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Perruthenate ion. Another metal oxo species able to promote the oxidative cyclisation of 1,5-dienes to 2,5-disubstituted *cis*-tetrahydrofurans

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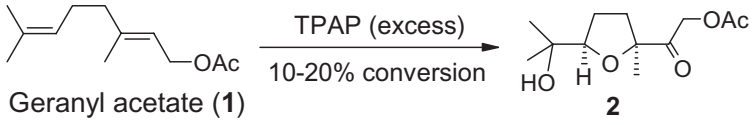
Abstract—Perruthenate ion, from tetrapropylammonium perruthenate (TPAP), in the presence of tetrabutylammonium periodate (TBAPI) as reoxidant catalyses the stereospecific and stereoselective oxidative cyclisation of 1,5-dienes to *cis*-2,5-disubstituted tetrahydrofurans in good to moderate yields. NMO also works as co-oxidant in the process but is less effective and at least 0.7 equiv TPAP are required. Acidic conditions promote the formation of THF diols. 1,5-Dienes with two terminal double bonds give poor yields of THF's or cleavage products.

The metal oxo reagents OsO_4, RuO_4 and MnO_4^- are the only known species able to accomplish the stereospecific and stereoselective conversion of 1,5-dienes to *cis*-2,5-bis(hydroxymethyl)tetrahydrofurans (*cis*-THF diols).[1] This is a very effective process by which four stereogenic centres are created in a single step from an achiral reagent with complete internal stereocontrol. Stereochemically complex tetrahydrofuran fragments, useful in the synthesis of biologically active natural substances, such as *Annonaceous* acetogenins,[2] can be easily accessed through the above processes.

Interest in this field appears still to be keen. Recent advances in the above chemistry include the MnO_4^--promoted formation of enantiomerically enriched mono-THF diols from dienones in the presence of a chiral phase-transfer catalyst,[1n] and an effective improvement of the OsO_4-catalysed oxidative cyclisation of 1,5-dienes to *cis*-THF diols,[1d,e] a process discovered a few years ago in our laboratories.[1c]

As a continuation of our studies in this area,[3] we report here the discovery of a novel oxidative process strictly related to the above-mentioned ones. In particular, perruthenate ion (RuO_4^-), from commercially available tetrapropylammonium perruthenate (TPAP),[4] in the presence of tetrabutylammonium periodate (TBAPI) or 4-methylmorpholine *N*-oxide (NMO) as reoxidants, can catalyse the stereoselective conversion of 1,5-dienes into 2,5-*cis*-disubstituted THF's.

In a preliminary experiment treatment of geranyl acetate (**1**, GA, Scheme 1) with excess TPAP (10 equiv) in CH_2Cl_2 cleanly afforded THF ketol **2**,[5a] but the process stopped at a ca. 10–20% conversion (Table 1). This result established the ability of the perruthenate ion to



Geranyl acetate (**1**) **2**

Scheme 1.

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Table 1

Entry	TPAP (equiv)	NMO (equiv)	2/GA[a]
1	10	—	1/4
2	0.05	20	1.5/1
3	0.1	3–5	1/1.5
4	0.5	10	2.3/1
5	0.7	10–12	1/0
6	1	2	2.3/1
7	1	3	3.6/1
8	1	4	12.0/1
9	1	5	1/0
10	2	3	5.7/1
11	2	4	7.3/1
12	3	4	1/0

[a] Calculated by ^{1}H NMR on the crude reaction mixture.

promote THF formation, therefore, our next objective was to force the process to completion.

