Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 9, pp. 2357-2364, 1995

0957-4166/95 $9.50+0.00

0957-4166(95)00312-6

The First Synthesis of All Possible Stereoisomers of the (*E*)-4,5-Dihydroxydec-2-enal, in Homochiral Form

Pietro Allevi,* Pierangela Ciuffreda, Giorgio Tarocco and Mario Anastasia

Dipartimento di Chimica e Biochimica Medica, Università di Milano, via Saldini 50, 20133 Milan, Italy

Abstract: The first synthesis of the four possible isomers of (*E*)-4,5-dihydroxydec-2-enal, a cytotoxic product of microsomal lipid peroxidation, is accomplished starting with D- and L-arabinose, D-ribose and D-lyxose by an identical reaction sequence. Each pentose was diacetonised and subjected to a Wittig reaction for the introduction of a four carbon chain. A selective cleavage of the terminal isopropylidene acetal and the oxidation of the diolic system affords a noraldehyde which is treated with (formylmethylene)triphenylphosphorane to afford the target molecule after regeneration of the diolic system.

In spite of a large body of literature concerning the synthesis and the study of the biological properties of (*E*)-4-hydroxyalk-2-enals, formed during microsomial lipid peroxydation (LPO),[1,2] only our previous paper[3] has appeared on the synthesis of the (*E*)-4,5-dihydroxydec-2-enal, a cytotoxic carbonyl product identified, apart from the stereochemistry, by Comporti and Esterbauer groups in peroxydised liver microsomial lipids.[4] Thus the exact configuration of the product deriving from biological sources is not know.

In our previous work[3] racemic *threo* and *erythro* compounds were obtained by a simple and rapid synthesis,[5] however, since these dihydroxyalkenals could occur *in vivo* in an optically active form, thus indicating that enzymes are involved in their biological formation, we planned the stereospecific synthesis of all possible stereoisomers of (*E*)-4,5-dihydroxydec-2-enal **1a-d**, in homochiral form, in order to allow the complete identification of the natural product by comparison.

In addition the availability of these interesting cytotoxic lipids could permit to study and to understand the mechanism of a large number of biological effects induced by LPO.

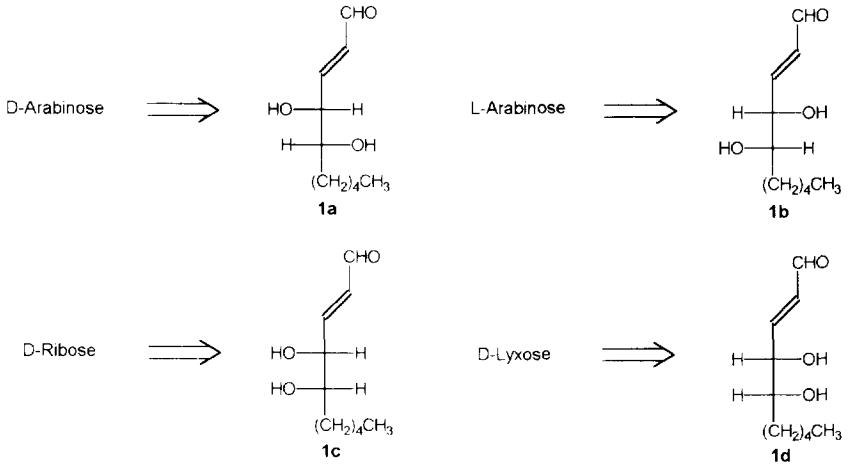
As an initial successful result we here report the obtaining of (*E*)-4,5-dyhydroxydec-2-enals **1a-d** starting with appropriate pentoses obtained by commercial sources.[6]

RESULTS AND DISCUSSION

The scheme shows the obtaining of **1a**, starting with the diacetonide **2a**, derived from D-arabinose. The route is representative of the general procedure which allows to obtain all isomeric aldehydes **1a-d** in homochiral form, preserving in the final molecule two of the three stereogenic centres of the starting pentoses.

