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A SHORT,THREE-COMPONENT TOTAL SYNTHESIS OF 12-HYDROXYEICOSA-5,8,14(Z), 10(E)-TETRAENOIC ACID (12-HETE) VIA THE CORRESPONDING KETONE

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Summary: A highly effective synthesis of (±)-12-HETE (1) from the components 2, 3 and 6 is described which employs a new class of cuprate reagents.

Since the first isolation of 12-HETE (1) as a product of arachidonic acid metabolism in blood platelets[1] the role of this substance and the corresponding hydroperoxide from which it is formed (12-HPETE) in biological systems has remained unclear. The recent identification of metabolites of 12-HPETE, specifically the 10-hydroxy-[2] and 8-hydroxy-11,12-epoxides,[3,4] and the finding that 12-HPETE (but not 12-HETE) stimulates leukotriene biosynthesis by leukocytes[5] indicate that this situation is subject to change. Because of the now growing importance of 12-HETE and 12-HPETE and the scarcity of the native compounds (which have been biosynthesized using platelets at only the microgram level) we have undertaken to devise a synthesis which is more effective than the original route developed in this laboratory several years ago.[6,7] Because known methodology for the total synthesis of HPETEs from the corresponding HETEs results in almost complete racemization[8] our targets have been (±)-12-HETE, the corresponding ketone and ketoxime. The last compound is of interest as a possible competitive inhibitor of the enzymes involved in conversion of 12-HPETE to 11,12-epoxides. The synthesis which has been developed involves the coupling of three simple and easily available components (2, 3 and 6) corresponding to the C(1) - C(4), C(5) - C(9), and C(10) - C(20) segments of 1.

The joining of components 3[9] and 2[10] presented unexpected problems. Only a 30% yield (at best) of the desired coupling product 4 could be obtained using iodide 3 and the Gilman cuprate derived from 2 (2 equiv) and cuprous bromide or iodide (1 equiv) under a range of conditions.[11] The use of a variety of other organocopper reagents proved even less satisfactory; dismal yields (2 - 10%) were obtained with reagents formed from 2 and CuCN (1 : 1 or 2 : 1),[12] $(CH_3)_2(CH_3O)CC{\equiv}CCu$ (1 : 1), C_6H_5SCu (1 : 1),[13] and (cyclo $C_6H_{11})_2NCuCNLi$ (1 : 1).[14] Successful coupling was achieved, however, using a reagent of a new type formed from 2 and n-$Bu_4NCu(CN)_2$[15] (1 : 1). A solution of the vinyllithium component 2 in tetrahydrofuran (THF) at -40° was treated with a suspension of 1 equiv of n-$Bu_4NCu(CN)_2$ and the mixture was brought to -25° and stirred for 2 hr. The OBO ester 3 (1.1 equiv) was added and the reaction mixture was worked up after a reaction time of 4 hr at -25°. Column chromatography on silica gel using 5 : 1 hexane - ether containing 1% of triethylamine provided the coupling product 4 in 69% yield.

Component 6 was prepared from 3(Z)-nonenal[16] in two steps: (1) reaction with lithium acetylide[17] in THF at -78° for 1 hr to give the corresponding ethynyl carbinol (95%); and (2) two phase Jones oxidation using ether at 25° for 2 hr, followed by rapid isolation and flash chromatography on Merck silica G-60 using methylene chloride as eluent to afford 6 in 97% yield. Because of the high reactivity of 6 it was normally prepared just before use in the next step.

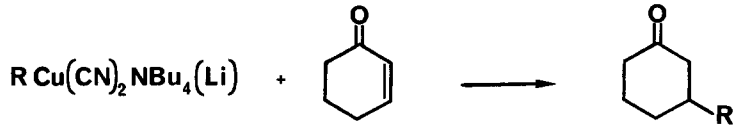
Treatment of 4 with 1 equiv of n-butyllithium in THF at -78° for 1.5 hr followed by reaction with 1 equiv of cuprous bromide dimethylsulfide complex in ether (1 hr at -50°) generated the Gilman vinylcopper reagent which was then allowed to react with 1.2 equiv acetylenic ketone 6 for ca. 1 min at -50° and quenched with 1.5 equiv of glacial acetic acid in methanol.[17] Extractive isolation and chromatography on silica gel using 3 : 1 hexane-ethyl acetate for elution gave the desired tetraenone 7 (68%); IR (film): 1645 $cm.^{-1}$; PMR (270 MHz, $CDCl_3$, δ): 7.53 (dd, J 15.8, 10.5Hz, 1H); 6.19 (d, J 15.8 Hz, 1H); 6.11 (dd, J 10, 10.5Hz, 1H); 5.83 (dt, J 10, 7Hz, 1H); 5.56 (m, 2H); 5.35 (m, 2H); 3.89 (s, 6H); 3.32 (d, J 5.5Hz, 2H); 3.04 (dd, J 7 Hz, 2H); 2.07 (m, 4H); 0.88 (t, 3H); 0.79 (s, 3H); R_f 0.48 (silica gel, 3 : 1 hexane-ethyl acetate).

