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A Practical Synthesis of (*R*)- and (*S*)-(*E*)-4-Hydroxyalk-2-enals, Cytotoxic Products of the Microsomal Lipid Peroxidation

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Abstract: The chemical synthesis of some (*S*)- and (*R*)-(E)-4-hydroxyalk-2-enals, important products of lipid peroxidation (LPO), has been carried out *via* enantiomerically pure 2-benzoyloxyaldehydes, chiral key intermediates obtained from two diastereomeric diepoxides deriving from D-mannitol. These aldehydes were transformed into the final compounds by Wittig condensation with (formylmethylene)triphenylphosphorane and regeneration of the hydroxy group.

Peroxidation of liver microsomial lipids leads to the formation of a number of aldehydes including alkanals, (*E*)-alk-2-enals and (*E*)-4-hydroxyalk-2-enals arising from polyunsaturated fatty acids bonded to phospholipids.[1] Of these carbonyls, (*E*)-4-hydroxyalk-2-enals have received much attention for their biological properties including mutagenicity, cytotoxicity[2,3] and the ability to induce heat shock protein synthesis.[4] However the chirality of the compounds isolated from biological media has not been clarified, probably for the lack of a simple method for obtaining standard compounds in homochiral form.

As part of a program devoted to study the physiological and pathophysiological properties of these (*E*)-4-hydroxyalk-2-enals, we were interested studying the influence of the absolute configuration of the stereogenic carbon atom on their biological properties. Thus we have recently reported two simple and general methods suitable for obtaining same important homochiral (*E*)-(4)-hydroxyalk-2-enals[5,6] and a method for obtaining the corresponding homochiral (*E*)-4-hydroxyalk-2-enoic acids by enzymatic resolution of their racemates.[7]

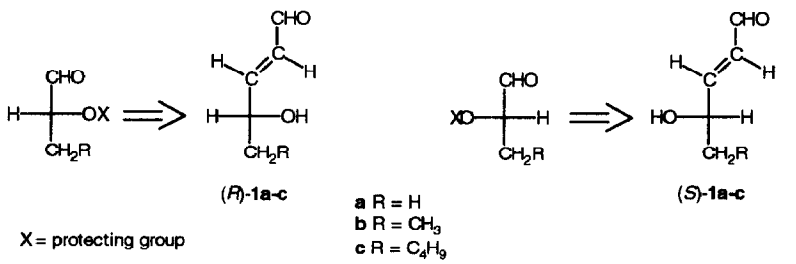
Before our results only one report had appeared describing the chemical resolution of (*E*)-4-hydroxynon-2-enal by means of a sorbic acid iron tricarbonyl complex.[8] However, while the present work was in progress, an enantioselective synthesis of (*E*)-4-hydroxynon-2-enal, (*E*)-4-hydroxydec-2-enal and (*E*)-4-hydroxyundec-2-enal was reported.[9] This synthesis involved a three-carbon homologation of an appropriate chiral epoxyaldehyde with methoxymethylenetriphenylphosporane. The epoxyaldehydes were on turn obtained by Sharpless asymmetric epoxidation[10] of appropriate allylic alcohols, improvement of the enantiomeric purity of the obtained epoxyalcohols by recrystallization, and Swern oxidation of the hydroxy group to carbonyl. However, the preparation of enantiomerically pure (*R*)- and (*S*)-(*E*)-4-hydroxypent-2-enal or (*E*)-4-hydroxyhex-2-enal, the first of which, in racemic form, is the more studied hydroxyaldehyde, remain unreported. This could be ascribed to the fact that the parent low molecular weight allylic alcohols are epoxidised with somewhat lower enantiomeric excess than more substituted allylic alcohols[11] and show special problems associated with the isolation and purification of the formed epoxyalcohols, which are water soluble and polymerise quite exothermically.[12]

Here we report a simple general method for obtaining homochiral short and long chain (*R*)- and (*S*)-(*E*)-4-hydroxyalk-2-enals by chemical synthesis starting with the diastereomeric diepoxides **2** and **3**, both obtainable from D-mannitol,[13,14] two stereogenic carbon of which are retained in the final compounds.

