Synthesis and characterization of some oxidized derivatives of citronellal ethylene acetal

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Three pairs of geometrical isomers corresponding to allylic monooxidation products of the trisubstituted olefin, citronellal ethylene acetal (**3**), were synthesized. These compounds were the *E* and *Z* isomers of 7-(1,3-dioxolan-2-yl)-2,6-dimethyl-2-hepten-1-ol, -1-al, and -1-oic acid (methyl ester), precursors for identifying the biodegradation products from citronellal and some of its derivatives. The *E* aldehyde (**4**) was obtained from **3** by the Sharpless procedure with catalytic quantities of selenium dioxide. The *E* ester (**5**) and *E* alcohol (**6**) were prepared in high isomeric purity (97–99%) from **4** with activated manganese dioxide and sodium borohydride, respectively. Selective ozonolysis of the isobutenyl group in **3** gave 5-(1,3-dioxolan-2-yl)-4-methyl-1-pentanal (**7**). Under the conditions used, ozone did not react with the ethylene acetal group. Acetal aldehyde (**7**) was stereoselectively converted to the *Z* alcohol (**8**) by a Wittig reaction. Manganese dioxide oxidation of **8** (98–99% *Z* isomer) to the *Z* aldehyde (**9**) and of **9** to the *Z* ester (**10**) was accompanied by partial *Z* to *E* isomerization. The distribution of *E* and *Z* isomers in crude reaction mixtures was determined by gas chromatography with a glass capillary column or by proton magnetic resonance spectroscopy.

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On a synthétisé trois paires d'isomères géométriques qui proviennent de la mono-oxydation allylique de l'oléfine trisubstitué, l'acétal éthylènique du citronellal (**3**). Ces composés sont les isomères *E* et *Z* du (dioxolanne-1,3 yl-2)-7 diméthyl-2,6 heptène-2 ol-1, de l'aldéhyde (al-1) et de l'acide (oique-1 sous forme d'ester méthylique) correspondants qui sont les précurseurs dans l'identification des produits de biodégradation du citronellal et de quelques-uns de ses dérivés. On a obtenu l'aldéhyde *E* (**4**) à partir du composé (**3**) en faisant appel au procédé de Sharpless avec des quantités catalytiques de bioxyde de sélénium. On a préparé l'ester *E*-(**5**) et l'alcool *E*-(**6**) avec une grande pureté isomérique (97–99%) en soumettant respectivement le composé **4** à une oxydation par le bioxyde manganèse activé et à une réduction au borohydrure de sodium. L'ozonolyse sélective du groupe isobuténylé du composé **3** donne le (dioxolanne-1,3 yl-2)-5 méthyl-4 pentanal-1 (**7**). Dans les conditions utilisées, l'ozone ne réagit pas avec l'acétal éthylènique. On a transformé d'une façon stéréosélective l'acétal-aldéhyde **7** en alcool *Z* (**8**) par une réaction de Wittig. L'oxydation du composé **8** (isomère *Z* à 98–99%) en aldéhyde *Z* (**9**) et du composé **9** en l'ester *Z* (**10**) par le bioxyde de manganèse s'accompagne d'une isomèrisation partielle de *Z* en *E*. On a déterminé la distribution des isomères *E* et *Z* des mélanges réactionnels bruts par chromatographie en phase vapeur avec un colonne capillaire en verre ou par la spectroscopie de rmn du proton.

[Traduit par le journal]

Several investigators have demonstrated that xenobiotics with the isobutenyl group are capable of undergoing metabolic oxidation in mammals according to eq. [1] (1–5). To explore such meta-

[1] $(CH_3)_2C{=}CHR \longrightarrow HOCH_2(CH_3)C{=}CHR + HC(=O)(CH_3)C{=}CHR + HOC(=O)(CH_3)C{=}CHR$

bolic transformations, authentic reference samples of the *E* (*trans*) and *Z* (*cis*) alcohols, aldehydes, and acids are required. In principle, these isomeric products are accessible from the substrate. Thus, it is known that *E* trisubstituted olefinic alcohols or aldehydes can usually be obtained by use of selenium dioxide chemistry (6–8) and that the cyanohydrins of conjugated *E* aldehydes have been converted to methyl esters of *E* trisubstituted olefinic acids with activated manganese dioxide in methanol (9). *Z* Trisubstituted alcohols of this particular type have been accessible with a special type of Wittig reaction (8), as demonstrated initially by Corey *et al.* (10, 11) and by Schlosser *et al.* (12–14). A new synthesis of *Z* trisubstituted olefinic alcohols by the Wittig reaction has also been reported (15).