With this aim, the use of the system TPAP (cat)/NMO/4 Å molecular sieves, known to accomplish alcohol oxidation,[4] was investigated.[6] Disappointingly, the use of 5–10% TPAP in the presence of 3–5 equiv of NMO, still gave only a modest 35–40% conversion of GA into THF **2** (Table 1, entry 3), once again obtained as the sole reaction product. However, complete GA consumption was reached in the presence of 0.7 equiv TPAP and excess NMO (10–12 equiv), affording **2** in a good 82% isolated (HPLC) yield (Table 1, entry 5; Table 2, entry 1). These conditions worked well with neryl acetate (**3**) and 2,6-dimethyl-2,6-octadienol diacetate (**4**) for which high yields (76% for both) of the expected THF products were obtained (Table 2, entries 3 and 5, respectively), but proved ineffective for the related geranic acid methyl ester (**6**), which gave no THF product while a 50% conversion was obtained for ethyl (*E*,*E*)-nonadeca-4,8-dienoate (**8**). Oxidation of both these dienes could be forced to completion only in the presence of larger amounts of both TPAP and NMO (2 equiv/25 equiv, entries 7 and 9, respectively); the fact that THF **7** from geranic acid methyl ester was obtained in 34% yield indicated that conjugation of one of the double bonds of the diene affected its reactivity (compare entries 1 and 7). This result is in sharp contrast with the oxidation of this substrate with RuO_4 for which yields comparable to, or higher than, that for the unconjugated GA are obtained.[1b] 2,5-Dimethyl-1,5-hexadiene (**10**) and 1,5-hexadiene (**11**) gave no THF product (entries 11 and 13) even with excess (up to 30 equiv) NMO.

Oxidations of geranyl acetate conducted with stoichiometric, or higher, amounts of TPAP were also tested (Table 1). With 1 equiv of TPAP at least 5 equiv of NMO were required for the process to go to completion (entry 9) and a further increase in NMO (up to 12 equiv) did not affect the yield of the THF, which was invariably in the 70–78% range. On the other hand, less NMO (4 equiv) required excess TPAP (3 equiv) (entry 12) but the process was faster (30 min) once again giving **2** in 82% yield.

All the above evidence can be summarised as follows. Both the TPAP and NMO amounts concur to push the reaction ahead. THF formation is strongly affected by the degree of alkylation of the diene: less alkylated dienes require higher amounts of reagents. In addition, 1,5-dienes possessing terminal double bonds are unreactive under the above conditions.

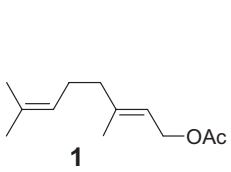
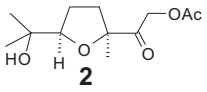
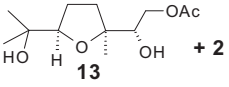
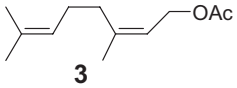
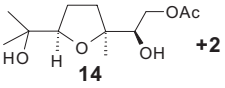
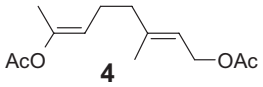
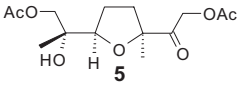
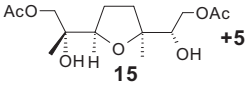
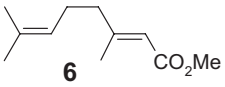
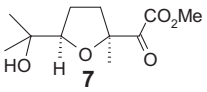
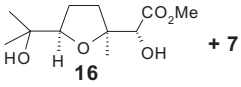
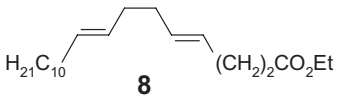
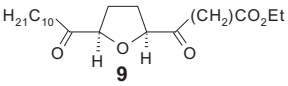
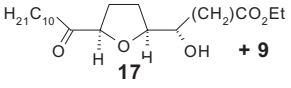
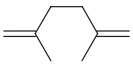
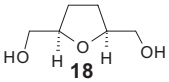
Due to the high amounts of reagents required, the above process appeared rather unattractive. Therefore, we turned our attention to the use of tetrabutylammonium periodate (TBAPI) as co-oxidant, a reagent able to deliver the periodate ion in an organic medium. Gratifyingly, 5% TPAP and 5 equiv of TBAPI gave, in 4.5 h, complete consumption of geranyl acetate and the formation of the THF ketone **2** and the corresponding diol **13**, as a ca. 1:1 mixture.[6] By leaving the mixture overnight the complete over-oxidation of **13** to **2** took place coincidentally giving the same 82% yield of THF **2** (Table 3, entry 1), as was obtained with the TPAP/NMO oxidising system described before.

