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RuO_4-catalysed oxidative cyclisation of 1,6-dienes to *trans*-2,6-bis(hydroxymethyl)tetrahydropyranyldiols. A novel stereoselective process

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Abstract

RuO_4 catalyses the stereoselective oxidative cyclisation of the 1,6-dienes, 7-methyl-1,6-octadiene and 1,6-heptadiene, to the corresponding *trans*-2,6-bis(hydroxymethyl)tetrahydropyranyldiols, in the presence of $NaIO_4$ as primary oxidant, in EtOAc:CH_3CN:H_2O (3:3:1) at 0°C for 4 min. A mechanistic hypothesis explaining the observed *trans*-2,6-stereochemical control is formulated. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: RuO_4; *trans*-THP diols; stereoselective process.

Some transition metal oxides in their high oxidation states are able to induce, in a stereoselective manner, the oxidative cyclisation of acyclic substrates to tetrahydrofuran rings (THFs) flanked by one or two hydroxymethyl groups (at the 2- and/or 5-positions), a recurrent structural motif in many biologically active natural products e.g. *Annonaceous* acetogenins.[1] In particular, *trans*-THFs can be obtained from 5-hydroxyalkenes using Re_2O_7/2,6-lutidine[2] or $(CF_3CO_2)ReO_3$/2,6-lutidine[3] while *cis*-THF products can be obtained from 1,5-dienes with MnO_4^-[4] (1.5–2 equiv.) or with catalytic amounts of either RuO_4[5] or OsO_4[6] in the presence of $NaIO_4$ as co-oxidant, as well as from 5,6-dihydroxyalkenes by using CrO_3.[7]

On the contrary, little is known about the ability of metal oxo species to induce the formation of tetrahydropyran (THP) rings. Only recently McDonald and Singhi[8] have reported that trishomoallylic alcohols can be transformed into *trans*-tetrahydropyranyl alcohols by acylperrhenate-induced *syn*-oxidative cyclisation by using $(CF_3CO_2)ReO_3$/$(CF_3CO)_2O$ in CH_2Cl_2.

In the present communication it is reported that the commercially available 1,6-dienes, 7-methyl-1,6-octadiene (**1**) and 1,6-heptadiene (**3**), can be stereoselectively cyclised to the corresponding *trans*-2,6-bis(hydroxymethyl)tetrahydropyranyldiols, **2** and **4**, respectively (Scheme 1), with catalytic amounts (5%) of RuO_4 (from $RuCl_3 \cdot 2H_2O$) in the presence of $NaIO_4$ (4 equiv.) as primary oxidant in EtOAc:CH_3CN:H_2O (3:3:1) at 0°C for a short time (4 min). These conditions have previously been used in a slightly modified form by Shing et al. for the RuO_4-catalysed 'flash-dihydroxylation' of alkenes.[9]

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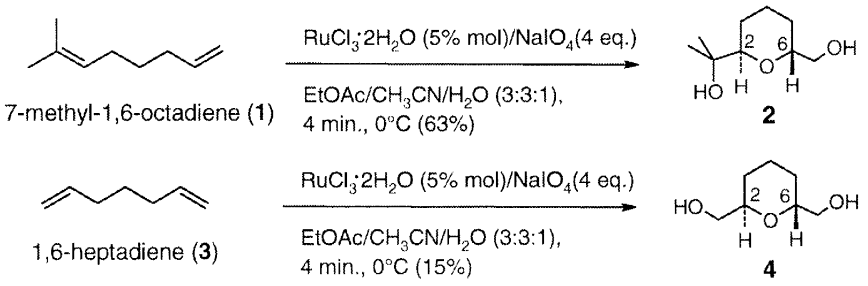


Scheme 1.

The reaction has been performed by adding $NaIO_4$ (4 equiv.) dissolved in H_2O to a suspension of $RuCl_3 \cdot 2H_2O$ in a mixture of EtOAc/CH_3CN at 0°C. The amount of solvent was adjusted so that the final composition of the mixture was 3:3:1 (EtOAc:CH_3CN:H_2O). Quenching the reaction was performed after 4 min by adding a saturated aqueous solution of $Na_2S_2O_3$. Shorter reaction times gave incomplete conversions. Extractive work-up (EtOAc) followed by HPLC afforded pure samples of compounds **2** and **4**. While THP **2** was obtained in a respectable 63% yield, compound **4** was recovered in a poor 15% yield. The reduction of the yield in the THP product by changing the substrate from **1** to **3** is in line with that observed for the MnO_4^--[4] and OsO_4-induced[10] oxidative cyclisation of 1,5-dienes to *cis*-THF for which lower yields are obtained when substrates embodying terminal double bonds are oxidised.

