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Short communication

An expeditious synthesis of 4-hydroxy-2(*E*)-nonenal (4-HNE), its dimethyl acetal and of related compounds

Laurent Soulère [a,b,c,*], Yves Queneau [a,b,c], Alain Doutheau [a,b,c]

[a] *ICBMS, Institut de Chimie et Biochimie Moléculaires et Supramoléculaires, université de Lyon, université Lyon 1, CNRS, UMR 5246, Lyon F-69622, France*
[b] *CPE Lyon, Villeurbanne F-69616, France*
[c] *Laboratoire de Chimie Organique, INSA-Lyon, 20 avenue Albert Einstein, Villeurbanne F-69621, France*

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Abstract

The facile one step synthesis of 4-hydroxy-2(*E*)-nonenal and its dimethyl acetal via a cross-metathesis reaction between commercially available octen-3-ol and acrolein or its dimethyl acetal is reported. The method was extended to the synthesis of C_6 and C_{12} 4-hydroxy-2(*E*)-enals, their dimethyl acetal and of the 4-hydroxy-2(*E*)-nonenoic acid (4-HNA).

Keywords: 4-Hydroxy-2(*E*)-nonenal (4-HNE); 4-Hydroxy-2(*E*)-alkenals; 4-Hydroxy-2(*E*)-alkenal dialkyl acetals; 4-Hydroxy-2(*E*)-nonenoic acid (4-HNA); Lipid peroxidation; Cross-metathesis

1. Introduction

Endogenic 4-hydroxyalkenals, which result from peroxidation of unsaturated fatty acid derivatives, are important compounds displaying various biological activities (Esterbauer et al., 1991; Robino et al., 2001). In particular 4-hydroxy-2(*E*)-nonenal (4-HNE) (Comporti, 1998; Petersen and Doorn, 2004) plays a major role in several biological processes such as oxidative stress (Poli and Schaur, 2000), apoptosis (Castello et al., 2005) and regulation of mitochondrial uncoupling (Echtay et al., 2003).

Consequently, several syntheses of 4-HNE and of its more stable dialkyl acetal precursor, have been reported in the literature. Since the first synthesis of 4-hydroxy-2(*E*)-alkenals by Esterbauer et al. more than 35 years ago using the reaction of the 3,3-diethoxypropynyl Grignard reagent on aldehydes and subsequent reduction of the triple bound followed by the hydrolysis of the acetal function (Esterbauer and Weger, 1967; Esterbauer, 1971), these syntheses were based on two sequential oxidation of 3(*Z*)-nonenol leading to 3,4-epoxynonenal further converted to 4-HNE in basic conditions (Gardner et al., 1992) or on Grignard reactions using the fumaraldehyde monodimethyl acetal with the 1-bromo-pentane (Grée and Carrié, 1986; Chandra and Srivastava, 1997). 4-Hydroxyalkenals are also accessible by DIBAL(H) reduction of 4-hydroxyalkenoic esters (Bacot et al., 2003) obtained from aldehydes using the Tanikaga conditions (Tanikaga et al., 1983). Very recently, Kurangi et al. (2006) reported the synthesis of 4-HNE using Wittig or Horner–Wardsworth–Emmons reactions between either a phosphorane or a phosphonate

* Corresponding author at: Laboratoire de Chimie Organique, INSA-Lyon, 20 avenue Albert Einstein, Villeurbanne F-69621, France. Tel.: +33 4 72 43 83 42; fax: +33 4 72 43 88 96.
E-mail address: laurent.soulere@insa-lyon.fr (L. Soulère).

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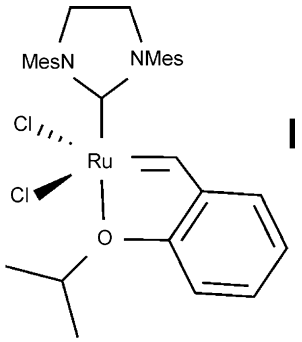


I

Scheme 1. Structure of the ruthenium catalyst **I**.

with glyoxal dimethyl acetal followed by the reduction of the carbonyl group and hydrolysis of the acetal function.

