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A New Convenient Method for the Synthesis of Chiral C_3-Synthons

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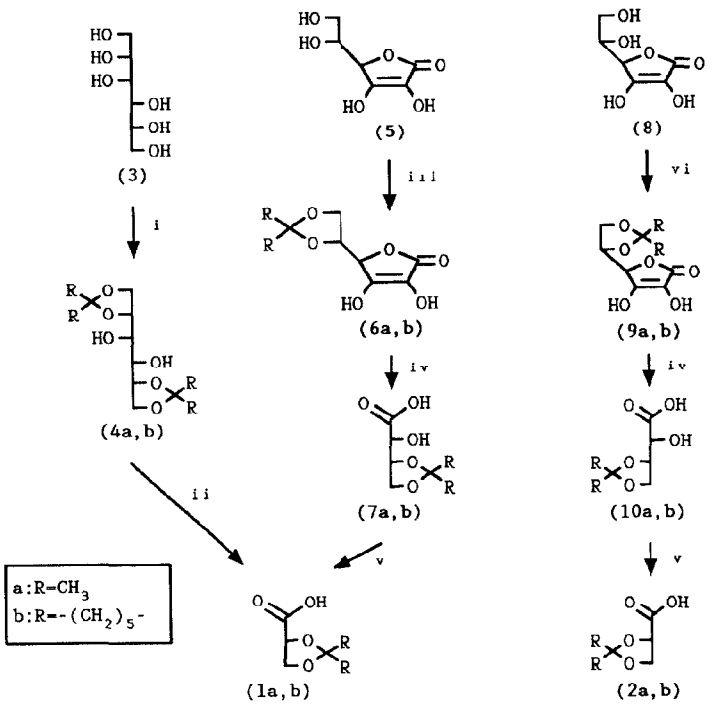
Abstract: Routes are described for the facile preparation of protected optically pure D- and L-glyceric acid (**1a,b; 2a,b**) starting from D-mannitol, D-isoascorbic acid and L-ascorbic acid. The key step is a ruthenium catalyzed oxidative cleavage of the vicinal diols **4a,b** or the α-hydroxy acids **7a,b; 10a,b.**

During the last decades there has been increasing interest in the synthesis of small chiral fragments which can be incorporated into optically active natural products and compounds of biological and synthetic importance[1]. Examples of such small versatile building blocks are optically pure D- and L-glyceric acid derivatives, which are applied in the synthesis of chiral natural and synthetic products[2]. Both enantiomers can be prepared starting from D- or L-serine[3] or by oxidation of the corresponding glycerol or glyceraldehyde derivatives by $KMnO_4$[2b,4]. More recently also a selective enzymatic oxidation of protected racemic glycerol[5] and an electrochemical oxidation of D-mannitol and D-isoascorbic acid[6] were reported to yield the 2,3-O-isopropylidene-D-glyceric acid (**1a**). In this paper we report a new facile method for the synthesis of enantiomerically pure 2,3-O-isopropylidene- or 2,3-O-cyclohexylidene-D- and L-glyceric acid (**1a,b; 2a,b**) by the ruthenium catalyzed oxidative cleavage of protected D-mannitol (**4a,b**), D-erythronic (**7a,b**) and L-threonic acid (**10a,b**) (Scheme I). By using this economically attractive method, both enantiomers of protected glyceric acid now become readily available starting from inexpensive carbohydrates and using inexpensive oxidizing agents.

Several oxidants are capable of cleaving the carbon-carbon bond in α-glycols. For the cleavage of carbohydrates the most commonly used reagents are lead tetraacetate and sodium periodate[7], which can be used under mild reaction conditions. However, for industrial applications they are too expensive and environmentally unacceptable. Since its introduction in organic chemistry in 1953[8], ruthenium tetroxide has been recognized as a powerful and versatile oxidizing agent[9]. Although numerous catalytic procedures have been developed[9-10] because of the high costs of ruthenium metal, only a few examples of ruthenium catalyzed oxidative cleavage reactions are known[11]. In 1970 Wolfe[11d] reported a $RuCl_3$-catalyzed hypochlorite oxidation of different organic compounds. Thus, cyclohexane-1,2-diol was cleaved to adipic acid using catalytic amounts of $RuCl_3$ and 6.2 equivalents of sodium hypochlorite. Under these reaction

conditions our substrates are fully deprotected and degraded. We have found however that under modified reaction conditions (see later) the cleavage of 1,2:5,6-di-O-isopropylidene- and 1,2:5,6-di-O-cyclohexylidene-D-mannitol (**4a,b**), 3,4-O-isopropylidene- and 3,4-O-cyclohexylidene-D-erythronic acid (**7a,b**) and 3,4-O-isopropylidene- and 3,4-O-cyclohexylidene-L-threonic acid (**10a,b**) affords 2,3-O-isopropylidene- and 2,3-O-cyclohexylidene-D- and L-glyceric acid (**1a,b; 2a,b**) in high yields (Scheme 1, Table 1).

