# A short method for the synthesis of hydroxyoleic acids

**Daniela Imperio,[1] Laura Morelli,[2] Luigi Panza[1]***

[1] Dipartimento di Scienze del Farmaco, Università del Piemonte Orientale, Largo Donegani 2, 28100 Novara, Italy.
[2] Dipartimento di Biotecnologie Mediche e Medicina Traslazionale, Università degli Studi di Milano, Via Saldini 50, 20133 Milano, Italy

***Correspondence:** Luigi Panza, Dip. di Scienze del Farmaco, L.go Donegani, 2 Novara – Italy

**Fax:**+390321375621; **Email:** luigi.panza@uniupo.it

**Running Title:** hydroxylated oleic acid

**Keywords:** hydroxyoleic acid, macrolactone, TEMPO, Grignard, natural products

**Abbreviations:** CPDA, 15-hydroxypentadecanoic acid; DIBAL-H, Diisobutylaluminium hydride; TEMPO, (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl; KHMDS, Potassium bis(trimethylsilyl)amide

## Abstract

Enzymatic or microbiological oxidation of oleic acid can afford azelaic acid as a building block for bioplastics. However, during the oxidation, the formation of hydroxylated byproducts is observed. To better follow the oxidation reaction, the availability of reference compounds is of great importance. To this aim, the synthesis of a series of oleic acids hydroxylated at ω - 1, ω - 2, ω - 3 positions is described without the use of protecting groups. The final products are obtained by partial lactone reduction to hydroxyaldehyde followed by Grignard addition, selective oxidation of the primary hydroxyl group, and Wittig reaction.

.

## 1 Introduction

Hydroxycarboxylic acids are a subclass of carboxylic acids of broad interest, ranging from short- (e.g. lactic acid) to long-chain components (Lipsa et al., 2010; Ranathunge et al, 2011), which can be obtained from natural sources or by chemical synthesis (Datta, 2004). Hydroxycarboxylic acids and their derivatives find multiple applications in different fields as dermopharmaceuticals and cosmetics (Green et al., 2009; Dal Farra et al., 2002), in the chemical modification of surfaces due to their attitude to forming self-assembling monolayers, and in the perfumery industry. As an example, 15-hydroxypentadecanoic acid (CPDA) is an important precursor of the most widely produced macrocyclic synthetic musk lactone, cyclopentadecanolide (Williams, 1999, Iuchi et al., 2010). Increasing interest towards hydroxycarboxylic derives from their use for the production of biodegradable polyesters which can substitute traditional plastics with lower environmental impact (Jem and Tan, 2020). Finally, many hydroxycarboxylic acids play important biological roles and are useful intermediates for organic synthesis (See e. g. Offermanns, 2017; Fráter, 1979). The biological relevance of hydroxylated fatty acids stimulated the development of their enantioselective preparation (Ren et al., 2010). In this context, we have been involved in a project for the exploitation of unsaturated fatty acids, derived from natural sources, for the synthesis of dicarboxylic acids as building blocks for polyesters.

## 2 Materials and methods

*General methods*

Flash column chromatography was performed on Merck silica gel 60 (0.040–0.063 mm) following the literature procedure (Still et al., 1978). Reactions were monitored by TLC on Merk silica gel 60 $F_{254}$ plates, and the compounds were detected by examination under UV light, when appropriate, and by charring with phosphomolybdate based reagent. Solvents were removed under reduced pressure below 40 °C. $CH_2Cl_2$ was dried and stored over 4 Å molecular sieves. All reactions (if not specifically including water as a reactant, solvent, or co-solvent) were performed under an Ar atmosphere, in oven-dried glassware. $^1$H NMR spectra were recorded in $CDCl_3$ at 300 MHz, $^{13}$C NMR spectra at 75 MHz, and Tetramethylsilane was used as an internal reference. Chemical shifts (δ) are given in parts per million (ppm); multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants (*J*) are reported in hertz. MS spectra were recorded on a Thermo Quest Finnigan LCQ™DECA spectrometer using electrospray ionization as indicated.

*General procedure for Bayer Villiger reaction*

The Bayer Villiger oxidation of cycloheptanone and cyclooctanone was performed as previously described (Rajabi et al., 2014).