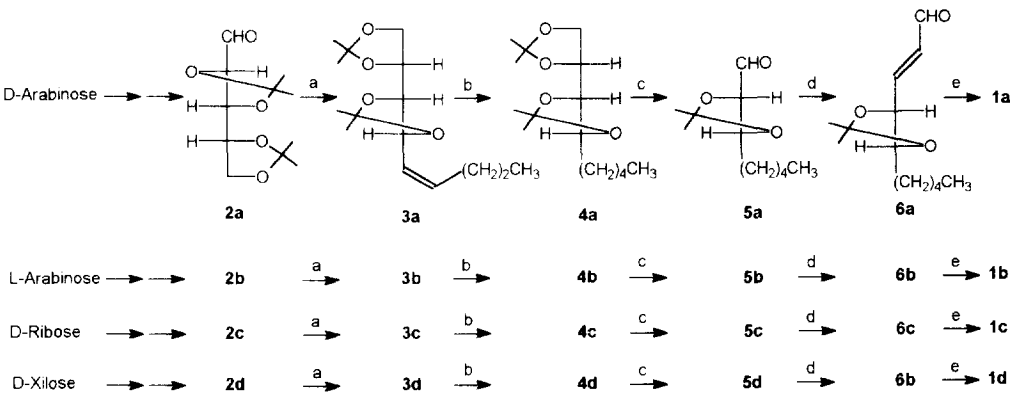
Wittig olefination, followed by catalytic hydrogenation, allows to build the hydrocarbon chain of **1a** without epimerisation next to the aldehyde function and alteration of the chiral integrity of the product.

FIGURE



In fact the Wittig olefination, using butyltriphenylphosphorane, occurs in high yield (85%) and affords the *Z* product **3a** accompanied only by a minor amount of the *E*-isomer (4.6%; ^{1}H NMR at 500 MHz). No epimerisation was observed even with the *erythro* isomers **3c-d** which are known to be easily epimerisable by bases[7] to the more stable *threo* diastereoisomers. Catalytic hydrogenation of **3a**, using palladium on carbon as catalyst, affords **4a** without endangering the geometry of the allylic stereogenic centre (^{1}H NMR at 500 MHz).

SCHEME



(a) $Ph_3P^+C_4H_9I^-$, C_6H_6, BuLi, 25°C, 2h (b) H_2, Pd/C, EtOH (c) H_5IO_6, Et_2O. (d) Ph_3P=CHCHO, C_6H_6, rt, 3h. (e) CF_3COOH, H_2O (9:1, -25°C, 0.5h).

The successive conversion of the diacetonide **4a** into the acetonide aldehyde **5a** (which is formed by the chemoselective cleavage of the 1,2-O-isopropylidene group and oxidation of the formed glycol) was obtained in one pot reaction, using periodic acid in diethylether, according to the procedure reported for

terminal isopropylidene acetals [8,9] By this route the aldehyde **5a** was always obtained together with considerable amounts (35-40%) of the starting diacetonide Several variations of the reaction conditions (temperature, concentration, nature of the solvent), attempted in order to improve the yields, do not afford useful results, in fact, in no case it was possible to obtain the disappearance of the starting diacetonide without a contemporary destruction of the target aldehyde **5a** On the other hand an alternative route including two steps was also practicable [3]

The successive two carbon homologation of **5a** was carried out in an efficient way using (formylmethylene)triphenylphosphorane [3] The Wittig reaction affords the unsaturated *E* aldehyde **6a** without epimerisation of the stereogenic centre at C-4, accompanied by minor amount of the unseparable (TLC) *Z* isomer (92 8, *E*:*Z*, ^{1}H NMR at 500 MHz) However the presence of minor quantity of the *Z* isomer was not a troublesome since during the acidic regeneration of the diolic system affording the target aldehyde **1a**, the *Z* isomer was transformed in a easily separable (column chromatography) furanosic impurity, deriving from the acetalisation of the *Z* unsaturated carbonyl with the 4-hydroxy group and successive dehydration [10]

Since the aldehyde **5a** (as each analogue **5b-d**) appeared to be sensitive to solvents (polymerise on standing varying its optical rotation without afford its diastereomer), in successive preparations we subjected the crude product, immediately after its obtaining by periodic acid treatment of **4a,** to the Wittig reaction which afforded the more stable aldehyde **6a**

Finally, the regeneration of the diolic system, performed by conventional acidic hydrolysis[3] of **6a**, afforded the target aldehyde **1a.**

An identical sequence of reactions afforded the others isomers **1b-d**, starting from L-arabinose, D-ribose and D-lyxose respectively

In order to check the enantiomeric purity of each obtained dihydroxyaldehydes **1a-d** and to provide analytical parameters useful for the identification of products derived from various biological sources, we studied a possible chromatographic separation of the isomeric (*E*)-4,5-dihydroxydec-2-enals **1a-d** After various attempts, we resulted in their separation by means of chiral HPLC analysis of their dibenzoates

In conclusion we have shown that all isomers of (*E*)-4,5-dihydroxydec-2-enal can be conveniently obtained by chemical elaboration of natural low cost precursors Their availability affords now the possibility to attribute the correct stereochemistry to the product formed during LPO and opens the way to perform biological investigations using the appropriate dihydroxyaldehyde **1a-d**

