Convenient Synthesis of Chiral Pyranones from Carbohydrates

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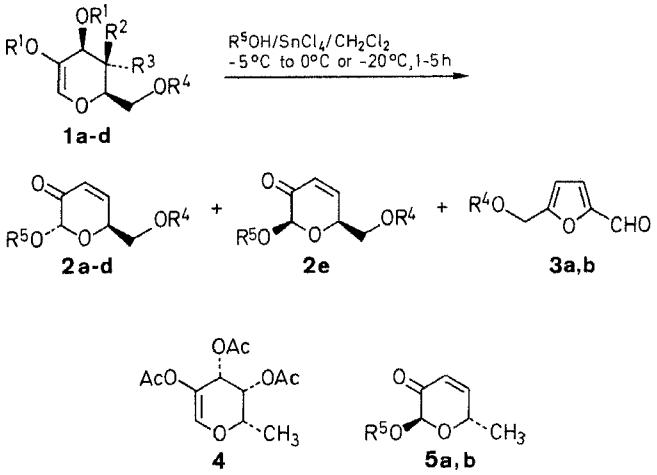
2-Acyloxyglycals (2-*O*-acyl-1,5-anhydrohex-1-enitols) having a D-*arabino* configuration (**1a, b**) react highly stereoselectively with alcohols in the presence of a stoichiometric amount of tin(IV) chloride at 0–5 °C to (2*S*, 6*S*)-6-acyloxymethyl-2-alkoxy-2*H*-pyran-3(6*H*)-ones **2** together with furaldehyde by-products **3**. In the case of 2-acyloxyglycals having a D-*lyxo* (**1c, d**) or an L-*lyxo* (**4**) configuration, reaction occurs readily at −20 °C to form the desired pyranones **2** or **5** without the formation of furaldehydes. All reactions showed high stereoselectivity for α-anomers in the formation of the acetal linkage, except the reaction of the tri-*O*-benzoyl derivative **1d** with methanol. The method reported allows the synthesis of chiral pyranones in higher yield and by a shorter route than the previously reported methods.

Chiral pyranoid sugar enones have been extensively used for the synthesis of a variety of asymmetric molecules, such as branched chain, amino, and rare sugars.[1] Since carbohydrate-derived enones also constitute adequate building blocks for the construction of natural products,[1,2] several approaches for their synthesis, including low-yielding[3,4] or multistep[5,6] methods, have been developed. We have recently reported[7] a short route for the preparation of the α-anomers of alkyl 3,4-dideoxyhex-3-enopyranosid-2-uloses (2-alkoxy-2*H*-pyran-3(6*H*)-one derivatives) and their enolic precursors, alkyl 3-deoxyhex-2-enopyranosides, by reaction of 2-acetoxyglycals with alcohols in the presence of *N*-iodosuccinimide. Depending upon the configuration of the starting 2-acetoxyglycal and the reaction conditions, enosides or enones were the preferred products. An acid-catalyzed mechanism was proposed for the rearrangement. This fact suggested that a Lewis acid could simultaneously produce the addition of the alcohol to 2-acyloxyglycals and the rearrangement. Furthermore, boron trifluoride[8] or stannic chloride[9] were used as catalysts in the allylic rearrangement of glycals.

We have now explored the reaction of 2-acyloxyglycal (2-*O*-acyl-1,5-anhydrohex-1-enitol derivatives, **1a–d, 4**) with 2-propanol, in the presence of tin(IV) chloride under various conditions (Table 1). The product distribution is affected by temperature, the concentration of stannic chloride and the configuration of the starting glycal. We have found that control of the temperature is essential. Thus, 2-acyloxyglycals having a D-*arabino* configuration (**1a, b**) gave two products, (2*S*, 6*S*)-6-acyloxymethyl-2-alkoxy-2*H*-pyran-3(6*H*)-one (**2a** or **2b**) and 5-acyloxymethyl-2-furaldehyde (**3a** or **3b**). The proportion of the latter product was diminished by conducting the reaction at −5 °C to 0 °C. At −20 °C or with less than a stoichiometric amount of tin chloride, starting glycals **1a, b** were recovered. 2-Acyloxyglycals having a D-*lyxo* configuration (**1c, d**) also produced furaldehyde by-products **3a** and **3b**, respectively, when



1	R^1	R^2	R^3	R^4
a	Ac	H	AcO	Ac
b	PhCO	H	$PhCO_2$	PhCO
c	Ac	AcO	H	Ac
d	PhCO	$PhCO_2$	H	PhCO

2	R^4	R^5	3	R^4	5	R^5
a	Ac	*i*-Pr	**a**	Ac	**a**	*i*-Pr
b	PhCO	*i*-Pr	**b**	PhCO	**b**	3-cholestanyl
c	Ac	3-cholestanyl				
d	PhCO	CH_3				
e	PhCO	CH_3				

Table 1. Reaction Conditions for the Formation of Pyranones **2**[a]