RESULTS AND DISCUSSION

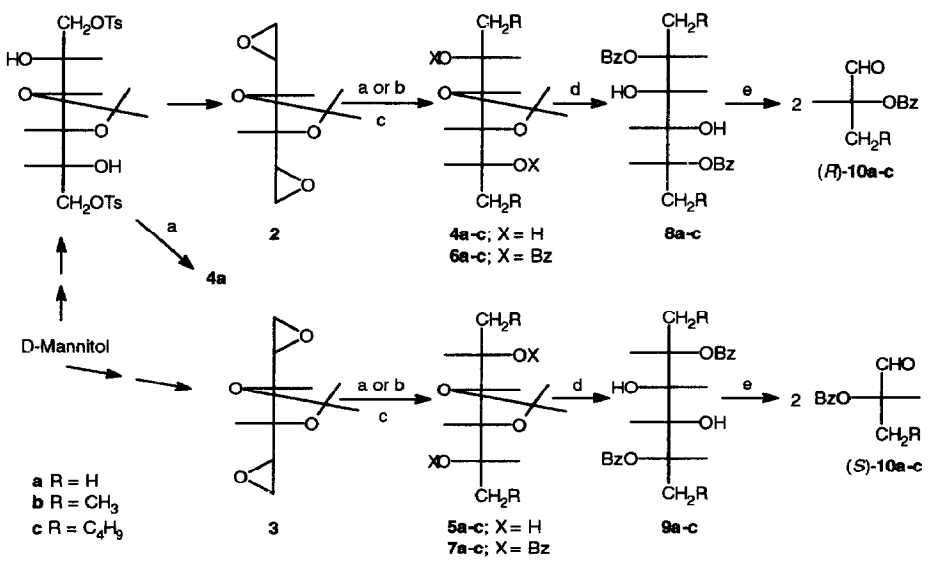
Since from the work developed by Depezay et al.[13,14] on the synthesis of coriolic acid and in leukotriene chemistry, (*R*)- and (*S*)-2-hydroxyaldehydes (suitably protected) appeared convenient chiral building blocks for the synthesis of (*R*)- and (*S*)-(E)-4-hydroxyalk-2-enals by Wittig reaction (Figure), we

FIGURE



planned to prepare these aldehydes by an unique procedure, starting with the diastereomeric diepoxyacetals **2** and **3**, prepared from D-mannitol[13,14] (Scheme 1).

SCHEME 1



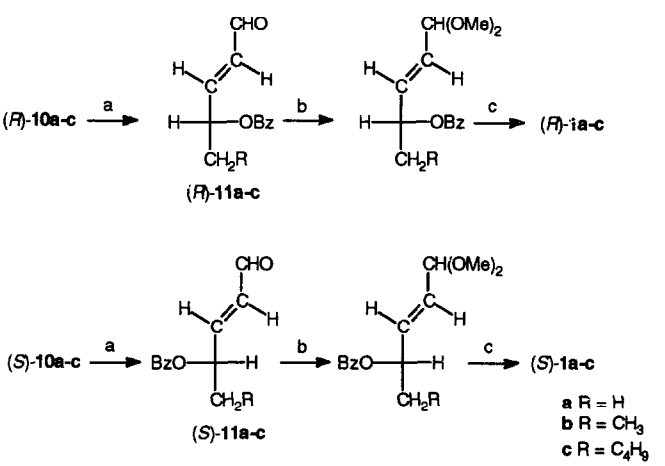
(a): for R = H, $LiEt_3BH$, THF, RT, 2h. (b): for R = alkyl, RMgBr / CuBr·SMe_2, THF, -45 °C then RT, 1h. (c): BzCl / Py, RT, 1h. (d): TFA / H_2O 9:1, 0 °C, 1h. (e): $Pb(OAc)_4$, C_6H_6, RT, 1h.

The first step of this procedure involves the nucleophilic opening of the epoxidic rings of compounds **2**, for the *R* series, and of compound **3**, for the *S* series. For the preparation of the shorter α-hydroxyaldehydes useful for obtaining (*R*)- and (*S*)-(E)-4-hydroxypent-2-enals [(*R*)- and (*S*)-**1a**] the opening was performed by lithium triethylborohydride reduction[15] which affords the diols **4a** and **5a**. The diol **4a** was also obtained by simple reduction of the ditosylate precursor[13] of **2** by the same hydride (Scheme 1).

