Tetrahedron Letters,Vol.25,No.1,pp 35 - 38,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

SYNTHESIS OF ± 8- and 9-HETES

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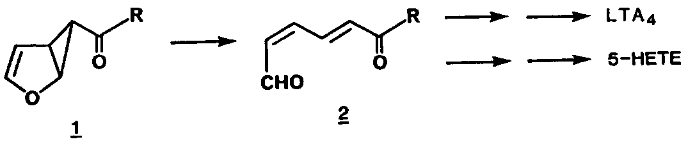
Summary: We describe the first total syntheses of ±8 and ±9 HETEs using the addition of diazoketones to furan followed by electrocyclic ring opening to provide the necessary cis-trans diene system.

We have recently described a method for the delivery of a diene of cis-trans geometry and illustrated the viability of the approach to the synthesis of ±5-HETE.[1]

Our choice of the next target, in order to test the generality of the synthetic method, was guided by the fact that of all the six possible HETEs described in mammalian systems, the 8- and 9-HETE isomers have not been the object of synthetic efforts to date. More importantly, whereas the 5-, 11-, 12- and 15-HETEs are well established natural products, whose biological activities are being investigated with great intensity, little is known about the 8- and 9-HETEs. The lack of standards has prevented the complete characterization of these substances. Although both 8- and 9-HETE have been shown to possess chemotactic activity,[2] unavailability of material has prevented thorough biological investigation.

We have over the past few years developed a method to produce compounds of type 2 by the highly efficient addition of diazo-carbonyl compounds to furan catalyzed by rhodium acetate dimer. Initially the reaction forms the carbene addition product, cyclopropylfuran 1, which then undergoes electrocyclic ring opening to the cis-trans dicarbonyl compound. In our first synthesis of LTA$_4$ we have used intermediate 1 (R=OEt) as our main starting point.[3] The key step in the synthesis of ±5-HETE was the use of bicyclic system 1 ($R=(CH_2)_3COOH_3$ - Scheme 1) as a precursor, for the delivery of the cis-trans diene 2, the carbonyl serving as a precursor for -OH group.



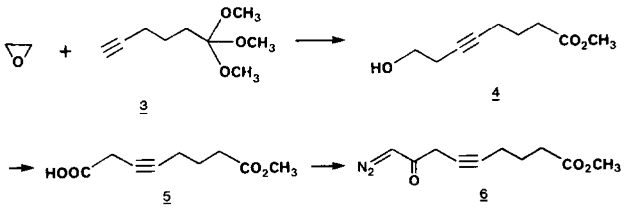
As we have pointed out earlier, the HETEs have in common the structural feature comprising a cis-trans diene and a hydroxy group adjacent to the trans double bond. By varying the R group in the bicyclic system 1 (Scheme 1) to incorporate the necessary features, one can synthesize any of the desired HETEs. Schemes 1 and 2 describe how this was accomplished in the case of 8- and 9-HETE, and show how the synthesis was completed.