Starting Compound	Glycal/$SnCl_4$ mole ratio	Temperature (°C)	Product Distribution[b] (%)
1a	1:1	−5 to 0	**2a** (60), **3a** (40)
	1:2	−5 to 0	**2a** (55), **3a** (45)
	2:1	0	–[c]
	1:1	−20	–[c]
1b	1:1	−5 to 0	**2b** (60), **3b** (40)
	1:1	−20	–[c]
1c	1:1	0	**2a** (80), **3a** (20)
	1:1	−20	**2a** (>95)
1d	1:1	0	**2b** (70), **3b** (30)
	1:1	−20	**2b** (>95)

[a] Reactions were performed in dichloromethane, with 2-propanol (1.5–2.0 mole equivalents), reaction time 1 h.
[b] Determined from integrated ^{1}H-NMR spectra.
[c] The starting compound was recovered.

reacted at 0°C, but at −20°C they rearranged readily to the desired **2a** or **2b** without furaldehyde formation. 2-Acyloxyglycal **4**, having the L-*lyxo* configuration, rearranged analogously to **1c, d** at −20°C with 2-propanol to give pyranone **5a** (Table 2). Having established the optimum temperature and glycal / tin chloride ratio, we extended the reaction to other alcohols, methanol and cholestanol. The results under optimized condition are summarized in Table 2.

The procedure here described has the following advantages:

- High stereoselectivity for α-anomers in the formation of the acetal linkage. The only instance in which the β-isomer was formed, was in the reaction of **1d** with methanol.
- The starting 2-acyloxyglycals are readily obtained from aldohexoses, via the glycopyranosyl bromides,[7,8] in excellent yields (80–90%).
- Pyranones are obtained in much higher yield as compared to other methods. For example, compound **2a** was obtained in ~68% yield from D-galactose, whereas for a similar pyranone[5] a 37% yield was reported in a multistep preparation from methyl α-D-glucopyranoside.
- Benzoylated derivatives that did not rearrange by *N*-iodosuccinimide[7] are effectively transformed into pyranones by the stannic chloride promoted reaction.

6-Acyloxymethyl-2-alkoxy-2*H*-pyran-3(6*H*)-ones 2 and 5; General Procedure:

A solution of the 2-acyloxyglycal derivative[7,8] (**1a–d**; **4**; 1 mmol) and the alcohol (1.5–2 mmol) in anhydrous CH_2Cl_2 (20 mL) is cooled to −5°C to 0°C (**1a, b**) or to −20°C (**1c, d, 4**) and $SnCl_4$ (1.2 mmol) is then added. The reaction is monitored by TLC (silica gel, Merck precoated sheets). When the starting material was completely consumed (1–5 h; see Table 2) the mixture is diluted with CH_2Cl_2 (150 mL) and washed with sat. aq. $NaHCO_3$ (2 × 50 mL) followed by brine (50 mL). The organic extract is dried ($MgSO_4$) and evaporated. The residue is column chromatographed with hexane/EtOAc 6:1 as eluent (except for compounds **2c** and **5b** for which hexane/EtOAc 9:1 is used) (see Table 2).

5-(Acetoxymethyl)-2-furaldehyde (3a) and 5-(Benzoyloxymethyl)-2-furaldehyde (3b):

Compounds **3a** and **3b** are isolated as by-products in the reaction of the 2-acyloxyglycals **1a, b** (Table 1). The ^{1}H- and ^{13}C-NMR of **3b** are in good agreement with data reported in the literature.[10]

Table 2. Reaction of 2-Acyloxyglycals with Alcohols in the Presence of Tin (IV) Chloride to Give Pyranones **2a–e**, **5a–b**