For the synthesis of the α-hydroxyaldehydes useful for obtaining both enantiomers of the **1b** and **1c** the opening of the epoxides by a nucleophilic attack of an appropriate carbon atom chain was required. This result was previously satisfactory obtained by Depezay group[14] by opening the diepoxides by means of lithium acetylides or of dibutylcopperlithium.[14] In our work a regiospecific alternative opening of the diepoxides was performed by means of an appropriate alkylmagnesium bromide in the presence of cuprous bromide-dimethylsulfide.[16] In fact, using this reagent couple no opening of the epoxides by the halogen was observed. On the contrary, when cuprous iodide and/or an alkylmagnesium iodide were used as copper(I) and alkyl chain sources, the iodohydrin formation was the main product of the reaction.

In all cases, each of the crude diols **4a-c** and **5a-c**, derived by the nucleophilic opening of the diepoxides, allowed two molecules of an enantiomerically pure aldehyde **10a-c** to be obtained. The result was obtained through the sequence of reaction including the protection of the hydroxy groups, the hydrolysis of the acetonide group and the cleavage of the 3,4-diol system.[13, 14] The final part of the synthesis was then accomplished by a two carbon homologation of the obtained 2-benzoyloxyaldehydes (*R*)- and (*S*)-**10a-c** by Wittig condensation with (formylmethylene)triphenylphosphorane[17] and regeneration of the 4-hydroxy group (Scheme 2).

SCHEME 2



(a): $(C_6H_5)_3PCHCHO$, C_6H_6, reflux, 6h. (b): $HC(OMe)_3$ / montmorillonite clay K-10, CH_2Cl_2, RT, 1h. (c): MeOH / MeONa 0.1M, RT, 20h followed by Dowex 50W-H, RT, 1h.

As previously observed for the acetylated homochiral (E)-4-hydroxyalk-2-enals, a direct regeneration of the allylic hydroxy group by alkaline hydrolysis of the 4-benzoate caused the decomposition of the product α,β–unsaturated system, or its reaction with the alcoholic solvent.[5,18] However, the saponification of the

acetoxy group by equilibration with sodium methoxide in methanol occurred in good yields after protection of the aldehydic function as the corresponding dimethylacetals,[18] by treatment with methylorthoformiate.[5] After a simple acidification with ion exchange resin of the saponification mixture, the regeneration of the aldehydic group also occurred and the (E)-4-hydroxyalk-2-enals (*R*)- and (*S*)-**1a-c** were obtained.

By this route the hydroxyaldehydes (*R*)- and (*S*)-**1a-c** were obtained in high enantiomeric purity (>95%) as established by ^{1}H NMR, using the corresponding Mosher esters[20] which allowed also to establish the absolute configuration of the stereogenic center[21] for compounds previously unreported.

In conclusion, our method represents the first chemical route which allows to synthesise in high enantiomeric purity the more important (*R*)-and (*S*)-4-hydroxyalk-2-enals, formed in lipid peroxidation. In particular the method allows to obtain both enantiomers of (*E*)-4-hydroxypent-2-enals and (*E*)-4-hydroxyhex-2-enals overcoming the use of short chain chiral epoxyalcohols[9] which pose special problems with respect to product isolation and/or the stability. The method complements our previous preparation of these (E)-4-hydroxyalk-2-enals by enzymatic separation of racemates, the enzymic resolution being generally preferred when low amounths of aldehydes are required. The present method allows also to obtain homochiral 2-hydroxyaldehydes, useful for other syntheses.

EXPERIMENTAL SECTION

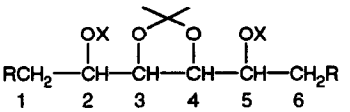
The ^{1}H NMR spectra (500.13 MHz) were recorded with Bruker AM-500 spectrometer in $CDCl_3$ at 303 K and were referenced to $CHCl_3$ at 7.24 ppm. HPLC analyses were carried out on a Merck superspher 100 RP-18 column, 4mm x 25 cm, the flow rate was 1 ml/min and the detection was performed at 220 nm. TLC were carried out on silica gel HF_{254} microplates. Column chromatography refers to flash chromatography. Usual work-up refers to washing the organic layer with water, drying over Na_2SO_4, and evaporating the solvent under reduced pressure. All products showed satisfactory elemental analyses.

