A Practical Preparation of α-Hydroxy and α,β-Dihydroxy Aldehydes, Useful Intermediates for the Synthesis of Arachidonic Acid Metabolites, starting with D-Glyceraldehyde Acetonide

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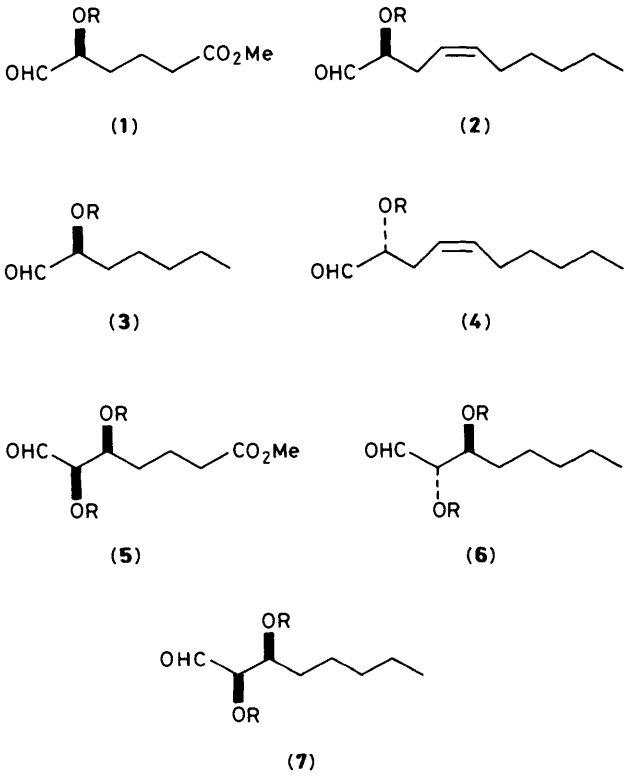
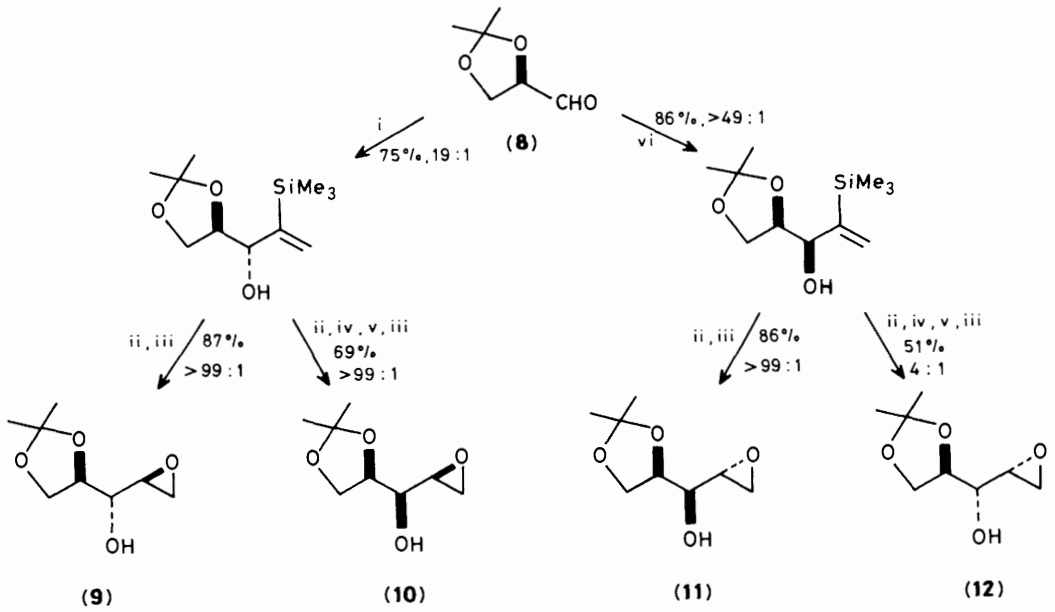
Optically active α-hydroxy and α,β-dihydroxy aldehydes, useful intermediates for synthesis of lipoxygenase metabolites of arachidonic acid, are synthesized highly diastereoselectively starting with readily available D-glyceraldehyde acetonide.

