Reactions of 1,5-Dienes with Ruthenium Tetraoxide: Stereoselective Synthesis of Tetrahydrofurandiols[‡]

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An improved procedure for the ruthenium tetraoxide catalysed oxidation of 1,5-dienes, employing 0.05 equiv. of the catalyst $RuO_2 \cdot 2H_2O$, 2.5 equiv. of $NaIO_4$ as a stoichiometric oxidant, and a biphasic solvent system of AcOEt/$(CH_3)_2CO$/H_2O (2:1:1, v/v/v), is presented. Reactions of 1,5-dienes **1**, **3**, and **5** furnished the new *cis*-tetrahydrofuran products **2**, **4**, **6**, and **7** with total stereospecificity. The structures of the products have been established on the basis of NMR and MS data, as well as chemical evidence. Application of this procedure to geranyl acetate (**8**) and neryl acetate (**12**) afforded the *cis*-tetrahydrofuran derivatives **9**, **10**, and **13** in high yields, accompanied by small amounts of *trans*-tetrahydrofurandiols **11** and **14**. These products are the same as those obtained by Sharpless et al. upon RuO_4-catalysed oxidation of **8** and **12** in the biphasic solvent system $CCl_4/CH_3CN/H_2O$ (2:2:3, v/v/v), but our procedure has the advantages of higher stereospecificity, a greater material recovery (about 90%), and a more simple work-up. The oxidation of 1,5-dienes proceeds stereoselectively by *syn* oxygen addition to both double bonds. The formation of tetrahydrofuran derivatives is presumed to involve initial addition of RuO_4 to one double bond of the 1,5-diene to give a ruthenium(VI) diester, which subsequently undergoes conversion into the cyclic ether with participation of the second double bond.

Introduction

The use of ruthenium tetraoxide as an organic oxidant was first reported in 1953 by Djerassi and Engle.[1] Since then, it has been used in both stoichiometric and catalytic procedures for a variety of oxidative transformations.[2−6] The oxidation of alkenes with ruthenium tetraoxide has been reported to give only scission products, i.e. ketones, aldehydes, or carboxylic acids.[7] An improved procedure for the cleavage of alkenes and for some organic functional group oxidations using a catalytic amount of RuO_4 and a stoichiometric amount of sodium metaperiodate in the biphasic solvent system $CCl_4/CH_3CN/H_2O$ (2:2:3, v/v/v) was reported in 1981 by the Sharpless group.[8] In this work, it was reported that reactions of the 1,5-dienes geranyl acetate and neryl acetate with RuO_4 gave products containing a tetrahydrofuran moiety that were formed by *cis* oxygenation of both double bonds,[8] the reactions being analogous to the permanganate oxidations of these substrates reported in 1965 by Klein and Rojahn.[9] The 2,5-disubstituted tetrahydrofuran moiety is a structural motif that is commonly encountered in polyoxygenated natural products.[10−12] Permanganate oxidation of 1,5-dienes represents a simple procedure for the preparation of heterocyclic systems containing oxygen and has been employed in the synthesis of tetrahydrofuran moieties in molecules of biological interest such as the polyether antibiotics monensin[13,14] and ionomycin.[13,15]

Previously, we have reported that oxidation of a number of monoene steroids,[16] conjugated diene steroids,[17] and alkenes[18] with RuO_4 leads almost exclusively to 1,2-diols and/or α-hydroxy ketones. Interestingly, some steroidal 1,3-dienes having double bonds located in a hindered position furnished mainly epoxy diols and epoxy ketols upon treatment with RuO_4.[17,19] Furthermore, we have recently demonstrated that these reactions proceed through ruthenium(VI) diesters.[20−22] In order to explore the generality of the reaction of 1,5-dienes with RuO_4, to find the optimal reaction conditions, and to shed light on the mechanism of the reaction, we have subjected some 1,5-dienes to RuO_4-catalysed cyclization.

Results and Discussion

Treatment of 2,5-dimethyl-1,5-hexadiene (**1**, Scheme 1) with $RuO_2/NaIO_4$ in a biphasic solvent system of ethyl acetate, acetone, and water (2:1:1, v/v/v) at room temperature gave tetrahydrofurandiol **2** in 50% yield. The HR FABMS of compound **2** showed an MH^+ ion peak at m/z = 161.1196, corresponding to the molecular formula $C_8H_{16}O_3$. Analysis of HR FABMS and ^{13}C NMR spectroscopic data showed **2** to be a cyclic symmetric molecule derived from *cis* oxygenation of both double bonds, with a plane of symmetry bisecting the C-3/C-4 bond. Specifically, the ^{13}C NMR spectrum of **2** showed only four signals at δ = 25.4 (2-CH_3 and 5-CH_3), 34.0 (C-3 and C-4), 69.1 (2-HO*C*H_2 and 5-HO*C*H_2) and 84.3 (C-2 and C-5), the latter being a typical chemical shift value for C-2 and/or C-5 tetrahydrofuran carbon atoms.[11] The ^1H NMR spectrum confirmed the symmetry of the molecule showing a single proton signal for the two methyl groups at δ = 1.18 (s, 6

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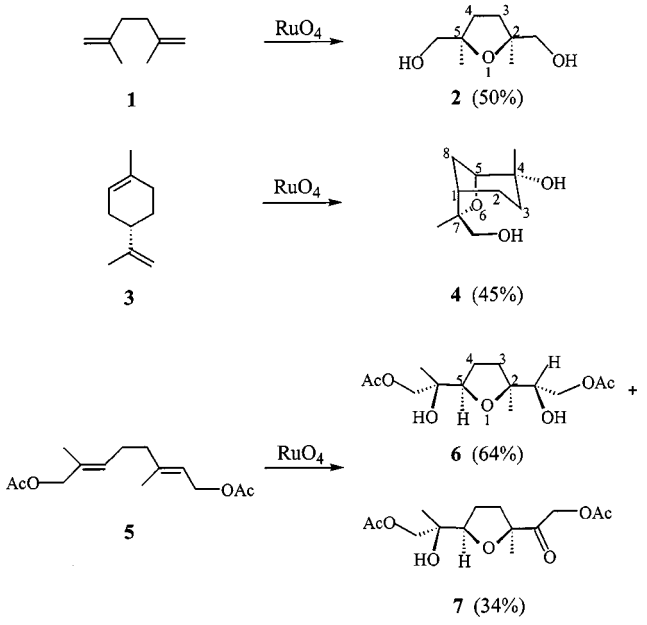