*General procedure for lactone reduction*

To a solution of the lactone (8 mmol) in dichloromethane (40 mL) under argon at -78°C, 1.1 equivalents of a 1 M solution of DIBAL-H in heptane was slowly added. After about 1 h TLC (cyclohexane/acetone 7:3) showed the almost complete disappearance of the starting lactone. The reaction was immediately quenched with methanol at -78°C and the mixture poured into 1 M aqueous HCl (100 mL), then extracted with dichloromethane (3x30 mL). The organic layer was washed with saturated NaCl (1 x 50 ml), dried with $Na_2SO_4$, and filtered. The organic layer was concentrated in vacuo at room temperature to yield about 750 mg of a colorless oil (the non-complete recovery of the product can be attributed to its partial solubility in water). Due to the instability observed during the attempted purification of aldehydes 4a and 4b (see Results and discussion) all the aldehydes were directly used as crude after having recorded only the $^1$H NMR spectrum.

**8-hydroxyoctanal (4a).** Prepared according to the general procedure. Crude compound **4a** was obtained in 74% yield as a colorless oil contaminated by a small amount of the starting lactone and of the over-reduced diol. $^1$H NMR (300 MHz, $CDCl_3$): 9.62 (t, 1H, *J* = 1.8 Hz, CHO), 3.52 (br s 1H, OH) 3.45 (t, 2H, *J* = 6.6 Hz, $CH_2OH$), 2.31 (dt, 2H, *J* = 7.3, 1.8 Hz, C*H*$_2$CHO), 1.8-1.2 (m, 12H, $CH_2$).

**7-hydroxyheptanal (4b).** Prepared according to the general procedure. Crude compound **4b** was obtained in 76% yield as a colorless oil contaminated by a small amount of the starting lactone and of the over-reduced diol. $^1$H NMR (300 MHz, $CDCl_3$): 9.72 (t, 1H, *J* = 1.7 Hz, CHO), 3.62 (t, 2H, *J* = 6.5 Hz, $CH_2OH$), 2.41 (dt, 2H, *J* = 7.3, 1.7 Hz, C*H*$_2$CHO), 1.8-1.2 (m, 9H, $CH_2$ and OH).

**6-hydroxyhexanal (4c).** Prepared according to the general procedure. Crude compound **4c** was obtained in 73% yield as a colorless oil contaminated by a small amount of the starting lactone and of the over-reduced diol. $^1$H NMR (300 MHz, $CDCl_3$): 9.75 (t, 1H, *J* = 1.8 Hz, CHO), 3.63 (t, 2H, *J* = 6.4 Hz, $CH_2OH$), 2.43 (dt, 2H, *J* = 7.3, 1.8 Hz, C*H*$_2$CHO), 1.7-1.3 (m, 9H, $CH_2$ and OH).

*General procedure for the Grignard addition to hydroxy aldehydes*

To a solution of 4 equivalents of the proper Grignard reagent in 15 mL of diethyl ether under nitrogen atmosphere, at -20°C, a solution of 6 mmol of the hydroxy aldehyde in 10 ml of THF were slowly added. The resulting mixture was stirred 2 hours while allowing the mixture to warm to room temperature. The reaction was quenched with a saturated aqueous $NH_4Cl$ (5 mL) and the pH adjusted to 2 with 1 M HCl. The mixture was extracted with ethyl acetate (3x30 ml). The organic solutions were combined, dried over $Na_2SO_4$, concentrated in vacuo, and purified by flash column chromatography (cyclohexane/ethyl acetate/acetone 7:2.5:0.5) to give the product as a colorless oil.

**Nonane-1,8-diol (5a)** (Hashimoto et al., 2014). Prepared according to the general procedure. Compound **5a** was obtained in 36% yield as a colorless oil. The data are in agreement with the

