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A New Stereoselective Synthesis of (E,Z)-Conjugated Hydroxy-Dienes, Key Intermediates for the Synthesis of HETES

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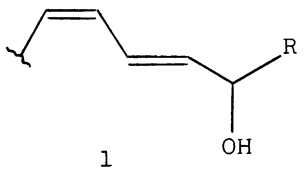
A general and highly stereoselective synthesis of (E,Z)-conjugated hydroxy-dienes is described and its synthetic utility is illustrated by the synthesis of precursors of (±)-LTA_4 methyl ester and (±)-5-HETE respectively.

Recently a new major pathway has been discovered for arachidonic acid metabolism which involves the conversion of this acid into the monohydroxyeicosatetranoïc acids (HETES) by the action of lipoxygenases .[1] These monohydroxylated metabolites possess important biological properties and have been the subject of active investigations. It has been pointed out that all the HETES have a common structural moiety 1 involving a (E,Z)-conjugated diene and a hydroxy group adjacent to the E double bond.



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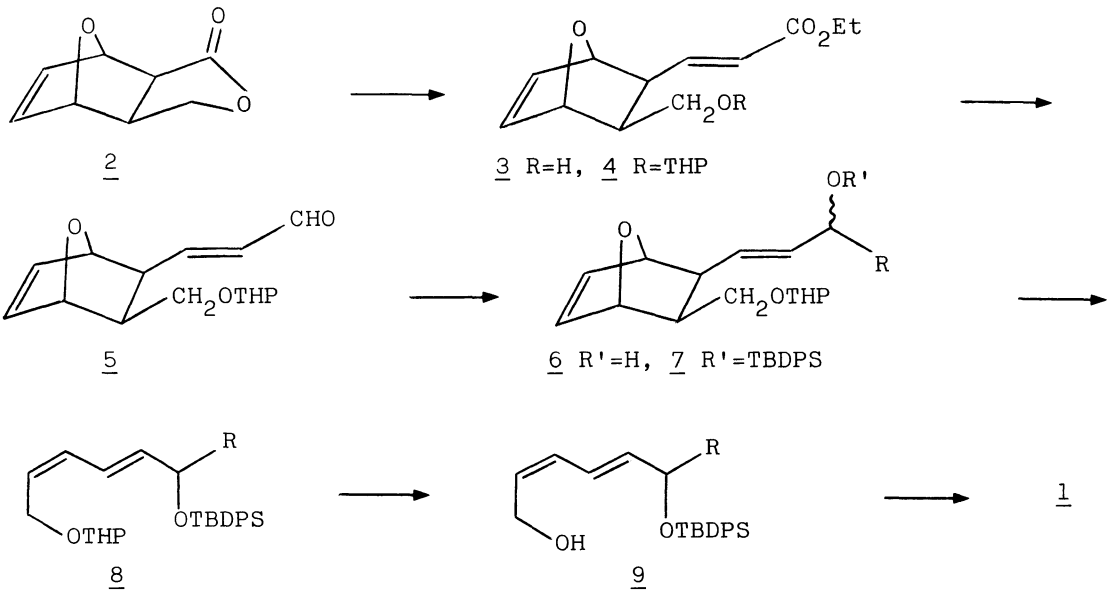
Two general approaches to these hydroxy-dienes have been recently described : the stereoselectivity of the first approach [2] is not very high (EZ/ZZ = 75-80/25-20) and in the second one [3] the Z double bond is generated via a Wittig reaction, the stereoselectivity being not specified. We report in this note a highly stereo selective synthesis of hydroxy-dienes 1 and its application to the synthesis of precursors of (±)-LTA_4 and (±)-5-HETE.