EXPERIMENTAL SECTION

Nuclear magnetic resonance spectra were recorded at 303 K on Bruker AM-500 spectrometer operating at 500 13 MHz for ^{1}H and 125 76 MHz for ^{13}C All chemical shifts are reported in ppm relative to $CHCl_3$ fixed at 7 24 ppm for the ^{1}H spectra and relative to $CDCl_3$ fixed at 77 00 ppm for the ^{13}C spectra. Signal multiplicity was designated according to the following abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet All reactions were monitored by thin-layer chromatography (TLC) carried out on 0 25 mm E. Merck silica gel plates (60 F_{254}) using UV light or 50% sulphuric acid and heat as developing agent. E. Merck 230 - 400 mesh silica gel was used for flash column chromatography.[11] Optical rotations were measured for 1% $CHCl_3$ solutions Usual work-up refers to washing the organic layer with water, drying over Na_2SO_4, and evaporating the solvent under reduced pressure

The starting material for the synthesis of **1a-d** were 2,3:4,5-di-*O*-isopropylidene-D-*arabino*-pentose (**2a**), 2,3:4,5-di-*O*-isopropylidene-L-*arabino*-pentose (**2b**), 2,3:4,5-di-*O*-isopropylidene-D-*ribo*-pentose (**2c**) and 2,3:4,5-di-*O*-isopropylidene-D-*lyxo*-pentose (**2d**). They were obtained from the appropriate commercial pentose by application of literature methods which include the transformation into the diethyl dithioacetal,[12] protection as diisopropylidene derivative[13] and regeneration of the aldehydic group.[9] Compounds **2a-d** showed the following properties

2,3:4,5-di-*O*-isopropylidene-D-*arabino*-pentose (**2a**): an oil; $[\alpha]_D^{20}$ = -17.9, lit[13] -16.1 (*c* 4.51, $CHCl_3$); ^1H NMR, δ 9.74 (1H, d, J = 1.4 Hz, H-1), 4.38 (1H, dd, J = 6.3, 1.4 Hz, H-2), 4.15 (1H, ddd, J = 6.3, 6.3, 3.5 Hz, H-4), 4.11 (1H, dd, J = 8.4, 6.3 Hz, H-5a), 4.05 (1H, dd, J = 6.3, 6.3 Hz, H-3), 3.95 (1H, dd, J = 8.4, 3.5 Hz, H-5b), 1.43, 1.40, 1.36, 1.33 (4 x 3H, 4 x s, isopropylidene methyls); ^{13}C NMR, δ 199.58 (C1), 111.61, 109.75, 83.03 (C2), 77.55 (C3), 76.27 (C4), 66.72 (C5), 26.79, 26.49, 26.07, 24.89. Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.46; H, 7.79.

2,3:4,5-di-*O*-isopropylidene-L-*arabino*-pentose (**2b**): an oil; $[\alpha]_D^{20}$ = +17.2, lit[14] +15.2 (*c* 3.82, $CHCl_3$); ^1H and ^{13}C NMR spectra are superimposable with those of **2a**. Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.51; H, 7.83.

2,3:4,5-di-*O*-isopropylidene-D-*ribo*-pentose (**2c**): an oil; $[\alpha]_D^{20}$ = -10.5, ^1H NMR, δ 9.68 (1H, d, J = 1.9 Hz, H-1), 4.56 (1H, dd, J = 7.0, 1.9 Hz, H-2), 4.26 (1H, dd, J = 7.0, 7.0 Hz, H-3), 4.08 - 4.04 (2H, m, overlapping of H-5a and H-4), 3.87 (1H, dd, J = 7.7, 3.5 Hz, H-5b), 1.50, 1.37, 1.34, 1.27 (4 x 3H, 4 x s, isopropylidene methyls), ^{13}C NMR, δ 197.53 (C1), 111.19, 110.08, 81.71 (C2), 78.74 (C3), 73.51 (C4), 67.45 (C5), 27.28, 26.62, 25.37, 25.04. Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.15; H, 7.98.

2,3:4,5-di-*O*-isopropylidene-D-*lyxo*-pentose (**2d**): an oil; $[\alpha]_D^{20}$ = -37.6, ^1H NMR, δ 9.64 (1H, d, J = 2.5 Hz, H-1), 4.34 - 4.29 (2H, m, overlapping of H-3 and H-2), 4.14 (1H, ddd, J = 7.0, 7.0, 4.0 Hz, H-4), 4.05 (1H, dd, J = 8.0, 7.0 Hz, H-5a), 3.80 (1H, dd, J = 8.0, 7.0 Hz, H-5b), 1.58, 1.40, 1.39, 1.29 (4 x 3H, 4 x s, isopropylidene methyls), ^{13}C NMR, δ 202.09 (C1), 111.48, 110.07, 80.89 (C2), 79.15 (C3), 73.41 (C4), 65.67 (C5), 26.85, 26.16, 25.27, 25.08. Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.42; H, 8.03.