literature. $^1$H NMR (300 MHz, $CDCl_3$): 3.75 (sext, 1H, *J* = 6.5 Hz, C*H*OH) 3.58 (t, 2H, *J* = 6.6 Hz, C$H_2$OH), 2.2-2.0 (br, 2H, OH), 1.6-1.2 (m, 12H, $CH_2$), 1.14 (d, 3H, *J* = 6.3 Hz, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): 68.3 (CHOH), 62.9 ($CH_2$OH), 39.2, 32.7, 29.6, 29.4, 25.7, 25.6 ($CH_2$), 23.5 ($CH_3$). EI-MS *m/z* = 183.1 [M+$Na^+$]. **Nonane-1,7-diol (5b).** Prepared according to the general procedure. Compound **5b** was obtained in 41% yield as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): 3.56 (t, 1H, *J* = 6.5 Hz, C$H_2$OH) 3.45 (m, 1H, C*H*OH), 2.3 (br, 2H, OH), 1.6-1.2 (m, 12H, $CH_2$), 0.88 (t, 3H, *J* = 7.4 Hz, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): 73.2 (CHOH), 62.7 ($CH_2$OH), 36.8, 32.6, 30.1, 29.5, 25.8, 25.6, 9.9 ($CH_3$). EI-MS *m/z* = 183.2 [M+$Na^+$]. **Nonane-1,6-diol (5c)** (Perkins et al., 1990). Prepared according to the general procedure. Compound **5c** was obtained in 46% yield as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): 3.63 (t, 2H, *J* = 6.5 Hz, C$H_2$OH), 3.62 (m, 1H, C*H*OH), 1.6-1.3 (m, 12H, $CH_2$), 0.91 (t, 3H, *J* = 7.8 Hz, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): 71.4 (CHOH) 62.4 ($CH_2$OH), 39.7, 37.3, 32.6, 25.8, 25.4, 18.9, 14.2 ($CH_3$). EI-MS *m/z* = 183.2 [M+$Na^+$].

*General procedure for the oxidation of diols **5a-c** to hydroxy aldehydes **6a-c***

To a solution of the diol (about 500 mg) in dichloromethane (16 mL), KBr (40 mg in 1 mL of water, 0.1 molar eq) and TEMPO (5.2 mg, 0.01 molar eq) were added. The mixture was cooled to in an ice bath and a mixture obtained from 7.9 mL of a commercial bleach solution and 7.9 mL of a saturated solution of $NaHCO_3$ (pH between 7 and 8) was slowly added while monitoring the reaction by TLC (cyclohexane/acetone 7:3). After 20 min TLC showed only a small amount of the starting diol. The reaction was quenched with $FeSO_4$ (5 mL, sat. aqueous solution), then extracted with dichloromethane (3x20 mL). The organic layer was washed with saturated NaCl (1 x 30 ml), dried with $Na_2SO_4$, and filtered. The organic layer was concentrated in vacuo to yield about 460 mg of a colorless oil. The obtained hydroxy aldehydes were immediately used for the following Wittig reaction. The $^1$H NMR revealed, as expected, the presence of some unreacted starting diol.

**8-hydroxynonanale (6a).** Prepared according to the general procedure. Compound **6a** was obtained in 82% yield as a colorless oil and immediately used for the following Wittig reaction. $^1$H NMR (300 MHz, $CDCl_3$): 9.64 (t, 1H, *J* = 1.7 Hz, CHO), 3.63 (m, 1H, C*H*OH), 2.51 (dt, 2H, *J* = 7.0, 1.7 Hz, C$H_2$CHO), 1.6-1.2 (m, 10H, $CH_2$), 1.16 (d, 3H, *J* = 6.5 Hz, $CH_3$). The peak of OH group could not be assigned unambiguously.

**7-hydroxynonanal (6b).** Prepared according to the general procedure. Compound **6b** was obtained in 89% yield as a colorless oil and immediately used for the following Wittig reaction. $^1$H NMR (300 MHz, $CDCl_3$): 9.76 (t, 1H, *J* = 1.6 Hz, CHO), 3.52 (m, 1H, C*H*OH), 2.43 (dt, 2H, *J* = 7.2, 1.6 Hz, C$H_2$CHO), 1.7-1.3 (m, 10H, $CH_2$), 0.93 (t, 3H, *J* = 7.4 Hz, $CH_3$). The peak of OH group could not be assigned unambiguously.

**6-hydroxynonanal (6c).** Prepared according to the general procedure. Compound **6c** was obtained in 86% yield as a colorless oil and immediately used for the following Wittig reaction. $^1$H NMR (300 MHz, $CDCl_3$): 9.77 (t, 1H, *J* = 1.6 Hz, CHO), 3.64 (m, 1H, C*H*OH), 2.45 (dt, 2H, *J* = 7.2, 1.6 Hz, C$H_2$CHO), 1.6-1.3 (m, 10H, $CH_2$), 0.92 (t, 3H, *J* = 6.7 Hz, $CH_3$), The peak of OH group could not be assigned unambiguously.

**9-Bromononanoic acid (8).** 9-Bromononanoic acid **8** was prepared according to a literature procedure (Amara et al., 2009).

**8-(Carboxyoctyl)triphenylphosphonium bromide (9).** Compound **9** was prepared according to literature procedures (Wube et al., 2011; Thurnhofer and Vetter, 2007).

