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AN EFFICIENT AND GENERAL METHODOLOGY FOR THE SYNTHESIS OF THE HETES: SYNTHESIS OF (±)-5-HYDROXY-6-TRANS-8,11,14-CIS-EICOSATETRAENOIC ACID (5-HETE)

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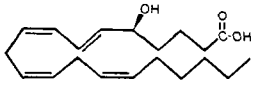
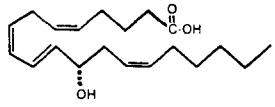
SUMMARY: The facile synthesis of (±)5-HETE illustrates a general synthetic approach to the HETES in which the key step involves the oxidative ring opening of an appropriately substituted furan nucleus.

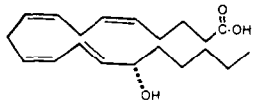
The conversion of arachidonic acid into the monohydroxyeicosatetraenoic acids (HETES) by the action of the lipoxygenases and the subsequent conversion of the HETES to the leukotrienes has recently received much interest.[1] In connection with a program in our laboratories directed toward the preparation of leukotriene analogs, an efficient and general synthesis of the HETES in reasonable quantities was mandated.[2] Any successful approach must permit construction of the cis-trans diene unit with an allylic hydroxyl moiety **1** common to all the HETES.



5-HETE

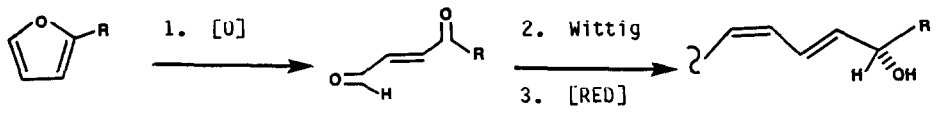


12-HETE



15-HETE

Preparation of the required structural unit **1** was rationalized from an appropriately substituted furan **2** which might be oxidatively cleaved to the unsaturated 1,4-dicarbonyl intermediate **3**. Further elaboration of **3** by Wittig olefination and reduction of the ketone carbonyl would provide the necessary cis-trans diene allylic hydroxyl unit **1**.



2 3 1

As an illustration of this approach, the total synthesis of (±)5-HETE is described.[3] The synthesis begins by converting 3-(2-furyl)-1-propanol **4**[4] to the chloride **5** (Ph_3P, CCl_4, 70°, 1 hr.) in 70% yield. The chloride **5** was converted to the methyl ester **6** (1. Mg, THF, reflux; 2. $ClCO_2Me$, RT) in 80% yield. At this point it was not possible to efficiently oxidatively open the furan ring with MCPBA[5] or PCC[6] - the former afforded no ring opened product and the latter could not be induced to give more than a 25% conversion under a variety of conditions.[7] Therefore, recourse was made to an earlier procedure[8] wherein **6** was converted first to the dimethoxy ester[9] **7** (Br_2, MeOH, Na_2CO_3, -30°) in 79% yield followed by ring opening[10] to **8** (H_2O, 45°, 30 min.) in 75% yield. The cis isomer **8** was converted[10] quantitatively to trans **9**[11] (I_2, ether, RT, 10 min.). The enedione **9** was subjected to Wittig olefination with (Z, Z)-3,6-dodecadienyltriphenylphosphonium bromide[12] (KOtBu, THF, 0°) to afford **11** in 51% yield. The keto ester **11** was reduced ($NaBH_4$, MeOH, 0°) to alcohol **12** in 65% yield, which was hydrolyzed (LiOH, IPA, H_2O, RT, 1 hr.) to afford (±)5-HETE in 95% yield.

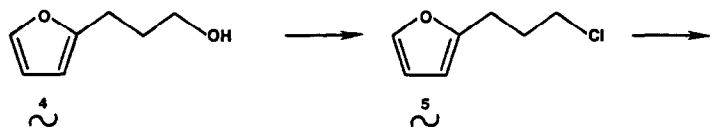
Advantages of this approach include the straightforward nature of the synthetic scheme which obviates the need for any tedious separations and the generality which is realized by appending the appropriate R group to the furan ring in **3**.

ACKNOWLEDGEMENTS

The author expresses appreciation to Mr. Steven Schmidt for providing the precursor to the phosphonium bromide **10** and to Drs. James Summers and Dee W. Brooks for helpful discussions.