In the last years, olefin metathesis proved to be a versatile tool in organic synthesis. The development of new catalysts for cross-metathesis or ring closure metathesis has indeed promoted the use of this reaction for the total synthesis of natural products (Prunet, 2003, 2005; Piscopio and Robinson, 2004; Villar et al., 2007). Particularly, the Hoveyda–Grubbs catalyst 2nd Generation **I** (Scheme 1) has been efficiently employed for the synthesis via cross-metathesis of various functionalized olefins (Kingsbury et al., 1999; Connon and Blechert, 2003).

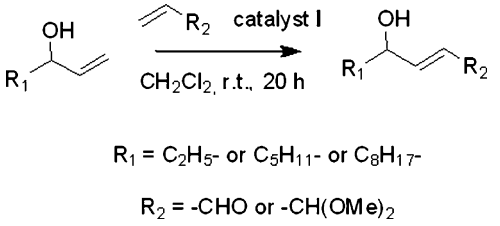
To our knowledge, only one 4-hydroxy-alkenal (4-hydroxy-2(*E*)-hexenal) has been prepared using cross-metathesis as an intermediate in the total synthesis of a natural compound (BouzBouz et al., 2004). None example are known in the case of 4-hydroxyalkenal dialkyl acetals.

Here we describe a facile one step synthesis of 4-HNE, 4-hydroxy-2(*E*)-hexenal (4-HHE), 4-hydroxy-2(*E*)-dodecenal (4-HDE) and their corresponding dimethyl acetal using the cross-metathesis reaction between readily available allylic alcohols and acrolein or acrolein dimethyl acetal, respectively, using **I** as catalyst. The method was also applied to the synthesis of the 4-hydroxy-2(*E*)-nonenoic acid (4-HNA) via its *tert*-butyl ester.

2. Results and discussion

The synthetic approach used to prepare 4-hydroxy-2(*E*)-alkenals and their related acetals is based on a cross-metathesis reaction between allylic alcohols and an excess of acrolein or acrolein dimethyl acetal (3 equiv.) (Scheme 2).

The reaction was performed in dry, oxygen free dichloromethane in the presence of the ruthenium catalyst **I** (0.025 equiv.). Monitoring of the reaction by TLC showed the appearance of a more polar product compared to the allylic alcohol. Purification of the crude reaction product by flash column chromatography furnished the corresponding 4-hydroxy-2(*E*)-alkenals or acetal derivatives. In the case of acetal derivatives, triethylamine (0.1%) was added to the eluant to avoid the hydrolysis of the acetal group on silica gel. The identification of all compounds was based on the comparison of ^{1}H NMR spectra with literature data (see Section 3).



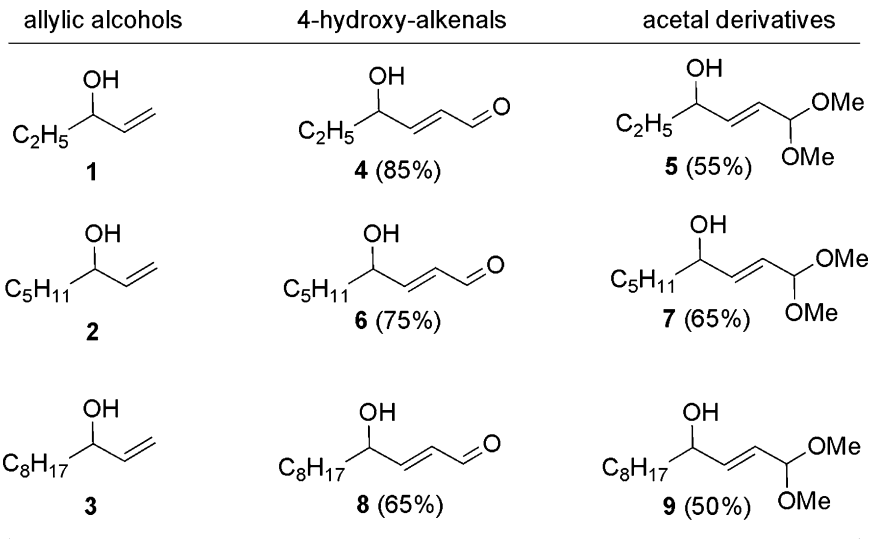
Scheme 2. Synthetic route to 4-hydroxy-2(*E*)-alkenals and to their related acetal derivatives.