*General procedure for the Wittig reaction*

To a suspension of 2 equivalents of the phosphonium salt 9 in 15 mL of tetrahydrofuran, under nitrogen atmosphere, at -78°C, 3 equivalents of a 0.5 M solution of KHMDS in toluene was slowly added and the mixture warmed at 0°C and stirred for 30 min. After cooling down again the mixture to -78°C, 1 mmol of the hydroxy aldehyde in 4 ml of THF was slowly added. The mixture was stirred 2 hours while allowing it to warm slowly to -35°C. The reaction was quenched with a saturated aqueous $NH_4Cl$ (5 mL) and the pH adjusted to 2 with 1 M HCl. The mixture was extracted with ethyl acetate (3x30 ml). The organic solutions were combined, dried over $Na_2SO_4$, concentrated in vacuo, and purified by flash column chromatography (n-hexane/ethyl acetate 7:3 or cyclohexane/ethyl acetate 7:3) to give the product as a colorless oil.

**(*Z*)-17-Hydroxyoctadec-9-enoic acid (1a).** Prepared according to the general procedure. Compound **1a** was obtained in 28% yield as a colorless oil. $^{1}$H NMR (300 MHz, $CDCl_3$): 5.33 (m, 2H, CH=CH), 3.79 (m, 1H, C*H*OH), 2.32 (t, 2H, *J* = 7.4 Hz, $CH_2C$=O), 1.99 (m, 4H, $CH_2C$=), 1.8-1.2 (m, 20H), 1.18 (d, 3H, *J* = 6.2 Hz, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): 179.0 (COOH) 130.2, 129.8 (CH=CH), 68.4 (CHOH), 39.4, 34.2, 29.8, 29.75, 29.7, 29.5, 29.4, 29.3, 29.1, 29.0, 27.3, 25.9, 24.9, 23.5 ($CH_3$). EI-MS *m/z* = 297 [M-H$^-$].

**(*Z*)-16-Hydroxyoctadec-9-enoic acid (1b).** Prepared according to the general procedure. Compound **1b** was obtained in 31% yield as a yellowish oil. $^{1}$H NMR (300 MHz, $CDCl_3$): 6.5-6.0 (Br, 2H, OH and COOH), 5.32 (m, 2H, CH=CH), 3.52 (m, 1H, C*H*OH), 2.30 (t, 2H, *J* = 7.4 Hz, $CH_2C$=O), 1.99 (m, 4H, $CH_2C$=), 1.7-1.2 (m, 20H), 0.91 (t, 3H, *J* = 7.4 Hz, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): 179.2 (COOH) 129.9 (CH=CH), 73.5 (CHOH), 36.8, 34.1, 30.0, 29.8, 29.7, 29.4, 29.2, 29.1, 29.0, 27.22, 27.17, 25.6, 24.8, 9.9 ($CH_3$). EI-MS *m/z* = 297 [M-H$^-$].

**(*Z*)-15-Hydroxyoctadec-9-enoic acid (1c).** Prepared according to the general procedure. Compound **1c** was obtained in 35% yield as a colorless oil. $^{1}$H NMR (300 MHz, $CDCl_3$): 6.5-6.0 (Br, 2H, OH and COOH), 5.34 (m, 2H, CH=CH), 3.61 (m, 1H, C*H*OH), 2.33 (t, 2H, *J* = 7.4 Hz, $CH_2C$=O), 2.01 (m, 4H, $CH_2C$=), 1.7-1.2 (m, 20H), 0.92 (t, 3H, *J* = 6.8 Hz, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): 179.3 (COOH) 130.1 and 129.8 (CH=CH), 71.9 (CHOH), 39.7, 37.4, 34.1, 29.9, 29.6, 29.1, 29.04, 29.0, 27.3, 27.2, 25.4, 24.8, 18.9, 14.2 ($CH_3$). EI-MS *m/z* = 297 [M-H$^-$].

## 3 Results and discussion

Starting from esters rich in oleic acid, oxidative cleavage of the double bond produces nonanedioic (azelaic) acid together with nonanoic (pelargonic) acid. Azelaic acid can be used for polyester production while pelargonic acid can be considered as a by-product. Chemical oxidation is industrially feasible (Bieser et al., 2018) but a possible alternative is the biological oxidation, which can become economically and environmentally convenient (see e. g. Brenna et al., 2020). Our group has been involved in a project for the exploitation of oleic acid from natural sources for the synthesis of dicarboxylic acids as building blocks towards biodegradable polyesters. Within this context, we published the synthesis of a series of nonanoic acids, hydroxylated at different positions (Rajabi et al., 2014).

