 50 MHz with a Bruker WP-200 spectrometer operating in the F.t. mode at ~35°. Most assignments were confirmed by heteronuclear decoupling experiments. Unless otherwise noted, samples for ^{1}H-n.m.r. and ^{13}C-n.m.r. spectroscopy were dissolved in (^{2}H)chloroform containing tetramethylsilane as the internal standard (δ 0.00). Anhydrous $MgSO_4$ was used to dry the organic phase collected after solvent extraction.

*General procedure for the $SnCl_4$-catalyzed allylic rearrangement of 3,4-di-*O-*acetyl-*L-*rhamnal* (**1**) *with an alcohol.* — In accordance with the method of Grynkiewicz *et al.*[9], to a solution of glycal **1** (1.00 g, 4.67 mmol) in dichloromethane (20 mL) containing the alcohol (9.70 mmol) was added a solution of $SnCl_4$ in dichloromethane (1.1 mL, 0.22M; 5 mol%). The resulting mixture was stirred at 25° for the period of time indicated in Table I, quenched with saturated aqueous $NaHCO_3$ (~5 mL), and then extracted (3 × 15 mL) with dichloromethane. The organic phases were combined, washed with saturated aqueous NaCl (~5 mL), dried, and evaporated to furnish a syrup that was a mixture of the alkyl 4-*O*-acetyl-2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside as the major component and the corresponding β-L anomer as the minor component. The anomeric ratios were determined by g.l.c. (OV-225; initial temperature, 70°; rate of temperature rise, 6°/min; final temperature, 130°), and are given in Table I.

Physical constants and elemental analyses of pure compounds (as judged by

TABLE II

ANALYTICAL DATA FOR COMPOUNDS **2**–**7** AND **11**–**14**

Compound	$[\alpha]_D$ *(degrees)*		*Anal.*			
	Observed[a]	*Reported (Ref.)*	*Calc.*		*Found*	
			C	*H*	*C*	*H*
2	−186	−187 (Ref. 6)				
3	−153	−154 (Ref. 7)				
4	−116	−103 (Ref. 8)				
5	−141		61.66	8.47	61.78	8.52
6	−132		63.13	8.83	63.29	8.88
7	−87	−85.0 (Ref. 6)				
11	+31	+32.4 (Ref. 12)				
12	+109	+119 (Ref. 13)				
13			58.05	7.58	57.93	7.63
14			60.73	8.92	60.53	8.95

[a] For solutions in chloroform (*c* 1.0) at 25°.

t.l.c. and ^{1}H-n.m.r. spectroscopy) are given in Table II. ^{1}H-N.m.r. and ^{13}C-n.m.r. spectral data are presented in Tables III and IV, respectively.

*$SnCl_4$-catalyzed equilibration of methyl 4-O-acetyl-2,3,6-trideoxy-α-*L-erythro-*hex-2-enopyranoside* (**2**) *and the corresponding β-*L *anomer* (**7**). — To a solution at 25° of compound **2** (250 mg, 1.35 mmol) in dichloromethane (6 mL) was added a solution of $SnCl_4$ in dichloromethane (0.32 mL, 0.02M). The resulting mixture was stirred for 30 min at 25°, quenched with saturated aqueous $NaHCO_3$ (2 mL), and extracted with dichloromethane (3 × 5 mL). The organic phase was washed with saturated aqueous NaCl (5 mL), dried, and evaporated to furnish a syrup that was a mixture of compound **2** and the corresponding β-L anomer **7** in the ratio 5.1:1, as estimated by g.l.c.

The corresponding β-L anomer **7**, on treatment with $SnCl_4$, likewise furnished an anomeric mixture of compounds **2** and **7** in the ratio 5:1, as determined by g.l.c.

*Multi-gram preparation of methyl 4-O-acetyl-2,3,6-trideoxy-α-*L-erythro-*hex-2-enopyranoside* (**2**). — 3,4-Di-*O*-acetyl-L-rhamnal (**1**; 5.00 g, 23.4 mmol) dissolved in dichloromethane (100 mL) was treated with methanol (1.55 g, 48.4 mmol) and 5.5 mL of a solution (0.22M) of $SnCl_4$ in dichloromethane as described in the general procedure. Chromatography of the resulting mixture of compounds **2** and **7** on a column of silica gel (6:1 hexane–ethyl acetate) afforded compound **2** (2.95 g, 15.9 mmol) and a mixture of compounds **2** and **7** (1.05 g, 5.66 mmol). To this mixture in dichloromethane (100 mL) was added glycal **1** (3.80 g, 17.8 mmol), and the resulting solution was treated with methanol (1.17 g, 36.7 mmol) and $SnCl_4$ in dichloromethane (5.5 mL, 0.22M) as already described. Chromatography of the resulting mixture of compounds **2** and **7** on the *same* column of silica gel now afforded compound **2** (2.96 g, 15.9 mmol) and a mixture of compounds **2** and **7**