Scheme 1. Reactions were performed at 25 °C using 0.05 equiv. of the catalyst $RuO_2{\cdot}2H_2O$ and 2.5 equiv. of $NaIO_4$ as a stoichiometric oxidant in a biphasic solvent system of AcOEt/$(CH_3)_2CO$/H_2O (2:1:1, v/v/v) and were allowed to proceed for a few minutes

H, 2-CH_3 and 5-CH_3) and only one AB system centred at δ = 3.46 (J = 11.1 Hz) for the two CH_2OH groups. As a final confirmation of the structure, treatment of **2** with Ac_2O/pyridine (1:2, v/v) gave the expected diacetylated product.

Oxidation of (4*S*)-isopropenyl-1-methylcyclohexene [(*S*)-(−)-limonene] (**3**) with the system $RuO_2/NaIO_4$ as described for **1** afforded a 45% yield of **4** along with cleavage products (about 50% yield). Combined HR FABMS (MH^+ ion peak at m/z = 187.1313) and ^{13}C NMR spectroscopic analyses of **4** indicated a molecular formula of $C_{10}H_{18}O_3$, showing it to be a bicyclic compound. Two of the oxygen atoms in this formula are present in OH groups, whereas the third must be incorporated in a tetrahydrofuran ring, as indicated by the unsaturation count and by inspection of the ^{13}C NMR spectrum, which showed signals at δ = 84.8 and 84.3 compatible with the presence of an ethereal bridge in the molecule.[11] DEPT and ^{13}C NMR spectra of **4** showed resonances arising from one CHO methine group at δ = 84.8 (C-5), one CH_2O methylene group at δ = 65.8 (7-CH_2OH), and two quaternary carbon atoms at δ = 84.3 (C-7) and 72.5 (C-4). Furthermore, the AB system centred at δ = 3.78 (J = 11.4 Hz) and the doublet at δ = 3.94 (J = 6.6 Hz) in the ^1H NMR spectrum of **4** confirmed the presence of CH_2O and CHO groups in the molecule, while the shift of the sole AB system from δ = 3.78 in **4** to δ = 4.29 in its acetylated derivative supported the presence of CH_2OH and confirmed the ethereal character of the CHO group. Selective H-H decoupling experiments of **4** and its acetylated derivative revealed the proton connectivities and allowed us to obtain full proton assignments. Specifically, the oxymethine proton signal at δ = 3.94 (5-H) was seen to be correlated with the methylene proton signal at δ = 2.30 (8-H_{eq}), which appears as a dddd showing (a) a geminal coupling (^2J = 12.6 Hz) with the signal at δ = 1.63 attributed to 8-H_{ax}, (b) two vicinal couplings with protons 5-H and 1-H (^3J = 6.6 and 4.4 Hz, respectively), and (c) a W-type coupling (^4J = 2.4 Hz) with 2-H_{eq}. The stereochemistry at the C-4, C-5, and C-7 stereogenic centres was deduced on the basis of the connectivities observed in an NOESY experiment. NOESY cross-peaks between the signals at δ = 1.63 (8-H_{ax}), 1.45 (2-H_{ax}), and 1.15 (4-CH_3) defined (*R*) stereochemistry at C-4. Strong correlations were also detected between the signals at δ = 1.29 (7-CH_3), 2.30 (8-H_{eq}), and 1.96 (1-H), suggesting a mutual *cis* relationship between the relevant protons. This means that the stereochemistry at C-7 is (*R*). This conclusion was also corroborated by Dreiding molecular modelling analysis of the possible cyclization products.