Synthesis of (*R*)-and (*S*)-2-benzoyloxyaldehydes (*R*)- and (*S*)-10a-c. General Procedures.

i) Synthesis of (2R,3R,4R,5R)- and (2S,3R,4R,5S)-2,5-dibenzoyloxy-3,4-O-(1-methyletylidene)-3,4-hexanediol **(6a)** *and* **(7a)**. The diol **4a** was obtained by reduction with lithium triethylborohydride of the diepoxide **2** or of its parent ditosylate.[13] The diol **5a** was obtained by similar reduction of the diastereomeric diepoxide **3**.[13]

To a solution of the appropriate diepoxide (or ditosilate) (5 mmol) in THF (7 ml), cooled to 0 °C (ice bath), lithium triethylborohydride (20 mmol of a 1.5 M solution in THF) was added and the ice bath removed. After a 2 h stirring at room temperature, the excess hydride was decomposed with water and the organoborane was oxidised with H_2O_2 (10 ml of a 30% aqueous solution) and NaOH (10 ml of a 3 N aqueous solution) at 0 °C for 45 min. Then the THF layer was separated and the aqueous layer was extracted with diethyl ether-hexane (1:1; v/v). The combined organic extracts were worked-up to afford crude (2*R*,3*R*,4*R*,5*R*)-3,4-O-(1-methylethylidene)-2,3,4,5-hexanetetraol (**4a**; 85% yield) or (2*S*,3*R*,4*R*,5*S*)-3,4-O-(1-methylethylidene)-2,3,4,5-hexanetetraol (**5a**; 83% yield). A sample of **4a**, purified by flash chromatography (eluting with hexane-AcOEt; 1:1; v/v) showed: mp 87-89 °C; $[\alpha]_D^{20}$ = -9.6, *c* 1, $CHCl_3$. A similarly purified sample of the diol **5a**, an oil, showed $[\alpha]_D^{20}$ = +23.2, *c* 1, $CHCl_3$. The ^{1}H NMR data for **4a** and **5a** are reported in the Table.

Table. ^{1}H NMR chemical shifts in ppm and coupling constants in Hz for compounds **4a-c, 5a-c, 6a-c, 7a-c**



Compound	R	X	Protons		
			1 and 6	2 and 5	3 and 4
4a	H	H	1.29 d (6.5)	3.76 dq, 3.75 dq (6.5, 1.5)	3.61 AB pattern
4b	CH_3	H	1.81 ddq (14.0, 7.5, 2.5) 1.48 ddq (14.0, 7.5, 7.5)	3.54 ddd, 3.52 ddd (7.5, 5.0, 2.5)	3.68 AB pattern
4c	C_4H_9	H	1.77-1.70 overlapping	3.54 ddd, 3.52 ddd (11.0, 5.0, 2.5)	3.62 AB pattern
5a	H	H	1.23 d (6.5)	3.72 dq, 3.70 dq (6.5, <1)	3.78 AB pattern
5b	CH_3	H	1.51 dq (7.5, <1)	3.40 dt (7.5, 7.5)	3.90 A_2 pattern
5c	C_4H_9	H	1.54-1.43 overlapping	3.47 ddd (9.0, 9.0, 4.5)	3.89 A_2 pattern
6a	H	Bz	1.42 d (6.5)	5.31 dq, 5.30 dq (6.5, 1.5)	4.18 AB pattern
6b	CH_3	Bz	1.84-1.76 overlapping	5.24 ddd, 5.23 ddd (7.5, 7.5, 4.0)	4.26 AB pattern
6c	C_4H_9	Bz	1.79-1.67 overlapping	5.31 ddd, 5.30 ddd (7.5, 7.5, 4.0)	4.24 AB pattern
7a	H	Bz	1.42 d (6.5)	5.33 dq, 5.32 dq (6.5, 1.5)	4.05 AB pattern
7b	CH_3	Bz	1.87 ddq (14.0, 9.0, 7.5) 1.76 ddq (14.0, 7.5, 5.0)	5.23 ddd (9.0, 5.0, <1)	4.00 A_2 pattern
7c	C_4H_9	Bz	1.80-1.69 overlapping	5.30 ddd (9.0, 5.0, <1)	3.99 A_2 pattern

For pursuing the synthesis, each crude diol (**4a** or **5a**; 5 mmol) was benzoylated by treatment with benzoyl chloride (12 mmol) in pyridine (5 ml) at 0 °C for 1 h. Usual work-up afforded, starting from **4a**, the

