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# Improved $RuO_4$-catalysed oxidative cyclisation of geraniol-type 1,5-dienes to *cis*-2,5-bis(hydroxymethyl)tetrahydrofuranyldiols

Vincenzo Piccialli* and Nicola Cavallo

*Dipartimento di Chimica Organica e Biochimica, Università degli Studi di Napoli, 'Federico II', Via Cynthia 4,*
*80126 Naples, Italy*

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**Abstract**—The oxidation of some representative 1,5-dienes based on the geraniol and nerol carbon skeletons, namely geranyl acetate (**1**), geranic acid methyl ester (**5**), *trans,trans*-2,6-dimethyl-2,6-octadiene-1,8-diol diacetate (**9**), neryl acetate (**13**) and neroic acid methyl ester (**16**), has been performed using catalytic amounts of $RuO_4$ (from $RuO_2{\cdot}2H_2O$, 4%) in the presence of $NaIO_4$ (4 equiv.) as co-oxidant in the solvent mixture $EtOAc/CH_3CN/H_2O$ (3:3:1) at 0°C for 4 min. These conditions assure a degree of stereoselectivity for the geraniol-type dienes higher than that obtained under the Sharpless conditions [$RuCl_3{\cdot}(H_2O)_n$ (2.2%), $NaIO_4$ (3.1 equiv.), $CCl_4/CH_3CN/H_2O$ (2:2:3), 0°C], furnishing the *cis*- and *trans*-THF diol products in 62–70 and 6–9% yields, respectively. In addition, the amount of the *cis*-THF, C-2 overoxidised, product is strongly reduced (2–7%). A comparison with the related $MnO_4^-$-induced process, tested on the same substrates, was made. © 2001 Elsevier Science Ltd. All rights reserved.

In 1981 Sharpless et al.[1] reported that geranyl acetate (**1**) and neryl acetate (**13**) (Scheme 1), two isomeric 1,5-dienes, underwent 'abnormal' oxidation by the $RuCl_3{\cdot}(H_2O)_n$ (2.2%)/$NaIO_4$ (3.1 equiv.) system in the biphasic solvent mixture $CCl_4/CH_3CN/H_2O$ (2:2:3) (0°C, 15 min) in that oxidative cyclisation products, namely a mixture of *cis*- and *trans*-2,5-bis(hydroxymethyl)tetrahydrofuranyldiols (*cis*- and *trans*-THF diols, **2**/**14** and **3**/**15**, respectively, ca. 3:1) were obtained in place of the expected double bond scission products. This reaction was similar to that promoted by $KMnO_4$ ($KMnO_4$, acetone/$H_2O$ 9:1, $CO_2$, −10/−30°C) with the same substrates, mostly studied by Klein and Rojahn,[2a] and Walba et al.[2b,2c] who tested the reactivity of some representative 1,5-dienes.

As for the stereochemical outcome of the two processes, the four newly created stereogenic centres [C*(*O*H)-C*(*O*-THF ring)C*-C*(*O*H)] are formed by the *cis*-addition of two oxygen atoms across both double bonds of the diene through two successive stereospecific steps.[3] In addition, for the $MnO_4^-$-promoted process, the THF-forming step proceeds with a high stereocontrol providing solely the *cis*-THF isomer. For the $RuO_4$-catalysed process the degree of stereocontrol for this step is less, since a mixture of *cis*- and *trans*-THF diols is obtained. In addition, a minor, but not negligible, amount of a *cis*-THF 2-keto-derivative (18% for both **1** and **13**) was also obtained from the $RuO_4$-induced process. Due to the above drawbacks, little attention has been paid to this process and, to our knowledge, it has found no synthetic application. On the contrary, the $MnO_4^-$-involving process has received much consideration from synthetic chemists having been introduced as a key-step in some complex synthetic sequences.[4]

More recently our group has discovered that the oxidative cyclisation of dienes **1** and **13** to *cis*-THF diols can also be accomplished by using the related oxide $OsO_4$ in catalytic amounts and $NaIO_4$ as co-oxidant in DMF.[5] As for the stereochemistry of the produced THF ring, this process is equivalent to that mediated by $MnO_4^-$ since it furnishes the *cis*-THF diol product.