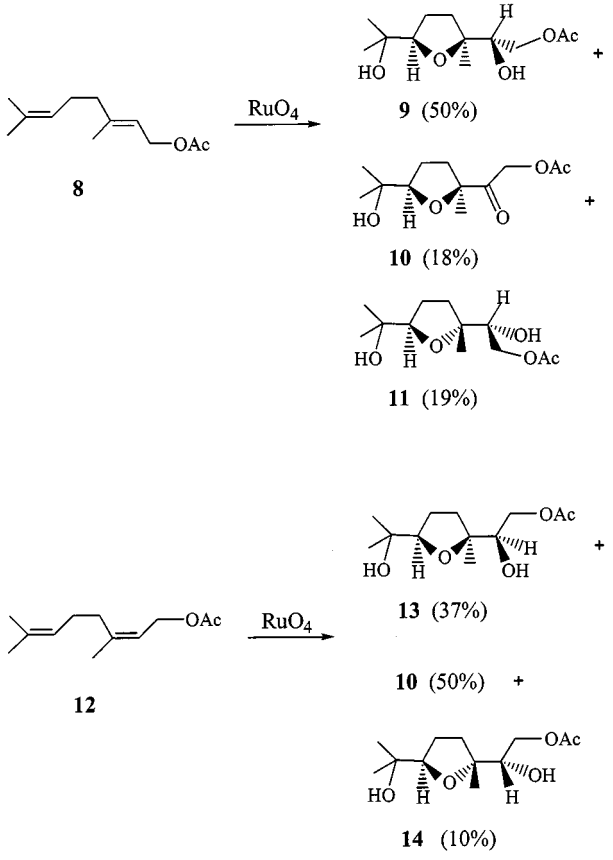
Treatment of *trans*,*trans*-2,6-dimethyl-2,6-octadiene-1,8-diol diacetate (**5**) with $RuO_2/NaIO_4$ as described for **1** afforded tetrahydrofurandiol diacetate **6** and tetrahydrofuran ketol diacetate **7** in yields of 64% and 34%, respectively. Compound **6** showed an MH^+ ion peak (HR FABMS) at m/z = 305.1627, corresponding to the molecular formula $C_{14}H_{24}O_7$. A combination of mass spectrometric and ^{13}C NMR spectroscopic data showed the presence in the molecule of an oxygen-containing ring and two OH groups. Specifically, ^{13}C NMR signals at δ = 84.4 and 81.9 were indicative of a tetrahydrofuran ring.[11] The presence of the alcohol functions was indicated by ^{13}C NMR resonances at δ = 74.8 and 72.6 and was further supported by the presence of a signal of two exchangeable protons at δ = 2.97 (br. s, 2 H, 2 OH) in the ^1H NMR spectrum. Treatment of **6** with Ac_2O/pyridine (1:2, v/v) gave a monoacetate derivative, indicating one of the two alcohol groups to be tertiary. The presence of the mono-THF ring was established by EIMS fragment ions at m/z (%) = 201 (60) [M^+ − $AcOCH_2$-CHOH] and 187 (25) [M^+ − $AcOCH_2C(CH_3)OH$]. The ^1H NMR spectrum of **6** showed the presence of a pure AB system centred at δ = 4.08 (J = 11.0 Hz) attributable to the 5-C(CH_3)(OH)CH_2OAc protons. A series of H-H decoupling experiments on product **6** allowed us to assign signals at δ = 4.33 (dd, J = 11.6 and 3.0 Hz) and 4.04 (dd, J = 11.6 and 8.5 Hz) to the 2-CH(OH)CH_2OAc protons, as the AB part of an ABM system; the M part was constituted by the proton signal at δ = 3.68 [dd, J = 8.5 and 3.0 Hz, 2-C*H*(OH)CH_2OAc]. A resonance at δ = 3.93 (dd, J = 8.4 and 6.0 Hz), which showed a correlation with the methylene protons, 4-CH_2, at δ ≈ 2.29−1.55, was attributed to 5-H. DEPT experiments and consideration of the ^{13}C chemical shifts of the THF unit permitted an assignment of all the carbon signals. In particular, the quaternary carbon atom C-2 and the methine carbon atom C-5 of the tetrahydrofuran moiety resonated at δ = 84.4 and 81.9, respectively, the signal of the hydroxymethine group directly linked to C-2 was seen at δ = 74.8, while the quaternary carbon atom $AcOCH_2C(CH_3)OH$ linked to C-5 gave a signal at δ = 72.6. The downfield shift of the proton signal at δ = 5.10 (dd, J = 8.6 and 2.6 Hz) of the acetylated derivative of **6**, as compared to δ = 3.68 in **6** itself, confirmed the assignment

of this signal to the 2-C*H*(OH)CH_2OAc proton. Finally, to obtain information about the relative stereochemistry at C-2 and C-5, NOE difference spectroscopy experiments (NOEDS) were carried out on **6**. Irradiation of the 2-methyl group [δ = 1.18 (s, 2-CH_3)] led to a strong enhancement of the signal due to the methine proton of the tetrahydrofuran ring [δ = 3.93 (5-H)]. This result clearly indicated a *cis* relationship between these groups.

Compound **7** was identified by analysis of its spectral data and by chemical correlation with compound **6**. In fact, oxidation of the secondary alcohol function of **6** with CrO_3/pyridine gave a product that exhibited chromatographic and spectroscopic properties identical to those of compound **7**. The presence of a ketone group in **7** was inferred from its ^{13}C NMR spectrum, which showed a signal at δ = 206.2. Moreover, the ^{13}C NMR spectrum also featured resonances characteristic of a carbon atom bearing a tertiary hydroxy group {δ = 71.6 [5-*C*(CH_3)(OH)CH_2OAc]}, a quaternary carbon atom of a tetrahydrofuran moiety [δ = 87.9 (C-2)], one oxymethine carbon atom [δ = 83.2 (C-5)], and two AcO*C*H_2 carbon atoms (δ = 69.4 and 65.3). The ^{1}H NMR spectrum showed two AB systems, one centred at δ = 4.97 (J = 17.4 Hz) attributable to the protons of the AcOCH_2 unit adjacent to the ketone carbon atom, and the other at δ = 4.09 (J = 11.4 Hz) attributable to the 5-C(CH_3)(OH)CH_2OAc protons. A proton signal at δ = 3.99 (dd, 1 H, J = 8.8 and 6.4 Hz) was assigned to 5-H on the basis of H-H decoupling experiments.

The stereochemistries of the cyclization products **2** and **6** were confirmed by comparison of their spectral data with those of authentic samples prepared from 1,5-dienes **1** and **5** by *syn* stereospecific reaction with $KMnO_4$, as described for the reactions of geranyl and neryl acetates with this reagent.[9] The main products obtained from these reactions were indistinguishable (^{1}H NMR, ^{13}C NMR, MS) from compounds **2** and **6** obtained with RuO_4. Thus, $KMnO_4$ oxidation of **1** afforded **2** in 30% yield, while reaction of **5** furnished a 50% yield of **6**. The above outcome indicated that RuO_4 oxygen addition to 1,5-dienes is a *syn* stereospecific reaction akin to the cyclization of 1,5-dienes with MnO_4^-.[23−27] In the case of the cyclic diene **3**, however, reaction with $KMnO_4$ did not afford the *cis*-tetrahydrofuran **4** but only cleavage products.