(2*R*,3*R*,4*R*,5*R*)-2,5-dibenzoyloxy-3,4-O-(1-methyletylidene)-3,4-hexanediol (**6a**; 90% yield) which showed: mp 64-66 °C; $[\alpha]_D^{20}$ = -23.0, *c* 1, $CHCl_3$ and, starting from **5a**, the (2*S*,3*R*,4*R*,5*S*)-2,5-dibenzoyloxy-3,4-O-(1-methyletylidene)-3,4-hexanediol (**7a**; 85% yield), an oil with $[\alpha]_D^{20}$ = +37.9, *c* 1, $CHCl_3$. The ^1H NMR data for **6a** and **7a** are reported in the Table.

ii) Synthesis of the benzoyloxy compounds **6b-c** *and* **7b-c.** To a magnetically stirred suspension of the appropriate alkylmagnesium bromide (20 mmol) in diethyl ether (10 ml), $CuBr{\cdot}SMe_2$ (0.5 mmol) was added. After stirring at -45 °C for 2 h, the appropriate diepoxide (**2** or **3**; 5 mmol) in THF (15 ml) was added. After 1 h at room temperature, the mixture was poured into a saturated NH_4Cl aqueous solution and worked-up to give, after flash chromatography (eluting with hexane-AcOEt; 7:3; v/v) pure dialkylation products **4b-c** or **5b-c**. The following yields and properties were observed for these compounds: **4b** (73%; an oil; $[\alpha]_D^{20}$ = +10.8, *c* 1, $CHCl_3$), **4c** (77%; mp 54-55 °C; $[\alpha]_D^{20}$ = +23.9, *c* 1, $CHCl_3$), **5b** (70%; an oil; $[\alpha]_D^{20}$ = +18.8, *c* 1, $CHCl_3$), **5c** (75%; an oil; $[\alpha]_D^{20}$ = +1.4, *c* 1, $CHCl_3$). The ^1H NMR data for **4b-c** and **5b-c** are reported in the Table.

However crude diols could be directly benzoylated by treatment with benzoyl chloride (12 mmol) in pyridine (5 ml) for 30 min at 0 °C and 1 h at room temperature, to afford, after usual work-up and flash chromatography (eluting with hexane-AcOEt; 9:1; v/v), the dibenzoates **6b-c** or **7b-c** with the following yields and properties: **6b** (86%; an oil; $[\alpha]_D^{20}$ = +21.8, *c* 1, $CHCl_3$), **6c** (89%; an oil; $[\alpha]_D^{20}$ = +37.7, *c* 1, $CHCl_3$), **7b** (90%; mp 93-94 °C; $[\alpha]_D^{20}$ = -4.0, *c* 1, $CHCl_3$), **7c** (88%; an oil; $[\alpha]_D^{20}$ = -3.0, *c* 1, $CHCl_3$; lit:[14b] $[\alpha]_D^{20}$ = -2, $CHCl_3$). The ^1H NMR data for **6b-c** and **7b-c** are reported in the Table.

iii) Hydrolysis of the acetonide group of **6a-c** *and* **7a-c.** The hydrolysis was performed treating each acetonide **6a-c** or **7a-c** (4 mmol) with aqueous trifluoroacetic acid (50 ml, 90%) for 1 h at 0 °C. After dilution with water, usual work-up and flash chromatography (eluting with hexane-AcOEt; 6:4; v/v) afforded the corresponding diol **8a-c** or **9a-c** with the following yields and properties: **8a** (74%; mp 68-69 °C; $[\alpha]_D^{20}$ = +36.6, *c* 1, $CHCl_3$), **8b** (78%; an oil; $[\alpha]_D^{20}$ = +69.0, *c* 1, $CHCl_3$), **8c** (70%; an oil; $[\alpha]_D^{20}$ = +68.4, *c* 1, $CHCl_3$), **9a** (74%; mp 100-102 °C; $[\alpha]_D^{20}$ = +47.5, *c* 1, $CHCl_3$), **9b** (72%; an oil; $[\alpha]_D^{20}$ = -6.4, *c* 1, $CHCl_3$), **9c** (76%; mp 68-69 °C; $[\alpha]_D^{20}$ = -9, *c* 1, $CHCl_3$; lit:[14b] mp 67 °C; $[\alpha]_D^{20}$ = -13, CH_2Cl_2). The ^1H NMR data for **8a-c** and **9a-c** are reported in the Table.

