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STEREOSPECIFIC TOTAL SYNTHESIS OF (5.6)-DiHETE ISOMERS

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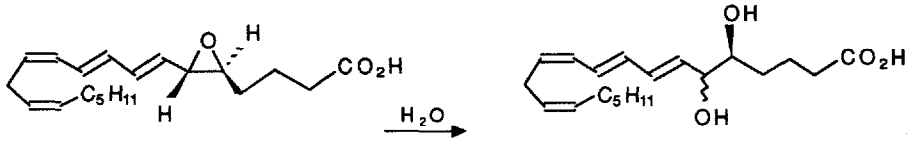
Abstract : The first highly practical stereocontrolled synthesis of the four diastereoisomeric (5,6)-DiHETEs is described using the acetonides of D-and L-glyceraldehyde as a source of chirality. Their spectral and physico-chemical properties are also described.

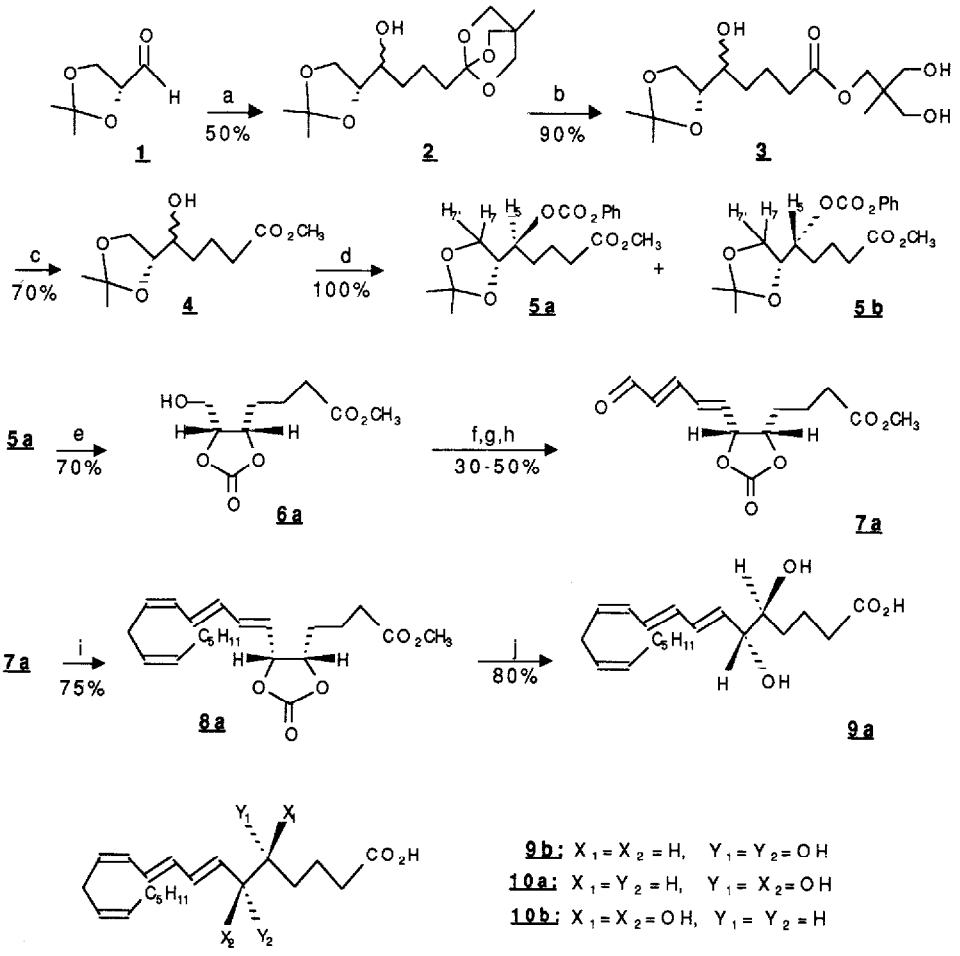
Although known for some years as non enzymatic hydrolysis product of (5S,6S)-LTA_4, the diastereoisomeric (5,6)-dihydroxy -7,9 -trans -11,14 -cis-eicosatetraenoic acids (5,6-DiHETEs[1]) epimeric at the carbon 6 with retention of the (S) chirality at the carbon 5 showed quite important biological activities like chemotaxis and chemokinesis on human neutrophils [2a], contractile potency on guinea pig pulmonary parenchymal strips [2b] and induction of arachidonic acid cyclooxygenase products release [2b].