Synthesis of (*Z*)-1,2:3,4-diisopropylidenedioxynon-5-enes 3a-d. General procedure.

Butyltriphenylphosphonium iodide (10.7 g, 24 mmol) was suspended in anhydrous benzene (200 mL) under an atmosphere of argon. A solution of butyllithium in hexane (1.5 mL, 1.6 M, 24 mmol) was added dropwise under stirring. The resulting yellow suspension was heated to 50 °C (1 h) and then was cooled to room temperature and added dropwise of a solution of the appropriate diisopropyloxyaldehyde **2a-d** (4.6 g, 20 mmol) dissolved in benzene (50 mL). The mixture was stirred at 25 °C (2 h) under argon, then it was diluted with ethyl acetate (200 mL) and filtered on a pad of Celite. Usual work-up and column chromatography (eluting with hexane-ethyl acetate; 100:5, v/v), afforded the compounds **3a-d** contamined by the corresponding chromatographycally inseparable *E* isomer (3-5%, ^1H NMR).

Compounds **3a-d** showed the following yields and properties:

(*Z,2R,3S,4R*)-1,2:3,4-diisopropylidenedioxynon-5-ene (**3a**; Y = 85%): an oil; $[\alpha]_D^{20}$ = -11.2; ^1H NMR, δ 5.64 (1H, ddd, *J* = 10.5, 7.7, 7.7 Hz, H-6), 5.39 (1H, dddd, *J* = 10.5, 9.1, 1.4, 1.4 Hz, H-5), 4.66 (1H, dd, *J* = 9.1, 7.0 Hz, H-4), 4.11 (1H, ddd, *J* = 7.0, 6.3, 6.3 Hz, H-2), 4.05 (1H, dd, *J* = 8.4, 6.3 Hz, H-1a), 3.89

(1H, dd, *J* = 8.4, 6.3 Hz, H-1b), 3.70 (1H, dd, *J* = 7.0, 7.0 Hz, H-3), 2.17 - 2.07 (2H, m, overlapping of H-7a and H-7b), 1.40 (2H, ddq, *J* = 7.7, 7.7, 7.7 Hz, H_2-8), 1.40, 1.39, 1.36, 1.31 (4 x 3H, 4 x s, isopropylidene methyls), 0.91 (3H, t, *J* = 7.7 Hz, H_3-9), *E* isomer (4.6%) 5.81 (1H, ddd, *J* = 15.4, 7.0, 7.0 Hz, H-6), 5.47 (1H, dddd, *J* = 15.4, 7.0, 1.4, 1.4 Hz, H-5). Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.48; H, 9.77.

(*Z,2S,3R, 4S*)-1,2:3,4-diisopropylidenedioxynon-5-ene (**3b**, Y = 87%): an oil; $[\alpha]_D^{20}$ = +11.5; ^{1}H NMR spectrum is superimposable with that of **3a**. Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.73; H, 9.60.

(*Z,2R,3S,4S*)-1,2:3,4-diisopropylidenedioxynon-5-ene (**3c**, Y = 89%): an oil; $[\alpha]_D^{20}$ = +35.9; ^{1}H NMR, δ 5.65 (1H, dddd, *J* = 11.0, 8.0, 8.0, 1.0 Hz, H-6), 5.43 (1H, dddd, *J* = 11.0, 9.5, 1.7, 1.7 Hz, H-5), 4.97 (1H, ddd, *J* = 9.5, 5.5, 1.0 Hz, H-4), 4.08-4.00 (3H, m, overlapping of H-3, H-2 and H-1a), 3.89 (1H, dd, *J* = 8.0, 5.0 Hz, H-1b), 2.12 - 2.03 (2H, m, overlapping of H-7a and H-7b), 1.39 (2H, ddq, *J* = 7.7, 7.7, 7.7 Hz, H_2-8), 1.42, 1.36, 1.34, 1.29 (4 x 3H, 4 x s, isopropylidene methyls), 0.89 (3H, t, *J* = 7.7 Hz, H_3-9), *E* isomer (3.5%) 5.77 (1H, ddd, *J* = 15.4, 7.0, 7.0 Hz, H-6), 5.48 (1H, dddd, *J* = 15.4, 7.0, 1.4, 1.4 Hz, H-5). Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.56; H, 9.76.

