Pergamon

Tetrahedron Letters 42 (2001) 7741–7745

TETRAHEDRON LETTERS

# Oxidative cyclization of 1,4-dienes to yield 2,3,5-trisubstituted tetrahydrofuran-diols

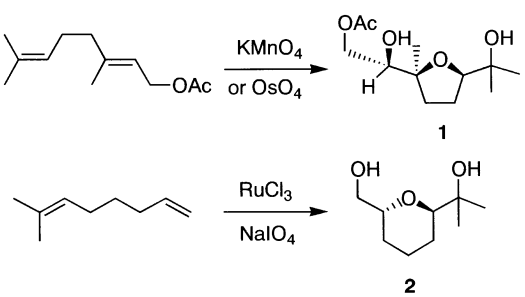
Benjamin Travis and Babak Borhan*

*Department of Chemistry, Michigan State University, East Lansing, MI 48824, USA*

Received 25 May 2001; revised 27 August 2001; accepted 29 August 2001

**Abstract**—$KMnO_4$ and $OsO_4$ catalyze the oxidative cyclization of 1,4-dienes to provide 2,3,5-trisubstituted tetrahydrofuran-diols in 30% yield. This reaction proceeds stereoselectively via a proposed [3+2] cycloaddition. Competing oxidative pathways are the major non-productive processes that reduce the yield of the reaction; however, four stereogenic centers are established in one-step.

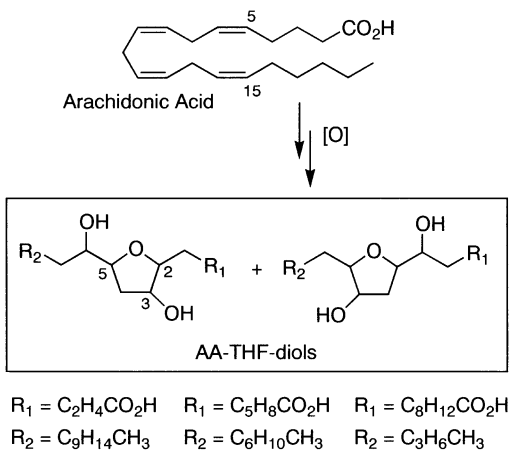

The development of methodologies to prepare substituted tetrahydrofurans (THFs) stereoselectively has become an area of great interest due to the increasing reports of their biological activity in areas such as polyether antibiotics and *Annonaceous* acetogenins.[1,2] An intriguing approach for the synthesis of these types of molecules is the oxidative cyclization of 1,5-dienes to prepare 2,5-disubstituted THF ring **1** (Scheme 1). This 1,5-diene oxidative cyclization has been reported with $KMnO_4$[3–6] or $OsO_4$[7–9] as oxidants and is believed to proceed through a [3+2] cycloaddition. The reaction generally provides the desired THF products in 40–60% yield with excellent stereoselectivity. A similar methodology has recently been reported for 1,6-dienes[10] in which $RuCl_3$ mediated oxidation stereoselectively prepares 2,6-disubstituted tetrahydropyran-diols such as **2** (Scheme 1).




**Scheme 1.** Oxidative cyclization of 1,5- and 1,6-diene reactions.

We are interested in studying the biological significance of 2,3,5-trisubstituted tetrahydrofuran-diols (THF-diols) derived from the oxidative metabolism of arachidonic acid (Scheme 2).[11] This has led us to investigate the feasibility of securing these structural motifs by the oxidative cyclization of 1,4-dienes. Herein, we report the results of subjecting 1,4-dienes to various oxidative conditions in an attempt to access 2,3,5-trisubstituted THF-diols.

Initial experiments began with the oxidative cyclization of methyl linoleate (**3**), using $KMnO_4$ in aqueous ace-




**Scheme 2.** 2,3,5-Trisubstituted THF-diols derived from arachidonic acid.

*Keywords*: oxidative cyclization; $OsO_4$; 1,4-dienes; 2,3,5-trisubstituted THF-diols; Oxone®.