Finally, application of our procedure for RuO_4-catalysed oxidation to the 1,5-dienes geranyl acetate (**8**) and neryl acetate (**12**) afforded *cis*-tetrahydrofuran derivatives in high yields. Thus, oxidation of **8** with RuO_2/$NaIO_4$ in the biphasic solvent system AcOEt/$(CH_3)_2CO$/H_2O (2:1:1, v/v/v) at 25 °C furnished compounds **9** (50%), **10** (18%), and **11** (19%), while carrying out the same reaction on **12** afforded the *cis*-tetrahydrofuran products **13** (37%) and **10** (50%) along with *trans*-tetrahydrofurandiol **14** (10%) (Scheme 2). As can be noted in Scheme 2, the products obtained from geranyl and neryl acetate were the same as those obtained by the Sharpless group upon RuO_4-catalysed oxidation of **8** and **12** in the biphasic solvent system CCl_4/CH_3CN/H_2O (2:2:3, v/v/v).[8] However, our procedure was characterized by a higher stereospecificity, a greater material recovery

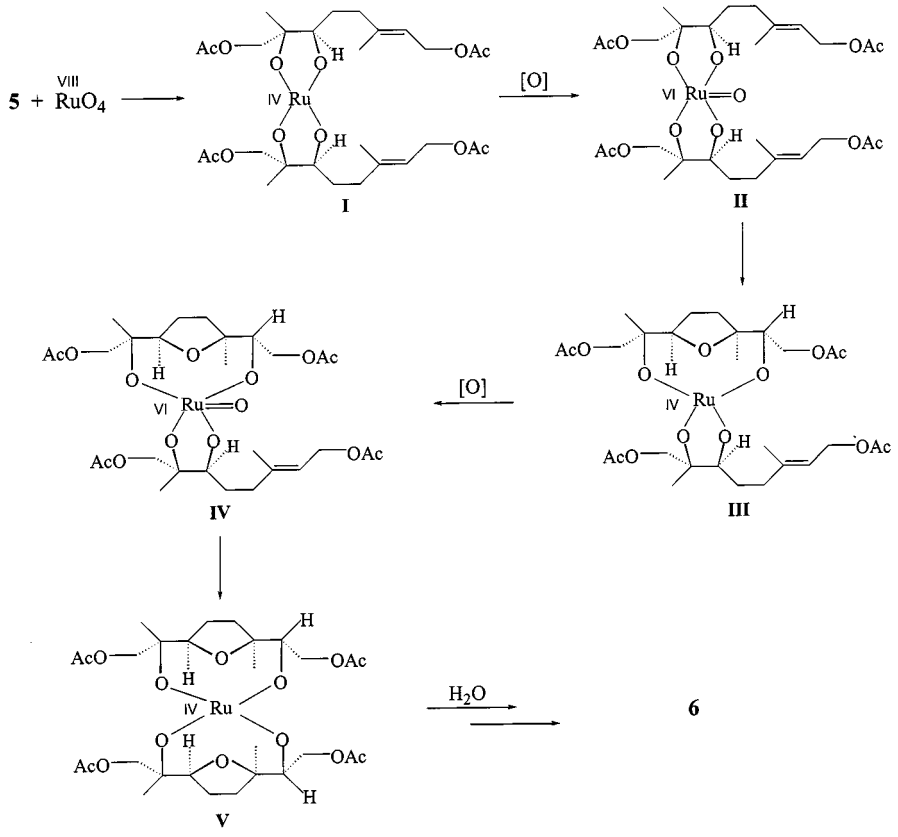


Scheme 2. RuO_4-catalysed oxidation of geranyl acetate and neryl acetate in the biphasic solvent system AcOEt/$(CH_3)_2CO$/H_2O (2:1:1, v/v/v)

(about 90%), and a more simple work-up. To complete our study on the oxidation of geranyl and neryl acetates, we carried out the reactions with $KMnO_4$ according to the procedure of Klein and Rojahn.[9] In this way, *cis*-tetrahydrofurandiol **9** and *cis*-tetrahydrofuran ketol **10** were obtained from **8** in yields of 42% and 10%, respectively, while oxidation of **12** afforded a 29% yield of ketol **10** and a 28% yield of *cis*-tetrahydrofurandiol **13**. Thus, the yields of the *cis*-tetrahydrofuran derivatives achieved by RuO_4 oxidation of **1**, **5**, **8**, and **12** according to our procedure are higher than those achieved by permanganate oxidation.

Conclusion

In this work, we have presented an improved procedure for the ruthenium tetraoxide catalysed oxidation of 1,5-dienes, which uses 0.05 equiv. of the catalyst RuO_2·2H_2O, 2.5 equiv. of $NaIO_4$ as a stoichiometric oxidant, and a biphasic solvent system of AcOEt/$(CH_3)_2CO$/H_2O (2:1:1, v/v/v). Oxidations of geranyl acetate (**8**) and neryl acetate (**12**) have been found to efficiently afford the *cis*-tetrahydrofuran derivatives **9** (50%), **13** (37%), and **10** (18% yield from geranyl acetate; 50% yield from neryl acetate), along with small amounts of the *trans*-tetrahydrofurandiols **11** (19%) and **14** (10%) (Scheme 2). These products are the same as those obtained by the Sharpless group upon RuO_4-catalyzed oxidation of **8** and **12** in the biphasic solvent system CCl_4/



Scheme 3. Proposed mechanism for RuO_4-catalyzed oxidation of 1,5-dienes to form *cis*-tetrahydrofuran products

