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The First Synthesis of *Threo*- and *Erythro*-(*E*)-4,5-Dihydroxydec-2-enals Carbonyls Related to the Peroxidation of Liver Microsomal Lipids

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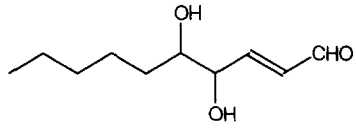
Abstract: ***The first synthesis of threo and erythro (E)-4,5-dihydroxydec-2-enals, aldehydes related to the lipid peroxidation is accomplished by reaction of α-benzoyloxheptanal with the Grignard reagent of 3,3-diethoxy-1-propyne and lithium aluminum hydride reduction. Acetonization of the diol system allows a simple chromatographic separation of the diastereoisomers, the geometry of which was established by ^{1}H and ^{13}C NMR experiments and was confirmed by an independent synthesis of (E,4R,5R)-4,5-O-isopropylidene-4,5-dihydroxydec-2-enal from D-mannitol.***

In recent years many researches have focused on the biological properties of some aldehydes such as 4-hydroxynonenal, 4-hydroxyhexenal and malondialdehyde, originating from the peroxidation of liver microsomal lipids.[1] The interest for these carbonyls arises from evidence that they are causally involved in some of the pathophysiological effects associated with oxidative stress in cells and tissues. In addition to these compounds other carbonyls such as (*E*)-4,5-dihydroxydec-2-enal, are also formed during microsomal lipid peroxidation, but their biological properties have been hardly studied due to lack of synthetic methods to obtain them.[1b]

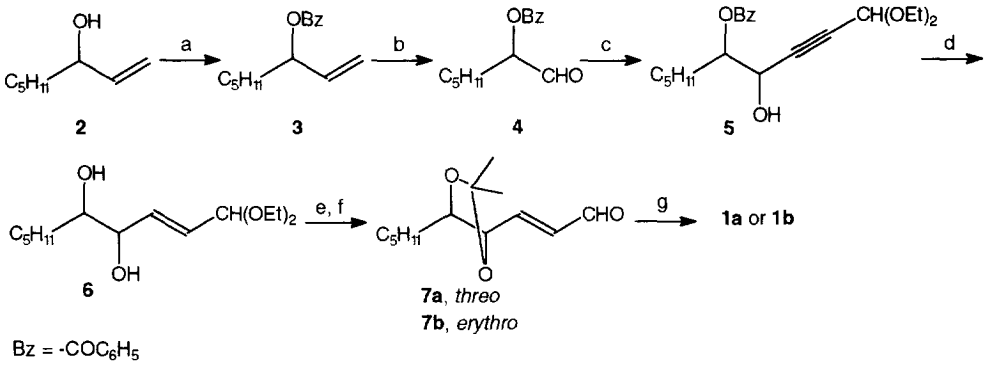
Our interest in studying the pathophysiological properties of the products formed during microsomal lipid peroxidation,[2] and the most general consideration about the utility of these compounds for studies on their biological interactions, prompted us to obtain both *threo*- and *erythro*-(E)-4,5-dihydroxydec-2-enals **1a** and **1b**. In addition the availability of **1a** and **1b** could permit the establishment of the relative stereochemistry of the hydroxy groups in the 4,5-dihydroxydec-2-enal isolated from liver microsomes after NADPH-Fe-induced peroxidation and identified mainly by means of mass spectrometry of the free aldehyde and of its derivatives.[3]



1a, *threo*
1b, *erythro*

The synthesis of **1a** and **1b**, here reported (Scheme 1), includes, as a key step, a three carbon homologation of the 2-benzoyloxyheptanal with the Grignard reagent of 3,3-diethoxy-1-propyne.[4] The successive reduction of the triple bond with lithium aluminum hydride, in conditions similar to those reported by Esterbauer for the synthesis of (*E*)-4-hydroxynon-2-enal,[4] causes the simultaneous regeneration of the

5-hydroxy group and affords a mixture of dihydroxyacetals **6**, unseparable by usual column chromatography. Since also the corresponding dihydroxyaldehydes, formed by simple acidic resin treatment of **6**, were unseparable, we attempted to raise up the steric differences between these diastereoisomers by protecting the diol system by cyclic acetonization with the aim to make possible their chromatographic separation.