In this communication, we report an improved procedure for the $RuO_4$-catalysed oxidative cyclisation of 1,5-dienes based on the geraniol carbon skeleton, to the corresponding *cis*-THF diols; the results obtained are compared with those from the related $MnO_4^-$-induced process. Our attention was primarily focused on dienes based on geraniol- or nerol-type carbon skeletons since a preliminary investigation conducted in our group on the $RuO_4$-induced cyclisation of some substituted 1,5-dienes[6] has shown that synthetically useful yields can

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* Corresponding author. Tel.: 39-81-674111; fax: 39-81-674393; e-mail: vinpicci@unina.it

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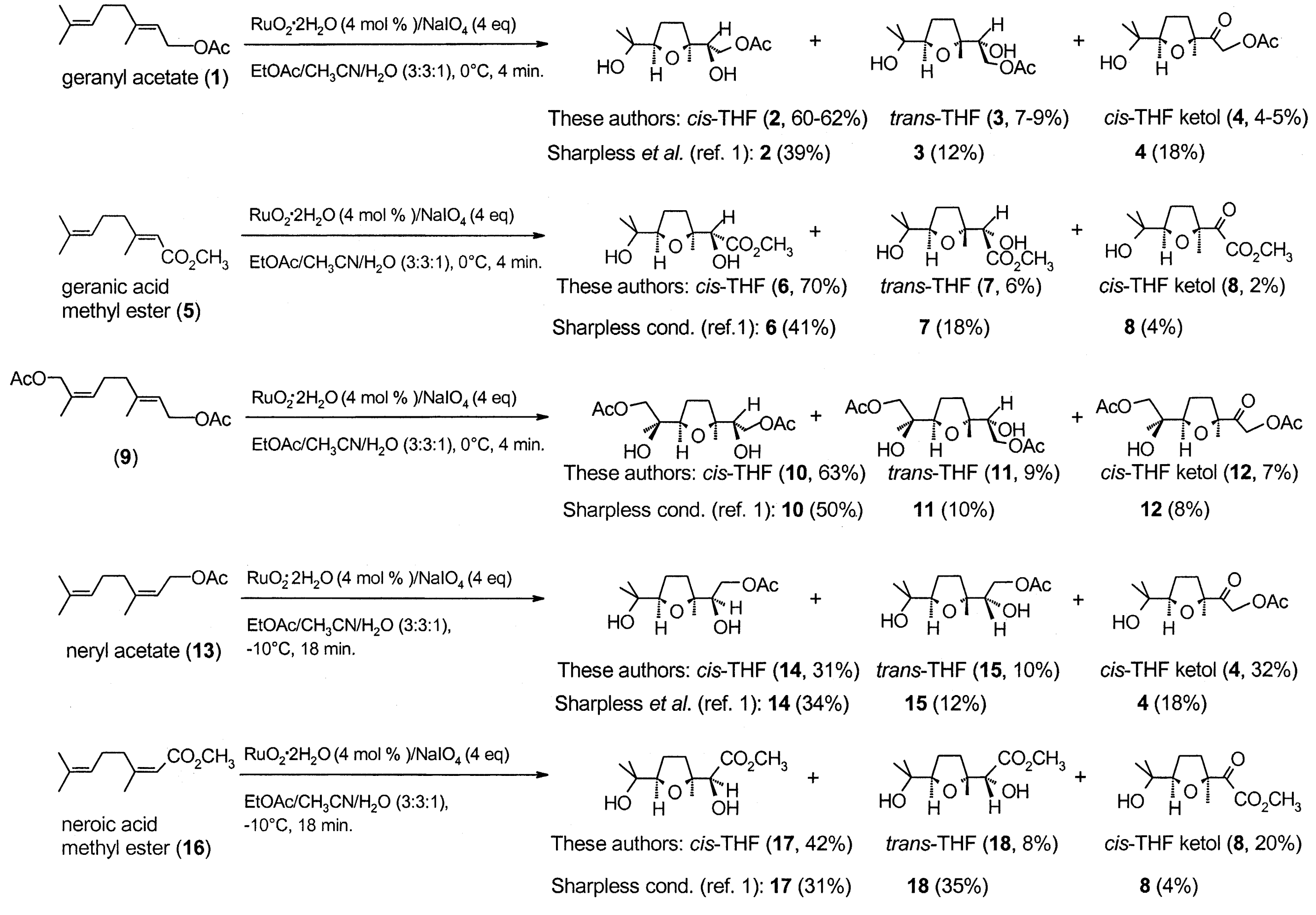