Among the possible byproducts generated by biological oxidation of oleic acid, hydroxylated derivatives at the terminal positions can be found in the oxidized products mixture (see e. g. Garg et al., 2016; Aranda et al., 2018). Hydroxylated oleic acids can also be found in sophorolipids (Zerkowski and Solaiman, 2006).

To help the systematic screening of products and byproducts formed during wild type or mutant microbiological oxidation of oleic acid, it is therefore of great utility to have in-hand standard compounds for reaction monitoring and precise product quantification.

In this paper, we describe the synthesis of ω-1, ω-2, and ω-3 hydroxy oleic acids **1a-c** (Figure 1) to be used as standards for the biological oxidation of oleic acid.

Insert Figure 1

To the best of our knowledge, mainly enzymatic or microbiological production of these compounds is described (Brenna et al., 2020), although an example of the synthesis of 16-hydroxyoleic (paleic) acid appeared in the literature (Watanabe et al., 2010).

The synthesis of ω – 1, ω – 2, and ω – 3 hydroxy oleic acids **1a-c** was planned as shown in retrosynthetic Scheme 1.

Insert Scheme 1

Our strategy was planned to avoid the use of protecting groups and to use, whenever possible, environmentally friendly reactions. The hydroxy aldehydes **6a-c** were identified as key intermediates (Scheme 2). Their reaction with the Wittig reagent obtained from (8-carboxyoctyl)triphenylphosphonium bromide **9** (Scheme 3) will give the desired hydroxyoleic derivatives.

The synthesis of hydroxy aldehydes **6a-c** started with the Baeyer-Villiger oxidation of cyclooctanone **2a** and cycloheptanone **2b** respectively, to produce the eight- and seven-carbon lactones **3a-b** as previously described (Rajabi et al., 2014). *ε*-Caprolactone **3c** is commercially available and was

used as purchased. The reduction of lactones **3a-c** to the corresponding hydroxy aldehydes **4a-c** was performed with DIBAL-H as described in the literature (Soubhye et al., 2010). Some difficulties were found during this reduction for 8 and 9 membered lactones, as the formation of some diol, was observed before the complete disappearance of the starting lactone. Moreover, the corresponding hydroxy aldehydes were unstable, especially 7- and 8-hydroxyhexanal (**4a** and **4b** respectively). Attempts to purify the hydroxy aldehydes gave insoluble solid degradation products. Therefore, the crude product obtained from DIBAL-H was directly submitted to the Grignard reaction with an excess of the proper Grignard reagent allowing to obtain the diols **5a-c** in moderate yields.

Insert Scheme 2

The selective oxidation of the primary hydroxyl group of the diols **5a-c** to the corresponding hydroxy aldehydes **6a-c** was performed with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and sodium hypochlorite giving satisfactory results (Anelli et al., 1987). The reaction was very fast, selective, and exploited cheap reagents being the only expensive TEMPO used in catalytic amount (0.01 molar equivalents with respect to the diol).

The Wittig reagent required for the final step of the synthesis, 9-(triphenylphosphoranylidene) nonanoic acid, was obtained starting from 9-bromononanol **7**, considering that 9-bromononanoic acid **8** is very expensive (Scheme 3).

Insert Scheme 3

9-Bromononanol **7** was oxidized to 9-bromononanoic acid **8** in almost quantitative yield by the action of nitric acid as described in the literature (Amara et al., 2009). Treatment of **8** with triphenylphosphine gave the corresponding phosphonium salt **9** as a yellow wax (Wube et al., 2011).

Eventually, the Wittig reaction between the ylide, generated by treatment of 2 equivalents of the phosphonium salt **9** with potassium bis(trimethylsilyl)amide (KHMDS), and the hydroxy aldehydes **6a-c** gave the desired hydroxyoleic acids **1a-c**. It has to be noted that, although the Wittig reagent formed with KHMDS is described to give the double bond exclusively as *Z* isomer (Watanabe et al., 2010), we also observed the formation of a small amount of the *E* isomer (For a discussion of the stereoselectivity of the Wittig reaction with carboxy ylides, published after we finished our work, see Suganuma and Kobayashi, 2019).