±8-HETE

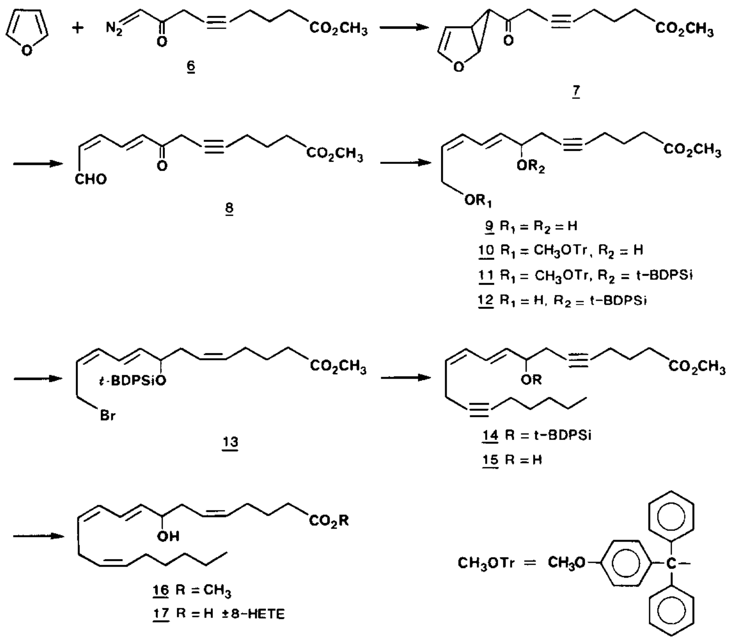
The synthesis of the ±8-HETE begins with the preparation of the appropriate diazo-ketone 6. The acetylide anion of ortho-ester 3[4] was used to alkylate ethylene oxide (LiNH$_2$/NH$_3$, excess ethylene oxide; -33°C) followed by acidic workup (1N HCl) to give 4 in 90% yield. Jones oxidation of 4 (8N Jones reagent, 5 equiv., 0°C) gave acid 5 which was treated with oxalyl chloride [(COCl)$_2$/DMF, 1 drop/ benzene, 1 h] followed by diazotization (excess CH$_2$N$_2$, 0°C 16 h) afforded diazo-ketone 6 in 57% yield from 4. Addition of 6 to furan was catalyzed by [Rh(OAc)$_2$]$_2$ (5 weight % catalyst, neat furan; 2 h at RT) and produced a mixture of 7, 8 and the cis-cis isomer of 8 (~50:40:10; ratios by ^{1}HNMR integration). The cyclopropylyl furan adduct 7 was slowly converted to 8 on standing, and the final composition of the reaction mixture was 75-80% 8, and 20-25% of cis-cis isomer, in 90% yield (based on diazo-ketone 6). The unstable dicarbonyl compound 8 is highly prone to isomerization and was not purified, but immediately reduced (NaBH$_4$/CeCl$_3$/(CH$_3$)$_2$CHOH/H$_2$O, pH=7, 0°C) thereby "freezing" the cis-trans geometry as the stable diol 9 obtained in 50-60% yield. A convenient protection, de-protection scheme was used to selectively block the secondary alcohol. First, the primary alcohol was tritylated as its mono-methoxy trityl ether (MeOTrCl/py; -10°C) giving 10 followed by silylation of the secondary alcohol (t-BuDPSiCl/DMF/imidazole 0°C). Regeneration of the free primary alcohol was achieved (80%/HOAc/H$_2$O/THF) affording 12 in 56% overall yield from diol 9. Alcohol 12 was converted to the bromide 13 (CBr$_4$,(ϕ$_2$PCH$_2$)$_2$/CH$_2$Cl$_2$, 0°C) in 90-95% yield. Chain extension to give the C-20 carbon skeleton was achieved by displacing the bromide with the cuprate of 1-heptyne (Me$_2$S CuBr/BuLi/1-heptyne, 1.5 eq @-78°C added to 13 in THF @ -78°C; warm to RT and add HMPA, 16 h) gave 14 in 80% yield. The silyl group was removed (n-Bu$_4$NF/THF, 3 equiv; 5 h RT) in 78% yield, and the resulting alcohol was semi-hydrogenated (H$_2$/Lindlar, hexanes containing 1% py). We were disappointed to discover that the diene was competitively reduced along with the acetylene[5] affording as much as 30-40% over-reduced products of 16. The final yield of 16 after HPLC purification was 20%. Saponification of 16 (LiOH,DME/H$_2$O 5:1) quantitatively afforded ±8-HETE.[6]

