Selective ruthenium-catalyzed oxidation of 1,2:4,5-di-O-isopropylidene- β -D-fructopyranose and other alcohols with NaOCl

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Typical Experimental procedure for oxidation of 1,2:4,5-di-O-isopropylidene- β -D-fructopyranose (compound 1)

In a typical experiment, a 2-neck pear-shaped flask was equipped with a magnetic stirrer, an addition funnel and a pH electrode, the latter connected to a Metrohm pH-stat device, consisting of a pH meter, an Impulsomat and a Dosimat. The following reagents (see Table 1) were then added in the order stated: catalyst precursor (prepared according to the literature¹); Methyl t-butyl ether (MTBE, containing the GLC internal standard); NaOCl. The biphasic mixture was stirred vigorously until the organic phase assumed a yellow-green colour and the aqueous phase was colourless. The substrate was then added rapidly dropwise with a pipette while stirring, once dissolved in the remaining solvent.

The oxidant was then added dropwise via the addition funnel, typically over 2 hour. During this phase, pH was kept constant at 9.5 by addition of HCl 2.0 M via Dosimat. After the addition of the oxidant was completed, pH was observed to drop and was therefore kept constant at the chosen value by Dosimat addition of NaOH 2.0 M for the rest of the experiment (typically 5 hours overall). The reaction was carried out at room temperature. The reaction was monitored by taking samples of the organic phase regularly and analysing the mixture by GLC after adsorption of the catalyst on a Celite pad (retention times and response factors were determined by calibration based on pure samples). When complete conversion was reached (typically after 3h), the final workup involved phase separation and evaporation of MTBE from the organic phase to yield the crude product (ca. 95% of the final amount).

The aqueous phase was extracted with CH₂Cl₂ after neutralisation with NaHCO₃ followed by evaporation to yield a second crop (ca. 5% of the final amount).

Table 1: reagents used

Reagents	Equivalents	Mmoles	Comments
Fructose diacetone (1)	1.0	2.0	gift from <i>Catalytica</i>
1,2,4-trichlorobenzene (TCB)	0.2	0.4	GC internal standard
NaOCl, aqueous sol (1.0 M)	3.0	6.0	Aldrich, iodometric title
[Pr ₄ N][RuO ₄] (TPAP)	0.01	0.02	See text

¹ (a) Griffith, W. P. et al *J. Chem. Soc. Chem. Comm.* **1987**, 1625. (b) Ley, S. V. et al, *Synthesis*, **1994**, 639.

MTBE, 10 ml			HPLC grade
HCl (2.0 M), NaOH (2.0 M)			Used for pH control

GLC data showed complete conversion and high selectivity to **2** after 3 hours, which was chosen as reaction time in the scaled-up experiments for which results are also shown below.

Table 2: GLC data

t (h)	% Conv.	% Yield	% S to 2	pH
1	82	65	79	9.45
3	>99	86	86	9.50
5	>99	80	80	9.50

Table 3: isolated yields of 1,2:4,5-di-O-isopropylidene- β -D-erythro-2,3-hexadiulo-2,6-pyranose (**2**) for scaled-up experiments.

1 , g (mmol)	2 , g (mmol)	% Yield
0.52 (2)	0.30 (1.2)	60
1.30 (5)	0.85 (3.3)	66
5.20 (20)	3.83 (14.8)	74
10.40 (40)	8.18 (31.7)	79

In all cases the product showed to be >99% pure by NMR and GLC at complete conversion of **1**.

In a separate experiment (2 mmol scale), the pH control procedure was replaced by use of a NaHCO₃/Na₂CO₃ buffer (pH 9.5). After 4 hours, GC data showed 98% conversion of **1** and 90% yield of **2**.

Recycling experiments

A series of experiments was carried out to test the activity of the catalytic system after recycling. The procedure described in a recent patent² was used to recycle the catalyst from its low valent state, presumably RuO₂. Compound **1** was used as substrate for recycling tests. Conditions: **1**, 2 mmol; TPAP, 0.02 mmol; NaOCl (0.7 M) 6 mmol added over 3h; MTBE 10 ml; TCB 1 mmol, RT, 4h; pH 9.50. After the run was completed, the organic phase containing **1**, **2** and TCB was separated after addition of NaOH to pH 11, which forces the catalyst into the water phase. Then the catalyst was back-extracted from the aqueous phase by addition of NaOCl (0.2 mmol) and MTBE

² M. Kakuda, T. Okamoto, T. Onozawa, H. Kurata, *Eur Patent Appl* EP1069103 (2001).

(10 ml overall), at pH 6. To the yellow solution so obtained, the substrate was added as a solid. The oxidation protocol was then applied as described above. The procedure was repeated for 3 cycles and the results are reported in Table 4 (below) and Figure 1 (see manuscript).

Table 4: Catalyst recycling for the Ru-catalysed bleach oxidation of **1** to **2**.

Cycle	%C	%Y*	%S to 2
1	99	83	83
2	85	70	82
3	80	62	78
4	78	53	68

**GC yields.*