(5S, 6S) - LTA_4 (5,6) - DiHETEs : mixture of epimers

More recently, two independent groups reported the biosynthesis of the same diastereoisomeric (5S,6R)-DiHETE using two different mammal cells preparations [3]. An efficient approach of the two key intermediate (5S,6R) and (5S,6S) carbonates of **7** type, starting respectively from 2-deoxy-D-ribose and L-xylose, has been previously described[4]. For a careful biological evaluation, we needed not only the natural (5S,6R) DiHETE but also the three other diastereoisomers. We report here the first simple and general synthesis of the four enantiomers 5,6-DiHETEs, from a single readily available starting material 2,3-O-isopropylideneglyceraldehyde.

Condensation of the lithio derivative of 1-(3-bromopropyl)-4-methyl-(2,6,7)-trioxabicyclo-(2.2.2) octane [5] with an excess of D-glyceraldehyde acetonide **1** [6] in anhydrous THF at -78°C gives an unseparable mixture of the two diastereoisomeric alcohols **2** [7] (50% yield). The ortho-OBO ester moiety of **2** can be efficiently converted to the methoxycarbonyl function through its successive acidic hydrolysis (CH_3CO_2H-aqueousTHF:90%) followed by transesterification of **3** (K_2CO_3 -CH_3OH : 70%) .



a : 1eq. 1- (3-bromopropyl)- 4 methyl- (2,6,7)- trioxabicyclo- (2.2.2) octane, 2eq. tBuLi, anh. THF, - 78°C, 15 min; then 2 eq. of **1** , THF, - 78°C, 2h.; **b** : THF- H_2O-AcOH 2-1- 4, 20°C, 1h. ; **c** : anh. K_2CO_3, anh. MeOH, 20°C, 1h30 ; **d** : 1.8 eq. PhOCOCl , 4.4 eq. anh. pyridine, anh. CH_2Cl_2 , 20°C, 2 h ; **e** : THF- H_2O- TFA 10-1-1, 20°C, 20h ; **f** : 1.1 eq. $(COCl)_2$, 2.4 eq. DMSO, anh. THF, - 78°C, 10 min. ; then 1 eq. **6a** , THF, - 60°C, 15 min. ; then 2.1 eq. anh. TEA, 30 min., - 60°C, 30 min., 0°C ; **g** : 1.2 eq. Triphenylphosphoranylidene-crotonaldehyde, anh. CH_2Cl_2 , 20°C, 3 h. ; **h** : cat. I_2 , anh. CH_2Cl_2 , 20°C, 4h ; **i** : 1.15 eq. 3-(Z)-nonenyltriphenylphosphonium bromide, 1.05 eq. BuLi, 15 eq. HMPA, anh. THF, 30 min., - 78°C; then **7a** , - 78°C to 0°C, 3h. ; **j** : MeOH / NaOH (10 N) 9-1 , 20°C,1h.

The quantitative derivatization of **4** using standard conditions (Py, CH_2Cl_2, PhOCOCl, 20°C) affords the two acetonides **5a** (erythro) and **5b** (threo) [8]. The crucial step separation (100% yield) of these diastereoisomers is easely performed by Low Pressure Liquid Chromatography ; Merk Lichroprep Si 60 (15-25 µ) : hexane -ethylacetate 4-1, λ = 257nm, d=3.0 ml /mn . **5a** / **5b** : 85 /15, (12 mn , 85% yield) / (14.8 min, 15% yield).