* Corresponding author. Tel.: 517-355-9715x138; fax: 517-353-1793; e-mail: borhan@cem.msu.edu

0040-4039/01/$ - see front matter 
PII: S0040-4039(01)01609-4

tone. This provided the desired 2,3,5-trisubstituted THF-diols (**4** and **5**) as a 1:1 regioisomeric mixture in a very modest 20% yield (Table 1). Analysis of $^{1}H$, $^{13}C$, HMQC, and COSY NMR identified the products as **4** and **5**,[12] and the peracetylated compounds **4a** and **5a**[13] allowed the relative ring stereochemistry to be defined as 2-*trans*-3,5-*cis*. Similar to other 2,3,5-trisubstituted THF-diol stereoisomers obtained from linoleic acid oxidation and cyclization reported previously, these compounds were also inseparable using standard chromatographic techniques.[14] Attempts to increase the yield in this system were unsuccessful on all fronts including both acidic and basic conditions, and using different solvents.

Attempts to cyclize **3** with catalytic $OsO_4$ and $NaIO_4$ did provide **4** and **5**, but again in only 20% yield. Oxidative cyclization with catalytic $RuCl_3$ and $NaIO_4$ was also an inefficient process,[10] only providing a 12% yield of **4** and **5** (Table 1).

As expected, we found 1,2-diols (**6**) or tetraols (**7**) in the crude reaction mixture. These alcoholic byproducts could have come from a competitive hydrolytic pathway of the intervening osmate ester. Aldehydes (**8**) were also found in both $KMnO_4$ and $NaIO_4$ reactions. These reagents are known to oxidatively cleave compounds such as **6** to yield the aldehydic products.[15,16]

In an attempt to hinder the hydrolysis of the intermediate osmate ester, numerous anhydrous solvents were used with $OsO_4$ and different co-oxidants. With only a few exceptions, compounds **4** and **5** were formed to no appreciable degree. To summarize these results, using standard conditions (**3**, $NaIO_4$, $OsO_4$ 1:4:0.05), no product was observed with $CH_2Cl_2$, toluene, ethyl acetate, diethyl ether, *t*BuOH, and hexanes. In all cases starting material was recovered with trace amounts of diols also being produced. THF and acetonitrile, respectively, yielded 8 and 10% of the desired products **4** and **5**. Notably, DMF provided compounds **4** and **5** in an improved yield of 30%. It is possible that with the more polar solvents such as acetonitrile, THF, and DMF there is a charge stabilizing effect if the mechanism involves a charged species (Scheme 4). The higher yield could also be due to better solvation of the reagents in more polar solvents.

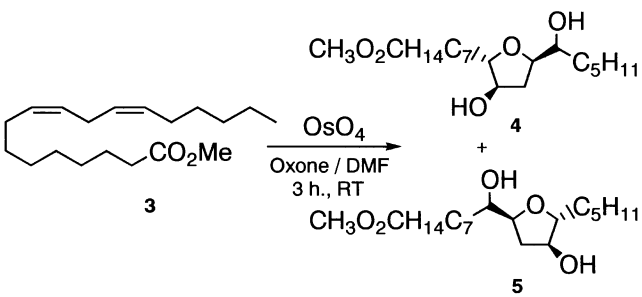
Attempts to vary the co-oxidant (Table 2) showed that only a few of these provided the desired compound in greater than 10% yield. Primarily, the products obtained were diols and/or aldehydes. The co-oxidants that did yield product were $KClO_3$, 2-iodoxybenzoic acid (IBX), $KIO_4$, and Oxone®.

Interestingly, Oxone®, a mono potassium peroxysulfate salt, was unique not only because it did provide a 20% yield, which was comparable to the initial $KMnO_4$ and $OsO_4/NaIO_4$ systems, but also this reaction had fewer number of byproducts making the work-up more facile. With DMF as the solvent, Oxone® based reactions also yielded 30% of the desired oxidatively cyclized product.