Starting Glycal	Alcohol	Reaction Time (h)	Product	Yield[a] (%)	mp[b] (°C)	$[\alpha]_D$[c]	Molecular Formula[d] or Lit. Data	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J(Hz)	^{13}C-NMR ($CDCl_3$/TMS)[f] δ
1a	2-propanol	5	**2a**	51	–	+ 3°	$[\alpha]_D$ +3°[7]	4.23, 4.38 (dd, 2H, C$\underline{H}_2$R); 4.78 (m, 1H, H-6); 4.98 (br s, 1H, H-2); 6.16 (dd, 1H, H-4, $J_{4,5}$ = 10.8, $J_{4,6}$ = 2.7); 6.97 (dd, 1H, H-5, $J_{5,6}$ = 1.8)	64.6 (C$\underline{H}_2$R); 66.8 (C-6); 96.1 (C-2); 126.1 (C-4); 147.1 (C-5); 188.7 (C-3)
1c	2-propanol	1	**2a**	84					
1b	2-propanol	5	**2b**	42	–	− 7°	$C_{16}H_{18}O_5$ (290.3)	4.49, 4.63 (dd, 2H, C$\underline{H}_2$R); 4.94 (m, 1H, H-6); 5.00 (br s, 1H, H-2); 6.22 (dd, 1H, H-4, $J_{4,5}$ = 11.0, $J_{4,6}$ = 2.8); 7.06 (dd, 1H, H-5, $J_{5,6}$ = 1.8)	65.1 (C$\underline{H}_2$R); 66.9 (C-6); 96.3 (C-2)–126.2 (C-4); 147.0 (C-5); 188.5 (C-3)
1d	2-propanol	1	**2b**	75					
1c	3-cholestanol	3	**2c**	70	83–84	+ 33°	$C_{35}H_{56}O_5$ (556.8)	4.23, 4.38 (dd, 2H, C$\underline{H}_2$R); 4.81 (m, 1H, H-6); 5.02 (br s, 1H, H-2); 6.18 (dd, 1H, H-4, $J_{4,5}$ = 11.0, $J_{4,6}$ = 2.6); 6.95 (dd, 1H, H-5, $J_{5,6}$ = 1.8)	64.7 (C$\underline{H}_2$R); 66.9 (C-6); 96.4 (C-2); 126.3 (C-4); 146.9 (C-5); 188.5 (C-3)
1d	methanol	2	**2d** + **2e**	95 (**2d** + **2e**)	85–86	− 40°	mp 85.5–86°[9] $[\alpha]_D$ −39.6°	4.47, 4.63 (dd, 2H, C$\underline{H}_2$R); 4.81 (br s, 1H, H-2); 4.85 (m, 1H, H-6); 6.20 (dd, 1H, H-4, $J_{4,5}$ = 10.8, $J_{4,6}$ = 2.6); 7.05 (dd, 1H, H-5, $J_{5,6}$ = 1.6)	64.9 (C$\underline{H}_2$R); 66.9 (C-6); 98.6 (C-2); 126.0 (C-4); 147.0 (C-5); 188.8 (C-3)
			2e		–	−105°	$[\alpha]_D$ −111.8°[9]	4.57, 4.65 (dd, 2H, C$\underline{H}_2$R); 4.85 (br s, 1H, H-2); 4.84 (m, 1H, H-6); 6.23 (dd, 1H, H-4, $J_{4,5}$ = 10.7, $J_{4,6}$ = 2.0); 7.10 (dd, 1H, H-5, $J_{5,6}$ = 2.9)	65.8 (C$\underline{H}_2$R); 70.8 (C-6); 98.2 (C-2); 126.0 (C-4); 146.5 (C-5); 188.1 (C-3)
4	2-propanol	1.5	**5a**	62	–	− 66°	$C_9H_{14}O_3$ (170.2)	1.38 (d, 3H, CH_3); 4.69 (m, 1H, H-6); 4.88 (br s, 1H, H-2); 6.04 (dd, 1H, H-4, $J_{4,5}$ = 10.5, $J_{4,6}$ = 2.6); 6.91 (dd, 1H, H-5, $J_{5,6}$ = 1.5)	20.0 (CH_3); 64.1 (C-6); 95.9 (C-2); 124.0 (C-4); 152.2 (C-5); 189.1 (C-3)
4	3-cholestanol	1	**5b**	54	130–131	− 14°	$C_{33}H_{54}O_3$ (498.8)	1.37 (d, 3H, CH_3); 4.69 (m, 1H, H-6); 4.95 (br s, 1H, H-2); 6.05 (dd, 1H, H-4, $J_{4,5}$ = 10.5, $J_{4,6}$ = 2.5); 6.90 (dd, 1H, H-5, $J_{5,6}$ = 1.8)	20.2 (CH_3); 64.3 (C-6); 96.0 (C-2); 124.2 (C-4); 152.1 (C-5); 189.2 (C-3)

[a] Yields after purification by column chromatography, or after recrystallization.
[b] Uncorrected, determined in a Thomas-Hoover apparatus.
[c] Determined at 20°C in a Perkin Elmer Model 141 polarimeter, for 1% solutions in chloroform.
[d] Satisfactory microanalyses obtained: C ±0.29, H ±0.30.
[e] Recorded on a Varian XL 100 spectrometer at 100.1 MHz. Signals for the protons of the enone moiety are reported.
[f] Recorded on a Varian XL 100 spectrometer at 25.2 MHz. Signals for the carbons of the enone moiety are reported.

^{1}H-NMR ($CDCl_3$): δ = 2.12 (s, 3 H, CH_3); 5.40 (s, 2 H, CH_2); 6.64 (d, 1 H, $J_{3,4}$ = 3.6 Hz, H-4); 7.20 (d, 1 H, H-3); 9.62 (s, 1 H, CHO).

^{13}C-NMR ($CDCl_3$): δ = 20.7 (CH_3); 57.8 (CH_2); 112.5 (C-4); 121.5 (C-3); 153.0, 155.5 (C-2, C-5); 169.5 ($CH_3\underline{C}O$); 177.7 (CHO).

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