# 4 Conclusions

In conclusion, a common strategy for the synthesis of a series of hydroxyoleic acids was accomplished without the use of protecting groups. The obtained compounds will be used as reference compounds for the study of enzymatic or microbiological oxidation of oleic acid.

## Acknowledgements

Regione Piemonte (Biochem project n. 0147000173) is gratefully acknowledged for financial support.

*The authors have declared no conflict of interest.*

## References

Amara, N., Mashiach, R., Amar, D., Krief, P., Spieser, S. A. H., Bottomley, M. J., Aharoni, A., Meijler M. M. (2009) Covalent Inhibition of Bacterial Quorum Sensing. *Journal of the American Chemical Society*, **131**:10610-10619 https://doi.org/10.1021/ja903292v.

Anelli, P. L., Biffi, C., Montanari, F., Quici S. (1987) Fast and selective oxidation of primary alcohols to aldehydes or to carboxylic acids and of secondary alcohols to ketones mediated by oxoammonium salts under two-phase conditions. *Journal of Organic Chemistry* **52**:2559-2562, https://doi.org/10.1021/jo00388a038.

Aranda, C., Olmedo, A., Kiebist, J., Scheibner, K., del Río, J. C., Martínez, A. T., Gutiérrez, A. (2018) Selective epoxidation of fatty acids and fatty acid methyl esters by fungal peroxygenases. *ChemCatChem* **10**:3964-3968 https://doi.org/10.1002/cctc.201800849.

Bieser, A., Borsotti, G., Digioia, F., Ferrari, A., Pirocco, A. (2018) Continuous process of

oxidative cleavage of vegetable oils. Patent US2018044277.

Brenna, E., Colombo, D., Di Lecce, G., Gatti, F. G., Ghezzi, M. C., Tentori, F., Tessaro, D., Viola, M. (2020) Conversion of oleic acid into azelaic and pelargonic acid by a chemo-enzymatic route. *Molecules* **25**, 1882 https://doi.org/10.3390/molecules25081882.

Dal Farra, C., Domloge, N. & Peyronel, D. (2002) Use of a mixture designed to reduce secretion of sebum in a cosmetic or dermatological composition. Patent WO2002072053.

Datta, R. (2004) Hydroxycarboxylic acids, in *Kirk-Othmer Encyclopedia of Chemical Technology*, **13**:1-22 John Wiley & Sons https://doi.org/10.1002/0471238961.0825041804012020.a01.pub2.

Fráter, G. (1979) Über die Stereospezifität der α-Alkylierung von β-Hydroxycarbonsäureestern. Vorläufige Mitteilung. *Helvetica Chimica Acta*, **62**:2825-2828 https://doi.org/10.1002/hlca.19790620832.

Garg, S., Yu, X., Jin, H., Yandeau-Nelson, M., Nikolaou, B., Rizhski, L. (2016) Materials and methods for production of bi-functional fatty acids in recombinant bacteria. Patent, US2016168603.

Green, B. A., Yu, R. J. & Van Scott, E. J. (2009) Clinical and cosmeceutical uses of hydroxyacids *Clinics in Dermatology*, **27**:495-501 https://doi.org/10.1016/j.clindermatol.2009.06.023.

Hashimoto, T., Hirose, D. Taniguchi, T. (2014) Direct Synthesis of 1,4-Diols from Alkenes by Iron-Catalyzed Aerobic Hydration and C-H Hydroxylation. *Angewandte Chemie International Edition*, **53**:2730–2734, https://doi.org/10.1002/anie.201308675.

Iuchi, Y., Hyotanishi, M., Miller, B. E., Maeda, K., Obora, Y. & Ishii, Y. (2010) Synthesis of ω-hydroxy carboxylic acids and α, ω-dimethyl ketones using α, ω-diols as alkylating agents. *Journal of Organic Chemistry*, **75**:1803-1806 https://doi.org/10.1021/jo9027165.

Jem, K. J. & Tan, B. (2020) The development and challenges of poly (lactic acid) and poly (glycolic acid). *Advanced Industrial and Engineering Polymer Research*, **3**:60–70 https://doi.org/10.1016/j.aiepr.2020.01.002.

Lipsa, R., Tudorachi, N. & Vasile, (2010) C. Poly (α-hydroxyacids) in biomedical applications: synthesis and properties of lactic acid polymers. e-*Polymers*, 1-43 https://doi.org/10.1515/epoly.2010.10.1.946.

Midland, M. M. & Lee P. E. (1981) Asymmetric synthesis of hydroxy carboxylic acids *Journal of Organic Chemistry*, **46**:3933-3934 https://doi.org/10.1021/jo00332a043.