(*Z,2R,3R,4R*)-1,2:3,4-diisopropylidenedioxynon-5-ene (**3d**, Y = 68%): an oil; $[\alpha]_D^{20}$ = -22.7; ^{1}H NMR, δ 5.63 (1H, ddd, *J* = 11.2, 7.0, 7.0 Hz, H-6), 5.42 (1H, dddd, *J* = 11.2, 9.8, 1.7, 1.7 Hz, H-5), 4.90 (1H, dd, *J* = 9.8, 6.0 Hz, H-4), 4.12-4.06 (2H, m, overlapping of H-3 and H-2), 3.93 (1H, dd, *J* = 8.5, 6.0 Hz, H-1a), 3.48 (1H, dd, *J* = 8.5, 6.0 Hz, H-1b), 2.10 (1H, dddt, *J* = 15.0, 7.0, 7.0, 1.7 Hz, H-7a), 1.98 (1H, dddt, *J* = 15.0, 7.0, 7.0, 1.7 Hz, H-7b), 1.39 (2H, ddq, *J* = 7.7, 7.7, 7.7 Hz, H_2-8), 1.51, 1.41, 1.37, 1.33 (4 x 3H, 4 x s, isopropylidene methyls), 0.90 (3H, t, *J* = 7.7 Hz, H_3-9), *E* isomer (3.2%) 5.72 (1H, ddd, *J* = 15.4, 7.0, 7.0 Hz, H-6). Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.80; H, 9.54.

Synthesis of 1,2:3,4-diisopropylidenedioxynonanes 4a-d. General procedure.

The appropriate compound **3a-d** (5.4 g, 20 mmol) in ethanol (200 mL) was hydrogenated over palladium on carbon (0.5 g, 10%) at room temperature and atmospheric pressure. Then the catalyst was removed by filtration on a pad of Celite and the solution was evaporated to give the corresponding saturated compound **4a-d** in nearly quantitative yields and with the properties below reported.

(*2R,3S,4R*)-1,2:3,4-diisopropylidenedioxynonane (**4a**): an oil; $[\alpha]_D^{20}$ = +18.5; ^{1}H NMR, δ 4.09 (1H, dd, *J* = 8.5, 6.5 Hz, H-1a), 3.99 (1H, ddd, *J* = 7.5, 6.5, 5.0 Hz, H-2), 3.92 (1H, dd, *J* = 8.5, 5.0 Hz, H-1b), 3.88 (1H, ddd, *J* = 8.0, 7.5, 3.5 Hz, H-4), 3.53 (1H, dd, *J* = 7.5, 7.5 Hz, H-3), 1.70 (1H, dddd, *J* = 14.5, 11.0, 6.5, 3.5 Hz, H-5a), 1.52 (1H, dddd, *J* = 14.5, 10.5, 8.0, 5.0 Hz, H-5b), 1.38, 1.36, 1.33, 1.32 (4 x 3H, 4 x s, isopropylidene methyls), 0.87 (3H, t, *J* = 7.0 Hz, H_3-9), ^{13}C NMR, δ 109.48, 108.65, 81.10 (C3), 80.49 (C4), 77.20 (C2), 67.60 (C1), 33.66, 31.83, 27.35, 26.99, 26.63, 25.61, 25.27, 22.52, 13.96. Anal. Calcd for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36. Found: C, 66.27; H, 10.19.

(*2S,3R,4S*)-1,2:3,4-diisopropylidenedioxynonane (**4b**): an oil; $[\alpha]_D^{20}$ = -18.3; ^{1}H and ^{13}C NMR spectra are superimposable with those of **4a**. Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.14; H, 10.36. Found: C, 66.25; H, 10.47.

(*2R,3S,4S*)-1,2:3,4-diisopropylidenedioxynonane (**4c**): an oil; $[\alpha]_D^{20}$ = +5.2; ^{1}H NMR, δ 4.12 (1H, ddd, *J* = 9.5, 5.0, 4.5 Hz, H-4), 4.07 - 4.02 (2H, m, overlapping of H-1a and H-2), 3.91 - 3.86 (2H, m, overlapping of H-1b and H-3), 1.36 (6H, s, two of the isopropylidene methyls), 1.30, 1.29 (2 x 3H, 2 x s, two

of the isopropylidene methyls), 0.87 (3H, t, J = 7.0 Hz, H_3-9), ^{13}C NMR, δ 109.48, 107.76, 78.85 (C3), 77.91 (C4), 73.48 (C2), 67.84 (C1), 31.81, 29.20, 28.15, 26.70, 26.13, 25.52, 25.52, 22.53, 13.96. Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.14, H, 10.36. Found: C, 66.07, H, 10.29.

(2R,3R,4R)-1,2:3,4-diisopropylidenedioxynonane (**4d**): an oil; $[\alpha]_D^{20}$ = +15.1; ^1H NMR, δ 4.12 (1H, ddd, J = 7.5, 7.0, 7.0 Hz, H-2), 4.07 (1H, ddd, J = 9.0, 6.0, 3.5 Hz, H-4), 4.02 - 3.98 (2H, m, overlapping of H-1a and H-3), 3.62 (1H, dd, J = 7.5, 7.5 Hz, H-1b), 1.47, 1.42, 1.35, 1.34 (4 x 3H, 4 x s, isopropylidene methyls), 0.87 (3H, t, J = 7.0 Hz, H_3-9), ^{13}C NMR, δ 109.37, 108.46, 78.46 (C3), 76.70 (C4), 74.75 (C2), 65.97 (C1), 31.61, 30.03, 27.70, 26.44, 26.00, 25.50, 25.25, 22.40, 13.82. Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.14, H, 10.36. Found: C, 66.23, H, 10.19.