**Scheme 1.**

only be obtained when at least one of the two double bonds of the diene is trisubstituted. This is in line with that observed for the related $MnO_4^-$-mediated process.[2,3] Also relevant to our choice is the fact that the *cis*-2,5-bis(hydroxymethyl)tetrahydrofuranyldiol products derived from the cyclisation of dienes of the above type, or closely related structures, are very often key synthetic sub-targets included in the structure of a variety of naturally occurring metabolites, such as the triterpenes quassiols,[7a] eurilenes,[7b] and teurilene,[7c] ionophores[7d] such as monensin, lonomicin and ionomycin, *Eunicea sp.* cembranoids (uprolides D and E),[7e] or a variety of *Annonaceous* acetogenins,[7f] many of which show interesting biological activities and/or cytotoxic properties.

In particular, when the cyclisation of compounds **1**, **5** and **9**,[8] possessing the geraniol carbon skeleton, was accomplished with $RuO_2 \cdot 2H_2O$ (4%)/$NaIO_4$ (4 equiv.) for a short time (4 min), in the biphasic system EtOAc/$CH_3CN/H_2O$ (3:3:1),[9] an increased yield of the *cis*-THF diol products **2**, **6** and **10** over their *trans*-THF isomers **3**, **7** and **11**, respectively, was observed when compared with the yields obtained under the Sharpless conditions[1] and, furthermore, the C-2 'overoxidised' products (**4**, **8** and **12**) were also obtained in low yields (2–7%) (Scheme 1). The typical procedure is as follows. The diene (1 mmol) was dissolved in a 1:1 $CH_3CN$/EtOAc mixture (6 mL each) followed by addition of $H_2O$ (2 mL). To the rapidly stirred mixture, $NaIO_4$ (855 mg, 4 mmol) and $RuO_2 \cdot 2H_2O$ (5.3 mg, 0.04 mmol) were added in sequence. After 4 min the reaction was quenched by addition of a saturated $Na_2S_2O_3 \cdot 5H_2O$ solution (2–3 mL) until the brown mixture became blue and stirred for a further 1–2 min. Extraction (EtOAc) followed by HPLC purification (hexane/EtOAc 4:6 then $CHCl_3/CH_3OH$ 97:3 for some unresolved fractions) afforded pure samples of all the reaction products.[10]

Scheme 1 shows a comparative picture of the data obtained subjecting dienes **1**, **5**, **9**, **13** and **16**[8] to the above procedure and to the one used by Sharpless et al.[1] It is to be noted that data concerning the $RuO_4$ oxidation of dienes **5**, **9** and **16** under the Sharpless conditions is not available in the literature (Ref. 1 only reports the oxidation of **1** and **13**). Therefore, the data relative to the oxidation of these substrates with the Sharpless procedure have been obtained by us. All the oxidative processes were repeated twice giving reproducible yields. The best yields were obtained with geranic acid methyl ester **5**, which gave the *cis*-THF diol **6** in 70% yield, while geranyl acetate **1** and its 8-acetoxyderivative **9** gave the expected *cis*-THF diols **2** and **10** in 60 and 63% yields, respectively. These results are clear evidence that the presence of electron-withdrawing groups conjugated with, or adjacent to, one of the double bonds of the diene increases the yield of the process. This also seems to be valid under the Sharpless conditions. A similar trend was found by Shing et al. for the 'flash hydroxylation' of alkenes with RuO$_4$.[11] We believe that this point and the possible mechanistic implications are worthy of further studies. Reaction times shorter than 4 min gave incomplete conversion. In particular, if the oxidation of **1** is quenched after 3 min, 20% of the starting material is recovered and the yield derived from the reacted diene increases to 63%.