Scheme 1



Scheme 1. *Reagents and conditions*: ia), 2,2-dimethoxypropane, $SnCl_2$ (cat.)[12]; ib), cyclohexanone, BF_3 (cat.)[13]; iia), NaOCl, $RuCl_3$ (cat.), pH = 8, room temperature, 30 min.; iib) NaOCl, $RuCl_3$ (cat.), H_2O/dichloroethane/acetonitrile, pH = 8, 4 h; iiia), 2,2-dimethoxypropane, acetone, $SnCl_2$ (cat.), reflux, 30 min. (100 %); iiib), 1,1-dimethoxycyclohexane, $SnCl_2$ (cat.), EtOAc, reflux, 30 min. (99 %); iv, H_2O_2, $CaCO_3$[14]; v, NaOCl, $RuCl_3$ (cat), pH = 8, room temperature, 30 - 60 min.; via), 2,2-dimethoxypropane, acetone, $SnCl_2$ (cat.), reflux, 5 min. (94 %); vib), 1,1-dimethoxycyclohexane, EtOAc, $SnCl_2$ (cat.), reflux, 30 min (93 %).

In a typical procedure sodium hypochlorite (13 wt% in water, 0.4 mole) was added dropwise over a period of 0.5 h to a well stirred solution of 1,2:5,6-di-O-isopropylidene-D-mannitol (**4a**, 0.087 mole) and $RuCl_3.xH_2O$ (0.002 mole) in water (400 ml, pH = 8, room temperature). The pH was maintained at 8 by adding a 5 M NaOH-solution. The reaction mixture was then concentrated in vacuo at 60 °C to a solid

residue, which was taken up in hot ethanol. Concentration of the filtrate gave sodium 2,3-O-isopropylidene-D-glycerate (**1a**, 0.165 mole, 95 %) {$[\alpha]_D$ = +32.6 (c = 0.98, H_2O), lit.[15] $[\alpha]_D$ = 30.1 (c = 1.03, H_2O)}.

Table 1. α-Glycol cleavage catalyzed by ruthenium(III) chloride[a].

substrate	time (min)	$[sub]_{t=0}$ (mole/l)	NaOCl (eq./mole)	product	yield[b] (%)
4a	30	0.2	4.5	**1a**	95
4b[c]	240	0.3	6	**1b**	64
7a	30	0.7	2	**1a**	99
7b	60[d]	0.35	2	**1b**	93
10a	30	0.7	2	**2a**	95
10b	60[d]	0.35	2	**2b**	99

[a] Reactions carried out at room temperature and pH = 8 in H_2O using 0.025 equivalents $RuCl_3.xH_2O$ per mole substrate. [b]Isolated as the sodium salt. [c] Two phase system (H_2O/dichloroethane/acetonitrile). [d] Reaction temperature 35 °C.

In contrast to Wolfe's experiments[11d], the pH was controlled throughout the process, which is essential in order to obtain a high selectivity. Reactions at too low or too high pH are attended by deprotection, degradation or racemisation.

Preliminary results indicate that other ruthenium catalysts, homogeneous as well as heterogeneous, are also able to cleave α-glycols. The yields in solution (not isolated) of 2,3-O-isopropylidene-D-glyceric acid (**1a**) in the cleavage of 1,2:5,6-di-O-isopropylidene-D-mannitol (**4a**) vary from moderate to very good (Table 2).

Table 2. Cleavage of 1,2:5,6-di-O-isopropylidene-D-mannitol (**4a**) catalyzed by various ruthenium catalysts[a]

oxidant (eq./mole)	time (min)	catalyst	yield[b] (%)
NaOCl (4.5)	30	$RuCl_3.xH_2O$	97
NaOCl (8)	45	$Pb_2[Ru_{1.33}Pb_{0.67}{}^{4+}]O_{6.5}$[c]	90
NaOCl (4.5)	120	Ru-Dowex W50-X8[d]	70
NaOCl (6.5)	45[e]	5 % Ru/C	98
NaOCl (4)	30	TPAP[f]	93
NaOCl(8)	100[e]	-	39[g]

[a] Reactions carried out at room temperature and pH = 8 (0.2 M **4a** in H_2O) using 0.025 equivalents of catalyst per mole **4a**. [b]Yield in solution determined by HPLC (as described by Dijkgraaf[15]). [c] Prepared as described by Horowitz[16]. [d] Prepared by stirring a mixture of $RuCl_3.xH_2O$ and Dowex 50W-X8 during 16 h. [e] Reaction temperature 60 °C. [f] Tetrapropylammonium perruthenate (TPAP)[4]. [g] Conversion is 54 %.

In conclusion our procedure constitutes a very mild and efficient method for the cleavage of protected α-glycols and could find broad use in carbohydrate chemistry. The use of a cheap oxidizing agent such as sodium hypochlorite, a heterogeneous catalyst (easily separated from the reaction mixture) and inexpensive carbohydrates as substrates, make this method also interesting for industrial applications.

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