The problem of obtaining reference oxidation products arose during investigations (unpublished) on the elucidation of metabolic pathways for citronellal (**1**) and stereoisomeric mixtures of its *N*-acetyloxazolidine derivative (**2**), two insect repellents with the isobutenyl group (16). However, it was evident that neither of these unsaturated monoterpenoids would withstand the reaction conditions necessary for stereoselective synthesis of both series of isomers, so a potentially versatile intermediate to **1** and **2** was selected instead. This paper describes the chemistry that has been explored during the synthesis of *E* and *Z* alcohols, aldehydes, and acids (as methyl esters) of citronellal ethylene acetal (**3**). It is planned to use these derivatives of **3** for identifying the biodegradation products from metabolic experiments with **1** and **2**.

Results and discussion

trans-*Oxidized derivatives of* 3

Clark *et al.* (17) had already prepared **4** by the regioselective oxidation of **3** with selenium dioxide in ethanol. In this work, a new procedure from Sharpless and co-workers (7, 18) was used in which **3** was oxidized in methylene chloride solution with

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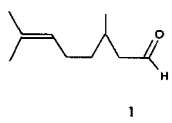
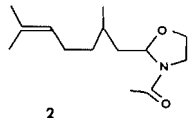


1



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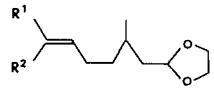
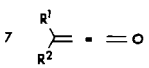


3 $R^1 = R^2 = CH_3$
4 $R^1 = CHO, R^2 = CH_3$
5 $R^1 = CO_2CH_3, R^2 = CH_3$
6 $R^1 = CH_2OH, R^2 = CH_3$



7

8 $R^1 = CH_3, R^2 = CH_2OH$
9 $R^1 = CH_3, R^2 = CHO$
10 $R^1 = CH_3, R^2 = CO_2CH_3$

a mixture of selenium dioxide and *tert*-butylhydroperoxide. The main product was **4**, as determined by spectral analysis of a sample from column chromatography. The *E* stereochemistry for **4** was indicated from the nmr spectrum because a signal for the unsaturated aldehyde proton was seen at 9.4 ppm. A signal for the aldehyde proton of the *Z* isomer would appear downfield near 10 ppm if it was present in detectable amounts (6, 19). The nmr analysis of the crude reaction product mixture gave no evidence for the presence of the *Z* aldehyde, so it was concluded that this reaction had proceeded with high (> 95%) stereoselectivity.

By employing a method from Crombie *et al.* (20) for converting related *E* trisubstituted olefinic aldehydes to *E* methyl esters, **4** gave the desired *E* acetal ester (**5**). The structure of **5** was confirmed by elemental and spectral analysis on a purified sample. Analysis of crude samples by glass capillary gas chromatography (capillary gc) showed **5** as a major component. A minor component, comprising 1–2% of the mixture, was also seen with a shorter retention time. It was apparent that the oxidation of **4** proceeded with little, if any, *E* to *Z* isomerization. In fact, only one olefinic proton was seen in the nmr spectrum of **5** and it resonated at the expected position (6.8 ppm) for an *E* trisubstituted olefinic ester of this type (6).

Alcohol (6) had previously been prepared by the incomplete oxidation of **3** with selenium dioxide in ethanol and pyridine (21). In the present investigation, **6** was obtained by reduction of **4** with sodium borohydride. The product from this reaction showed a major component and a minor component with a peak area ratio of 97:3 by capillary gc. Under conditions for electron impact mass spectrometry (ei-ms) combined with capillary gc, these two components gave nearly identical mass spectra, thus indicating that the *Z* isomer of **6** was probably present. Both components gave small $M - 1$ ions, which are characteristic ions in related ethylene acetals (22), and the base peak at *m/z* 73 was seen for the oxonium ($C_3H_5O_2$) ion (23). The latter ion was the base peak in the ei-ms of all of the compounds examined.

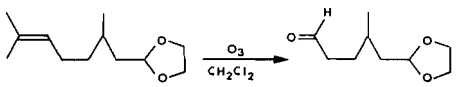
Confirmatory evidence for the presence of the *Z* isomer of **6** in samples from the reduction of **4** with sodium borohydride came from the independent synthesis of this isomer (discussed later). Additional evidence was also obtained by reducing the methyl ester function in **5** with lithium borohydride. The same isomeric alcohols, in approximately the same ratio (98:2), were found by capillary gc. This experiment also confirmed that **5** was formed from **3** with approximately 98% stereoselectivity.

