Tetrahedron Letters,Vol.24,No.47,pp 5185-5188,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

A NEW GENERAL METHOD FOR THE SYNTHESIS OF LIPOXYGENASE PRODUCTS: PREPARATION OF ±5-HETE

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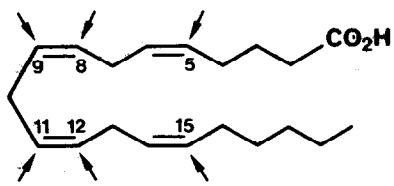
SUMMARY: Recognizing 3 as the basic common unit in the structures of all HETEs, a general synthetic approach is proposed. As an illustration of this method, the synthesis of ±5-HETE was accomplished using the masked diene 8.

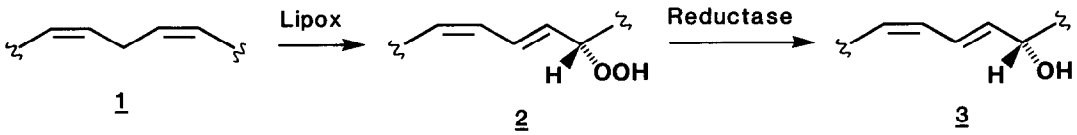
The metabolism of arachidonic acid to yield prostaglandins, thromboxane and prostacyclin has been extensively studied. The major first step in the biosynthesis is the introduction of a hydroperoxy group in the 11 position by the cyclooxygenase enzyme. More recently, a major new pathway for arachidonic acid metabolism has been discovered.[1] The enzymes involved, the lipoxygenases, introduce (as was the case for the cyclooxygenase) a hydroperoxy radical in positions 5, 8, 9, 11, 12 or 15. The mono-hydroxylated metabolites (HETEs) have been implicated as chemotactic factors and as inhibitors of the 5-lipoxygenase enzyme,[2] however, the field is still too new to know the potential importance of these products. Natural products derived from 5-lipoxygenase (i.e. leukotrienes) continue to be the subjects of intensive investigation.



Oxidation sites of Arachidonic acid

Upon closer examination of the process leading to the introduction of a hydroperoxy group by a lipoxygenase, it becomes apparent that regardless of the position involved, the net result in all cases is the transformation, shown in Equation I, in which a "skipped" diene from arachidonic acid 1 is converted to a conjugated diene 2, having a cis-trans olefin geometry and the hydroperoxy group assumes the S configuration, for 5, 12 and 15 HPETEs. The 11-position gives rise to the R hydroperoxy group, and as yet both 8 and 9 HPETEs and HETEs have not been fully characterized with regard to absolute stereochemistry. Hydroperoxide 2 is enzymatically reduced to produce the HETE, 3, which retains all the structural features of 2. This structure is common to the primary lipoxygenase products identified from natural sources: namely, 5, 8, 9, 11, 12, 15 HPETEs and HETEs. We have sought a general approach to the syntheses of these natural products focusing on the cis-trans diene alcohol 3 common to all the HETEs.

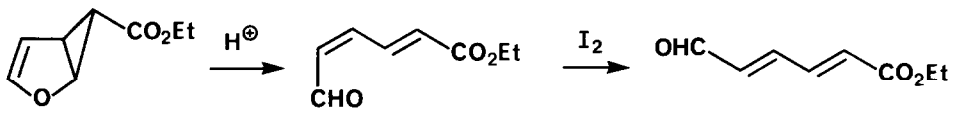
Equation 1



1 2 3

In our first synthesis of slow-reacting substance of anaphalaxis or SRS-A we used synthon 6 prepared as described in Equation II.[3]