Offermanns, S. (2017) Hydroxy-carboxylic acid receptor actions in metabolism. Trends in Endocrinology & Metabolism, **28**:227-236 https://doi.org/10.1016/j.tem.2016.11.007.

Perkins, M. V., Fletcher, M. T., Kitching, W., Drew, R. A. I., Moore C. J. (1990) Chemical studies of rectal gland secretions of some species of *Bactrocera dorsalis* complex of fruit flies (diptera: Tephritidae). *Journal of Chemical Ecology*, **16**:2475–2487 https://doi.org/10.1007/BF01017470.

Rajabi, M., Lanfranchi, M., Campo, F., Panza, L. (2014) Synthesis of a series of hydroxycarboxylic acids as standards for oxidation of nonanoic acid *Synthetic Communications*, **44**:1149–1154 https://doi.org/10.1080/00397911.2013.853800.

Ranathunge, K., Schreiber, L. & Franke, R. (2011) Suberin research in the genomics era—New interest for an old polymer. *Plant Sci*ence, **180***:*399-413 https://doi.org/10.1016/j.plantsci.2010.11.003.

Ren, Q., Ruth, K., Thöny-Meyer, L., Zinn, M. (2010) Enantiomerically pure hydroxycarboxylic acids: current approaches and future perspectives. *Applied Microbiology and Biotechnology*, **87**:41–52 https://doi.org/10.1007/s00253-010-2530-6.

Soubhye, J., Prévost, M., Van Antwerpen, P., Zouaoui Boudjeltia, K., Rousseau, A., Furtmüller, P. G., Obinger, C., Vanhaeverbeek, M., Ducobu, J., Nève, J., Gelbcke, M., Dufrasne, F. (2010) Structure-based design, synthesis, and pharmacological evaluation of 3-(aminoalkyl)-5-fluoroindoles as myeloperoxidase inhibitors. *Journal of Medicinal Chem*istry*,* **53**:8747–8759, https://doi.org/10.1021/jm1009988.

Still, W. C., Kahn, M., Mitra, A. (1978) Rapid chromatographic technique for preparative separations with moderate resolution. *Journal of Organic Chemistry*, **43**:2923-2925 https://doi.org/10.1021/jo00408a041.

Suganuma, Y., Kobayashi, Y. (2019) Formation of COOH-Ylides, and their reactivities and selectivities in Wittig reactions. *Synlett*, **30**:333-337, https://doi.org/10.1055/s-0037-1611958.

Thurnhofer, S.; Vetter, W. (2007) Synthesis of (S)-(+)-enantiomers of food-relevant (n-5)-monoenoic and saturated anteiso-fatty acids by a Wittig reaction. *Tetrahedron* **63**:1140–1145 https://doi.org/10.1016/j.bmc.2010.10.060.

Watanabe, T., Kurata, I., Hayashi, C., Igarashi, M., Sawa, R., Takahashi, Y., Akamatsu, Y. (2010) The synthesis of paleic acid, an antimicrobial agent effective against *Mannheimia* and *Pasteurella*, and its structurally related derivatives *Bioorganic and Medicinal Chemistry Letters*, **20**:5843-5846 https://doi.org/10.1016/j.bmcl.2010.07.115.

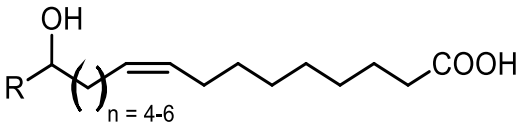
Williams, A. S. (1999) The synthesis of macrocyclic musks. *Synthesis,* 1707-1723 https://doi.org/10.1055/s-1999-3581.

Wube, A. A.,Hùfner, A., Thomaschitz, C., Blunder, M., Kollroser, M., Bauer, R., Bucar, F. (2011) *Bioorganic and Medicinal Chemistry*, **19**:567-579 https://doi.org/10.1016/j.bmc.2010.10.060.

Zerkowski, J. A., Solaiman, D. K. Y. (2006) Synthesis of polyfunctional fatty amines from sophorolipid-derived 17-hydroxy oleic acid. *Journal of the American Oil Chemists' Society*, **83**:621-628 https://doi.org/10.1007/s11746-006-1248-1.