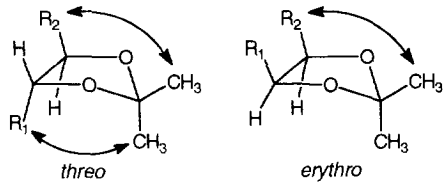


Scheme 1

(a) BzCl (1.1 molar eq), Py (0.3 mL/mmol), CH_2Cl_2 (0.3 mL/mmol), 25°C, 30 min; 95%. (b) OsO_4 (0.027 molar eq), H_2O-Dioxane (7 mL/mmol, 1:3, v:v), then $NaIO_4$ (3.2 molar eq), 25°C, 12 h; 58%. (c) $IMgC{\equiv}CH(OEt)_2$ (1 molar eq), Et_2O-THF (0.7 mL/mmol, 1:2, v:v), -15°C, 2 h; 62%. (d) $LiAlH_4$ (4.5 molar eq), Et_2O (1.4 mL/mmol), -15°C for 1 h, then 25°C for 24 h; 55%. (e) Dowex 50Wx4, Me_2CO (2 mL/mmol), 25°C, 1 h. (f) Flash chromatography eluting with hexane-AcOEt (100:5, v:v); **7a**, 38%; **7b**, 40%. (g) CF_3COOH-H_2O (1.9 mL/mmol, 9:1, v:v), 0°C, 0.25 h; 62%.

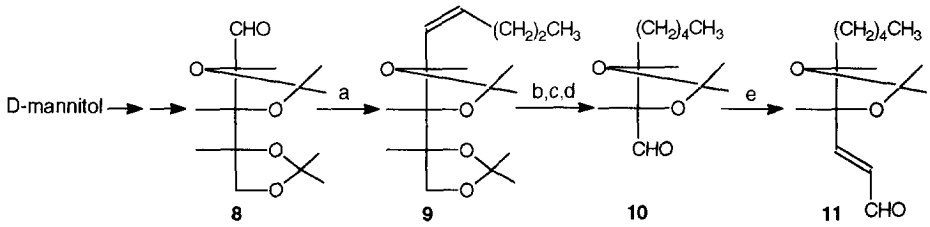
In fact treatment of crude **6** with acetone under acidic catalysis, followed by chromatographic separation, which also complete the regeneration of the aldehydic group, allowed to obtain in pure form the *threo*-isomer **7a** and the *erythro*-isomers **7b**. [5]

The relative configuration of the stereocenters at C(4) and C(5) in **7a** and **7b** was derived from ^{13}C and ^{1}H NMR evidence.[6] In fact the acetonide methyl groups in the *erythro* couple **7b** have a higher degree of magnetic non-equivalence[6] due to a higher difference in the steric 1,3 interactions with the alkyl chains with respect to *threo* one **7a** (Figure): the acetonide methyl groups of **7b** show a $\Delta\delta_C = 2.53$ ppm and a $\Delta\delta_H = 0.11$ ppm whereas those of **7a** show less noticeable differences ($\Delta\delta_C = 0.65$ and $\Delta\delta_H = 0.03$ ppm respectively).[7]



Figure

The assignment of the *threo* structure to the less polar (in the used solvent)[5] couple of enantiomers **7a** was unequivocally confirmed by obtaining by an independent synthesis the (*E,4R,5R*)-4,5-*O*-isopropylidene-4,5-dihydroxydec-2-enal **11**, one of the enantiomers forming the *threo* couple **7a** (Scheme 2), through the following reaction sequence: Wittig olefination of the known[8] aldehyde **8**, catalytic hydrogenation of the formed double bond, selective hydrolysis of the terminal isopropylidene ketal followed by glycol cleavage and final Wittig homologation with (formylmethylene)triphenylphosphorane.