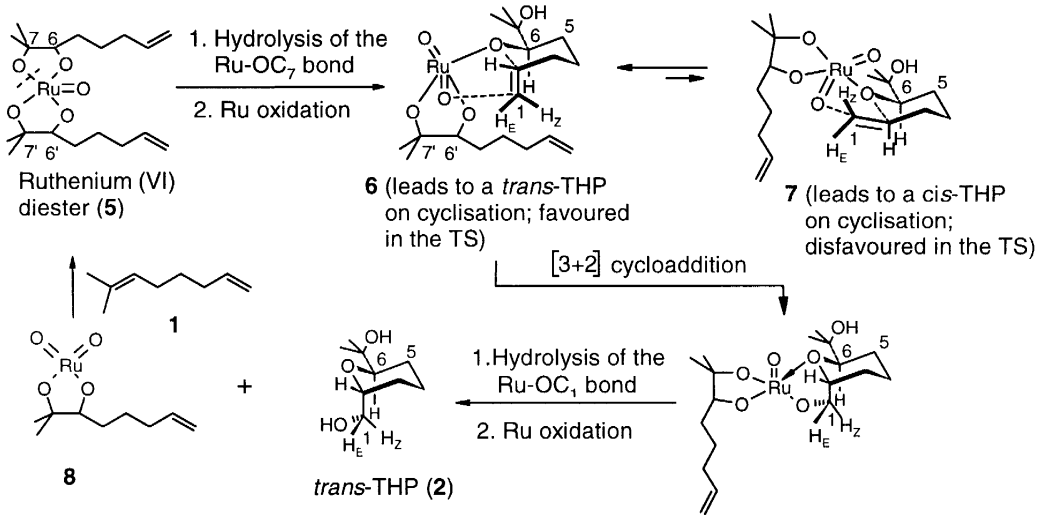
Unambiguous assignment of the structure of *trans*-THP **2** came from its synthesis by acid-catalysed [HCl (1 M):THF:H_2O, 0.5:3:7, 15 min] cyclisation of the diepoxide obtained from diene **1** by reaction with *m*-CPBA ($CHCl_3$, 0°C, 8 h), which also provided a sample of the *cis*-isomer of **2** (ratio *cis*:*trans* ca. 1:1; 60% overall yield).

While the proton spectra of the above *cis*- and *trans*-THP diols recorded in $CDCl_3$ showed overlapping of signals for the H-2 and H-6 protons with the C*H*$_2$-OH resonances, the acetyl derivatives of both showed a good proton dispersion in the 3.5–4.5 ppm region allowing assignment of their stereochemistry by NOE experiments. In particular, NOE enhancements of the methylene protons of the CH_2OAc group linked to C-6 in **2**, on irradiation of the H-2 proton, coupled with the absence of an NOE effect between this proton and H-6, were in agreement with the *trans* stereochemistry for this compound.

The *trans* stereochemistry in **4** was established by performing a dynamic NMR experiment[11] on its diacetyl derivative. In particular, the appearance of ^{1}H NMR signals of the protons geminal to oxygen resonating in the 3.5–4.5 ppm region of the spectrum was monitored while lowering the temperature. In going from −10 to −110°C, an increased complexity of this spectral region was noticed and at −90°C the decoalescence for a signal attributable to one of the two C*H*$_2$OAc protons was clearly observed. This evidence, indicating a 'freezing' of the chair–chair interconversion, is only compatible with the *trans* stereochemistry in **4**, since, in principle, the number of resonances for the corresponding *cis*-THP isomer would be unaffected by the lowering of temperature, due to symmetry reasons.

The *trans* stereoselectivity of the RuO_4-catalysed process can be rationalised by applying to the ruthenium(VI) diester intermediate of the process (**5**, Scheme 2) a model strictly similar to that proposed by McDonald and Singhi to account for the acylperrhenate-induced formation of *trans*-THP alcohols from trishomoallylic alcohols.[8] In particular, the closure of the *trans*-THP ring in the case of diene **1** can be hypothesised to involve the cyclisation of an intermediate species (**6**/**7**), in turn derived from **5** by partial hydrolysis (scission of the Ru–OC_7 bond), followed by oxidation at Ru, in a conformational arrangement (**6**) affected in the transition state by a smaller number of destabilising *gauche* interactions. The only difference between McDonald's and this model resides in the dimeric nature of the ruthenium diester[12] and, thus, in the hybridisation (pentacoordination) at the ruthenium centre. On the other hand, it cannot be excluded a priori that the cyclisation could involve the monomeric ruthenate ester **8** in which

case hydrolysis of the Ru–OC_7 bond, followed by Ru oxidation, would generate a species having the same tetrahedral geometry of the perrhenate ester intermediate of McDonald's process.



Scheme 2.

Experiments are in progress to establish if the above-described RuO_4-induced cyclisation process is stereospecific as well as general in scope, by synthesising suitably substituted 1,6-dienes.

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