CH_3CN/H_2O (2:2:3, v/v/v). However, our procedure is characterized by a higher stereospecificity, a greater material recovery (about 90%), and a more simple work-up. Application of our procedure to 1,5-dienes **1**, **3**, and **5** furnished the new *cis*-tetrahydrofuran products **2** (50%), **4** (45%), **6** (64%), and **7** (34%) with total stereospecificity (Scheme 1). The lack of *trans* selectivity observed for the reactions of **1** and **5** is difficult to explain, while oxidation of the more strained cyclic diene **3** necessarily proceeds by *syn* oxygen addition to both double bonds, as we have noted from analysis of Dreiding molecular models. It seems probable that the initial step in the formation of a *cis*-tetrahydrofurandiol (**2**, **4**, **6**, **9**, or **13**) involves cycloaddition of RuO_4 to one double bond of two 1,5-diene molecules to afford a cyclic ruthenium(IV) diester (**I**, Scheme 3). This is believed to be rapidly oxidized by $NaIO_4$ to give the cyclic ruthenium(VI) diester **II**, containing an Ru=O group. This intermediate could then undergo intramolecular addition to the second neighbouring double bond to give the cyclic ruthenium(IV) diester **III**, following a pathway similar to that suggested by Baldwin[26] and modified by Wolfe[25] for the permanganate-induced oxidative cyclization of 1,5-dienes. Intermediate **III** yields **V**. Finally, hydrolysis of **V** produces the observed *cis*-tetrahydrofuran product **6** and RuO_2, which is then reintegrated into the catalytic cycle. Support for the pathway set out in Scheme 3 is provided by the fact that we have recently proven the existence of a cyclic ruthenium(VI) diester akin to the postulated intermediate **II** (Scheme 3).[20,22]

Furthermore, we have carried out $KMnO_4$ oxidations of compounds **1**, **3**, **8**, and **12** according to the procedure of Klein and Rojahn. In all cases, the yields of the *cis*-tetrahydrofuran derivatives were lower than those achieved applying our procedure for RuO_4 oxidation to the same 1,5-dienes.

In conclusion, our procedure can be envisaged as being applicable to the construction of polyoxygenated natural products and of molecules of biological interest, such as polyether antibiotics, which are characterized by the frequent occurrence of 2,5-disubstituted tetrahydrofuran moieties.

Experimental Section

General Remarks: Fourier transform IR (FT-IR) spectra were obtained with a Perkin−Elmer 1760-X FT-IR spectrophotometer. − ^1H and ^{13}C NMR spectra were recorded with Bruker WM 200 and 400 spectrometers with samples in $CDCl_3$ solution. Proton chemical shifts are referenced to the residual $CHCl_3$ signal (δ = 7.26). ^{13}C NMR chemical shifts are referenced to the solvent ($CDCl_3$: δ = 77.0). 2D NMR spectra were recorded at 500 MHz with a Bruker AMX-500 spectrometer with samples in $CDCl_3$ solution. The multiplicities of the ^{13}C NMR resonances were determined by DEPT experiments. − Electron-impact mass spectra (EIMS) were recorded with a Trio 2000 mass spectrometer. − HR FAB mass spectra were obtained with a VG Autospec mass spectrometer. − High-performance liquid chromatography (HPLC) separations

were performed with a Varian 2510 apparatus equipped with a Waters R403 dual cell refractometer, using a semi-preparative Hibar LiChrosorb Si-60 (250 × 10 mm) column. − Column chromatography was carried out on Merck silica gel 40 (70−230 mesh). − Thin-layer chromatography (TLC) was performed on precoated silica gel F_{254} plates (0.25 mm thick, Merck). The reactions were monitored by TLC with visualization by iodine until all the starting material had been consumed.

RuO_4 Oxidation of 2,5-Dimethyl-1,5-hexadiene (1): To a stirred solution of $RuO_2{\cdot}2H_2O$ (13 mg, 0.10 mmol, 0.05 equiv.) and $NaIO_4$ (1.073 g, 5.04 mmol, 2.5 equiv.) in acetone (8 mL) and water (8 mL), a solution of 2,5-dimethyl-1,5-hexadiene (**1**, 222 mg, 2.02 mmol, 1 equiv.) in ethyl acetate (16 mL) was added at 25 °C. The reaction was instantaneous, as revealed by TLC and, after 3 min, was terminated by adding a few drops of ethanol. The mixture was then diluted with ethyl acetate and the phases were separated. The aqueous phase was extracted twice with ethyl acetate and three times with $CHCl_3$. The combined organic extracts were dried with Na_2SO_4, filtered, concentrated to dryness, and the residue was chromatographed by HPLC on a semi-preparative Si-60 column eluting with $CHCl_3/CH_3OH$ (98:2, v/v, φ = 2.5 mL/min) to give 161 mg of tetrahydrofurandiol **2** (50%, t_R = 17 min) as a colourless oil.

Compound 2: FT-IR (film): $\tilde{\nu}$ = 3400, 1051 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.98 (br. s, 2 H, 2 OH), 3.53 (d, 2 H, *J* = 11.1, part of an AB system centred at δ = 3.46, 2-C*H*$_a$H$_b$OH and 5-C*H*$_a$H$_b$OH), 3.39 (d, 2 H, *J* = 11.1, part of an AB system centred at δ = 3.46, 2-CH$_a$*H*$_b$OH and 5-CH$_a$*H*$_b$OH), 2.18 (m, 2 H, part of an AA′BB′ system centred at δ = 1.96, 3-H$_a$ and 4-H$_a$), 1.74 (m, 2 H, part of an AA′BB′ system centred at δ = 1.96, 3-H$_b$ and 4-H$_b$), 1.18 (s, 6 H, 2-CH_3 and 5-CH_3). − ^{13}C NMR ($CDCl_3$, 100.1 MHz): δ = 84.3 (C-2 and C-5), 69.1 (2-*C*H$_2$OH and 5-*C*H$_2$OH), 34.0 (C-3 and C-4), 25.4 (2-CH_3 and 5-CH_3). − FABMS: *m*/*z* = 161 [MH^+]. − HR FABMS: *m*/*z* (assignment, relative intensities) = 161.1196 ([MH^+], $C_8H_{17}O_3$ requires 161.1178, 100), 143.1098 ([$MH^+ - H_2O$], $C_8H_{15}O_2$ requires 143.1072, 15).