TABLE III

^{1}H-N.M.R. SPECTRAL DATA FOR COMPOUNDS **2–14**

Compound	Chemical shifts (δ) and coupling constants[a]					
	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6}$)	H-6
2	4.86bs	5.81–5.84m		5.06m (9.2)	3.95dq (6.3)	1.24d
3	4.98bs	5.76–5.89m		5.06d (9.2)	3.98dq (6.2)	1.21–1.26m[b]
4	5.07m[c]	5.78–5.90m		5.07m[c] (9.2)	4.01dq (6.3)	1.19d
5	5.07s[c]	5.73–5.87m		5.05 (9.3)	4.01dq (6.4)	1.16–1.27m[b]
6	5.26bs	5.67–5.84m		5.01m (9.2)	4.04dq (6.3)	1.19d
7	5.06bs[c]	5.84–5.92m		5.03m[c] (6.5)	3.86dq (6.5)	1.32d
8	5.13bs	—5.89m—		5.05m (6.4)	3.84dq (6.4)	1.31d
9	5.22d (1.6)	—5.94m—		5.06m (6.4)	3.91dq (6.6)	1.36d
10	5.20m	5.81–5.89m		5.03m	4.06dq (6.2)	1.10–1.34m[b]
11	6.34dd[d] (6.1)	4.81dd (2.6)	3.81m[c] (6.3)	3.13dd (8.7)	3.81m[c] (6.5)	1.36d
12	6.38dd[e] (6.1)	4.74dd (3.0)	5.31ddd (6.0)	3.28dd (8.1)	4.01dq (6.5)	1.38d
13	6.40dd[f] (6.2)	4.85dd (3.0)	3.90m (5.8)	5.03dd (7.5)	4.06dq (6.6)	1.30d
14	4.81bs	6.05d (10.3)	5.76ddd (5.1)	3.52m (8.8)	3.78dq (6.2)	1.30d

[a]Hz in parentheses [b]Overlapping signals with those of the alkyl protons [c]Overlapping signals. [d]$J_{1,3}$ 1.3 Hz [e]$J_{1,3}$ 1.3 Hz [f]$J_{1,3}$ 1.4 Hz.

TABLE IV

^{13}C-N.M.R. SPECTRAL DATA FOR COMPOUNDS **2–7** AND **11–14**

Compound	Chemical shifts (δ)					
	C-1	C-2	C-3	C-4	C-5	C-6
2	95.4	129.8[a]	127.8[a]	70.9	64.7	17.7
3	89.0	129.6[a]	128.8[a]	71.1	64.4	18.0
4	96.8	130.3[a]	127.6[a]	69.5	71.2	18.3
5	94.2	129.6[a]	128.1[a]	70.9	64.6	17.7
6	93.7	—138.2–127.7[b]—		70.9	64.9	17.6
7	92.8	129.3[a]	128.5[a]	71.1	64.6	18.0
11	144.7	99.7	77.6[a]	81.3	73.7[a]	17.1
12	145.7	99.0	70.3	80.2	73.6	17.0
13	144.9	99.5	74.1	71.6	72.6	16.4
14	95.6	130.4[a]	126.7[a]	78.2	65.5	18.2

[a]These assignments may be interchanged. [b]Signals overlapping those of the aromatic carbon atoms.

(950 mg, 5.12 mmol). Thus, 5.91 g (31.8 mmol, 77%) of **2** was isolated, together with 950 mg (5.12 mmol) of a mixture of compounds **2** and **7**, corresponding to a 90% yield of **2** + **7**.

*Preparation of 3,4-di-O-methyl-*L*-rhamnal* (**11**), *3-O-acetyl-4-O-methyl-*L*-rhamnal* (**12**), *and 4-O-acetyl-3-O-methyl-*L*-rhamnal* (**13**). — To a solution of L-rhamnal* (10.0 g, 77 mmol), iodomethane (33 g, 235 mmol), and imidazole (5 mg) in oxolane (120 mL) at 10° was added a suspension of NaH (5.6 g, 50% dispersion in oil, 0.115 mol; freed from oil by previously washing with hexane) in oxolane (10 mL). The resulting mixture was stirred for 2 h at 25°. T.l.c. (4:1 hexane–ethyl acetate) indicated the absence of L-rhamnal and the formation of a less-polar product (R_F 0.6) together with a more-polar product (R_F 0.1). Sodium iodide, which had separated as a white precipitate, was filtered off and the filtrate was evaporated to a syrup. Chromatography of the syrup on a column of silica gel (4:1 hexane–ethyl acetate) afforded the less-polar product **11** (7.60 g, 62%) as an oil and the more-polar product as a waxy solid. The latter was directly dissolved in pyridine (50 mL) and to the resulting mixture at 0° was added an excess of acetic anhydride (5 mL). The mixture was stirred for 12 h at 25°. T.l.c. (4:1 hexane–ethyl acetate) now indicated the formation of two products (R_F 0.5 and 0.45). The mixture was quenched with water (~10 mL) and extracted with three 15-mL portions of dichloromethane. The organic phase was dried and evaporated to a syrup. Chromatography on a column of silica gel (6:1 hexane–ethyl acetate) afforded compound **12** (265 mg, 2%) and compound **13** (1.72 g, 13%), both as colorless oils.

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*Prepared from the diacetate **2** by Zemplén deacetylation with sodium methoxide.