Lowering the temperature in hopes of reducing the rates of competing reactions and to increase the yield of the desired products **4** and **5** did not result in any improvements. Experiments at both 0 and –40°C actually lowered the yield of **4** and **5** providing 20 and 12%, respectively. Elevating the temperature to 50°C was also ineffective and lowered the yield to 13%. The rate of addition of the co-oxidant was also varied from the standard one portion addition. This was achieved by dissolving the co-oxidant in an appropriate solvent and slowly adding the solution via syringe pump over the course of 10 h. These attempts had absolutely no effect on the yield of the isolated product which remained at 20%.

While the results of our optimization studies did not increase the isolated yield, we still find this to be an intriguing reaction since it sets four stereocenters in a simple one pot reaction. This prompted us to see if the reaction was scaleable. Using our best reaction conditions for the oxidative cyclization, i.e. Oxone® (4 equiv.) and $OsO_4$ (0.05 equiv., 2.5% in *t*BuOH) in DMF (0.1 M), we scaled the reaction up to 5 mmol (1.5 g) of **3**. This did indeed provide **4** and **5** in 30% yield.[17] Detailed analysis of the reaction byproducts showed no diol or aldehyde products. Instead this reaction

**Table 1.** Oxidative cyclization of **3** to **4** and **5**




| Oxidant (equiv.) | Co-oxidant | Solvent | Yield (%) |
|---|---|---|---|
| $KMnO_4$ (6) | – | Acetone/$H_2O$ | 20 |
| $OsO_4$ (0.05) | $NaIO_4$ | Acetone/$H_2O$ | 20 |
| $RuCl_3$ (0.05) | $NaIO_4$ | EtOAc/ACN/$H_2O$ | 12 |

**Table 2.** Co-oxidant effects on the cyclization of **3**[a]

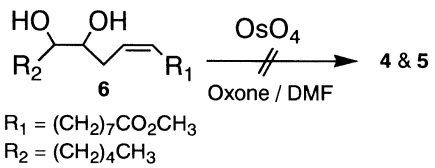
| Co-oxidant | Yield (**4** and **5**) (%) | Co-oxidant | Yield (**4** and **5**) (%) |
|---|---|---|---|
| NMO | 0[b] | IBX | 5[b] |
| $KIO_3$ | 0[b] | $KClO_3$ | 8[b] |
| *t*-BuOOH | 0[b] | Oxone® | 20[d] |
| $H_2O_2$ | 0[c] | $KIO_4$ | 20[b] |
| DMP | 0[c] | Oxone® | 30[e] |

[a] All reactions were performed using $OsO_4$ (0.1 equiv., 4% in $H_2O$) with co-oxidant (4 equiv.) in aqueous acetone.
[b] 1,2-Diol products were observed.
[c] Products were not identifiable.
[d] C9 and C7 carboxylic acid products were observed.
[e] DMF was the solvent.

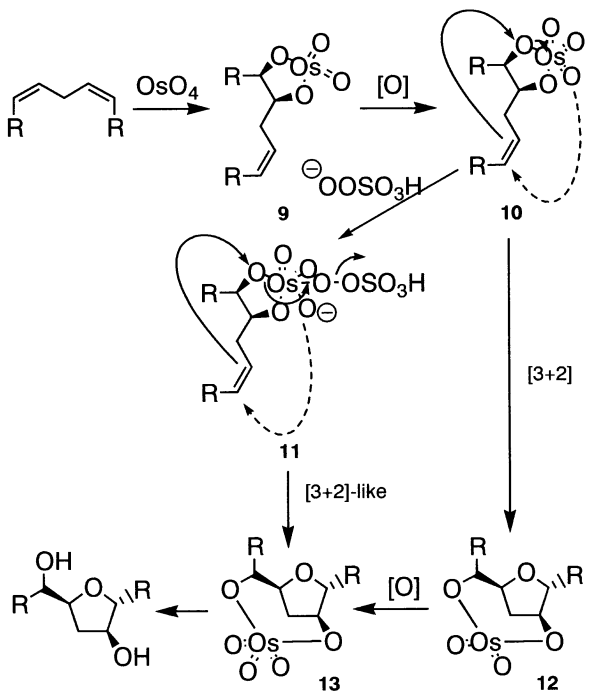
revealed only the formation of carboxylic acids from oxidatively cleaved olefins.