Acetylation of 2: Compound **2** was acetylated in the standard manner with pyridine/Ac_2O (2:1). After stirring the mixture at room temperature overnight, standard workup of the crude residue by TLC (hexane/AcOEt, 6:4, v/v) gave the pure diacetyl derivative. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 4.02 (d, 2 H, *J* = 11.1, part of an AB system centred at δ = 3.96, 2-C*H*$_a$H$_b$OAc and 5C*H*$_a$H$_b$OAc), 3.87 (d, 2 H, *J* = 11.1, part of an AB system centred at δ = 3.96, 2-CH$_a$*H*$_b$OAc and 5-CH$_a$*H*$_b$OAc), 2.07 (s, 6 H, 2 CH_3COO), 1.99 (m, 2 H, part of an AA′BB′ system centred at δ = 1.89, 3-H$_a$ and 4-H$_a$), 1.80 (m, 2 H, part of an AA′BB′ system centred at δ = 1.89, 3-H$_b$ and 4-H$_b$), 1.27 (s, 6 H, 2-CH_3 and 5-CH_3).

RuO_4 Oxidation of (*S*)-(−)-Limonene (3): A mixture of (*S*)-(−)-limonene (**3**, 355 mg, 2.60 mmol, 1 equiv.), $RuO_2{\cdot}2H_2O$ (17 mg, 0.13 mmol, 0.05 equiv.), and $NaIO_4$ (1.390 g, 6.53 mmol, 2.5 equiv.) in ethyl acetate (20 mL), acetone (10 mL), and water (10 mL) was stirred for 15 min. Thereafter, the reaction was terminated and the mixture was worked up as described for **1**. Separation of the products by HPLC on a Hibar Lichrosorb Si-60 column, eluting with $CHCl_3/CH_3OH$ (96:4, v/v, φ = 2.5 mL/min), gave pure samples of 4-hydroxy-7-hydroxymethyl-4,7-dimethyl-6-oxabicyclo[3.2.1]octane (**4**) (218 mg, 45% yield, t_R = 19 min) as a colourless oil.

Compound 4: FT-IR (film): $\tilde{\nu}$ = 3446, 1031 cm^{-1}. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 3.99 (d, 1 H, *J* = 11.4 Hz, part of an AB system centred at δ = 3.78, 7-C*H*$_2$OH), 3.94 (d, 1 H, *J* = 6.6 Hz, 5-H), 3.57 (d, 1 H, *J* = 11.4 Hz, part of an AB system centred at δ = 3.78, 7-C*H*$_2$OH), 3.15 (br. s, 2 H, 2 OH), 2.30 (dddd, 1 H, *J* = 12.6, 6.6, 4.4, and 2.4 Hz, 8-H$_{eq}$), 1.96 (m, 1 H, 1-H), 1.83−1.65 (overlapped multiplets, 3 H, 3-CH_2 and 2-H$_{eq}$) 1.63 (d, 1 H, *J* = 12.6 Hz, 8-H$_{ax}$), 1.45 (extensive multiplet, 1 H, 2-H$_{ax}$), 1.29 (s, 3 H, 7-CH_3), 1.15 (s, 3 H, 4-CH_3). − ^{13}C NMR ($CDCl_3$, 100.1 MHz): δ = 84.8 (C-5), 84.3 (C-7), 72.5 (C-4), 65.8 (7-CH_2OH), 40.1 (C-1), 35.6 (C-8 or C-3), 33.8 (C-8 or C-3), 24.5 (7-CH_3 or 4-CH_3), 24.4 (C-2), 24.4 (7-CH_3 or 4-CH_3). − FABMS: *m*/*z* (%) = 209 (40) [M + Na^+], 187 (75) [MH^+], 169 (100) [$MH^+ - H_2O$]. − EIMS: *m*/*z* (%) = 168 (9) [$M^+ - H_2O$], 155 (100) [$M^+ - CH_2OH$, α-cleavage of the cyclic ether], 153 (22) [$M^+ - H_2O - CH_3$], 150 (8) [$M^+ - 2\,H_2O$], 137 (34) [$M^+ - H_2O - CH_2OH$], 125 (64) [$M^+ - CH_2OH - 2\,CH_3$]. − HR FABMS: *m*/*z* = 187.1313 ([MH^+], $C_{10}H_{19}O_3$ requires 187.1334).

Acetylation of Compound 4: Compound **4** was acetylated as described for **2**. − ^1H NMR ($CDCl_3$, 200 MHz) δ = 4.41 (d, 1 H, *J* = 11.3 Hz, part of an AB system centred at δ = 4.29, 7-CH_2OAc), 4.18 (d, 1 H, *J* = 11.3 Hz, part of an AB system centred at δ = 4.29, 7-CH_2OAc), 3.93 (d, 1 H, *J* = 6.8 Hz, 5-H), 2.30 (m, 1 H, 8-H$_{eq}$), 2.11 (s, 3 H, CH_3COO), 2.04 (m, 1 H, 1-H), 1.84−1.67 (overlapped multiplets, 3 H, 3-CH_2 and 2-H$_{eq}$) 1.64 (d, 1 H, *J* = 12.4 Hz, 8-H$_{ax}$), 1.33−1.55 (m, 1 H, 2-H$_{ax}$), 1.26 (s, 3 H, 7-CH_3), 1.15 (s, 3 H, 4-CH_3). − EIMS: *m*/*z* (%) = 228 (4) [M^+], 168 (47) [M^+ − AcOH], 155 (100) [$M^+ - CH_3COOCH_2$, α-cleavage of the cyclic ether], 153 (25) [$M^+ - CH_3COOH - CH_3$], 150 (26) [$M^+ - CH_3COOH - H_2O$], 137 (21) [$M^+ - H_2O - CH_3COOCH_2$], 125 (93) [$M^+ - 2\,CH_3 - CH_3COOCH_2$].