Hydroxyicosatetraenoic acids (HETEs), leukotriene B_4 (LTB_4), and lipoxins are important metabolites of arachidonic acid, and their total synthesis has attracted much interest in recent years.[1] These metabolites all have hydroxy-bearing chiral centre(s) and a conjugated polyalkene unit. Previous studies have revealed that the carbon chain elongation of α-hydroxy aldehydes and/or α,β-dihydroxy aldehydes *via* a Wittig reaction provides an effective method for preparation of these metabolites. Thus, 14(*R*)-lipoxin B was prepared from the aldehydes (**1**) and (**6**),[2] 14(*S*)-lipoxin B from (**1**) and (**7**),[2] lipoxin A from (**3**) and (**5**),[3] LTB_4 from (**1**) and (**4**),[4] 12-*epi*-LTB_4 from (**1**) and (**2**),[4] and 5-HETE from (**1**).[5] So far these aldehydes have been prepared from discrete starting materials, most frequently from sugars such as D- and L-arabinose, 2-deoxy-D-ribose, and L-xylose.† We report here the synthesis of all these aldehydes (**1**)—(**7**) starting from a single chiral material, D-glyceraldehyde acetonide (**8**).‡ Recently we reported the highly stereoselective preparation of four possible diastereoisomers of the epoxy alcohols (**9**)—(**12**) from (**8**) according to the procedure shown in Scheme 1.[8,9] Starting with the aldehydes (**9**), (**10**), and (**11**), we planned to prepare the aldehydes (**1**)—(**7**) by the procedure shown in Scheme 2 and it has been successful. The procedure is based

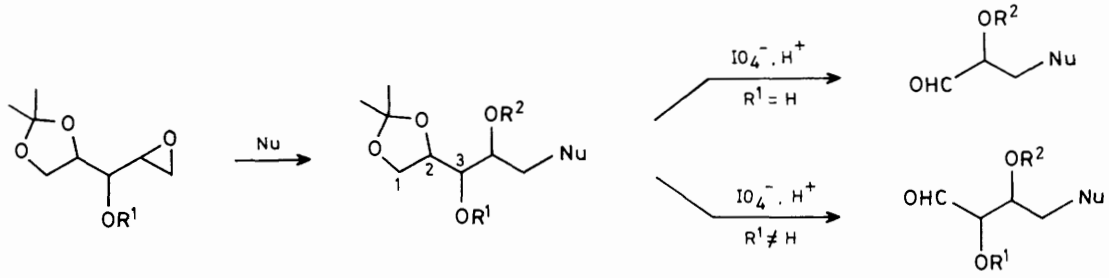


† For other methods for preparation of these aldehydes, see ref. 6.

‡ Depezay and his coworkers have prepared (**2**) and (**4**) from mannitol, see ref. 7.



Scheme 1. *Reagents and conditions:* i, $[H_2C{=}C(SiMe_3)Cu(Me)CN]LiMgBr$; ii, Bu^tOOH, V^{5+}; iii, Bu^tOK, Bu^n_4NF; iv, $(COCl)_2$, Me_2SO then NEt_3; v, L-Selectride; vi, $H_2C{=}C(SiMe_3)Cu$.