We believe that the carboxylic acid byproducts formed in our reactions are produced via an $OsO_4$ assisted cleavage of the olefins to aldehydes. The aldehydes are then further oxidized with Oxone® independently to carboxylic acids.[18,19] This competition occurs with comparable rates to that of the oxidative cyclization of 1,4-dienes. Further work in this area is forthcoming.

Walba[20] has reported a similar method of oxidative cyclization using a Cr(VI) compound to prepare 2,5-disubstituted THF rings from 5,6-dihydroxyalkenes. We thought that diol **6** might be a possible intermediate so it was independently synthesized from the corresponding mono epoxide. While Walba's mechanism with Cr(VI) might be an alternative explanation for the observed cyclization in our systems, treatment of **6** with conditions that yield oxidative cyclization did not produce any THF-diol product. This suggests that the diol is not involved as a possible reaction intermediate (Scheme 3).




**Scheme 3.**




**Scheme 4.** Proposed mechanistic pathways for the 1,4-diene oxidative cyclization.

Analysis of our results shows a scaleable reaction with both a solvent and temperature dependence. These insights made us reevaluate the conventional [3+2] cycloaddition mechanistic viewpoint.

Piccialli and co-workers propose a concerted [3+2] cycloaddition to form the THF core which is consistent with the observed relative stereochemistry of both 1,5-dienes reported previously,[8] and the 1,4-diene reported here (Scheme 4). The first step involves formation of an osmate ester **9**, followed by oxidation to the osmate **10**. It is postulated that this intermediate undergoes a [3+2] cycloaddition to yield **12**, followed again by oxidation of the osmate ester. Finally, hydrolysis of the osmium complex **13** yields the cyclized product and regenerates $OsO_4$. An alternate mechanism where intermediate **10** is further activated by the co-oxidant Oxone® is also plausible (Scheme 4). Compound **11** can undergo a [3+2]-like cycloaddition in which the last step is the expulsion of bisulfate. The intermediacy of **11** may be responsible for the apparent solvent dependence of the reaction.

Alternatively, a [2+2] cycloaddition of $OsO_4$ followed by a second [2+2] intramolecular cycloaddition of the osmaoxetane with the remaining olefin can be envisioned. The putative bis-osmaoxetane can rearrange to yield intermediate **12**, as first described by Walba and co-workers.[21,22] Although the [2+2] mechanism is plausible,[23] recent experimental and theoretical calculations by Houk, Sharpless, and Singleton favor the [3+2] cycloaddition of $OsO_4$ to olefins, and find that the [2+2] formation of the osmaoxetane and the subsequent ring expansion are prohibitively high energy processes ($\sim$42 kcal/mol and $\sim$30 kcal/mol, respectively).[24]

Fig. 1 illustrates a three-dimensional representation of the two reactive intermediates obtained from 1,5-diene (**14**) and 1,4-diene (**10**). The approach of the olefinic carbon to the osmate ester oxygen which will eventually become the THF ring oxygen is hindered by the neighboring alkyl group. This is not the case with the 1,5-diene in which the neighboring group is a methylene and does not pose a bulky presence. In the 1,5-diene case there is good overlap between the olefin and both oxygen atoms that are incorporated into the 2,5-THF-

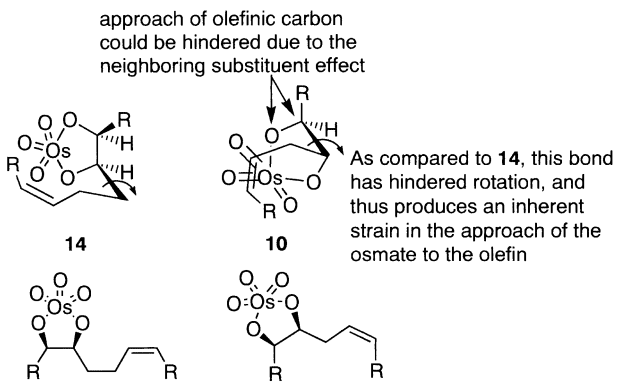
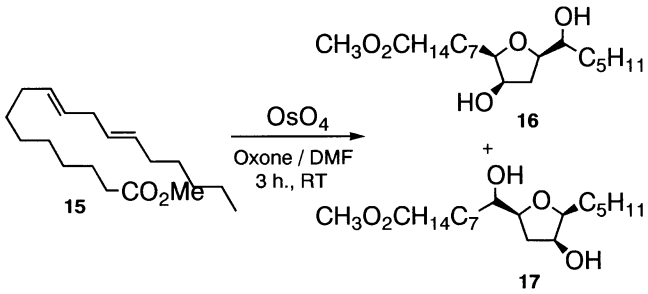