As expected (Cossy et al., 2001; Chatterjee et al., 2003), only the (*E*) isomer was obtained as shown by ^{1}H NMR spectra ($^3J_{H2–H3}$ = 15.4, 15.6 or 15.8 Hz) of crude products.

We thus prepared the 4-hydroxy-2(*E*)-hexenal (4-HHE, **4**) and the corresponding acetal (**5**) from penten-3-ol (**1**) in 85% and 55% yield, respectively, the 4-hydroxy-2(*E*)-nonenal (4-HNE, **6**) and the related acetal (**7**) from octen-3-ol (**2**) in 75% and 65% yield, respectively, and the 4-hydroxy-2(*E*)-dodecenal (**8**) and the related acetal (**9**) from undecen-3-ol (**3**) in 65% and 50% yield, respectively (Scheme 3).

The synthetic approach proved also to be efficient for the preparation of the 4-hydroxy-2(*E*)-nonenoic acid (4-HNA), a marker of lipid peroxidation resulting from the metabolism of 4-HNE (Guichardant et al., 2004; Brichac et al., 2007). Previous works described the multistep synthesis of this acid as a result of the reaction of the pentenyl trichloromethyl carbinol (Shamshina and Snowden, 2006) or the 4-chloro-3(*Z*)-nonenoic acid (Kawashima et al., 1988) in aqueous NaOH as last step. We prepared the 4-hydroxy-2(*E*)-nonenoic acid in a two steps sequence: a cross-metathesis reaction between the octen-3-ol (**2**) and the *tert*-butyl acrylate leading to the 4-hydroxy-2(*E*)-nonenoic acid *tert*-butyl ester **10** in 65% yield; this ester was then deprotected in high yield to the 4-HNA (**11**) (Scheme 4).

To summarize we described here the use of cross-metathesis for the convenient and efficient synthesis of 4-HNE and related biologically relevant compounds. This synthetic approach was found to give good yields and



Scheme 3. Structure of the allylic alcohols used as starting materials and of the synthetic 4-hydroxy-2(*E*)-alkenals and their corresponding dimethyl acetals.

to be rapid and easy to carry out with commercially or readily available starting materials.

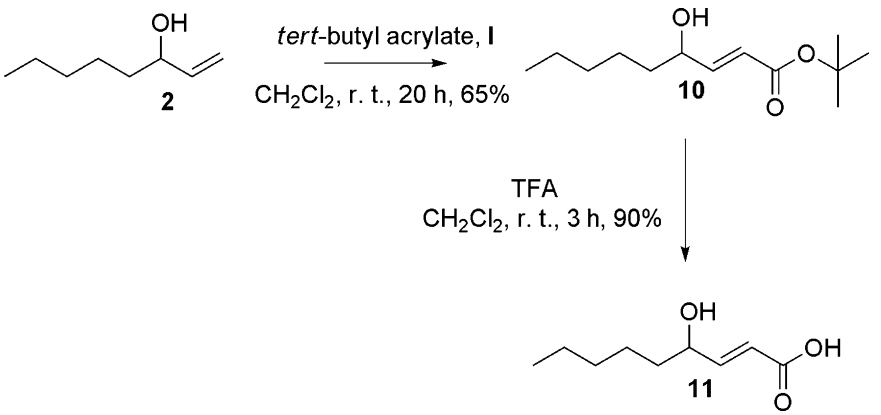
3. Experimental procedures

3.1. Materials

All chemicals (allylic alcohols **1** and **2**, acrolein, acrolein dimethyl acetal and the catalyst **I**) were purchased from Sigma–Aldrich. Undecen-3-ol was prepared from nonanal and vinyl magnesium bromide (Ramiandrasoa and Descoins, 1990). The reactions were performed under nitrogen and were monitored by thin-layer chromatography on Silica Gel 60 F254 (Merck); detection was carried out by charring with a 5% phosphomolybdic acid solution in ethanol containing 10% of H_2SO_4. Silica gel (Kieselgel 60, 70–230 mesh ASTM, Merck) was used for flash chromatography. The ^1H (300 MHz) and ^{13}C (75 MHz) spectra were recorded with a Bruker ALS300 or DRX300 spectrometer. The signal of the residual protonated solvent was taken as reference. Chemical shift (δ) and coupling constants (J) are reported in ppm and Hz, respectively. IR spectra were recorded on a Nicolet Magna 550 FT-IR Spectrometer.