iv) Oxidation of **8a-c** *and* **9a-c** *to (R)- and (S)-2-benzoyloxyaldehydes (R)- and (S)-***10a-c.**. Each diol **8a-c** or **9a-c** (1.3 mmol) was dissolved in benzene (12 ml) and treated with lead tetraacetate (1.56 mmol) at room temperature for 1 h. Then the mixture was filtered on a pad of Celite and worked-up to afford the crude aldehydes and, after flash chromatography (eluting with hexane-AcOEt; 7:3; v/v), the pure aldehydes (*R*)- or (*S*)-**10a-c** with the following yields and properties: (*R*)-**10a** {87%; an oil; $[\alpha]_D^{20}$ = -8.5, *c* 1, C_6H_6; ^1H NMR: δ 9.65 (1H, d, *J* < 1 Hz, H-1), 5.29 (1H, dq, *J* = 6.5 and < 1 Hz, H-2), 1.51 (3H, d, *J* = 6.5 Hz, H_3-3); lit:[22] $[\alpha]_D^{20}$ = -30.8, C_6H_6, the specific rotations of this *R*-benzoyloxyaldehyde and of its enantiomer (*S*)-**10a** depend of the degree of polymerisation and change even in the sign. Our date agree in the sign with those reported by Hobbs[22] and contrast with those reported for *S* enantiomer by Murayama.[23] In our synthesis the crude benzoyloxyaldehydes (*R*)- and (*S*)-**10a** were generally directly used for accomplishing the synthesis}, (*R*)-**10b** (85%; an oil; $[\alpha]_D^{20}$ = +43.2, *c* 1, $CHCl_3$; ^1H NMR:δ 9.36 (1H, d, *J* < 1 Hz, H-1), 5.16 (1H, ddd, *J* = 7.5, 5.0, < 1 Hz, H-2), 1.99 (1H, ddq, *J* = 14.0, 7.5, 5.0 Hz, H-3), 1.93 (1H, ddq, *J* = 14.0, 7.5, 7.5 Hz, H'-3)), (*R*)-**10c** (82%; an oil; $[\alpha]_D^{20}$ = +36.6, *c* 1, $CHCl_3$; ^1H NMR:δ 9.62 (1H, d, *J* < 1 Hz, H-1), 5.20 (1H,

ddd, J = 7.5, 5.0, < 1 Hz, H-2), 1.98 - 1.83 (2H, overlapping, H_2-3)) (*S*)-**10a** (90%; an oil; $[\alpha]_D^{20}$ = +10.3, *c* 1, C_6H_6; lit:[23] $[\alpha]_D^{20}$ = -28, C_6H_6) (*S*)-**10b** (80%; an oil; $[\alpha]_D^{20}$ = -42.4, *c* 1, $CHCl_3$), (*S*)-**10c** (79%; an oil; $[\alpha]_D^{20}$ = -35.9, *c* 1, CH_2Cl_2; lit:[14b] $[\alpha]_D$ = -31, CH_2Cl_2)). The ^{1}H NMR data for (*S*)-**10a-c** were identical in all respects with those of their enantiomers (*R*)-**10a-c** .

Synthesis of (*R*)- and (*S*)-(E)-4-hydroxyalk-2-enals (*R*)- and (*S*)-1a-c.