±9-HETE

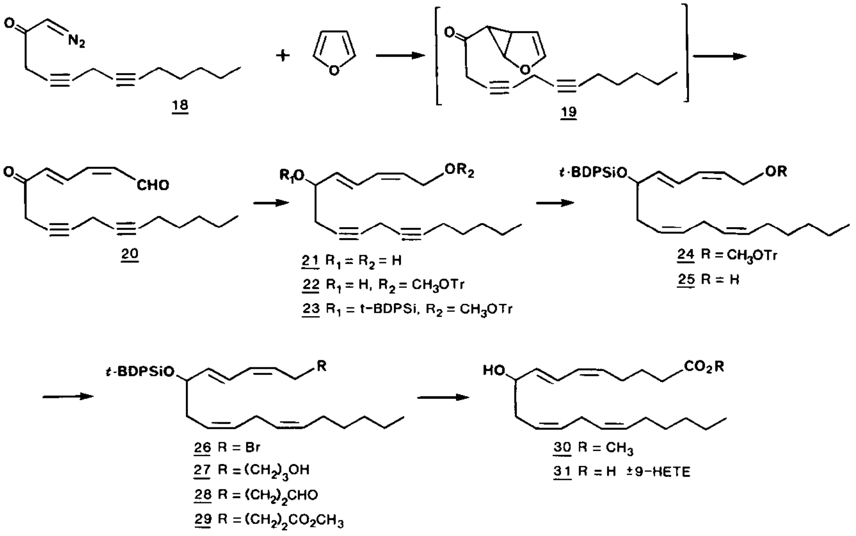
The configuration of the cis-trans diene geometry in 8-HETE mandates the choice of diazo-ketone 6 bearing carbons C$_1$ to C$_9$ of the final product. By contrast, in 9-HETE, recognition of the cis-trans diene suggests construction of the target molecule in the opposite sense and diazo-ketone 18 was chosen, bearing carbons C$_8$ to C$_{20}$ in the natural product. We begin the synthesis of ±9-HETE using diazo-ketone 18. The preparation of 18 from the corresponding homo-propargyl alcohol[7] paralleled the route described for diazo-ketone 6. Addition of 18 to furan catalyzed by [Rh(OAc$_2$)]$_2$, give 20 via intermediate 19 and reduction to the diol 21 proceeded as expected in 40-50% overall yield from 18. The same protection scheme, tritylation followed by silylation produced the protected ethers 23 in 67% yield. We attempted the semi-hydrogenation of 23 and were gratified to discover that diene over-reduction products amounted to less than 5%, and an 80% yield of alcohol 25 was obtained after removal of the methoxy trityl group. We reasoned that the bulky methoxy-trityl and silyl groups flanking both sides of the diene effectively mask it from the catalyst surface and prevent over-reduction.[8]



SCHEME 1 - SYNTHESIS of ±8-HETE



SCHEME 2 - SYNTHESIS of ±9-HETE



Using the previously described conditions, the alcohol 25 was transformed to the bromide 26 in 90-95% yield. Homologation to the C-20 chain was effected using the Normant Grignard[9] $ClMg(CH_2)_3OMgCl$ (6 equiv of Grignard added to bromide THF/HMPA 1:1 @ -40°C, warming to RT overnight) to give a 50% yield of 27. A very mild two step oxidation procedure was used to complete the synthesis. Moffat oxidation[10] (DCC/py/TFA in ϕH/DMSO, RT, 16 h) followed by a second oxidation,[11] ($NaClO_2/(CH_3)_3COH/H_2O$ pH 4.5/2-methyl-2-butene) provided the acid which was esterified (CH_2N_2) affording a 50% yield from silyl ether 29. Removal of the silyl (n-Bu_4NF/THF) provided ±9-HETE Me-ester 30 in 81% yield. Saponification ($LiOH/DME/H_2O$) gave a quantitative yield of the natural product 31.[5]

In summary, we have demonstrated the versatility of the rhodium (II) catalyzed addition of diazo-ketones to furan to provide requisite precursors to HETEs. Recognition and delivery of the cis-trans diene are the paramount features in our approach. Finally, we have shown that the diazo-ketone chain may contain latent functionality (acetylene and/or esters) which may be unveiled at a later stage in the synthesis to produce the desired moiety.

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5. Lindlar catalyst purchased from Strem Chemicals, other Lindlar catalysts gave worse results.

6. Satisfactory spectral data obtained: IR, UV, HPLC, 400 MHz, ^{1}HNMR, GC-Mass Spec. (TMS ether, Me-ester).

7. Prepared using the procedure of K. Eiter, F. Lieb, H. Disselukotter, and H. Oediger, Justus Liebigs Ann. Chem., 658 (1978).

8. This reduction was found to be a general reaction when the diene is sufficiently masked. The same reduction was repeated on intermediate 11 in the 8-HETE synthesis with a large improvement in the yield, (94%) and no over-reduction.

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(Received in USA 4 October 1983)