RuO_4 Oxidation of *trans,trans*-2,6-Dimethyl-2,6-octadiene-1,8-diyl Diacetate (5): A mixture of *trans,trans*-2,6-dimethyl-2,6-octadiene-1,8-diyl diacetate (**5**, 208 mg, 0.82 mmol), $RuO_2{\cdot}2H_2O$ (5 mg, 0.04 mmol, 0.05 equiv.), and $NaIO_4$ (436 mg, 2.05 mmol, 2.5 equiv.) in ethyl acetate/acetone/water (32 mL, 2:1:1, v/v/v) was stirred at 25 °C. After 3 min, the reaction was terminated and the mixture was worked up in the standard manner. The recovered material was subjected to HPLC separation using $CHCl_3/CH_3OH$ (98:2, v/v, φ = 2.5 mL/min) as eluent to give 101 mg of tetrahydrofurandiol **6** (64% yield, t_R = 14.5 min) and 75 mg of tetrahydrofuran ketol **7** (34%, t_R = 5.5 min) as colourless oils.

Compound 6: ^1H NMR ($CDCl_3$, 400 MHz): δ = 4.33 [dd, 1 H, *J* = 11.6 and 3.0 Hz, A part of an ABM system, 2-CH(OH)C*H*$_2$OAc], 4.16 [1 H, *J* = 11.0 Hz, part of an AB system centred at δ = 4.08, 5-C(CH_3)(OH)C*H*$_2$OAc], 4.04 [dd, 1 H, *J* = 11.6 and 8.5 Hz, B part of an ABM system, 2-CH(OH)C*H*$_2$OAc], 4.00 [1 H, *J* = 11.0 Hz, part of an AB system centred at δ = 4.08, 5-C(CH_3)(OH)C*H*$_2$OAc], 3.93 (dd, 1 H, *J* = 8.4 and 6.0 Hz, 5-H), 3.68 [dd, 1 H, *J* = 8.5 and 3.0 Hz, M part of an ABM system, 2-C*H*(OH)CH_2OAc], 2.97 (br. s, 2 H, 2 OH), 2.29−1.55 (complex overlapped multiplets, 4 H, 3-CH_2 and 4-CH_2), 2.08 (s, 6 H, 2 CH_3COO), 1.18 (s, 3 H, 2-CH_3), 1.09 [s, 3 H, 5-C(C*H*$_3$)(OH)CH_2OAc]. − ^{13}C NMR ($CDCl_3$, 100.1 MHz): δ = 171.3 (CH_3COO), 171.1 (CH_3COO), 84.4 (C-2), 81.9 (C-5), 74.8 [2-*C*H(OH)CH_2OAc], 72.6 [5-*C*(CH_3)(OH)CH_2OAc], 69.5 [5-C(CH_3)(OH)*C*H$_2$OAc], 65.9 [2-CH(OH)*C*H$_2$OAc], 35.2 (C-3), 25.8 (C-4), 23.2 (2-CH_3), 20.9 (2 *C*H$_3$COO), 20.6 [5-C(*C*H$_3$)(OH)CH_2OAc]. − FABMS: *m*/*z* (%) = 437 (8) [M + Cs^+], 327 (6) [M + Na^+], 305 (23) [MH^+], 287 (100) [$MH^+ - H_2O$], 227 (15) [$MH^+ - H_2O$ − AcOH]. − EIMS: *m*/*z* (%) = 213 (46) [$M^+ - H_2O$ − $AcOCH_2$], 201 (60) [M^+ − $AcOCH_2CHOH$, α-cleavage of the cyclic ether], 187 (25) [M^+ − $AcOCH_2C(CH_3)OH$], 153 (35) [M^+ − AcOH − H_2O − $AcOCH_2$], 141 (100) [M^+ − AcOH − $AcOCH_2CHOH$], 127 (54) [M^+ − $AcOCH_2C(CH_3)OH$ − AcOH],

84 (81) [M^+ − $AcOCH_2CHOH$ − $AcOCH_2C(CH_3)OH$]. − HR FABMS: *m/z* = 305.1627 ([MH^+], $C_{14}H_{25}O_7$ requires 305.1600).

Acetylation of Compound 6: Compound **6** was acetylated as described for **2**. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.10 [dd, 1 H, *J* = 8.6 and 2.6 Hz, M part of an ABM system, 2-C*H*(OAc)-CH_2OAc], 4.37 [dd, 1 H, *J* = 12.5 and 2.6 Hz, A part of an ABM system, 2-CH(OAc)C*H*$_2$OAc], 4.07 [1 H, *J* = 11.1 Hz, part of an AB system centred at δ = 3.99, 5-C(CH_3)(OH)C*H*$_2$OAc], 4.03 [dd, 1 H, *J* = 12.5 and 8.6 Hz, B part of an ABM system, 2-CH(OAc)-C*H*$_2$OAc], 3.91 [1 H, *J* = 11.1 Hz, part of an AB system centred at δ = 3.99, 5-C(CH_3)(OH)C*H*$_2$OAc], 3.94 (dd, 1 H, *J* = 8.6 and 6.0 Hz, 5-H), 2.13 (s, 3 H, CH_3COO), 2.08 (s, 3 H, CH_3COO), 2.03 (s, 3 H, CH_3COO), 2.24−1.54 (complex overlapped multiplets, 4 H, 3-CH_2 and 4-CH_2), 1.23 (s, 3 H, 2-CH_3), 1.09 [s, 3 H, 5-C(C*H*$_3$)(OH)CH_2OAc]. − ^{13}C NMR ($CDCl_3$, 100.1 MHz): δ = 171.3 (CH_3*C*OO), 171.0 (CH_3*C*OO), 170.8 (CH_3*C*OO), 83.4 (C-2), 82.1 (C-5), 77.2 [2-*C*H(OAc)CH_2OAc], 71.5 [5-*C*(CH_3)(OH)CH_2OAc], 69.4 [5-C(CH_3)(OH)*C*H$_2$OAc], 63.2 [2-CH(OAc)*C*H$_2$OAc], 35.4 (C-3), 25.7 (C-4), 23.1 (2-CH_3), 21.0 (2 CH_3), 20.8 (CH_3), 20.2 (CH_3).