The absolute stereochemistry depicted for the major erythro compound **5a** was established by comparison with the physico-chemical properties of the pure erythro (5S,6R) standard **5c**, which have been prepared according to the sequence summarized reference[9] from compound **11**[10]; i) $(\alpha)_D$ for **5a** and **5c** - 7.6° (c= 0.5, acetone); ii) ^{1}H-NMR (300 MHz; $CDCl_3$) using the H_5 and H_7 proton patterns, H_5 (m): δ (**5a** and **5c**) = 4.90 ppm, H_7 (dd) : δ (**5a** and **5c**) =3.85 ppm ; threo isomer (**5b**) = 4.82 ppm and 3.80 ppm respectively). Therefore, the alkylation of D-glyceraldehyde acetonide **1** occurs according to Cherest and al.'s model[11] so that the major product was the anti-erythro alcohol. The acidic hydrolysis of the acetonide moiety of **5a** and the simultaneous formation of the cyclic carbonate affords in a one-pot sequence the erythro alcohol **6a** with 70 % yield[7]. Swern oxidation[12] of **6a** leads only to the unstable aldehyde which is immediately reacted with 3-oxo-1-propenylidene-triphenyl-phosphorane[13] in anhydrous dichoromethane to give a mixture of the 7E and 7Z **7a** . No partial epimerisation on the C_6 occured during oxidation (confirmed by the fact that no detectable amount of the other enantiomer was observed in HPLC). This mixture is smoothly isomerized to the pure (E) alkene **7a** using a dichloromethane catalytic iodine solution [7,8] (**7a** $J_{7,8}$ = 15.2 Hz; $J_{9,10}$ = 15.6 Hz ; 30-50% overall yield from **6a**).

Wittig condensation of **7a** with 2(Z)-octenylidene triphenylphosphorane at -78° in THF-HMPT proceeds stereospecifically as a cis olefination to give the protected tetraene **8a** [7,8] (75 % yield). The geometry of the characteristic triene (7E, 9E, 11Z) was confirmed by high-field ^{1}H-NMR ; 300MHz, $CDCl_3$; $J_{7,8}$ = 14.8 Hz; $J_{9,10}$ = 14.8 Hz; $J_{11,12}$ = 11.1Hz) and UV spectroscopy (λ max CH_3OH : 265.0, 275.0, 286.0 nm).

Standard alcaline hydrolysis provides the erythro (5S,6R)-DiHETE **9a** [8,14] with 80 % yield. Similarly, minor **5b** is converted to the threo (5R,6R)-DiHETE **9b** [8,14] with reproducible yields. By analogy, the same multi-step sequence starting from L-glyceraldehyde acetonide[15] affords the erythro (5R,6S)-DiHETE **10a** [8,14] as the major product and the threo (5S,6S)-DiHETE **10b** [8,14] as the minor one.

The biological evaluation of these four diastereoisomeric (5,6)-DiHETEs is under active investigation and will be reported in due course.

REFERENCES AND NOTES

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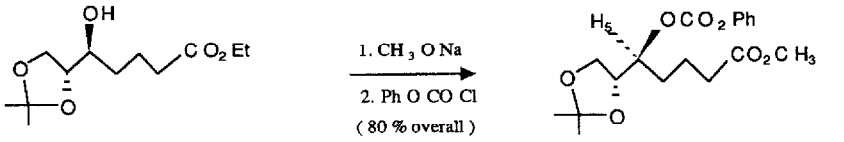
7. All new compounds have spectral data (IR, ^{1}H-NMR, MS) in full agreement with the proposed structures.
8. These compounds have the following chromatographic properties : TLC on silica gel plates Merck 60 F_{254} ; hexane-ethylacetate 7-3, **5a** (0.48), **5b** (0.42) ; hexane-ethylacetate 2-3, **7a** (0.40), **7b** (0.51) ; hexane-ethylacetate 7-3, **8a** (0.36), **8b** (0.45) ; TLC on reverse phase glass plates RP-18 Merck, methanol-water 9-1, **9a** or **10a** (0.50), **9b** or **10b** (0.47). HPLC analytical Zorbax Sil DuPont : hexane-ethylacetate 2-3, λ = 257nm, d = 1.0 ml /mn ; **7a** (11.2 min), **7b** (9.2 min) ; hexane-ethylacetate 4-1, **8a** (16.0 min), **8b** (10.4mn)
9.