The starting point of our synthesis (Scheme 1) is the lactone 2 easily available either in racemic [4] or in optically active form .[5]

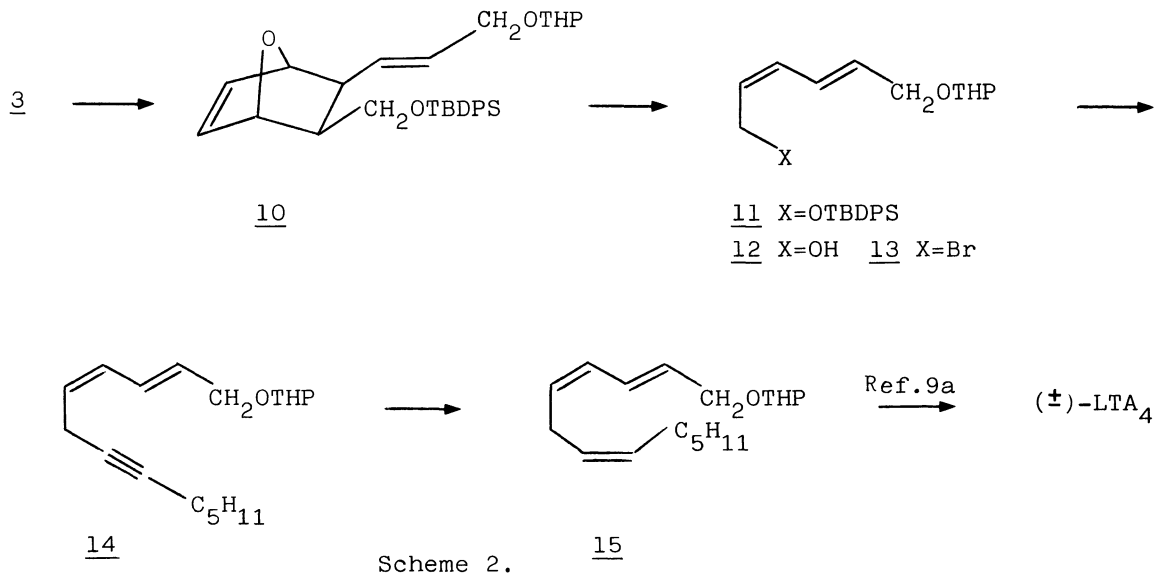
A one pot reduction (DIBAL, toluene, -78 °C) and Wittig-Horner olefination ($(EtO)_2POCH_2CO_2Et$, n-BuLi, -78 °C RT, 15 h) led to the pure trans ester 3 in 40-60% yield.[6] After protection of the hydroxy group (dihydropyran, ether, p-TsOH, 75%) the ester 4 was reduced (DIBAL, toluene, -78 °C, 80%) and the resulting alcohol was oxidized (MnO_2, CH_2Cl_2, 4 h, RT, 95%) to give the aldehyde 5. Nucleophilic addition of Grignard reagents (RMgBr, ether, 0 °C) provided alcohols 6 (70-90%) as mixtures of two diastereoisomers in practically equal proportions .[7] After silylation (TBDPSCl, DMF,

imidazole, 80%) the Z double bond was generated by a smooth retro-Diels-Alder reaction (xylene, 140 °C, 3 h, 80-85%) to provide (E,Z)-dienes 8. Deprotection of the primary alcohol (PPTS, ethanol, 55 °C, 3 h, 60%) afforded the (E,Z)-conjugated dienes 9, stereoisomerically pure as shown by ^{1}H NMR .[8] The allylic alcohols 9 can be then converted to the corresponding bromides and coupled with cuprates of acetylenic compounds to give dienes of type 1. The viability of this sequence is illustrated by the synthesis of (2E,4Z,7Z)-tridecatrienyl tetrahydropyranyl ether (15) and of methyl 10-hydroxy-5-(t-butyldiphenylsilyl)oxy-(6E,8Z)-decadienoate (19), key intermediates for the synthesis of (±)-LTA$_4$ methyl ester and (±)-5-HETE respectively.



Scheme 1.