**Figure 1.** Standard and 3-D projections of reactive intermediates **14** and **10**.




**Scheme 5.**

diol product. However, the strain of the 1,4-diene (**10**) hinders the approach of the olefinic carbon towards the osmate ester oxygen, and thus could prevent a good overlap of the atoms participating in the cycloaddition (Fig. 1). The relatively hindered approach and overcoming steric congestion in the case of 1,4-dienes could very well be the cause for the reaction to proceed, but only in modest yields.

Based on the aforementioned [3+2] cycloaddition pathway, and the observed stereoselectivity in the oxidative cyclization of **3** we predicted that under the same reaction conditions *trans*-methyl lineolate, **15**, would produce **16** and **17** with an all *cis* relative stereochemistry. This reaction did unambiguously provided the known all-*cis* THF-diol **16** and **17**[14] in a comparable 30% yield (Scheme 5).

In summary, the oxidative cyclization of 1,4-dienes is a feasible reaction and proceeds stereoselectively through a predictable [3+2] cycloaddition. Currently, only a 30% yield has been obtained which has been attributed to the strain of proposed intermediate **10**, and the competing oxidative pathways, notably, the oxidative cleavage of the olefins and the hydroxylations yielding diols and tetraols. The reaction is amenable to scale up with the oxidative cyclization of **3** (1.5 g, 5 mmol) providing a 30% yield of **4** and **5**. Efforts to further increase the yield and induce chirality are ongoing.

## Acknowledgements

Generous support was provided in part by Michigan State University Startup funds to B.B. and a grant from the Michigan Economic Development Corporation (GR-183). The authors wish to thank Professors Rob Maleczka and Ned Jackson for helpful discussions.