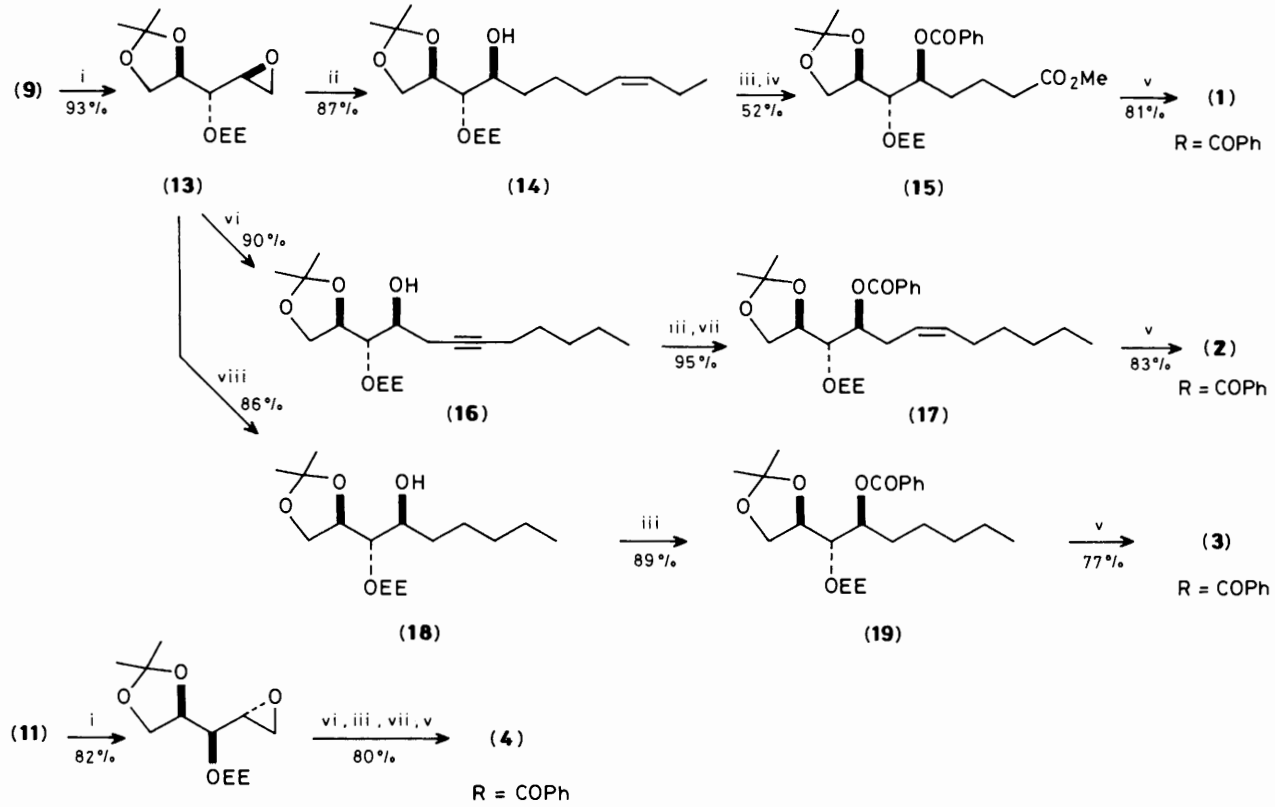


Scheme 2

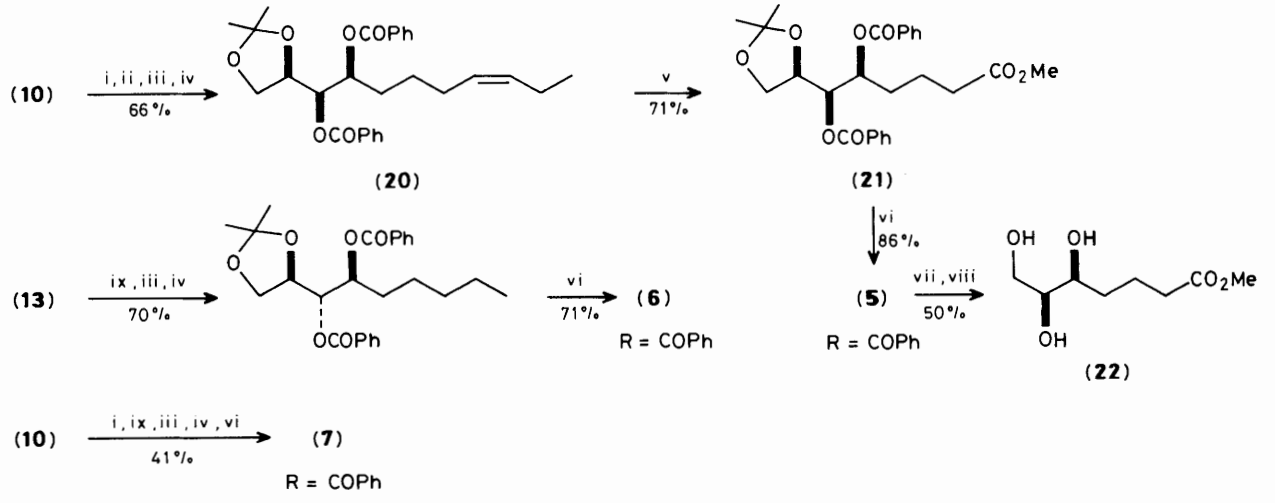
on the epoxide ring opening of one of the epoxy alcohols (**9**), (**10**), or (**11**) with an appropriate nucleophile (Nu) and the transformation of the resulting product into the α-hydroxy aldehyde and/or the α,β-dihydroxy aldehyde *via* oxidative cleavage of the C(2)–C(3) or C(1)–C(2) carbon bond, respectively, with IO_4^-.

The synthesis of (**1**) (R = COPh) from (**9**) was carried out as shown in Scheme 3. After protection of (**9**) as the ethoxyethyl (EE) ether, the resulting product (**13**) was treated with (*Z*)-hex-3-enylmagnesium bromide in the presence of a catalytic amount of CuI in Et_2O to afford (**14**) quantitatively. Oxidation of the benzoate of (**14**) with $NaIO_4$ in the presence of a catalytic amount of RuO_4[10] followed by esterification using CH_2N_2 gave (**15**) in 60% yield. Finally, (**15**) was treated with H_5IO_6 in MeOH–H_2O[11] (1 : 1) at room temperature for 4 h to yield (**1**) {R = COPh, $[\alpha]_D^{25}$ −35.7° (*c* 1.66, $CHCl_3$); lit. ref. 12: $[\alpha]_D^{23}$ −34.4° (*c* 1.3, $CHCl_3$)} in 81% yield. The aldehyde (**2**) (R = COPh) was prepared from the same starting material (**13**). In this case, the epoxide (**13**) was treated with the lithium anion of hept-1-yne in tetrahydrofuran (THF)-hexamethylphosphoric triamide (HMPA) to produce (**16**), which was then converted into (**17**) by benzoylation followed by semi-hydrogenation over Lindlar catalyst. Finally oxidative cleavage of (**17**) with H_5IO_6 gave (**2**) {R = COPh, $[\alpha]_D^{25}$ −16.3° (*c* 1.76, CH_2Cl_2); lit. ref. 7: $[\alpha]_D^{22}$ −16° (*c* 0.8, CH_2Cl_2)}. The epoxide (**13**) was also transformed into (**3**) {R = COPh, $[\alpha]_D^{25}$ −40.5° (*c* 1.55, $CHCl_3$)} in 59% overall yield by the reaction with Bu^nMgBr–CuI followed by oxidative cleavage of the resulting adduct after protection of the hydroxy group as the benzoyl ester. The aldehyde (**4**) {R = COPh, $[\alpha]_D^{25}$ +16.1° (*c* 1.52, CH_2Cl_2); lit. ref. 7: $[\alpha]_D^{22}$ +17° (*c* 1.4, CH_2Cl_2)}, which is the enantiomer of (**2**), was synthesized in 66% overall yield using the same method used for the preparation of (**2**) except that the aldehyde (**11**) instead of (**9**) was used as the starting material.