Equation 2

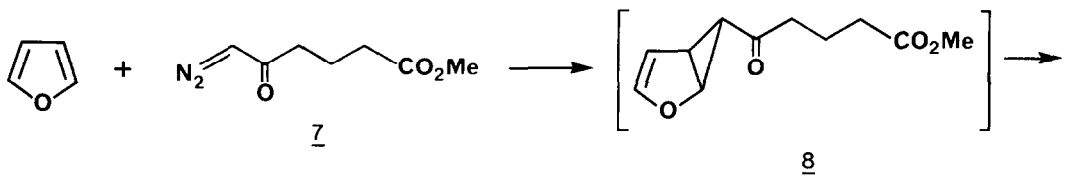


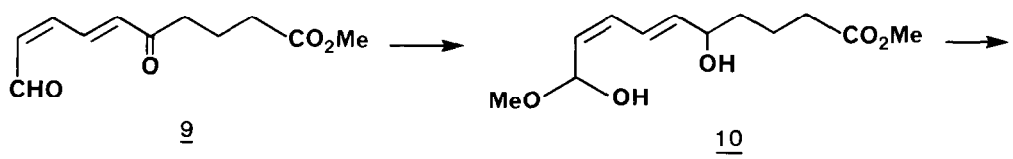
4 5 6

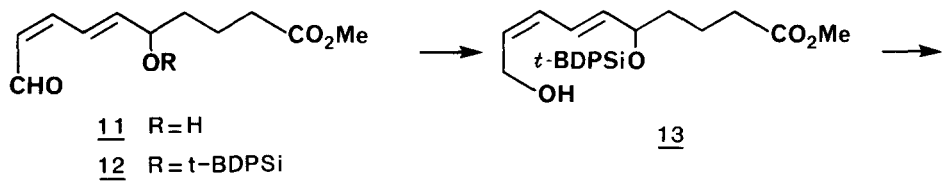
Considering the initial reaction product, 5, one realizes that this synthon has the desired features necessary for the construction of HETEs. The ester function can serve as the precursor to the OH group, the cis-trans olefin geometry is the desired one and the aldehyde can be regarded as a handle to elaborate the rest of the carbon chain. Thus, structures of type 4 may be considered to be masked dienes of the correct geometry for HETEs. This paper reports the first illustration of the proposed general method as applied to the preparation of ±5-HETE.[4]

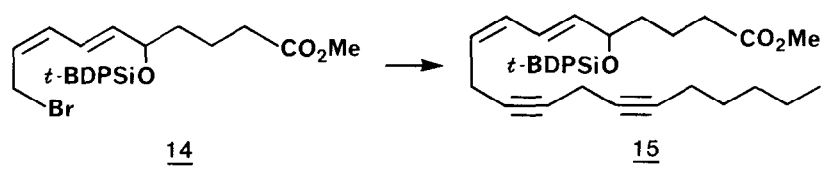
We begin the synthesis of 5-HETE with the preparation of diazo-ketone 7, from commercially available methyl 4-(chloroformyl) butyrate (excess CH_2N_2, 0° 16 h) in 94% yield. Addition of 7 to furan was catalyzed by $[Rh(OAc)_2]_2$ (5 weight %, catalyst, neat furan; 2 h at RT) and gave a mixture of 8, 9 and cis-cis isomer of 9 (~40:40:20; ratios determined by NMR integration). The bicyclic ketone 8 in contrast to 4, is not thermally stable and is not isolated, but directly transformed to 9 on standing or instantaneously by addition of a drop of AcOH. The final composition of the reaction mixture is 75-80% 9 and 20-25% of the cis-cis isomer, in 90-95% total yield.[5] At this point it was necessary to differentiate between the two carbonyl functions, and this was accomplished by a selective reduction-protection sequence, based on work by Luche.[6] Selective reduction of the ketone with concomitant hemi-acetal formation gave intermediate 10 ($NaBH_4/CeCl_3$/MeOH) at 0°C). Regeneration of the aldehyde ($AcOH/(CH_3)_2CO/H_2O$) and protection of the secondary alcohol (t-BDPSiCl, DMF, imidazole) afforded 12, which was reduced ($NaBH_4/CeCl_3/(CH_3)_2CHOH/H_2O$ affording alcohol 13, in 40-50% overall yield from 9.[7] The allylic alcohol was converted to the corresponding bromide 14 ($CBr_4/[\emptyset_2PCH_2+_2/CH_2Cl_2$); 30 min at 0° C) in 90-95% yield. Coupling of 14 with an excess of the mixed cuprate of 1,4 decadiyne (2 eq 1,4 decadiyne, 1 eq CuBr.Me_2S in THF cooled to -78°C, followed by treatment with 1 eq n-BuLi, warming to -40° C and addition of HMPA doubling the volume of the mixture; the cuprate is added to a THF solution of the freshly prepared bromide at 0°C) gave 15 with yields ranging 60-70%. Semi-hydrogenation of 15 (H_2/Lindlar/hexane containing 1% pyridine by volume; 15 min at RT)[8] followed by de-silylation (nBu_4NF/THF/HOAc 2 eq) provided ±5-HETE methyl ester in 61% combined yield. Hydrolysis (LiOH,DME/H_2O 5:1; 1 h at RT) afforded a quantitative yield of ±5-HETE, having identical spectral characteristics[9] compared with an authentic sample of chiral 5-HETE.[4]