Oxidation of the other 1,5-dienes under these conditions led to good yields of the expected THF products. In particular, dienes belonging to the geraniol series gave yields comparable to, or slightly higher than, those obtained by the process with NMO (Table 3, entries 2 and 3), while for the disubstituted diene **8** the yield was improved to 68% (entry 5). In some cases 10% TPAP proved more effective (entries 4–6). Geranic acid methyl ester was cyclised in a 41% yield (entry 4), but excess TBAPI (10 equiv) was required. The rather low yield for this process was due to the poor mass recovery after work-up. This behaviour is unclear and is peculiar to this conjugated diene. It is possible that the remainder of material for the mass balance could be made up of highly polar, water soluble, or volatile substances, given the high purity of crude **7**, as estimated from its ^{1}H NMR.

The behaviour of 2,5-dimethyl-1,5-hexadiene under the new conditions paralleled that of geranic acid methyl ester in that a THF product, lactone **12**,[5b] was obtained (note that the oxidation with TPAP/NMO gave no THF product), albeit in a poor 22% yield (entry 6). This product is likely to have been produced by over-oxidation of one of the primary alcohol functions of the initially formed THF diol to an aldehyde, followed by internal hemiacetalisation and further oxidation to give the lactone. The remaining material (ca. 70%) was made up of 2,5-hexanedione derived from cleavage of both double bonds. Though the yield of **12** is low, the possibility of obtaining, in a single step, a compound more complex than the parent THF diol, without additional protection–deprotection steps, appears nontrivial.[7] 1,5-Hexadiene still gave no THF, possibly due to the formation of volatile (C_4) aldehyde product(s) produced by scission, as observed for 2,5-dimethyl-1,5-hexadiene, and/or because of the volatility of the diene itself.

Thus, the process with TPAP/TBAPI is more efficient due to the acceptably low amounts of both reagents (TPAP 5–10%, TBAPI 5 equiv) used, higher yields for

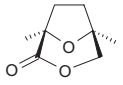
Table 2

Entry	1,5-Diene	TPAP (equiv)	NMO (equiv)	AcOH (equiv)	Product	Yield (%)
1	 **1**	0.7	12	—	 **2**	82
2		2	3	500	 **13**	**13** (55) **2** (22)
3	 **3**	0.7	12	—	**2**	76
4		2	2	500	 **14**	**14** (44) **2** (33)
5	 **4**	0.7	12	—	 **5**	76
6		2	2	500	 **15**	**15** (62) **5** (18)
7	 **6**	2	25	—	 **7**	34
8		4	5	500	 **16**	**16** (20) **7** (8)
9	 **8**	2	25	—	 **9**	59
10		4	15	500	 **17**	**17** (17) **9** (29)
11	 **10**	2	20	—	No THF	—
12		2	2	500	No THF	—
13	 **11**	2	20	—	No THF	—
14		2	2	500	 **18**	<5

some dienes, and the ability of this pair to force diene **10** to cyclise.

Our next objective was to seek out conditions to obtain THF diols. Based on the observation that the over-oxidation of the THF diol products initially formed in the process with TPAP/TBAPI was slow, an attempt was made to stop the oxidation at the diol stage. We were unable to obtain this product alone even quenching the process at an early stage (1–2 min); however, a

Table 3

Entry	1,5-Diene	TPAP/TBAPI (equiv)	Product	Yield (%)
1	**1**	0.05/5	**2**	82
2	**3**	0.05/5	**2**	76
3	**4**	0.05/5	**5**	79
4	**6**	0.1/10	**7**	41
5	**8**	0.1/5	**9**	68
6	**10**	0.1/5	 **12**	22

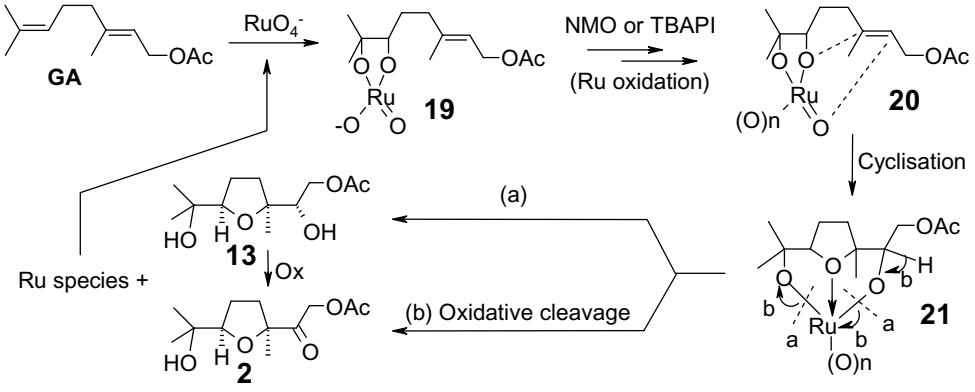


Figure 1.