11 Litt.[10] $(\alpha)_D$ + 9.4° (c = 4.6, $CDCl_3$) **5c** $(\alpha)_D$ - 7.6° (c = 0.5, acetone)

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    b) N.T.Anh, Top. Curr. Chem., 1980, **88**, 145.
12. K. Omura and D. Swern, Tetrahedron, 1978, **34**, 1651.
13. I. Ernest, A.J. Main and R. Menasse, Tetrahedron Lett., 1982, **23**, 167.
14. Physical data for **9a**, **10a** : ^{1}H-NMR (300 MHz, CD_3OD, TMS) δ 0.85 (t, 3H, J = 6.6Hz,), 1.20-1.40 (m, 6H), 1.45-1.80 (m, 4H), 2.05 (m, 2H), 2.15 (t, 2H, J = 7.1 Hz), 2.90 (t, 2H, J = 6.9 Hz) , 3.49 (m, 1H), 3.93 (dd,1H, J = 5.9, 7.1Hz), 5.25-5.45 (m, 3H), 5.75 (dd, 1H, J = 7.1, 14.8 Hz), 5.96 (dd, 1H, J = 11.3, 11.0 Hz), 6.18 (dd, 1H, J = 10.7, 14.3 HZ), 6.28 (dd, 1H, J = 14.8, 10.7 Hz), 6.50 (dd, 1H, J = 14.3, 11.3 Hz) ; MS (CI) m/z : 336, 153, 136 (100%), 117 ; RP - HPLC : DuPont Zorbax ODS (4,6 mm x 250 mm), MeOH-H_2O: 75-25, 1 ml / min flow rate, Rt = 25.5 min, monitored at 270 nm. UV (EtOH) : λ_{max} = 263 (35350), 272.5 (46040), 284 (35840)nm,

    9b, **10b** : ^{1}H-NMR (300 MHz, CD_3OD, TMS) δ = 0.85 (t, 3H, J = 6.5 Hz), 1.20-1.40 (m,6H), 1.45-1.85 (m, 4H), 2.04 (m, 2H), 2.23 (m, 2H), 2.90 (t, 2H, J = 6.9 Hz), 3.40 (m, 1H), 3.90 (dd, 1H, J = 5.3, 7.1 Hz), 5.25-5.42 (m, 3H), 5.70 (dd, 1H, J = 7.1, 14.8 Hz), 5.97 (dd, 1H, J = 11.3, 11.0 Hz), 6.18 (dd, 1H, J = 10.7, 14.5 HZ) , 6.30 (dd, 1H, J = 14.8, 10.7 Hz), 6.50 (dd, 1H, J = 14.5, 11. 3 Hz) ; MS (CI) m/z : 336, 252, 191, 135 (100%), 118 ; RP-HPLC : DuPont Zorbax ODS (4,6 mm x 250 mm), MeOH-H_2O 75-25, 1 ml / min flow rate, R_t = 28.5 min, monitored at 270 nm ; UV (EtOH) : λ_{max} = 263.6 (34730), 273.0 (45570), 284.1 (35370) nm.

    The optical rotation of **9a** : $(\alpha)_D^{22°C}$ = + 15° (c = 0.1, Et OH, n = 3, σ = 6.5) ; **10a** : $(\alpha)_D^{22°C}$ = -13 °(c = 0.1, Et OH, n = 3, σ = 1.3); **9b** : $(\alpha)_D^{22°C}$ = + 72° (c = 0.05 , Et OH, n = 4, σ = 8.7) ; **10b** : $(\alpha)_D^{22°C}$ = - 65 ° (c = 0.05, Et OH, n = 4, σ = 13.0) are not significative because of the low solubility and (or) low rotation. Nevertheless, a good optical correlation has been obtained for the carbonates of **8** type :

    8 (5S,6R), $(\alpha)_D^{22°C}$ = + 13.8° (c = 0.9, acetone)

    (5R,6S), $(\alpha)_D^{22°C}$ = - 13.7° (c = 0.8, acetone)

    (5R,6R), $(\alpha)_D^{22°C}$ = + 44.3° (c = 0.4, acetone)

    (5S,6S), $(\alpha)_D^{22°C}$ = - 46.3° (c = 0.8, acetone)
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