Compound 7: ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.06 (d, 1 H, *J* = 17.4 Hz, part of an AB system centred at δ = 4.97, 2-COC*H*$_2$OAc), 4.87 (d, 1 H, *J* = 17.4 Hz, part of an AB system centred at δ = 4.97, 2-COC*H*$_2$OAc), 4.17 [1 H, *J* = 11.4 Hz, part of an AB system centred at δ = 4.09, 5-C(CH_3)(OH)C*H*$_2$OAc], 4.00 [1 H, *J* = 11.4 Hz, part of an AB system centred at δ = 4.09, 5-C(CH_3)(OH)C*H*$_2$OAc], 3.99 (dd, 1 H, *J* = 8.8 and 6.4 Hz, 5-H), 3.14 (br. s, 1 H, OH), 2.10 (s, 3 H, C*H*$_3$COO), 2.06 (s, 3 H, C*H*$_3$COO), 1.37 (s, 3 H, 2-CH_3), 1.08 [s, 3 H, 5-C(C*H*$_3$)(OH)CH_2OAc]. − ^{13}C NMR ($CDCl_3$, 100.1 MHz): δ = 206.2 (2-*C*OCH_2OAc), 170.9 (CH_3*C*OO), 170.3 (CH_3*C*OO), 87.9 (C-2), 83.2 (C-5), 71.6 [5-*C*(CH_3)(OH)CH_2OAc], 69.4 (AcO*C*H$_2$), 65.3 (AcO*C*H$_2$), 35.7 (C-3), 25.2 (C-4), 23.7 (2-CH_3), 20.8 (2 *C*H$_3$COO), 20.3 [5-C(*C*H$_3$)(OH)CH_2OAc]. − FABMS: *m/z* (%) = 303 (67) [MH^+], 285 (100) [$MH^+ - H_2O$], 243 (9) [MH^+ − CH_3COOH], 225 (40) [$MH^+ - CH_3COOH - H_2O$], 202 (76) [MH^+ − $AcOCH_2CO$], 186 (35) [MH^+ − $AcOCH_2C(CH_3)OH$], 165 (14) [$MH^+ - 2\,CH_3COOH - H_2O$], 142 (42) [$MH^+$ − AcOH − $AcOCH_2CO$], 126 (18) [MH^+ − AcOH − $AcOCH_2(CH_3)OH$], 124 (24) [$MH^+ - H_2O$ − AcOH − $AcOCH_2CO$].

Chromium Trioxide/Pyridine Oxidation of Compound 6: To a solution of **6** in pyridine was added an excess of chromium trioxide/pyridine complex. The mixture was stirred at room temperature for 16 h, then diluted with water, and extracted with diethyl ether. HPLC purification on a Hibar LiChrosorb Si-60 column using hexane/AcOEt (1:1) as eluent afforded a product identical in all respects to the tetrahydrofuran ketol **7**.

RuO_4 Oxidation of Geranyl Acetate (8): To a stirred solution of $RuO_2{\cdot}2H_2O$ (3 mg, 0.02 mmol, 0.05 equiv.) and $NaIO_4$ (271 mg, 1.27 mmol, 2.5 equiv.) in acetone (4 mL) and water (4 mL), a solution of geranyl acetate (**8**, 100 mg, 0.51 mmol, 1 equiv.) in ethyl acetate (8 mL) was added at 25 °C. After 2 min, the reaction was terminated by adding a few drops of ethanol and the mixture was worked up as described for **1**. The crude products were separated by HPLC on a semi-preparative Si-60 column eluting with $CHCl_3$/CH_3OH (98:2, v/v, φ = 2.5 mL/min) to give 63 mg of *cis*-tetrahydrofurandiol **9** (50% yield, t_R = 15 min), 22 mg of *cis*-tetrahydrofuran ketol **10** (18%, t_R = 5.5 min), and 24 mg of *trans*-tetrahydrofurandiol **11** (19%, t_R = 13 min). Products **9**, **10**, and **11** show the same spectroscopic properties as authentic samples.[28]

RuO_4 Oxidation of Neryl Acetate (12): A mixture of $RuO_2{\cdot}2H_2O$ (3 mg, 0.025 mmol, 0.05 equiv.), $NaIO_4$ (271 mg, 1.27 mmol, 2.5 equiv.), and neryl acetate **12** (100 mg, 0.51 mmol, 1 equiv.) in ethyl acetate (8 mL), acetone (4 mL), and water (4 mL) was stirred for a few minutes at room temperature. After the usual workup, the crude products were subjected to HPLC separation on an Si-60 column eluting with $CHCl_3$/CH_3OH (98:2, v/v, φ = 2.5 mL/min) to afford 47 mg of *cis*-tetrahydrofurandiol **13** (37% yield, t_R = 14 min), 63 mg of *cis*-tetrahydrofuran ketol **10** (50%, t_R = 6 min), and 13 mg of *trans*-tetrahydrofurandiol **14** (10%, t_R = 12.6 min). Products **13**, **10**, and **14** show the same spectroscopic properties as authentic samples.[28]

Oxidative Cyclization of 1,5-Dienes 1, 5, 8, and 12 with $KMnO_4$: Compounds **1**, **5**, **8**, and **12** were oxidized to *cis*-tetrahydrofuran derivatives with $KMnO_4$ according to the procedure of Klein and Rojahn.[9] All the chromatographic and spectroscopic properties of the synthetic compounds proved to be essentially identical to those of compounds **2**, **6**, **9**, **10**, and **13** obtained by RuO_4 oxidation of the same 1,5-dienes. Specifically, $KMnO_4$ oxidation of **1** afforded **2** in 30% yield, while oxidation of **5** furnished **6** in 50% yield. Compounds **9** and **10** were obtained from geranyl acetate (**8**) in yields of 42% and 10%, respectively. Finally, $KMnO_4$ oxidation of neryl acetate afforded **13** and **10** in yields of 28% and 29% yield, respectively.

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