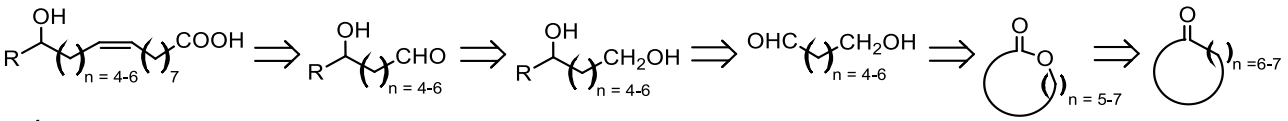
--

## Figures



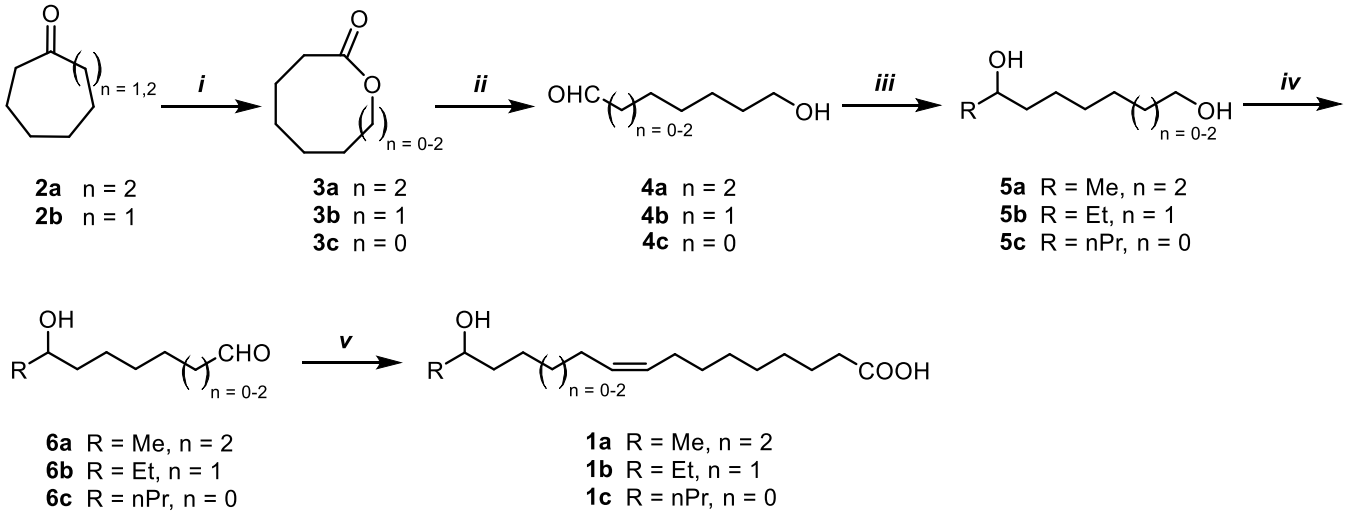

**1a** R = Me, n = 6
**1b** R = Et, n = 5
**1c** R = nPr, n = 4

Figure 1

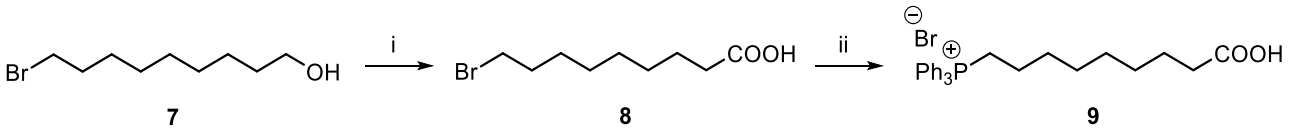



**1a** R = Me, n = 6
**1b** R = Et, n = 5
**1c** R = nPr, n = 4

Scheme 1




Scheme 2




Scheme 3

## Figure legends

**Figure 1.** Hydroxylated oleic acids to be used as standard products

**Scheme 1.** Retrosynthetic approach

**Scheme 2. (i)** mCPBA, $CH_2Cl_2$, r.t. several days, **(ii)** DIBAL-H, $CH_2Cl_2$, -78°C, **(iii)** PrMgBr for n = 0, EtMgBr for n = 1, or MeMgI for n = 2, THF, $Et_2O$, -20°C, **(iv)** NaClO, TEMPO, $CH_2Cl_2$, 0°C. **(v) 8**, KHMDS, THF, -78°C.

**Scheme 3. (i)** $HNO_3$, r.t. to 80°C. **(ii)** $Ph_3P$, toluene, reflux.