Synthesis of (*E*)-4,5-isopropylidenedioxydec-2-enals 6a-d. General procedure.

A solution of the appropriate compound **4a-d** (2.72 g, 10 mmol) in dry diethylether (50 mL) was added to a well-stirred suspension of periodic acid (3.42 g, 15 mmol) in dry diethylether (200 mL) at room temperature and under argon atmosphere. The suspension was stirred overnight and then was filtered, washed with water, and evaporated to give a residue constituted by the noraldehyde **5a-d** accompanied by unreacted starting material. The crude product was directly used in the next Wittig reaction.

[In first preparations, aldehydes **5a** and **5c** were purified by column chromatography (eluting with hexane-ethyl acetate, 80:20, v/v) and they have showed the following yields and properties.

(2S,3R)-2,3-isopropylidenedioxynonanal (**5a**, Y = 43%): an oil; $[\alpha]_D^{20}$ = -58.7; the optical rotation of this aldehyde changes fast on standing in solution and slowly when stored as pure oil at -20 °C, without epimerisation to its diastereomer **5d**. ^1H NMR δ 9.70 (1H, d, J = 2.1 Hz, H-1), 4.02 (1H, dt, J = 7.7, 6.0 Hz, H-3), 3.91 (1H, dd, J = 7.7, 2.1 Hz, H-2), 1.65 (2H, dt, J = 7.7, 6.0 Hz, H_2-4), 1.46, 1.40 (2 x 3H, 2 x s, isopropylidene methyls), 0.87 (3H, t, J = 7.0 Hz, H_3-9).

(2S,3S)-2,3-isopropylidenedioxynonanal (**5c**, Y = 40%): an oil; $[\alpha]_D^{20}$ = -6.9; the optical rotation shows a behaviour similar to that of **5a**. ^1H NMR δ 9.61 (1H, s, J = 3.5 Hz, H-1), 4.31 (1H, ddd, J = 8.5, 7.0, 4.5 Hz, H-3), 4.22 (1H, dd, J = 7.0, 3.5 Hz, H-2), 1.57, 1.39 (2 x 3H, 2 x s, isopropylidene methyls), 0.87 (3H, t, J = 7.0 Hz, H_3-9)].

The crude product deriving from the oxidation with periodic acid was dissolved in benzene (150 mL) and treated with (formylmethylene)triphenylphosphorane (3.34 g, 11 mmol). The resulting mixture was stirred at room temperature (3 h), diluted with diethylether (100 mL) and the formed triphenylphosphine oxide was filtered. Usual work-up and column chromatography (eluting with hexane-ethyl acetate, 100:5, v/v), afforded the corresponding pure compounds **6a-d** with the properties below reported.

(E,4R,5R)-4,5-isopropylidenedioxydec-2-enal (**6a**, Y = 42%): an oil; $[\alpha]_D^{20}$ = +13.1; ^1H NMR, δ 9.58 (1H, d, J = 7.7 Hz, H-1), 6.72 (1H, dd, J = 15.5, 5.5 Hz, H-3), 6.35 (1H, ddd, J = 15.5, 7.7, 1.5 Hz, H-2), 4.25 (1H, ddd, J = 8.5, 5.5, 1.5 Hz, H-4), 3.76 (1H, ddd, J = 8.5, 8.0, 5.0 Hz, H-5), 1.43, 1.40 (2 x 3H, 2 x s, isopropylidene methyls), 0.86 (3H, t, J = 7.0 Hz, H_3-10). *Z* isomer (8%) 10.13 (1H, d, J = 7.7 Hz, H-1), 6.44 (1H, dd, J = 11.0, 7.0 Hz, H-3), 6.07 (1H, ddd, J = 11.0, 7.7, 1.4 Hz, H-2), ^{13}C NMR, δ 192.93 (C1), 152.51 (C3), 132.56 (C2), 109.58, 80.52 (C5), 80.05 (C4), 32.01, 31.66, 27.12, 26.47, 25.52, 22.36, 13.88. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99, H, 9.80. Found: C, 69.19, H, 9.95.

(*E,4S,5S*)-4,5-isopropylidenedioxydec-2-enal (**6b**, Y = 40%) an oil, $[\alpha]_D^{20}$ = -13.0; ^1H and ^{13}C NMR spectra are superimposable with those of **6a**. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.12; H, 9.75.