Quasimolecular ions usually dominated the chemical ionization mass spectra (ci-ms) of these compounds and aided in confirming their structures. In the case of **3**, the loss of 60 amu from both the quasimolecular ion ($(M + 1) - 60$) and from the $M - 1$ ion ($(M - 1) - 60$) accounted for the major fragmentation pathways. With **4** and **6**, $(M - 1) - 60$ was more favorable. The most intense ion in **6** corresponded to $(M + 1) - 18$, a process observed in the ci-ms of saturated alcohols (24). Other prominent ions in **6** occurred at *m/z* 137 and *m/z* 135, which can be rationalized by $(M + 1) - 18 - 60$ and $(M - 1) - 18 - 60$ pathways. The most prominent fragment ion in **5** was seen at *m/z* 211, corresponding to $(M + 1) - CH_3OH$ (25).

Ozonolysis of 3

Synthetic approaches to the *Z* isomers of **4**, **5**, and **6** required that the olefinic bond in **3** first be cleaved and the product acetal aldehyde (**7**) subjected to a Wittig reaction. By employing a modification of the Wittig reaction for *Z* selectivity, where electrophilic substitution of intermediate β-oxido ylides with formaldehyde gave *Z* trisubstituted allylic alcohols directly (10–14), **7** should give the *Z* acetal alcohol (**8**).

A potential problem arose during the attempted synthesis of **7** by the ozonolysis of **3** (eq. [2]). This

[2] 

3 7

was because a number of acetals, including ethylene acetals, were known to react with ozone in ethyl acetate solution to give β-hydroxy esters (26–29). However, treatment of **3** with ozone at −78°C in methylene chloride solution gave one main product as detected by capillary gc. The nmr spectrum clearly indicated the formation of **7** since

an aldehyde signal (at 9.8 ppm), an acetal signal (at 4.9 ppm), and a four proton multiplet (at 3.6–4.1 ppm) for the methylene groups of the 1,3-dioxolane ring were present. The crude ozonolysis product was also examined by capillary gc in combination with ei-ms and ci-ms. By selected ion monitoring techniques, no evidence for the presence of β-hydroxy esters of **3** or **7** was obtained. The main component gave a weak molecular ion for **7** under ei conditions and the base peak (at *m/z* 73) suggested that the 1,3-dioxolane ring was present. Under ci-ms conditions, the most prominent ion of the main component occurred at *m/z* 173, which represented the quasimolecular ion for **7**. Ions were also seen at *m/z* 155 [(*M* + 1) − 18] and *m/z* 111 [(*M* − 1) − 60].

The crude material from ozonolysis experiments was purified by chromatography with silica gel and **7** was isolated in reasonable yields (40–80%). The use of high pressure liquid chromatography for purification of **7** was preferred. It was also important to stop the reaction as soon as **3** had disappeared and to use dimethylsulfide (30) as a reducing agent. The structure of **7** was confirmed by the synthesis of this aldehyde by reaction of **3** with osmium tetroxide and sodium periodate (Experimental section).

cis-*Oxidized derivatives of* **3**

The preparation of *Z* alcohol (**8**), and the subsequent conversion of **8** with manganese dioxide to *Z* aldehyde (**9**) and, via the cyanohydrin of **9**, to *Z* ester (**10**) depended on the functionalization of **7** with the hydroxyisopropenyl group. Since *Z* trisubstituted olefinic alcohols have been obtained from ketal aldehydes in this laboratory by a Wittig reaction (8), it was anticipated that acetal aldehyde (**7**) would behave analogously. In fact, the Wittig reaction on **7**, performed by adding **7** to a cold solution of ethylidenetriphenylphosphorane in THF, followed by the addition of *n*-butyllithium, formaldehyde, and water gave the desired **8**, in yields ranging from 0–50%. In comparison to dry paraformaldehyde or *s*-trioxane, gaseous formaldehyde, generated according to the procedure of Benkeser *et al.* (31), gave the best yield of **8**. The identity of **8** was confirmed from elemental analysis and from spectral comparisons to samples of the *E* alcohol (**6**). Noteworthy differences in nmr chemical shift values were apparent for the methyl, methylene, and vinyl protons of the isobutenyl group (Experimental section) and were in agreement with published values on isomers related to **6** and **8** (6, 8, 11). Capillary gc on samples of **8** showed that **6** was also present but only to the extent of 1–2%. Possible reasons for the remarkable stereoselectivity in this type of Wittig reaction have already been discussed (32).