REFERENCES

1. See for example, D.M. Bailey and F.B. Casey, Annual Reports in Medicinal Chemistry, **17**, 203 (1982).
2. Other HETE syntheses, 5-HETE: a. R. Zamboni and J. Rokach, Tetrahedron Lett., **24** (10), 999 (1983); b. J. Rokach, J. Adams and R. Perry, Tetrahedron Lett., **24** (47), 5185 (1983); 12-HETE: a. E.J. Corey, H. Niwa and J. Knolle, J. Am. Chem. Soc., **100**, 1942 (1978); b. E.J. Corey, K. Kyler and N. Raju, Tetrahedron Lett., **25** (45), 5115 (1984).
3. Satisfactory infrared, proton magnetic resonance, and mass spectral data were obtained on all intermediates.



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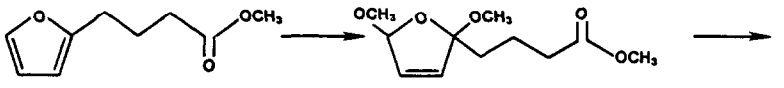

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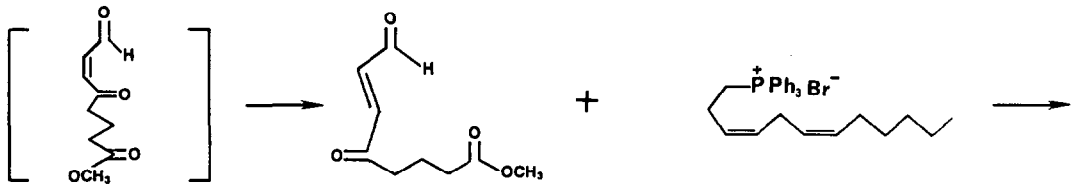

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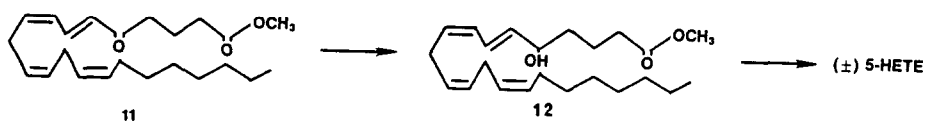

11 12

4. Alcohol **4** is commercially available. Alternatively, furan itself may be alkylated; see e.g., G. Buchi and H. Wuest, J. Org. Chem., **31**, 977 (1966).
5. P.D. Williams and F. LeGoff, J. Org. Chem., **46**, 4143 (1981).
6. G. Piancatelli, A. Sceltri and M. D'Auria, Tetrahedron, **36**, 661 (1980).
7. It is interesting to note that chloride **5** and the nitrile corresponding to ester **6** were smoothly oxidized in excellent yield by either reagent.
8. J. Levisalles, Bull Soc. Chim. France, 997 (1957).
9. A 1:1 cis/trans mixture, as determined from the 300 MHZ ^{1}H nmr spectrum, was produced.
10. J.A. Hirsch and A.J. Szur, J. Heterocyclic Chem., **9**, 523 (1972).
11. ^{1}H NMR (300 MHz, $CDCl_3$) for **9**: δ 9.79 (d, J=6Hz, 1H), 6.89 (d, J=16Hz, 1H), 6.79 (dd, J=6,16Hz, 1H), 3.69 (s, 3H), 2.81 (t, J=7Hz, 2H), 2.41 (t, J=7Hz, 2H), 2.00 (quint., J=7Hz, 2H).
12. Prepared in five steps by modification of the Rokach procedure[2a] as follows: Commercially available 2-octyn-1-ol was converted to the bromide (PBr_3, Pyr) in 82% yield. The bromide was then coupled to 4-butyn-1-ol (EtMgBr, THF, RT) in 91% yield. Reduction[13] of the diacetylene ("P-2" NiB) followed by bromination (PPh_3, CBr_4, CH_2Cl_2, RT, 2 hr.) afforded the cis diene which was converted to the phosphonium salt (PPh_3, EtOH, 80°, 2 days) in 80% yield over the three steps.
13. A small amount (ca. 5%) of the over reduced material was removed via chromatography on $AgNO_3$ impregnated silica gel.[14]
14. R.P. Evershed, E.O. Morgan and L.D. Thompson, J. Chrom., 350 (1982).

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