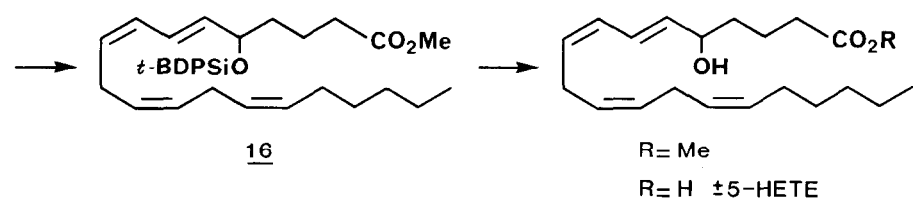
Scheme


+
N2
O
CO2Me
7
O
CO2Me
8


CO2Me
O
CHO
9
CO2Me
OH
MeO
OH
10


CO2Me
OR
CHO
11 R=H
12 R=t-BDPSi
CO2Me
t-BDPSiO
OH
13


CO2Me
t-BDPSiO
Br
14
CO2Me
t-BDPSiO
15


CO2Me
t-BDPSiO
16
CO2R
OH
R=Me
R=H ±5-HETE

ACKNOWLEDGEMENT

We wish to thank Dr. Joseph G. Atkinson for helpful discussions related to this work.

REFERENCES

1. For a recent review see, e.g. D.M. Bailey and F.B. Casey, Annual Reports in Medicinal Chemistry, 17, 203 (1982).

2. a) J.Y. Vanderhoek, R.W. Bryant and J.M. Bailey, J. Biol. Chem. 255, 10064 (1980).
b) Y. Arai, K. Shimoji, M. Konno, Y. Konishi, S. Okuyama, S. Iguchi, M. Yayashi, T. Miyamoto and M. Toda, J. Med. Chem. 26, 72 (1983).
c) E.J. Goetzl, Biochem, Biophys. Res. Comm. 101, 344 (1981).

3. J. Rokach, Y. Girard, Y. Guindon, J.G. Atkinson, M. Larue, R.N. Young, P. Masson and G. Holme, Tetrahedron Lett., 21, 1485 (1980).

4. We have recently published the first stereospecific syntheses of 5-HETE and its enantiomer. R. Zamboni and J. Rokach, Tetrahedron Lett., 10, 999 (1983).

5. The isomeric mixture was not separated at this stage and the minor cis-cis isomer was carried through in the synthesis. We find it convenient to separate the minor cis-cis isomer at compound 13 and this was accomplished by HPLC (see footnote 7 for conditions).

6. A.L. Gemal and J.L. Luche, J. Org. Chem., 44, 4187 (1979).

7. We have found that in some experiments a small amount of trans-trans isomer of 9 is formed. The desired cis-trans isomer was separated at this stage using normal phase HPLC on a Waters μ-porasil column eluting with hexanes/EtOAc 3:1.

8. Over-reduction of the diene occurred to the extent of 5-10% depending on the run. The only catalyst that was effective was the commercial Lindlar purchased from Strem Chemicals.

9. Satisfactory spectral data were obtained for all isolated and purified intermediates: ^{1}H NMR, IR, UV, TLC, HPLC.

(Received in USA 5 August 1983)