Scheme 2

(a) $Me(CH_2)_2$-CH=$P(C_6H_5)_3$ (1.3 molar eq), MeC_6H_5 (10 mL/mmol), 25°C, 2 h; 88%. (b) H_2 (1 atm), Pd/C, EtOH (15 mL/mmol), 25°C; 92%. (c) AcOH-H_2O (3 mL/mmol, 7:3, v:v), 40°C, 2 h; 62%. (d) $n$$Bu_4NIO_4$ (2 molar eq), CH_2Cl_2 (3 mL/mmol), 25°C, 3 h; 89%. (e) $(C_6H_5)_3$P=CHCHO (1.2 molar eq), C_6H_6 (10 mL/mmol), 25°C, 4 h; 87%.

Deketalization of **7a** and **7b** by treatment with aqueous trifluoroacetic acid afforded the final compound **1a** and **1b**.

The physicochemical properties of **1a** and **1b** were in agreement with the assigned structure and confirmed the constitutional formula and the geometry of the double bond assigned to the natural product by Benedetti and Esterbauer groups.[3] However, since a sample of compound of natural source was not available, at moment it was not possible to assign its complete steric structure. Work is in progress for isolating a sample of natural compound which could now permit a complete structure assignment.[9]

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5. The two diastereoisomers show the following chromatographic profiles: TLC (Kieselgel 60 F_{254}, Merk, eluent hexane-AcOEt 9:1 v:v): R_f 0.31 (**7a**) and R_f 0.24 (**7b**); HPLC (Hypersil ODS C-18, 10 cm x 4.6 mm, 3 µm, eluent CH_3CN-H_2O 1:1 v:v) R_t 10.8 min (**7a**) and R_t 9.0 min (**7b**); GLC (SPB-5, Supelco, 25 m x 0.75 mm, 90°C): R_t 10.8 min (**7a**) and R_t 13.0 min (**7b**).
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7. All compounds showed satisfactory elemental analyses and significant spectroscopic data (^{1}H- and ^{13}C-NMR, 500 MHz, $CDCl_3$) confirming the assigned structure. Compound **4**, an oil, shows the following signals attributed to the two diastereoisomeric components: δ 9.60 (1 H, d, J < 1 Hz, H-1), 5.18 (1 H, dd, J 8.5 and J 8.5 Hz, H-2). The diastereoisomeric mixture **5** shows: ^{1}H-NMR δ 5.26 (1 H, d, J 1.4 Hz, H-1), 5.19 (1 H, ddd, J 9.1, J 9.1 and J 4.5 Hz, H-5), 4.63 (1 H, dd, J 4.5 and J 1.4 Hz, H-4) for the first one and δ 5.24 (1 H, d, J 1.4 Hz, H-1), 5.20 (1 H, ddd, J 9.1, J 9.1 and J 5.5 Hz, H-5), 4.55 (1 H, dd, J 5.5 and J 1.4 Hz, H-4) for the second one. The *threo* isomer **7a**, an oil, shows: ^{1}H-NMR δ 9.58 (1 H, d, J 7.7 Hz, H-1), 6.72 (1 H, dd, J 15.5 and J 5.5 Hz, H-3), 6.35 (1 H, ddd, J 15.5, J 7.7 and J 1.5 