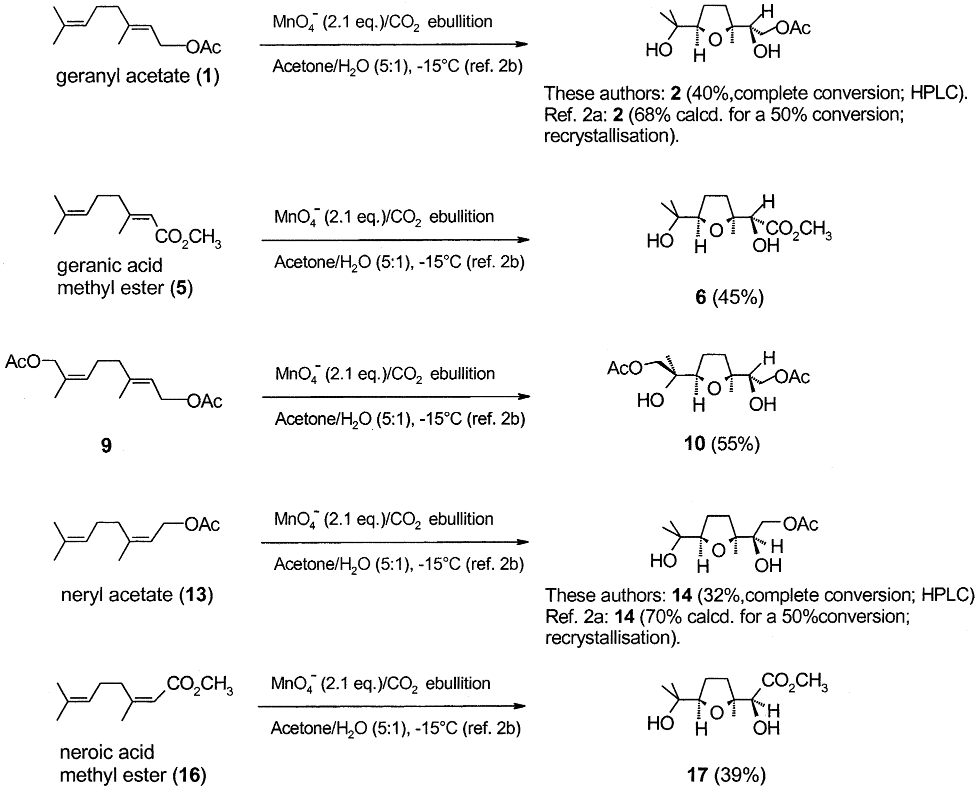
In order to evaluate the preparative utility of the above procedure, the oxidation of **1** with RuO$_4$ was carried out on a 15 mmol scale. Gratifyingly, an even higher yield (62 versus 60% obtained for the 1 mmol scale) of the *cis*-THF diol **2** was obtained.

Interestingly, when the nerol-type substrates neryl acetate (**13**) and neroic acid methyl ester (**16**), the $\Delta^2$ isomers of **1** and **5**, respectively, were oxidised using the above conditions, quite different results were obtained. In particular, the oxidative process was slower in both cases. Oxidation of **13** gave after 4 min at 0°C incomplete conversion (ca. 50%, $^1$H NMR) and the reaction mixture was largely made up of ketol **4**. On the other hand, when the same reaction was carried out at room temperature the reaction was complete within a 3–4 min period, but compound **4** was still obtained as the main product (>50%). A compromise was found at −10°C for 18 min; under these conditions the diene was completely consumed and almost equal amounts of *cis*-THF-diol **14** and ketol **4** were obtained (*cis*-THF **14**: 31%; *trans*-THF **15**: 10%; *cis*-THF ketol **4**: 32%).[10] Thus, under the new conditions no increase in the yield of *cis*-THF-diol **14** was registered with respect to yields from the process using Sharpless conditions and the *cis*-THF product **14** was half the amount obtained with its isomer **1**. Meanwhile, the yield of *cis*-THF ketol **4** was higher and, a comparison with the process involving **1** indicated that the increased stereoselectivity of the process is preserved, being the overall amount of cyclic *cis*-THF products (*cis*-THF-diol **14** plus *cis*-THF ketol **4**) approximately the same (63%=31+32%) as that obtained for diene **1** (66%=62+4%), and is higher than that obtained for the same diene under the Sharpless conditions (52%=34+18%).

Oxidation of the nerol-type diene **16** parallels that of **13** giving a similar distribution of products (*cis*-THF **17**: 42%; *trans*-THF **18**: 8%; ketol **8**: 20%)[10] and a decreased yield of the *cis*-THF diol **17**, compared to its $\Delta^2$-isomer **5** (42 versus 70%), was observed in this case as well. Note that an acceptable 62% (42+20%) yield of *cis*-THF products is obtained for this reaction too.

In principle, a method for overcoming the yield limitation for the *cis*-THF diol, from the process involving **13** and **16**, could be to recycle the *cis*-THF ketol by reintroducing the required chirality at C-2 through a diastereoselective reduction of its (C-2) ketone group. Preliminary reduction of **4** with NaBH$_4$ (EtOH, 15 min, rt) gave, however, only a very modest excess (20%) of the desired diastereomer **14**. Further studies should be carried out to search for suitable reducing agents able to carry out the required transformation.