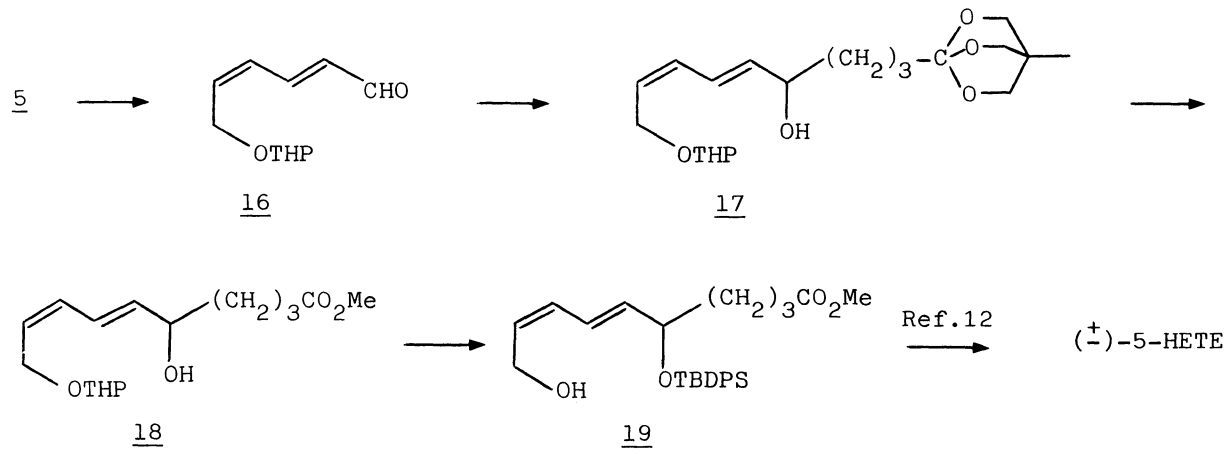
(2E,4Z,7Z)-tridecatrienyl tetrahydropyranyl ether (15) [9] was obtained from the bicyclic ester 3 (Scheme 2). After silylation of the primary alcohol (TBDPSCl, DMF, Imidazole, 93%) the ester group was reduced (DIBAL, toluene, 79%) and the created hydroxy group was protected (dihydropyran, pTsOH, 83%).



Scheme 2.

The protected diol 10 was then thermolyzed (xylene, 140 °C, 1 h) to give the (E,Z) diene 11 (stereoisomeric purity > 95% as shown by ^{1}H NMR). Desilylation (nBu_4NF, THF) and conversion to the bromide (CBr_4, $(\phi_2PCH_2)_2$, CH_2Cl_2) afforded the bromodiene 13 in 61% yield over the three steps. Coupling of 13 with an excess of the cuprate of 1-heptyne (5 equiv. 1-heptyne, 5 equiv. C_2H_5MgBr, 0.5 equiv. CuCl in THF ; the freshly prepared bromide 13 was added at room temperature to this solution and the mixture was heated 1 h at 60 °C) gave 14 in 65-71% yield. Semi-hydrogenation [10] of 14 (H_2, Lindlar, hexane containing 2% quinoline by volume, 1.5 h, RT) provided the triene 15 in 78% yield .[11] The synthesis of (±)-LTA_4 methyl ester via the phosphonate derived from 15 has been described by North .[9a]

Methyl 10-hydroxy-5-(t-butyldiphenylsilyl)oxy-(6E,8Z)-decadienoate (19) [12] was obtained following Scheme 3. Thermolysis of aldehyde 5 (xylene, 140 °C, 3 h) afforded the (E,Z)-diene 16 in 87% yield. Addition of the lithio OBO orthoester derived from 1-(3-bromopropyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane [13] to the aldehyde 16 (1.2 equiv. of bromo orthoester, 2.4 equiv. t-BuLi -78 °C, 15 min, followed by addition of 16, -78 °C, 30 min) gave the dienol 17 in 36% yield .[14] Hydrolysis [15] of 17, (AcOH, THF, H_2O (4:2:1), 1.5 h, RT) followed by transesterification (K_2CO_3, MeOH) furnished the methyl ester 18 in 66% yield for the two steps.



Scheme 3.

Protection of the secondary hydroxy group (TBDPSCl, DMF, imidazole) and deprotection of the primary alcohol (PPTS, ethanol, 55 °C) led to the (E,Z)-diene 19 as a unique stereoisomer as shown by H^1 NMR .[16] The synthesis of (±)-5-HETE by coupling of the bromide derived from 19 with the cuprate of 1,4-decadiyne followed by semi-hydrogenation and hydrolysis has been established by Rokach .[12]