For the preparation of **9**, pure samples of **8** were oxidized with activated manganese dioxide in hexane (9). Despite the high *Z* isomer content of **8** (98–99%), the nmr spectrum showed that the product was a mixture of isomeric aldehydes consisting predominantly of **9**. Thus, a main signal for the aldehyde proton in **9** resonated at 10.1 ppm and a minor signal was seen at 9.4 ppm which had the same chemical shift as the aldehyde proton for the *E* isomer (**4**). This *Z* to *E* isomerization, estimated at 25–30% in an experiment with a large excess of manganese dioxide, was reduced to 5–10% by the gradual addition of a minimum quantity of the reagent. Attempts to further suppress this isomerization were unsuccessful (Experimental section).

The **9** isolated from these experiments was an unstable compound and freshly isolated samples were used without purification for the synthesis of **10**. Cyanohydrin formation, followed by oxidation with manganese dioxide in methanol (as described for **5**), gave a mixture of **5** and **10**. This was confirmed by mass spectrometry. Capillary gc showed that there was from 15% to 32% of **5** in all samples of **10**. This amount was discernible in the nmr spectrum, particularly by comparison of chemical shifts for the vinylic proton. In **10**, this signal occurred at 5.9 ppm whereas the same signal for **5** was seen at 6.8 ppm.

The mass spectra of the isomeric pairs of esters and alcohols were very similar, especially under ei-ms conditions. A noteworthy difference in the ci-ms of **6** and **8** was apparent in the intensities of ions at *m/z* 153 [(*M* − 1) − 60] and *m/z* 197 [(*M* + 1) − 18]. Comparisons between the isomeric aldehydes were impractical because **9** was not amenable to capillary gc analyses.

The methodology described here illustrates a possible solution to the problem of obtaining authentic samples of the metabolites formed by eq. [1].

Experimental

Proton nuclear magnetic resonance (nmr) spectra were obtained on a Varian EM-360 A spectrometer using tetramethylsilane as the internal standard. Infrared spectra were taken as liquid films on a Perkin–Elmer Model 137 Infracord spectrophotometer. For capillary gc, a Hewlett–Packard 5838A instrument equipped with a model 18835B capillary inlet system was used. The glass column (22 m × 0.31 mm id) was wall coated with Carbowax 20M-terephthalic acid according to the method of Grob and Grob (33). Helium at a velocity of 30 cm/s served as the carrier gas and nitrogen at a flow rate of 30 mL/min was used as a make-up gas for the flame ionization detector. Samples were

injected by the split technique. The injector and detector temperatures were 225°C and 250°C, respectively. For mass spectrometry, a Hewlett–Packard 5985B gc–ms computer system was used with a glass capillary column (55 m × 0.31 mm id) coated with Carbowax 20M-terephthalic acid. Electron-impact mass spectra were recorded at 70 eV whereas positive chemical ionization mass spectra were recorded using isobutane as the reagent gas at a source pressure of 0.5 Torr. High pressure liquid chromatography was performed with a Waters Prep LC/System 500 A instrument equipped with a Prep PAK Silica cartridge (Waters Associates, Inc.). Mallinckrodt cc-7 silica gel was used for column chromatography. Elemental analyses were obtained from Dr. C. Daessle, Montreal, Quebec. Melting points and boiling points are uncorrected.

Citronellal (Eastman P312), *tert*-butylhydroperoxide (Aldrich 18,471-3), selenium dioxide (K and K, 17660), activated manganese dioxide (K and K, 28107), and ethyl triphenylphosphonium bromide (Aldrich E5, 060-4) were used as received. *n*-Butyllithium (Aldrich 18,617-1) was standardized by titration (34) before use. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride and then redistilled immediately before use from sodium and benzophenone. Evaporations were performed with a Büchi rotary evaporator at water aspirator vacuum and a bath temperature of 25–35°C.