35–45% yield of the THF diol was produced, as estimated by ^{1}H NMR. This evidence suggests that both the THF diol and ketol products were simultaneously formed from a common intermediate through parallel routes (see Fig. 1, later in the discussion).

The oxidative cyclisation process could be driven towards the formation of THF diols under acidic conditions. Precedents in OsO_4[1d,e] and MnO_4^-[1l,m,n] chemistry suggest the use of acidic conditions for these transformations. AcOH (500 equiv), TPAP 2 equiv and NMO 2–3 equiv were selected[6] as a good compromise in order that the THF diol would predominate over the corresponding THF ketone. In this manner oxidation of geraniol-type substrates gave the THF diols with acceptable 44–62% yields (Table 2, entries 2, 4 and 6) in short times (15–20 min). It is worth noting that Δ^2 isomeric **1** and **3** gave C-2 epimeric THF diols **13** and **14**, indicating that the process was stereospecific, as observed for the cyclisations promoted by the above related oxo-species.[1] Interestingly, no, or extremely slow, over-oxidation of the diol was observed under these conditions. In addition, the overall yields of THF products did not significantly change in comparison with the process without AcOH. For diene **8**, once again more forcing conditions were required (TPAP 4 equiv, NMO 15 equiv) to push the process to completion (entry 10). However, these conditions prevented the formation of the expected THF diol corresponding to diketone **9**, but allowed the formation of ketol **17**. Geranic acid methyl ester was still cyclised in an unsatisfactory 28% (overall) yield. The fact that THF diol **16** was obtained in 20% yield was encouraging and further proved the ability of AcOH to facilitate the diol formation. 2,5-Dimethyl-1,5-hexadiene (entry 12) still gave no THF, while 1,5-hexadiene gave only a <5% amount of the THF diol **18** (entry 14), isolated as its tosyl derivative, while no mono- or dialdehyde corresponding to **18** was detected.

The use of trifluoroacetic acid (TFA 20 equiv, TPAP 2 equiv, NMO 3 equiv) in place of AcOH was tested in the oxidation of GA, but slightly lower (ca. 10%) yields were obtained. On the other hand, the oxidation of the same substrate with TPAP/TBAPI under acidic conditions proved to be less clean compared with the analogous process in the presence of NMO. It must be pointed out, however, that fine tuning of the reaction conditions for these processes has not yet been carried out.

A doubt could arise about the possibility that the true oxidising agent could be RuO_4 produced in some way during the process. Though at the present level of knowledge this cannot be firmly ruled out, we believe that it is not plausible due to the too many differences with the analogous RuO_4-mediated process. In particular:

(a) A higher level of stereoselectivity was observed for the perruthenate-mediated cyclisation since no *trans*-THF isomer was formed, as is observed (in very low yields) in the process with RuO_4.[1b]
(b) No scission products were observed for geraniol-type substrates and for the unbranched diene. These products are generally formed in minor amounts as

side products in the process with RuO_4. In addition, the yields of the THF products obtained from these dienes are higher with the new process.

(c) The reactivity of geranic acid methyl ester appears to be quite different, at least under the tested conditions, from that of other geraniol-type substrates, probably due to conjugation. On the contrary, this substance gives the *cis*-THF product with yields comparable to, or higher than, that for GA and NA in the process with RuO_4.[1b]

(d) 1,5-Dienes possessing terminal double bonds were unreactive in the presence of TPAP but give the expected *cis*-THF diols with RuO_4.

In addition, some experiments aimed at excluding the formation of RuO_4 in the cyclising conditions have been carried out. In particular, *trans*-7-tetradecene in CH_2Cl_2 failed to give the expected scission or diol products, usually obtained with RuO_4, on treatment with excess TPAP (10 equiv) alone or with the $TPAP_{(cat)}$/NMO system,[8] while the same alkene gave heptanal on RuO_4 oxidation in the same solvent.