3.2. General procedure

To a solution of allylic alcohol (1 mmol, 1 equiv.) and acrolein (3 equiv.) or acrolein dimethyl acetal (3 equiv.) in dry, oxygen free CH_2Cl_2 was added the Hoveyda–Grubbs catalyst **I** (0.025 equiv.) in two equal portion at $t = 0$ and $t = 5$ h. After stirring for further 20 h



Scheme 4. Synthesis of the 4-hydroxy-2(*E*)-nonenoic acid (4-HNA, **11**).

at room temperature, the solvent was evaporated and the residue was purified by flash column chromatography (Et_2O/pentane: 50/50 for **4**, AcOEt/pentane: 30/70 for **6** and Et_2O/pentane: 40/60 for **8**) to give the 4-hydroxy-2(*E*)-alkenals or (Et_2O/pentane with 0.1% Et_3N: 50/50 for **5** and **7** and 40/60 for **9**) to give the 4-hydroxy-2(*E*)-alkenal dimethyl acetals. 4-Hydroxy-2(*E*)-hexenal (**4**, 4-HHE, 85% yield): IR (neat) ν_{max} 970, 1116, 1692, 2839, 2959, 3436 cm^{-1}; ^1H NMR (acetone, d_6) (BouzBouz et al., 2004): δ 0.97 (t, J = 7.5, 3H), 1.53–1.72 (m, 2H), 4.30 (d, J = 4.9, 1H), 4.32–4.40 (m, 1H), 6.26 (ddd, J = 1.9, 7.9 and 15.8, 1H), 7.02 (dd, J = 4.1, 15.8, 1H), 9.6 (d, J = 7.9, 1H); ^{13}C NMR (acetone, d_6): δ 9.6, 29.8, 71.9, 130.8, 161.0, 193.9.

4-Hydroxy-2(*E*)-nonenal (**6**, 4-HNE, 75% yield): IR (neat) ν_{max} 983, 1633, 1686, 2866, 2932, 3437 cm^{-1}; ^1H NMR (acetone, d_6) (De Montarby et al., 1989): δ 0.88 (t, J = 6.7, 3H), 1.29–1.36 (m, 4H), 1.40–1.70 (m, 4H), 4.28 (d, J = 5.3, 1H), 4.38–4.46 (m, 1H,), 6.25 (ddd, J = 1.7, 7.9 and 15.6, 1H), 7.01 (dd, J = 4.3, 15.6, 1H), 9.6 (d, J = 7.9, 1H); ^{13}C NMR (acetone, d_6): δ 14.2, 23.1, 25.5, 32.3, 37.1, 70.8, 130.8, 161.6, 194.0.

4-Hydroxy-2(*E*)-dodecenal (**8**, 65% yield): IR (neat) ν_{max} 983, 1135, 1692, 2855, 2925, 3447 cm^{-1}; ^1H NMR (acetone, d_6) (Iriye et al., 1990): δ 0.88 (t, J = 7.0, 3H), 1.28–1.33 (m, 10H), 1.39–1.68 (m, 4H), 4.27 (d, J = 5.3, 1H), 4.38–4.46 (m, 1H,), 6.25 (ddd, J = 1.9, 7.9 and 15.4, 1H), 7.02 (dd, J = 4.1, 15.4, 1H), 9.6 (d, J = 7.9, 1H); ^{13}C NMR (acetone, d_6): δ 14.3, 23.3, 25.9, 32.6, 38.2, 52.5, 71.7, 103.6, 126.7, 139.2.

4-Hydroxy-2(*E*)-hexenal, dimethyl acetal (**5**, 55% yield): IR (neat) ν_{max} 963, 1062, 1348, 1460, 2826, 2979, 3450 cm^{-1}; ^1H NMR (acetone, d_6) (Rees et al., 1995): δ 0.90 (t, J = 7.5, 3H), 1.45–1.55 (m, 2H), 3.24 (s, 6H). 3.80 (d, J = 4.9, 1H), 3.98–4.06 (m, 1H), 4.75 (d, J = 4.9, 1H), 5.58 (ddd, J = 1.5, 4.9 and 15.8, 1H), 5.83 (ddd, J = 1.1, 5.7 and 15.8, 1H); ^{13}C NMR (acetone, d_6): δ 9.9, 30.8, 52.4, 72.8, 103.4, 126.8, 138.6.