(*E,4R,5S*)-4,5-isopropylidenedioxydec-2-enal (**6c**, Y = 43%) an oil, $[\alpha]_D^{20}$ = +19.2; ^1H NMR, δ 9.58 (1H, d, *J* = 7.5 Hz, H-1), 6.69 (1H, dd, *J* = 15.5, 6.0 Hz, H-3), 6.31 (1H, ddd, *J* = 15.5, 7.5, 1.5 Hz, H-2), 4.72 (1H, ddd, *J* = 6.5, 6.0, 1.5 Hz, H-4), 4.26 (1H, ddd, *J* = 8.5, 6.5, 4.5 Hz, H-5), 1.49, 1.38 (2 x 3H, 2 x s, isopropylidene methyls), 0.87 (3H, t, *J* = 7.0 Hz, H_3-10). *Z* isomer was not detected in spectrum; ^{13}C-NMR, δ 192.86 (C1), 152.44 (C3), 133.06 (C2), 108.90, 78.14 (C5), 77.14 (C4), 31.48, 30.30, 27.77, 25.24, 25.80, 22.29, 13.79. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.78; H, 9.84.

(*E,4S,5R*)-4,5-isopropylidenedioxydec-2-enal (**6d**, Y = 42%) an oil; $[\alpha]_D^{20}$ = -18.9; ^1H and ^{13}C NMR spectra are superimposable with those of **6c**. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.87; H, 9.96.

Synthesis of (*E*)-4,5-dihydroxydec-2-enals 1a-d. General procedure.

The regeneration of diolic system was performed treating each acetonide **6a-d** (1.13 g, 5 mmol) with aqueous trifluoroacetic acid (10 mL, 90% v/v) at -25 °C (0.5 h). The solution was then poured into a mixture of ice and aqueous saturated $NaHCO_3$ solution and worked-up to give, after column chromatography (eluting with hexane-ethyl acetate, 60:40, v/v), each pure dihydroxyaldehyde **1a-d** with the properties below reported.

(*E,4R,5R*)-4,5-dihydroxydec-2-enal (**1a**, Y = 56%) an oil, $[\alpha]_D^{20}$ = +52.3, lit[5] +40.7 (*c* 1, $CHCl_3$), ^1H NMR, δ 9.52 (1H, d, *J* = 7.5 Hz, H-1), 6.82 (1H, dd, *J* = 15.5, 5.0 Hz, H-3), 6.34 (1H, ddd, *J* = 15.5, 7.5, 1.5 Hz, H-2), 4.21 (1H, ddd, *J* = 5.0, 5.0, 1.5 Hz, H-4), 3.56 (1H, ddd, *J* = 8.5, 5.0, 5.0 Hz, H-5), 0.85 (3H, t, *J* = 7.0 Hz, H_3-10). ^{13}C-NMR, δ 193.66 (C1), 156.27 (C3), 132.30 (C2), 73.98, 73.85, 33.14, 31.62, 25.20, 22.47, 13.90. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.32; H, 9.79.

(*E,4S,5S*)-4,5-dihydroxydec-2-enal (**1b**, Y = 56%) an oil, $[\alpha]_D^{20}$ = -52.0; ^1H and ^{13}C NMR spectra are superimposable with those of **1a**. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.57; H, 9.67.

(*E,4R,5S*)-4,5-dihydroxydec-2-enal (**1c**, Y = 57%) an oil, $[\alpha]_D^{20}$ = +33.9;), ^1H NMR, δ 9.52 (1H, d, *J* = 7.5 Hz, H-1), 6.85 (1H, dd, *J* = 15.5, 5.0 Hz, H-3), 6.36 (1H, ddd, *J* = 15.5, 7.5, 1.5 Hz, H-2), 4.38 (1H, ddd, *J* = 5.0, 5.0, 1.5 Hz, H-4), 3.78 (1H, ddd, *J* = 8.0, 4.5, 4.5 Hz, H-5), 0.85 (3H, t, *J* = 7.0 Hz, H_3-10); ^{13}C-NMR, δ 193.63 (C1), 154.81 (C3), 132.72 (C2), 74.171 (C4 and C5), 32.11, 31.62, 25.45, 22.46, 13.90. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.43; H, 9.58.

(*E,4S,5R*)-4,5-dihydroxydec-2-enal (**1d**, Y = 58%) an oil, $[\alpha]_D^{20}$ = -33.5; ^1H and ^{13}C NMR spectra are superimposable with those of **1c**. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.60; H, 9.88.