References

1) See for example :" The Leukotrienes, Chemistry and Biology," ed by L.W. Chakrin and D.M. Bailey, Academic Press, London (1984).
2) J. Rokach and J. Adams, Acc. Chem. Res., 18, 87 (1985) and references therein ; Y. Leblanc, B.J. Fitzsimmons, J. Adams, F. Perez, and J. Rokach, J. Org. Chem., 51, 789 (1986).
3) B.P. Gunn, Tetrahedron Lett., 26, 2869 (1985) ; B.P. Gunn and D.W. Brooks, J. Org. Chem., 50, 4418 (1985).
4) S. Tanako and K. Ogasawara, Synthesis, 1974, 42.
5) R. Bloch, E. Guibé-Jampel, and C. Girard, Tetrahedron Lett., 26, 4087 (1985).
6) A Wittig-Horner olefination of the isolated lactol led always to a mixture of ester 3 and of a tricyclic compound arising from an intramolecular Michael addition : see R. Bloch and M. Seck, Tetrahedron Lett., 28, 5819 (1987).
7) The transposition of this sequence to the synthesis of optically active 1 (starting from an enantiomer of 2) would demand a stereoselective addition of organometallic species to 7. Various solvents (ether, THF, HMPA), organometallics (RMgBr, RLi, RTi(OiPr)3) and hydroxyl protective groups (THP, TBDPS, MEM) have been tried but without any useful improvement of the selectivity : only small ratio changes from 50/50 to 60/40 have been observed by HPLC.
8) ^{1}H NMR (250 MHz, $CDCl_3$) for 9 (R = C_5H_{11}) :δ 7.3 - 7.7 (m, 10H), 6.1 (dd, J = 11.4, 16 Hz, 1H), 5.95 (dd, J = 11.4, 10.1 Hz, 1H), 5.6 (dd, J = 6, 16 Hz, 1H), 5.4 (dt, J = 10.1, 6.3 Hz, 1H), 4.15 (m, 1H), 4.1 (d, J = 6.3 Hz, 2H), 1.1 - 1.6 (m, 9H), 1.05 (s, 9H), 0.9 (t, J = 7 Hz, 3H).
9) For previous syntheses of (2E,4Z,7Z)-tridecatrienol see a) J.C. Buck, F. Ellis, and P.C. North, Tetrahedron Lett., 23, 4161 (1982) ; b) S. Tsuboi, T. Masuda, and A. Takeda, Chem. Lett., 1983, 1829.
10) Over reduction of the triene occurred to the extent of 5-20% depending on the run. The best catalyst found was the commercial Lindlar purchased from Fluka.
11) ^{1}H NMR (250 MHz, $CDCl_3$) for 15 :δ 6.64 (dd, J = 11.2, 15.2 Hz, 1H), 6.08 (dd, J = 11.2, 11 Hz, 1H), 5.85 (dt, J = 15.2, 6.2 Hz, 1H), 5.45 (m, 3H), 4.75 (m, 1H), 4.35 (m, 1H), 4.10 (m, 1H), 3.95 (m, 1H), 3.58 (m, 1H), 3.0 (dd, J = 6.2, 6 Hz, 2H), 2.1 (m, 2H), 1.3 - 1.9 (m, 12H), 0.95 (t, J = 7 Hz, 3H).
12) Previous synthesis of 19 : J. Rokach, J. Adams, and R. Perry, Tetrahedron Lett., 24, 5185 (1983).
13) E.J. Corey and N. Raju, Tetrahedron Lett., 24, 5571 (1983).
14) Addition of the lithio OBO orthoester to the bicyclic aldehyde 5 could also be effected but with poor yields (15 to 20%).
15) P.Y. Kwok, F.W. Muellner, C.K. Chen, and J. Fried, J. Am. Chem. Soc., 109, 3684 (1987).
16) ^{1}H NMR (250 MHz, $CDCl_3$) for 19 :δ 7.3 - 7.7 (m, 10H), 6.1 (dd, J = 11.3, 15 Hz, 1H), 5.95 (dd, J = 11.3, 11 Hz, 1H), 5.65 (dd, J = 15, 7 Hz, 1H), 5.5 (dt, J = 11, 7 Hz, 1H), 4.25 (m, 1H), 4.15 (d, J = 7 Hz, 2H), 3.6 (s, 3H), 2.2 (t, J = 7 Hz, 2H), 1.4 - 1.7 (m, 4H), 1.1 (s, 9H).

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