Hz, H-2), 4.25 (1 H, ddd, J 8.5, J 5.5 and J 1.5 Hz, H-4), 3.76 (1 H, ddd, J 8.5, J 8.0 and J 5.0 Hz, H-5), 1.43 and 1.40 (2 x 3 H, 2 x s, $C(C\underline{H_3})_2$); ^{13}C-NMR: δ 192.93 (C-1), 152.51 (C-3), 132.56 (C-2), 109.58 ($\underline{C}Me_2$), 80.52 and 80.05 (2 x >CHOR), 32.01 and 31.66 (2 x CH_2), 27.12 and 26.47 (2 x $C(\underline{C}H_3)_2$), 25.52 and 22.36 (2 x CH_2), 13.88 (C-10).The *erythro* isomer **7b**, an oil, shows: ^{1}H-NMR δ 9.58 (1 H, d, J 7.5 Hz, H-1), 6.69 (1 H, dd, J 15.5 and J 6.0 Hz, H-3), 6.31 (1 H, ddd, J 15.5, J 7.5 and J 1.5 Hz, H-2), 4.72 (1 H, ddd, J 6.5, J 6.0 and J 1.5 Hz, H-4), 4.26 (1 H, ddd, J 8.5, J 6.5 and J 4.5 Hz, H-5), 1.49 and 1.38 (2 x 3 H, 2 x s, $C(C\underline{H_3})_2$); ^{13}C-NMR: δ 192.86 (C-1), 152.44 (C-3), 133.06 (C-2), 108.90 ($\underline{C}Me_2$), 78.14 and 77.14 (2 x >CHOR), 31.48 and 30.30 (2 x CH_2), 27.77 and 25.24 (2 x $C(\underline{C}H_3)_2$), 25.80 and 22.29 (2 x CH_2), 13.79 (C-10). Compound **1a**, an oil, shows: ^{1}H-NMR δ 9.52 (1 H, d, J 7.5 Hz, H-1), 6.82 (1 H, dd, J 15.5 and J 5.0 Hz, H-3), 6.34 (1 H, ddd, J 15.5, J 7.5 and J 1.5 Hz, H-2), 4.21 (1 H, ddd, J 5.0, J 5.0 and J 1.5 Hz, H-4), 3.56 (1 H, ddd, J 8.5, J 5.0 and J 5.0 Hz, H-5). Compound **1b**, an oil, shows: ^{1}H-NMR δ 9.52 (1 H, d, J 7.5 Hz, H-1), 6.85 (1 H, dd, J 15.5 and J 5.0 Hz, H-3), 6.36 (1 H, ddd, J 15.5, J 7.5 and J 1.5 Hz, H-2), 4.38 (1 H, ddd, J 5.0, J 5.0 and J 1.5 Hz, H-4), 3.78 (1 H, ddd, J 8.0, J 4.5 and J 4.5 Hz, H-5). Compound **9**, an oil, shows: $[\alpha]_D^{25}$ -11.6 ($CHCl_3$, *c* 1); ^{1}H-NMR δ 5.64 (1 H, ddd, J 10.5, J 7.7 and J 7.7 Hz, H-6), 5.39 (1 H, ddt, J 10.5, J 9.1 and J 1.4 Hz, H-5), 4.66 (1 H, dd, J 9.1 and J 7.0 Hz, H-4), 4.11 (1 H, ddd, J 7.0, J 6.3 and J 6.3 Hz, H-2), 4.05 (1 H, dd, J 8.4 and J 6.3 Hz, H-1), 3.89 (1 H, dd, J 8.4 and J 6.3 Hz, H-1'), 3.70 (1 H, dd, J 7.0 and J 7.0, H-3), 1.40, 1.39, 1.36, 1.31 (4 x 3 H, 4 x s, 2 x $C(C\underline{H_3})_2$). Compound **10**, an oil, shows: $[\alpha]_D^{25}$ -58.7 ($CHCl_3$, *c* 1), **10** polymerizes on standing at -20°C continually increasing its optical rotation; ^{1}H-NMR δ 9.70 (1 H, d, J 2.1 Hz, H-1), 4.02 (1 H, dt, J 7.7 and J 6.0 Hz, H-3), 3.91 (1 H, dd, J 7.7 and J 2.1 Hz, H-2), 1.46 and 1.40 (2 x 3 H, 2 x s, $C(C\underline{H_3})_2$).
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