The synthetic method for preparation of the α,β-dihydroxy aldehyde derivatives (**5**)—(**7**) (R = COPh) is outlined in Scheme 4. The compound (**10**) was transformed into (**21**) in 47% yield by the five-step sequence which involved (i) protection as the ethoxyethyl ether; (ii) reaction with (Z)-hex-3-enylmagnesium bromide in the presence of a catalytic amount of CuI; (iii) acid-catalysed selective deprotection, (iv) benzoylation of the resulting diol to yield (**20**), and (v) RuO_4-catalysed oxidation[10] of (**20**) with $NaIO_4$ followed by esterification with CH_2N_2. Conversion of the dibenzoate (**21**) into (**5**) (R = COPh) was carried out using H_5IO_6 (86% yield).



Scheme 3. *Reagents and conditions:* i, H_2C=CHOEt, H^+; ii, (*Z*)-EtCH=CH[CH_2]$_2$MgBr, CuI (cat.), THF–Et_2O–Me_2S (5:3:1), −70 to +25 °C; iii, PhCOCl, *p*-$Me_2NC_5H_4N$ (cat.), C_5H_5N, 25 °C; iv, $NaIO_4$, $RuCl_3 \cdot 3H_2O$ (cat.), CCl_4–MeCN–H_2O (2:2:3), 25 °C, 1 h; CH_2N_2, Et_2O; v, H_5IO_6, MeOH–H_2O (1:1), 25—30 °C, 1—4 h; vi, LiC≡C[CH_2]$_4$Me, THF–HMPA (10:1), reflux, 5 h; vii, H_2 (1 atm.), 5% Pd–$BaSO_4$, quinoline, MeOH, 25 °C; viii, Bu^{n}MgBr, CuI (cat.), THF–Me_2S (7:1), −70 to +25 °C.



Scheme 4. *Reagents and conditions:* i, H_2C=CHOEt, H^+; ii, (*Z*)-EtCH=CH[CH_2]$_2$MgBr, CuI (cat.), THF–Et_2O–Me_2S (30:15:1), −70 to +25 °C; iii, 0.01 M HCl, THF, 25—30 °C; iv, PhCOCl, *p*-$Me_2NC_5H_4N$ (cat.), C_5H_5N; v, $NaIO_4$, $RuCl_3 \cdot 3H_2O$ (cat.), CCl_4–MeCN–H_2O (2:2:3), 30 °C, 2 h; CH_2N_2, Et_2O; vi, H_5IO_6, MeOH–H_2O (4—6:1), 25—30 °C, 1—4 h; vii, $NaBH_4$, MeOH; viii, NaOMe, MeOH, 25 °C, 1 h; ix, Bu^{n}MgBr, CuI, THF–Me_2S (7:1), −70 to +25 °C.

The high optical purity of (**5**) {R = COPh, $[\alpha]_D^{25}$ −65.0° (*c* 1.29, $CHCl_3$)} was confirmed by transformation into the corresponding triol (**22**) {$[\alpha]_D^{25}$ −12.5° (*c* 1.60, $CDCl_3$); literature value of the enantiomer of (**22**): $[\alpha]_D$ +11.9° (*c* 2.7, $CDCl_3$)}.[13] By a similar way, the aldehyde (**6**) {R = COPh, $[\alpha]_D^{25}$ −23.0° (*c* 1.13, $CHCl_3$)} and its diastereoisomer (**7**) {R = COPh, $[\alpha]_D^{25}$ −69.1° (*c* 2.07, $CHCl_3$)} were synthesized starting with (**13**) and (**10**), respectively.

The ready availability of D-glyceraldehyde acetonide (**8**) and high total stereoselectivites and good total yields of the present reaction readily make it possible to prepare the key intermediates (**1**)—(**7**) for the synthesis of the 5-HETE, LTB_4, 12-*epi*-LTB_4, and lipoxin A and B.

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