## References

1. Dutton, C. J.; Banks, B. J.; Cooper, C. B. *Nat. Prod. Rep.* **1995**, 165–181.
2. Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, 275–306.
3. (a) Baldwin, J. E.; Crossley, M. J.; Lehtonen, E. M. *J. Chem. Soc., Chem. Commun.* **1979**, 918–920; (b) Hammock, B. D.; Gill, S. S.; Casida, J. E. *J. Agric. Food Chem.* **1974**, *22*, 379–385.
4. Wolfe, S.; Ingold, C. F. *J. Am. Chem. Soc.* **1981**, *103*, 940–941.
5. Klein, E.; Rojhan, W. *Tetrahedron* **1965**, *21*, 2353–2358.
6. Walba, D. M.; Przybyla, C. A.; Walker, C. B. *J. Am. Chem. Soc.* **1990**, *112*, 5624–5625.
7. Champdore, M. de; Lasalvia, M.; Piccialli, V. *Tetrahedron Lett.* **1998**, *39*, 9781–9784.
8. Brown, R. C. D.; Hughes, R. M.; Keily, J.; Kenney, A. *J. Chem. Soc., Chem. Commun.* **2000**, 1735–1736.
9. Donohoe, T. J.; Winter, J. J. G.; Helliwell, M.; Stemp, G. *Tetrahedron Lett.* **2001**, *42*, 971–974.
10. Piccialli, V. *Tetrahedron Lett.* **2000**, *41*, 3731–3733.
11. Moghaddam, M. F.; Motoba, K.; Borhan, B.; Pinot, F.; Hammock, B. D. *Biochim. Biophys. Acta* **1996**, *1290*, 327–339.
12. Compound **4** and **5**: $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 4.05 (m, 1H), 3.98 (m, 1H), 3.93 (m, 1H), 3.78 (m, 1H), 3.63 (s, 3H), 2.26 (t, 2H, $J=7.4$ Hz), 2.21–2.12 (m, 1H), 1.83 (bd, 1H, $J=3.9$ Hz), 1.59–1.22 (b, 20H), 0.85 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ 174.2, 87.3, 80.2, 74.5, 71.9, 51.3, 33.9, 33.3, 32.9, 32.6, 31.6, 29.2, 29.0, 28.9, 25.8, 25.6, 24.7, 22.4, 13.9. HRMS (CI) calcd for $C_{19}H_{36}O_5$: 345.2641 $m/z$ (M+H). Observed: 345.2638 $m/z$.
13. Compound **4a** and **5a**: $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 4.99–4.95 (m, 1H), 4.88–4.85 (m, 1H), 3.98–3.89 (m, 2H), 3.63 (s, 3H), 2.36–2.23 (m, 1H and t, 2H, $J=7.5$ Hz), 2.02 (s, 6H), 1.82–1.80 (m, 1H), 1.79–1.25 (b, 20H), 0.84 (t, 3H, $J=1$ Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ 174.2, 170.8, 170.5, 83.3, 78.1, 77.8, 74.6, 51.4, 33.9, 33.4, 32.7, 31.6, 30.9, 29.2, 29.0, 28.9, 25.4, 25.2, 25.0, 24.8, 22.4, 21.1, 13.9. HRMS (CI) calcd for $C_{23}H_{40}O_7$: 429.2844 $m/z$ (M+H). Observed: 429.2849 $m/z$.
14. Borhan, B.; Nourooz-Zadeh, J.; Uematsu, T.; Hammock, B. D.; Kurth, M. J. *Tetrahedron* **1993**, *49*, 2601–2612.
15. Cainelli, G.; Contento, M.; Manescalchi, F.; Plessi, L. *J. Chem. Soc., Chem. Commun.* **1989**, 47–50.
16. Viski, P.; Szeverenyi, V.; Simandi, L. I. *J. Org. Chem.* **1986**, *51*, 3213–3214.
17. General procedure for oxidative cyclization: **3** (1.5 g, 5.01 mmol, 1 equiv.) was dissolved in DMF (50 mL). $OsO_4$ (2.5% in *t*BuOH, 0.0085 mmol, 0.05 equiv.) was added and stirred for 5 min. Oxone® (20.0 mmol, 4 equiv.) was added in one portion and stirred for an additional 3 h. The reaction was quenched with $Na_2SO_3$ (9 g) and stirred for a further 1 h. The reaction was diluted with EtOAc (150 mL) and filtered through Celite to remove the salts. The filter cake was rinsed with EtOAc (3×25 mL). The combined organics were washed with $H_2O$ (2×200 mL), 1N HCl (1×200 mL) and brine (1×200 mL). The organic layer was dried over anhydrous $Na_2SO_4$, filtered and evaporated under reduced pressure to provide a crude brown oil. Silica gel flash chromatography (30% EtOAc/Hexanes) provided products **4** and **5** (535 mg) in 30% yield as a clear colorless oil.

18. Webb, K. S.; Ruszkay, S. J. *Tetrahedron* **1998**, *54*, 401–410.
19. Bausmark, A. L.; Beeson, M.; Vasquez, P. C. *Tetrahedron Lett*. **1989**, *30*, 5567–5570.
20. Walba, D. M.; Stoudt, G. S. *Terahedron. Lett*. **1982**, *23*, 727–730.
21. Walba, D. M.; Wand, M. D.; Wilkes, M. C. *J. Am. Chem. Soc*. **1979**, *101*, 4396–4397.
22. Walba, D. M.; DePuy, C. H.; Grabowski, J. J.; Bierbaum, V. M. *Organometallics* **1984**, *3*, 498–499.
23. Gobel, T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl*. **1993**, *32*, 1329–1331.
24. DelMonte, A. J.; Haller, J. H.; Houk, K. N.; Sharpless, K. B.; Singleton, D. A.; Strassner, T.; Thomas, A. A. *J. Am. Chem. Soc*. **1997**, *119*, 9907–9908.