The different chemical behaviour within the pairs of isomers **1**/**13** and **5**/**16** under the new conditions is in sharp contrast with that shown under Sharpless condi-



These authors: **2** (40%,complete conversion; HPLC).
Ref. 2a: **2** (68% calcd. for a 50% conversion; recrystallisation).

These authors: **14** (32%,complete conversion; HPLC)
Ref. 2a: **14** (70% calcd. for a 50%conversion; recrystallisation).

**Scheme 2.**

tions that, in terms of distribution of reaction products, do not discriminate, or discriminate less (see **5**/**16**) between the two isomers (Scheme 1).

Referring to the effect of conjugation on the yield of the *cis*-THF diol product, it is worth pointing out that within both the pairs **1**(unconjugated)/**5**(conjugated) and **13**(unconjugated)/**16**(conjugated) yields for the process involving the conjugated species are 8–11% higher.

Obtaining higher yields of THF-ketol products in the, *slower*, oxidation of nerol-type dienes suggested that ketols could derive from the initially formed *cis*-THF diols through overoxidation by $RuO_4$. In order to validate this hypothesis, compound **2** was reacted with $RuO_4$ under the above conditions. After 4 min the reaction was quenched, worked-up as above, and analysed by HPLC and $^1H$ NMR. Indeed, 3–4% of ketol **4** was obtained.

It was interesting at this stage to compare the efficiency of the $RuO_4$-catalysed process performed under the above conditions with that of the analogous process promoted by the $MnO_4^-$ ion. To this end, the reaction of dienes **1**, **5**, **9**, **13** and **16** was performed under slightly modified Walba conditions[2b,13] ($KMnO_4$ 2 equiv., $CO_2$ ebullition, acetone/water (5:1)). The results obtained, along with those reported by Klein and Rojahn[2a,14] for **1** and **13**, are shown in Scheme 2. Yields of *cis*-THF-diols from geraniol derivatives fall in the range 40–55% and are lower than those obtained by the $RuO_4$ oxidation. On the contrary, the two processes gave very similar yields for the nerol-type dienes **13** and **16**. Also note that by performing the reaction under the Klein and Rojahn's conditions an appealing 68–70% yield is obtained at a 50% conversion. However, it is fair to say that three recycle steps would have to be carried out to reach a yield (60%) for the *cis*-THF diol **2**, comparable with that (60–62%) obtained in one-step from the oxidation with $RuO_4$.

Some other similarities between the two processes should be pointed out. In particular, the yield of *cis*-THF diol is affected both by the change of the $\Delta^2$ configuration and by conjugation, for the process with $MnO_4^-$ as well. In fact, within both the pairs **1**/**13** and **5**/**16** the yield of the product obtained from the oxidation of the *Z* (nerol-type) diene is 7–8% less than that obtained for the oxidation of the *E* (geraniol-type) isomer, while within the pairs **1**/**5** and **13**/**16** the yield obtained from the conjugated species is 5–7% higher, just as observed for the $RuO_4$-catalysed process.

Finally, we evaluated the effect of acetonitrile on the process with $RuO_4$, by oxidising diene **5** in the solvent mixture $EtOAc/H_2O$ (3:1) ($CH_3CN$ elimination). The results obtained indicate, as observed by others for related processes involving $RuO_4$,[1,11b] that acetonitrile plays a crucial role in the process. Without $CH_3CN$ the process is slower since at least 10 min are required in order for the reaction to proceed to completion, and a reduction of the overall recovered material, as well as of the *cis*-THF diol yield, is observed (10 min, HPLC: **6** 40%; **7** 17%; **8** 1%).

A speculative rationale explaining the increased yields of *cis*-THF diols **2**, **6** and **10** in the $RuO_4$-catalysed process performed under our conditions could be the following. $CH_3CN$ is miscible with both water and EtOAc and brings all the reacting species into contact in a single phase, thus increasing the rate of the oxidation. For dienes of the geraniol-type, it can be hypothesised that, under the above conditions, cyclisation leading to the *trans*-THF diol isomer and formation of the *cis*-THF ketol by overoxidation at C-2 are both slower processes than the cyclisation leading to the *cis*-THF diol. As for the nerol-type dienes **13** and **16**, the opposite $\Delta^2$ configuration slows the cyclisation processes (for **13** a 50% conversion is observed after 4 min at 0°C). However, for these substrates the overoxidation *cis*-THF diol→*cis*-THF ketol is still fast enough and most of the former is transformed into the latter in the time required for the diene to react.