2-(2,6-Dimethyl-5-heptenyl)-1,3-dioxolane (3)

This acetal was prepared from **1** (77 g, 0.5 mol), ethylene glycol (44.5 g, 0.72 mol), *p*-toluenesulfonic acid (0.1 g), and benzene as described in the literature (17). A center portion of the distillate gave **3** (57 g, 57.5% yield) as a colorless oil. Capillary gc (temperature programmed from 100°C to 130°C at 3°C/min) showed 78% of **3** with a retention time of 9.9 min. Pure samples of **3** were obtained in 48–52% overall yield by preparative hplc with 2% ethyl acetate in methylene chloride: bp 76–78°C (0.3 Torr) (lit (17) bp 125–130°C (18 Torr)); nmr ($CDCl_3$) δ: 5.17 (m, C=C*H*), 4.90 (t, J = 4 Hz, acetal *H*), 4.10–3.53 (m, OCH_2CH_2O), 2.43–1.13 (m, 13 *H*), 0.96 (d, J = 5 Hz, $CHCH_3$); ei-ms *m/z* (% relative abundance): 198 (M^+, 4), 197 (2), 121 (61), 113 (78), 73 (100); ci-ms: 199 (MH^+, 45), 197 (4), 139 (100), 137 (54).

5-(1,3-Dioxolan-2-yl)-4-methyl-1-pentanal (7)

Using an ozone-generating apparatus previously described in detail (8), **3** (14 g, 70 mmol) in methylene chloride solution (Caledon glass distilled, 300 mL) at −78°C was allowed to react with ozone until the starting material had just been consumed (gc evidence). With dual ozonizers and an oxygen flow rate of 12 L/h, the time of reaction was 7 h (± 30 min). The cold mixture was swept with nitrogen for 30 min and dimethylsulfide (10 mL) was added. The mixture was gradually allowed to approach room temperature with continuous stirring during 16–18 h. A crude oil (~ 18 g) was obtained by removing the volatiles on a rotary evaporator. Capillary gc (as described for **3**) showed a major component (> 70% of the mixture) with a retention time of 15.8 min. Samples of **7** (80–90% purity) were isolated in 40–60% yields by column chromatography with silicAR cc-7 and eluting with hexane–ether mixtures. Alternatively, **7** (75–95% purity) was obtained in 50–80% yields by preparative hplc using a solvent system of 4% ethyl acetate in methylene chloride: bp 72–76°C (0.3 Torr); ir: 1725 cm^{-1} (C=O); nmr ($CDCl_3$) δ: 9.78 (m, aldehyde *H*), 4.90 (t, J = 4 Hz, acetal *H*), 4.10–3.60 (m, OCH_2CH_2O), 2.70–2.10 (m, 2*H*), 2.06–1.20 (m, 5*H*), 0.98 (d, J = 5.5 Hz, $CHCH_3$); ei-ms *m/z* (% relative abundance): 172 (M^+, 0.2), 171 (2), 73 (100); ci-ms: 173 (MH^+, 100), 171 (5), 155 (48), 111 (13), 93 (19). During ci-ms analyses, ions at *m/z* 215 and 189 were monitored but these ions, which correspond to quasi-molecular ions for β-hydroxy esters of **3** and **7**, were absent.

Aldehyde **7** (a colorless liquid) gave a crystalline, deep red 2,4-dinitrophenylhydrazone derivative, which was recrystallized from THF–water: mp 214–218°C. *Anal.* calcd. for $C_{15}H_{20}N_4O_6$: C 51.13, H 5.72, N 15.90; found: C 51.41, H 5.49, N 15.74.

Alternatively, **7** was prepared by stirring a mixture of **3** (9.915 g, 50 mmol), osmium tetroxide (0.051 g dissolved in ether, 0.2 mmol), dioxane, and water for 30 min at room temperature. Sodium periodate (20 g, 94 mmol) was added during 1 h and the mixture was heated at 50°C for 24 h (35). The mixture was filtered and the white precipitate was washed with ether. The aqueous layer was extracted with ether and the combined organic extracts were washed with 5% aqueous sodium carbonate and with water. The organic extract was dried (Na_2SO_4) and concentrated on a rotary evaporator to give 7.38 g of a crude product. Column chromatography with silicAR cc-7 and hexane–ether mixtures gave 1.9 g (22% yield) of **7** which had a purity of 70% by gc.