The diastereomeric purity of compounds **1a-d** was checked by GLC analysis (SPB-5, Supelco, 25 m x 0.75 mm, 160 °C) of their cyclic methaneboronates, prepared by reaction with a 0.05 M solution of methaneboronic acid in anhydrous pyridine at 60 °C (0.5 h). The methaneboronates of the couple **1a** and **1b** showed R_t = 6.74 min, while those of the couple **1c** and **1d** showed R_t = 7.51 min.

The enantiomeric purity of compounds **1a-d** was checked by HPLC analysis of their dibenzoates, on a chiral column (LiChroCART 250-4 (*R,R*)-Whelk-01, 5 μm, Merck, eluent hexane-2-propanol 94:6 v/v), 1 mL/min, λ 222 nm). The dibenzoates deriving from enantiomers **1a** and **1b** showed R_t = 17.4 and 20.5 min respectively, while the dibenzoates of enantiomers **1c** and **1d** showed R_t = 17.1 and 19.4 min respectively.

The diastereomeric and enantiomeric purity of all compounds **1a-d** was always higher than 98%.

Acknowledgement

This work, supported by Regione Lombardia (Piano di Ricerche Finalizzate per il Settore Sanitario, progetto N° 1560), was dedicated to the memory of Prof. Martino Colonna.

REFERENCES AND NOTES

1. (a) Esterbauer, H.; Schaur, R.J.; Zollner, H. *Free Radical Biol. Med.*, **1991**, *11*, 81-128. (b) Esterbauer, H. in McBrien, D.C.H.; Slater, T.F.; Eds. *Free Radicals Lipid Peroxidation and Cancer*, London: Academic Press Inc., **1982**, 101-128.
2. (a) Allevi, P.; Anastasia, M.; Cajone, F.; Ciuffreda, P.; Sanvito, A. M. *Free Radical Biol. Med.*, **1995**, *18*, 107-116. (b) Allevi, P.; Anastasia, M.; Ciuffreda, P.; Sanvito, A. M. *Tetrahedron Asymmetry*, **1994**, *5*, 927-934. (c) Allevi, P.; Anastasia, M.; Ciuffreda, P. *J. Labelled Compd. Radiopharm.*, **1994**, *34*, 557-563. (d) Allevi, P.; Anastasia, M.; Cajone, F.; Ciuffreda, P.; Sanvito, A. M. *Tetrahedron Asymmetry*, **1994**, *5*, 13-16. (e) Allevi, P.; Anastasia, M.; Cajone, F.; Ciuffreda, P.; Sanvito, A. M. *J. Org. Chem.*, **1993**, *58*, 5000-5002. (f) Allevi, P.; Anastasia, M.; Ciuffreda, P.; Sanvito, A. M. *Tetrahedron Asymmetry*, **1993**, *4*, 1397-1400.
3. Allevi, P.; Cajone, F.; Ciuffreda, P.; Anastasia, M. *Tetrahedron Lett.*, **1995**, *36*, 1347-1350.
4. Benedetti, A.; Comporti, M.; Fulceri, R.; Esterbauer, H. *Biochim. Biophys. Acta*, **1984**, *792*, 172-181.
5. In our paper[3] we reported also the synthesis of the acetonide of the (*E,4R,5R*)-4,5-dihydroxydec-2-enal. The aldehyde was also obtained by Sharpless by an elegant procedure (Becker, H.; Soler, M.A.; Sharpless, K.B. *Tetrahedron*, **1995**, *51*, 1345-1376).
6. Other results, obtained by a different approach, based on the use of Sharpless dihydroxylation reagents which allows a "reagent-control strategy" of the stereochemistry, will be published in due course.
7. (a) Lee, A.W.M.; Martin, V.S.; Masamune, S.; Sharpless, K.B.; Walker, F.J. *J. Am. Chem. Soc.*, **1982**, *104*, 3515-3516. (b) Lee, A.W.M. *Magnetic Resonance in Chemistry*, **1985**, *23*, 468-469.
8. Wu, W.-L.; Wu, Y.-L. *J. Org. Chem.*, **1993**, *58*, 3586-3588.
9. Wu, W.-L.; Wu, Y.-L. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 3081-3086.
10. A similar transformation was observed for (*E*)-4-hydroxynon-2-enal (Seyfarth, H.E. *Chem. Ber.*, **1968**, *101*, 2283-2284).
11. Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.*, **1978**, *43*, 2923-2925.
12. (a) Zinner, H. *Chem. Ber.*, **1950**, *83*, 275-277. (b) Rollin, P.; Pougny, J.R. *Tetrahedron*, **1986**, *42*, 3479-3490.
13. Zinner, H.; Wittenburg, E.; Rembarz, G. *Chem. Ber.*, **1959**, *92*, 1614-1617.
14. Zinner, H.; Kristen, H. *Chem. Ber.*, **1964**, *97*, 1654-1658.

(*Received in UK* 31 *July* 1995)