*i) Wittig condensation of (R)- and (S)-***10a-c.** To a solution of the benzoyloxyaldehyde (*R*)- or (*S*)-**10a-c** (3.4 mmol) in benzene (50 ml) (formylmethylene)triphenylphosphorane (1.2 g, 4.0 mmol) was added and the mixture was refluxed for 6 h. The mixture was diluted with diethylether and the triphenylphosphine oxide was filtered. Usual work-up and flash chromatography (eluting with hexane-AcOEt; 9:1; v/v), afforded the corresponding pure (*R*)- or (*S*)-(E)-4-benzoyloxyalk-2-enals (*R*)- or (*S*)-**11a-c** with the following yields and properties: (*R*)-**11a** (72%; an oil; $[\alpha]_D^{20}$ = -86.2, *c* 1, $CHCl_3$; ^{1}H NMR:δ 9.58 (1H, d, J = 7.7 Hz, H-1), 6.30 (1H, ddd, J = 15.5, 7.7, 1.5 Hz, H-2), 6.86 (1H, dd, J = 15.5, 5.0 Hz, H-3), 5.84 (1H, ddq, J = 6.3, 5.0, 1.5 Hz, H-4)), (*R*)-**11b** (75%; an oil; $[\alpha]_D^{20}$ = -76.0, *c* 1, $CHCl_3$; ^{1}H NMR:δ 9.57 (1H, d, J = 7.7 Hz, H-1), 6.28 (1H, ddd, J = 15.5, 7.7, 1.5 Hz, H-2), 6.82 (1H, dd, J = 15.5, 5.0 Hz, H-3), 5.70 (1H, ddt, J = 6.3, 5.0, 1.5 Hz, H-4)), (*R*)-**11c** (73%; an oil; $[\alpha]_D^{20}$ = -68.0, *c* 1, $CHCl_3$; ^{1}H NMR:δ 9.57 (1H, d, J = 7.7 Hz, H-1), 6.27 (1H, ddd, J = 15.5, 7.7, 1.5 Hz, H-2), 6.83 (1H, dd, J = 15.5, 5.0 Hz, H-3), 5.75 (1H, ddt, J = 6.3, 5.0, 1.5 Hz, H-4)) (*S*)-**11a** (75%; an oil; $[\alpha]_D^{20}$ = +87.1, *c* 1, $CHCl_3$), (*S*)-**11b** (74%; an oil; $[\alpha]_D^{20}$ = +77.8, *c* 1, $CHCl_3$), (*S*)-**11c** (73%; an oil; $[\alpha]_D^{20}$ = +68.5, *c* 1, $CHCl_3$; lit:[14b] $[\alpha]_D^{20}$ = +67, CH_2Cl_2)). The ^{1}H NMR data for (*S*)-**11a-c** were identical in all respects with those of their enantiomers (*R*)-**11a-c**

ii) Regeneration of the 4-hydroxy-group. Each benzoyloxyaldehyde (*R*)- or (*S*)-**11a-c** (1 mmol) dissolved in dichloromethane (15 ml) was stirred with montmorillonite clay K-10 (200 mg) in trimethylorthoformiate[5] for 1 h. The mixture was filtered and worked-up to afford the crude benzoyloxyacetal (TLC, ^{1}H NMR) which was equilibrated with a methanolic solution of sodium methoxide (9 ml, 0.1 M) at room temperature for 20 h. The solution was treated with an acidic ion exchange resin (Dowex-50 W-hydrogen, 2 meq) at room temperature for 1 h under stirring and then was filtered. The solvent was evaporated and the crude residue was purified by flash chromatography (eluting with hexane-AcOEt; 7:3; v/v), to afford (*R*)- or (*S*)-**1a-c** with the following yields and properties: (*R*)-**1a** (67%; an oil; $[\alpha]_D^{20}$ = -45.7, *c* 1, $CHCl_3$), (*R*)-**1b** (69%; an oil; $[\alpha]_D^{20}$ = -53.0, *c* 1, $CHCl_3$; lit:[5] oil; $[\alpha]_D^{20}$ = -52.3, $CHCl_3$), (*R*)-**1c** (70%; an oil; $[\alpha]_D^{20}$ = -48.7, *c* 1, $CHCl_3$; lit:[5] oil; $[\alpha]_D^{20}$ = -48.2, $CHCl_3$), (*S*)-**1a** (72%; an oil; $[\alpha]_D^{20}$ = +55.6, *c* 1, $CHCl_3$, the difference in the absolute value with the *R* enantiomer can be explained considering the easy polymerisation of the compounds on standing at room temperature), (*S*)-**1b** (70%; an oil; $[\alpha]_D^{20}$ = +52.6, *c* 1, $CHCl_3$; lit:[5] oil; $[\alpha]_D^{20}$ = +51.6, $CHCl_3$), (*S*)-**1c** (72%; an oil; $[\alpha]_D^{20}$ = +48.0, *c* 1, $CHCl_3$; lit:[5] oil; $[\alpha]_D^{20}$ = +46.3, $CHCl_3$). The enantiomeric excess of the hydroxyaldehydes (*R*)- and (*S*)-**1a-c,** determined by HPLC and ^{1}H NMR (500 MHz) analyses of their (*R*) and (*S*) Mosher esters [(*R*)- and (*S*)-2-methoxy-2-phenyl-2-trifluoromethylacetates; (*R*)- and (*S*)-MTPA esters],[20, 21] were always major than 98%.

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