Along this line of reasoning, it can be speculated that other solvents such as acetone could play a role similar to that of $CH_3CN$. Thus, a mixture EtOAc/acetone/$H_2O$ could also work well. A preliminary experiment conducted on diene **1** in the (one-phase) mixture EtOAc/acetone/$H_2O$ 3:3:1 gave promising results. The reaction was rather clean but only a conversion of ca. 30–40% was observed after 4 min. Further work is in progress to test this three-solvent mixture by tuning the reaction conditions.

In conclusion, it appears that the above described conditions for the $RuO_4$-catalysed oxidative cyclisation of 1,5-dienes of geraniol-type to *cis*-THF diols are more advantageous in terms of time and yields than those previously reported for the same oxidant and for the process involving $MnO_4^-$. It is likely that the above procedure will find future synthetic applications.[15] Future work from our group will be aimed at rendering the above process diastereoselective through derivatisation of 1,5-dienes with suitable chiral auxiliaries,[16,2c] and at exploring the utility of the above procedure by its application to selected synthetic targets. In addition, other conditions will be tested to increase the yields for the less effective oxidation of nerol-type dienes.

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8. All chemicals were purchased from Aldrich. Compounds **1** and **13** were further purified by HPLC. Diene **9** was obtained by acetylation of *trans*,*trans*-2,6-dimethyl-2,6-octadiene-1,8-diol. Pure samples of geranic and neroic acid methyl esters (**13** and **16**) were obtained by methylation ($CH_2N_2$) of the commercially available mixture of the acids followed by HPLC separation.
9. These conditions have recently been shown to also induce the oxidative cyclisation of 1,6-dienes to *trans*-2,6-bis-(hydroxymethyl)tetrahydropyranyldiols: Piccialli, V. *Tetrahedron Lett.* **2000**, *41*, 3731–3733.
10. All the isolated substances gave satisfactory spectral data. The stereochemistry of the hitherto unknown compounds **6**, **7**, **17** and **18** was proven by correlation with known **2**, **3**, **14** and **15**, respectively. In particular, LAH reduction (0°C, 15 min) of the former compounds followed by acetylation ($Ac_2O$/py, rt, 16 h; 70–80% for two steps) afforded substances identical to those obtained from the latter by acetylation. That compound **10** was the expected *cis*-THF diol derived from the oxidation of **9**, was inferred by obtaining the same substance as the major reaction product from the oxidation of **9** with $KMnO_4$ (Scheme 2), having in mind that the $MnO_4^-$-involving process only produces *cis*-THF diols. Compound **11** had spectral properties (MS, $^1H$ and $^{13}C$ NMR) strictly similar to those exhibited by its isomer **10**. Definitive proof of its structure was provided by its correlation with both **3** and **10**. In particular, acetylation of **11** ($Ac_2O$/py, 16 h) followed by treatment with $RuCl_3\cdot(H_2O)_n/NaIO_4$ under the Sharpless conditions,[1] afforded a five-membered lactone product (C(6)=O), derived from the oxidative fission of the C6–C7 bond,[12] that was identical to the product obtained subjecting either *trans*-THF diols **13** and **10** to the same transformations. The structure of ketol **8** was proven by oxidation (C(2)–OH→C(2)=O) of *cis*-THF **17** with $TPAP_{(cat.)}/NMO$ in $CH_2Cl_2$ that provided a substance identical to **8**.
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12. A similar correlation procedure is reported in the supplementary material to Ref. 1.
13. Walba et al.[2b] used a 9:1 acetone–water mixture. We have observed that no significant change in time and yields is observed by using a 5:1 acetone–water mixture.
14. These authors originally used a $CO_2$ stream and 1.5 equiv. of $KMnO_4$. Later, Walba et al.[2b,2c] used $CO_2$ at ebullition and 2 equiv. of the oxidant. Less than 2 equiv. of oxidant give incomplete conversion.
15. Related chemistry with $OsO_4$ has been recently developed by others: Donohoe, T. J.; Winter, J. J. G.; Helliwell, M.; Stemp, G. *Tetrahedron Lett.* **2001**, *42*, 971–974. This work reports three examples of cyclisation of 1,5-dienes including one or both disubstituted double bonds in interesting synthetic yields.
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