(E) *(4) and* (Z) *(9) isomers of 7-(1,3-dioxolan-2-yl)-2,6-dimethyl-2-hepten-1-al*

By oxidation of 3 with selenium dioxide

Following the literature method (7), **3** (11.9 g, 60 mmol) was allowed to react with a mixture of selenium dioxide (3.32 g, 30 mmol), *tert*-butylhydroperoxide (15.4 mL of a 70% aqueous solution, 120 mmol), and methylene chloride (60 mL) for 60 h. The reaction mixture was worked up as described (18) to give 8.78 g of a faint yellow oil. Capillary gc (160–180°C at 2°C/min) showed a major component (~ 60%) with a retention time of 10.75 min. A pure sample of **4** (2.3 g, 18% yield) was obtained by column chromatography with silicAR cc-7 and eluting with hexane–ether mixtures: ir: 1670 cm^{-1} (C=O); nmr ($CDCl_3$) δ: 9.40 (s, aldehyde *H*), 6.48 (ragged t, J = 7 Hz, C=C*H*), 4.88 (t, J = 4 Hz, acetal *H*), 4.07–3.63 (m, OCH_2CH_2O), 2.63–2.10 (m, 2*H*), 1.93–1.20 (m, 8*H*), 0.98 (d, J = 5.5 Hz, $CHCH_3$); ei-ms *m/z* (% relative abundance): 212 (M^+, O), 211 (1), 73 (100); ci-ms: 213 (MH^+, 100), 195 (3), 151 (35).

By oxidation of 8 with activated manganese dioxide

A mixture of **8** (2.143 g, 10 mmol), manganese dioxide (8.69 g, 100 mmol, added in portions during five days), and hexane (250 mL) was stirred at 20°C for 6 days and then filtered. A yellow oil (1.94 g) was obtained by removal of the solvent on a rotary evaporator. Capillary gc with Carbowax 20M-TPA and with SP 2300 (20 m × 0.29 mm id) showed a complex mixture of products, including a small peak with the same retention time as **4**. The mixture showed **9** and **4** by nmr ($CDCl_3$): δ: 10.15 (s, ~ 0.9 *H*, aldehyde *H* for *Z* isomer), 9.40 (s, ~ 0.1 *H*, aldehyde *H* for *E* isomer). This experiment was repeated at 0°C, by adding a total of 200 mmol of manganese dioxide in portions during two days to a suspension of **8** (4.2 g, 20 mmol) in hexane (400 mL). The product (3.30 g) contained **9** and **4** in an approximate ratio of 90:10 (nmr evidence). The same isomeric ratio was found on repeating this experiment with the Attenburrow grade of manganese dioxide (12.5-fold mole excess added during 2 days), which was prepared here by the literature method (36). When manganese dioxide (20-fold mole excess) was added in one portion to a mixture of **8** at 0°C, the reaction was completed in 4 h and the ratio of **9**/**4** was 70:30 (nmr evidence). Storage of neat samples resulted in a gradual decomposition of **9** to unidentified products. The aldehyde nmr signal for **9** had completely disappeared after storage of samples at 0°C for six months.

(E) *(5) and* (Z) *(10) isomers of the methyl ester of 7-(1,3-dioxolan-2-yl)-2,6-dimethyl-2-hepten-1-oic acid*

By manganese dioxide oxidation of the cyanohydrin of 4

A solution of **4** (2.16 g, 10.2 mmol) in methanol (150 mL) was stirred with sodium cyanide (2.5 g, 51 mmol) and glacial acetic acid (1.0 mL) for 1 h. Activated manganese dioxide (17.73 g, 204

mmol) was then added and the mixture was stirred at room temperature for 90 h. The mixture was filtered, the filtrate evaporated on a rotary evaporator, and the residue dissolved in chloroform. Washing with water and evaporating the dried ($MgSO_4$) organic phase gave 2.06 g (83% yield) of a yellow oil. The residue gave a main peak (98%) at 13.37 min and a minor peak (2%) at 10.05 min when analyzed by capillary gc (as described for **4**). The sample was purified by column chromatography (silicAR cc-7) with hexane–ether mixtures to give **5** as a colorless oil: bp 80–85°C (0.05 Torr); ir: 1720 cm^{-1} (C=O); nmr ($CDCl_3$) δ: 6.77 (ragged t, J = 7 Hz, C=C*H*), 4.92 (t, J = 4 Hz, acetal *H*), 4.10–3.80 (m, OCH_2CH_2O), 3.75 (s, OCH_3), 2.47–2.00 (m, 2*H*), 1.93–1.13 (m, 8*H*), 0.99 (d, J = 5.5 Hz, $CHCH_3$); ei-ms *m/z* (% relative abundance): 242 (M^+, O), 241 (1), 73 (100); ci-ms: 243 (MH^+, 100), 211 (25), 183 (4), 181 (7). *Anal.* calcd. for $C_{13}H_{22}O_4$: C 64.43, H 9.15; found: C 64.67, H 9.43.