4-Hydroxy-2(*E*)-nonenal, dimethyl acetal (**7**, 65% yield): IR (neat) ν_{max} 977, 1070, 1370, 1467, 2853, 2939, 3436 cm^{-1}; ^1H NMR (acetone, d_6) (De Montarby et al., 1989): δ 0.88 (t, J = 6.8, 3H), 1.28–1.37 (m, 4H), 1.43–1.50 (m, 4H). 3.24 (s, 6H), 3.77 (d, J = 4.5, 1H), 4.06–4.11 (m, 1H), 4.75 (d, J = 4.9, 1H), 5.57 (ddd, J = 1.1, 4.9 and 15.4, 1H), 5.84 (ddd, J = 1.1, 5.0 and 15.4, 1H); ^{13}C NMR (acetone, d_6): δ 14.4, 23.3, 26.0, 30.0, 30.3, 32.6, 37.3, 71.0, 130.9, 161.7, 194.1.

4-Hydroxy-2(*E*)-dodecenal, dimethyl acetal (**9**, 50% yield): IR (neat) ν_{max} 971, 1055, 1355, 1457, 2855, 2954, 3425 cm^{-1}; ^1H NMR (acetone, d_6): δ 0.88 (t, J = 6.8, 3H), 1.26-1-34 (m, 10H), 1.43–1.51 (m, 4H). 3.24 (s, 6H), 3.77 (d, J = 4.5, 1H), 4.06–4.13 (m, 1H), 4.75 (d, J = 4.9, 1H), 5.58 (ddd, J = 1.1, 4.9 and 15.8, 1H), 5.84 (ddd, J = 1.1, 5.7 and 15.8, 1H); ^{13}C NMR (acetone, d_6): δ 14.4, 23.3, 26.3, 30.0, 30.3, 30.4, 32.6, 38.3, 54.47, 52.51, 71.7, 103.5, 126.7, 139.2. HR-MS (ESI) calcd for $C_{14}H_{28}NaO_3$ (MNa^+): 267.1936, found: 267.1935.

4-Hydroxy-2(*E*)-nonenoic acid *tert*-butyl ester (**10**): this compound (colourless oil) was prepared according the general procedure via a cross-metathesis reaction between the octen-3-ol (1 equiv.) and the acrylic acid *tert*-butyl ester (3 equiv.) in 65% yield. IR (neat) ν_{max} 996, 1260, 1314, 1659, 1715, 2853, 2936, 3429 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.89 (t, J = 6.8, 3H), 1.28–1.44 (m, 6H), 1.49 (s, 9H), 1.54–1.59 (m, 2H), 4.27–4.28 (m, 1H), 5.96 (dd, J = 1.5 and 15.4, 1H), 6.84 (dd, J = 4.9 and 15.4, 1H); ^{13}C NMR ($CDCl_3$): δ 13.9, 22.5, 24.8, 28.0, 31.6, 36.6, 71.1, 80.4, 121.9, 148.9, 165.8. HR-MS (CI) calcd for $C_{13}H_{25}O_3$ (MH^+): 229.1804, found: 229.1805.

4-Hydroxy-2(*E*)-nonenoic acid (**11**, 4-HNA): to a solution of **10** (0.06 g, 0.26 mmol) in CH_2Cl_2 (4 mL) was added TFA (2 mL). After 3 h of stirring at room temperature, 10 mL of toluene was added and the solvent was evaporated. The residue was purified by flash column chromatography (Et_2O/pentane: 70/30) to give a colourless oil (0.04 g, 90%). IR (neat) ν_{max} 1268, 1407, 1653, 1699, 2919, 3390 cm^{-1}; ^1H NMR ($CDCl_3$) (Alevi et al., 1993): δ 0.89 (t, J = 6.4, 3H), 1.31–1.45 (m, 6H), 1.56–1.64 (m, 2H), 4.31–4.37 (q, J = 5.0, 1H), 6.06 (d, J = 15.8, 1H), 7.05 (dd, J = 5.0 and 15.8); ^{13}C NMR ($CDCl_3$): δ 13.9, 22.4, 24.8, 31.5, 36.3, 71.1, 119.4, 152.6, 171.4.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.chemphyslip.2007.07.003.

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