Based on the above evidence and previous studies by Lee et al.[9] it seems reasonable that at least for the process conducted under neutral conditions, the first step could involve the formation of a cyclic ruthenium(V) diester **19** through attack of the perruthenate anion at one of the double bonds (Fig. 1). These authors reported that, for the oxidation of *trans*-cinnamate,[9] this species decomposes slowly to cleavage products, and also proposed that it is oxidised to a Ru(VI) species in a fast step.[9] These precedents agree well with the observation that no scission products were detected in our process and suggest that the transformation to a more oxidised ruthenium diester species **20** (note that (O)n only indicates a higher oxidation state for Ru), by the co-oxidant, or, in its absence, by the perruthenate ion itself, could follow. It seems rather obvious that this species should be different from the Ru(VI) species involved in the RuO_4-mediated cyclisation. Closure of the THF ring possibly through a [3+2] cycloaddition[1c,10] and release of the THF as a diol (path a) or ketol (path b) would then occur. On the other hand, cyclisation of diester **19** itself cannot be a priori ruled out. Finally, one can speculate that acidic conditions would facilitate THF release as the diol by favouring path b over path a in **21**.

In conclusion, we have discovered a new process for obtaining 2,5-disubstituted *cis*-tetrahydrofurans from 1,5-dienes. Conditions have been devised to obtain THF diols of more alkylated substrates. The process appears to be amenable for further improvement. Efforts towards this goal, as well as to induce chirality, are ongoing.

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5. (a) The structure of all the reaction products was proven by comparison with authentic samples synthesised from the same dienes through the related OsO_4-mediated cyclisation[1c,e] followed, where needed, by TPAP/NMO oxidation; (b) Lactone **12** was synthesised by TPAP/NMO oxidation of the parent THF diol, in turn obtained from 2,5-dimethyl-1,5-hexadiene with $KMnO_4$.[1f]
6. Typical procedure for the TPAP/NMO and TPAP/NMO/AcOH processes. To the diene in CH_2Cl_2 were sequentially added 4 Å molecular sieves (500 mg/mmol), NMO dissolved in CH_2Cl_2 (ca. 15 mg/mL) and TPAP, at rt, under stirring. When the reaction was complete (TLC monitoring) the mixture was concentrated and filtered through a pad of silica gel eluting with $CHCl_3$/MeOH ($9{:}1 \rightarrow 8/2$). The organic phase was concentrated in vacuo taken up in $CHCl_3$ and washed with 0.1 M HCl, saturated $NaHCO_3$ solution and water, then dried over Na_2SO_4 and concentrated under reduced pressure. Pure THF products were obtained by HPLC (hexane/EtOAc mixtures). The process with AcOH, was performed as above; the acid was added to the reaction mixture before TPAP. The solubility of NMO in CH_2Cl_2/AcOH was ca. 30 mg/mL. The use of molecular sieves appears not to affect appreciably both processes but their presence facilitates the work-up.

Typical procedure for the TPAP/TBAPI process. To the diene in CH_2Cl_2 were sequentially added TBAPI (ca. 10 mg/mL) and TPAP, at rt, with stirring. When the reaction was complete (TLC monitoring) an excess of a saturated $Na_2S_2O_3 \cdot 5H_2O$ solution was added and the mixture stirred for 30 min whereupon the whole was poured into a separatory funnel and the phases were separated. The aqueous phase was further extracted with $CHCl_3$. The organic phase was evaporated, taken up in EtOAc and washed twice with a saturated $Na_2S_2O_3 \cdot 5H_2O$ solution, dried over Na_2SO_4 and concentrated in vacuo. Pure THF products were obtained by HPLC (hexane/EtOAc mixtures).

7. See, for example, the synthesis of related D-chitaric acid reported in Ref. 1e.
8. After a prolonged treatment $a < 5\%$ of (*E*)-tetradec-6-en-5-one was obtained.
9. (a) Lee, D. G.; Chang, V. S.; Helliwell, S. *J. Org. Chem.* **1976**, *41*, 3644–3646; (b) Lee, D. G.; Helliwell, S. *Can. J. Chem.* **1984**, *62*, 1085–1092.
10. Travis, B.; Borhan, B. *Tetrahedron Lett.* **2001**, *42*, 7741–7745, and references cited therein.