By manganese dioxide oxidation of the cyanohydrin of ***9***

A crude sample of **9** (1.9 g, ~ 9 mmol) in methanol (150 mL) was allowed to react with sodium cyanide (2.45 g, 50 mmol) and glacial acetic acid (1.0 mL), then with activated manganese dioxide (17.39 g, 200 mmol) for 160 h at 20°C as described for the preparation of **5**. A yellow oil (2.05 g, 90% yield) was isolated. Capillary gc (as described for **4**) showed **10** at 10.05 min and **5** at 13.37 min in a ratio of 82:18. Column chromatography (silicAR cc-7) with hexane–ether mixtures gave predominantly **10** as a colorless oil: bp 96–100°C (0.05 Torr); ir: 1720 cm^{-1} (C=O); nmr ($CDCl_3$) δ: 5.93 (ragged t, J = 7 Hz, C=C*H*), 4.93 (t, J = 4 Hz, acetal *H*), 4.10–3.80 (m, OCH_2CH_2O), 3.76 (s, OCH_3), 2.73–2.10 (m, 2*H*), 2.00–1.00 (m, 8*H*), 0.98 (d, J = 5.5 Hz, $CHCH_3$); ei-ms *m/z* (% relative abundance): 242 (M^+, 0.1), 241 (1), 73 (100); ci-ms: 243 (MH^+, 100), 211 (44), 183 (5), 181 (16). *Anal.* calcd. for $C_{13}H_{22}O_4$: C 64.43, H 9.15; found: C 64.17, H 9.16.

In three additional experiments on this oxidation (as described), crude samples of **10** contained from 15–25% of the *E* isomer (**5**) (capillary gc and nmr evidence). The ratio of **10/5** was 68:32 in another experiment with manganese dioxide prepared by the method of Attenburrow *et al.* (36).

(E)*(6) and* (Z)*(8) isomers of 7-(1,3-dioxolan-2-yl)-2,6-dimethyl-2-hepten-1-ol*

By reduction of ***4*** *with sodium borohydride*

A crude sample of **4** (1.83 g, 8.6 mmol) in 95% ethanol (30 mL) at 6°C was treated dropwise with a solution of sodium borohydride (1.085 g, 29.0 mmol) in 95% ethanol (30 mL; pH adjusted to 8 with NaOH) during 45 min. The mixture was stirred at room temperature for 18 h. Acetone (15 mL) was added and the solvents were evaporated on a rotary evaporator. The residue was dissolved in saturated brine and extracted with ether. The ether extract was dried ($MgSO_4$) and evaporated. There was obtained 1.636 g (88.6%) of **6** which eluted at 18.02 min under conditions of capillary gc analysis (as described for **4**). An analytically pure sample, as a colorless oil, was obtained by column chromatography (silicAR cc-7), eluting with hexane–ether mixtures: bp 82–84°C (0.1 Torr); ir: 3490 cm^{-1} (OH); nmr ($CDCl_3$) δ: 5.40 (ragged t, J = 7 Hz, C=C*H*), 4.90 (t, J = 4 Hz, acetal *H*), 4.10–3.63 (m, OCH_2CH_2O and CH_2OH), 1.93 (broad s, CH_2OH, exchanged with D_2O), 1.67 (s, $C=CCH_3$), 2.30–1.10 (m, 7*H*), 0.95 (d, J = 5.5 Hz, $CHCH_3$); ei-ms *m/z* (% relative abundance): 214 (M^+, O), 213 (0.5), 113 (59), 73 (100); ci-ms: 215 (MH^+, 13), 213 (11), 197 (100), 155 (5), 153 (93), 137 (25), 135 (62). *Anal.* calcd. for $C_{12}H_{22}O_3$: C 67.25, H 10.35; found: C 67.34, H 10.46.

By reduction of ***5*** *with lithium borohydride*

To a mechanically stirred suspension of lithium borohydride (0.022 g, 1.0 mmol) in THF (5 mL) was added dropwise a solution of **5** (0.1 g, 0.41 mmol) in THF (3 mL). The mixture was stirred under an argon atmosphere for 16 h at 20°C, then heated under reflux for 21 h. Water was added and the pH was adjusted to 1 with 0.1 *N* hydrochloric acid. The product was isolated by extraction with ethyl acetate. The organic extracts were washed with water and saturated brine, then dried ($MgSO_4$) and concentrated on a rotary evaporator. The colorless oil (51 mg) when subjected to capillary gc (as described for **4**) and gc–ms showed the *E* alcohol (**6**, ~ 56% of the mixture) and the *Z* alcohol (**8**, ~ 1%). A component at 14.13 min (~ 27%) was identified by capillary gc–ms as the saturated alcohol, 7-(1,3-dioxolan-2-yl)-2,6-dimethyl-1-heptanol: ei-ms *m/z* (% relative abundance): 216 (M^+, O), 215 (1), 73 (100); ci-ms: 217 (MH^+, 100), 215 (5), 199 (8), 155 (44), 137 (11).

By reaction of ***7*** *in the Wittig reaction*

The preparation of ethylidenetriphenylphosphorane from ethyltriphenylphosphonium bromide (19.45 g, 52.4 mmol) and *n*-butyllithium (52.4 mmol) in THF (125 mL) was performed at 0°C as previously described (8). Aldehyde **7** (9.0 g from hplc, 52.4 mmol) was added by syringe at −78°C and, after 20 min of mechanical stirring, another 52.4 mmol of *n*-butyllithium was added. After 45 min, the Dry Ice bath was replaced by crushed ice. When the temperature was −5°C, formaldehyde gas (~ 3 g, freshly generated from 11.1 g of dried paraformaldehyde (31)) was delivered above the reaction mixture during 10 min. The color changed from deep red to creamy white during the delivery of formaldehyde. After stirring at 20°C for 12 h, the product was isolated as described (8). Distillation of the crude product *in vacuo* gave a volatile fraction (1.5 g, bp 57–98°C at 0.1 Torr) and another fraction (bp 98–120°C at 0.1 Torr) which was identified as **8** (4.86 g, 43.4%). Capillary gc (as described for **4**) on the first fraction showed several components. Two major components were seen with retention times of 2.8 and 2.9 min. These were tentatively identified by capillary gc–ms as 3-methyl-6-octen-1-al ethylene acetal (a 1:1 mixture of *E* and *Z* isomers); ei-ms *m/z* (% relative abundance); 184 (M^+, O), 183 (1), 73 (100) for both isomers; ci-ms showed prominent ions at 185, 125, and 123. Capillary gc on the second fraction from distillation showed a main peak (75–85% of the mixture) with a retention time of 15.85 min. This fraction was purified by column chromatography (silicAR cc-7) with hexane–ether mixtures, followed by redistillation. A pure sample of **8** was obtained as a colorless oil: bp 107°C (0.1 Torr); ir: 3490 cm^{-1} (OH); nmr ($CDCl_3$) δ: 5.26 (ragged t, J = 7 Hz, C=C*H*), 4.90 (t, J = 4 Hz, acetal *H*), 4.11–3.63 (m, OCH_2CH_2O and CH_2OH), 2.05 (broad s, CH_2OH, exchanged with D_2O), 1.80 (s, $C=CH_3$), 2.33–1.13 (m, 7*H*), 0.95 (d, J = 5.5 Hz, $CHCH_3$), ei-ms *m/z* (% relative abundance): 214 (M^+ O), 213 (0.5), 113 (60), 73 (100); ci-ms: 215 (MH^+, 16), 213 (5), 197 (50), 153 (100), 137 (17), 135 (35). *Anal.* calcd. for $C_{12}H_{22}O_3$: C 67.25, H 10.35; found: C 67.05, H 10.60.

This reaction was repeated as described except gaseous formaldehyde (generated by heating paraformaldehyde in a vessel connected to the reaction flask by means of glass tubing) was used. Delivery of formaldehyde above the surface of the reaction, which was at −15°C, ultimately gave **8** in 43% yield. Delivery of formaldehyde below the surface of the reaction (at −78°C) resulted in the formation of a thick solid from which **8** was isolated in 25% yield. Addition of paraformaldehyde directly to the reaction mixture (at 0°C, −5°C, or −78°C) gave **8** in yields ranging from 11–29%. None of the desired **8** was isolated when excess *s*-trioxane (added at −5°C) was used as the source of formaldehyde. Volatile side products accounted for the majority of material in these experiments.

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