Reduction of 7 with sodium borohydride in methanol at -40° for 15 min afforded after extractive isolation and chromatography on silica gel (3 : 1 hexane-ethyl acetate containing 1% triethylamine for elution) the OBO ortho ester of (±)-12-HETE (92%). This ester was converted to (±)-12-HETE in quantitative yield by exposure to sodium bisulfate in 1 : 1 dimethoxy ethane-water (pH ca. 3) at 0° for 30 min, basification to 0.15 M in lithium hydroxide and stirring at 25° for 1 hr, acidification to pH 3 and extraction. The (±)-12-HETE so obtained was spectroscopically identical (by IR, UV, 270 MHz PMR) with previously synthesized 12-HETE.[6]

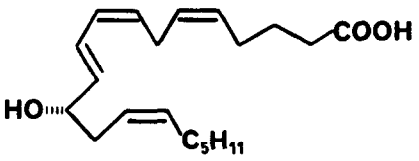
The oxime 9, an analog of 12-HPETE, was prepared by reaction of 7 with excess hydroxylamine hydrochloride-sodium acetate in methanol at 0° for 30 min followed by extractive isolation and chromatography to give 8 (90%), and subsequent cleavage of the OBO ortho ester as described above.

In our opinion the synthesis of 1 and 9 outlined herein is the method of choice for the preparation of these substances and also the analog of 12-HETE derived from eicosapentaenoic acid.[18]

Because of the remarkable effectiveness in coupling with the iodo OBO ester 3 of the copper reagent formed from vinyllithium 2 and $Bu_4NCu(CN)_2$, we have investigated the reaction of this type of reagent with 2-cyclohexenone (1.1 equiv) for a number of organolithium reagents according to the equation:

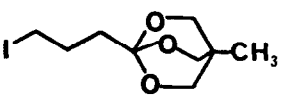


The yields based on organolithium reagent used (1 : 1 with $Bu_4NCu(CN)_2$) for reaction in THF at -50° for 1 hr were as follows: R = n-Bu, 97%; R = phenyl, 92%; R = vinyl, 66%; R = 1(Z)-heptenyl, 77%. These results indicate potentially high utility of this type of cuprate in synthesis, especially when a valuable organolithium reagent which should not be wasted is involved. The reagents listed above were obtained as nearly homogeneous THF solutions which had excellent stability at -25° under nitrogen.[19]

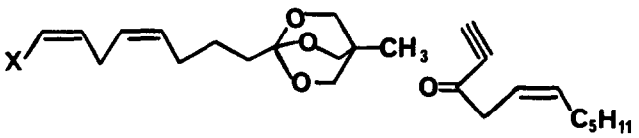


1

2



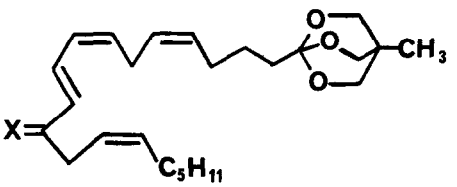
3



4 X = Bu_3Sn

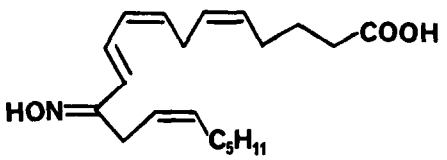
5 X = Li

6



7 X = O

8 X = NOH



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References and Notes

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7. For other more recent syntheses of various HETEs see (a) E. J. Corey and J. Kang, J. Am. Chem. Soc., 103, 4618 (1981); and (b) J. Rokach, J. Adams, and R. Perry, Tetrahedron Letters, 24, 5185 (1983).

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9. The iodo OBO ortho ester 3 was prepared in 85% yield from the corresponding bromide with concentrated sodium iodide (10 equiv) in acetone at reflux in the presence of 1 equiv of sodium bicarbonate. See E. J. Corey and N. Raju, Tetrahedron Letters, 24, 5571 (1983).

10. The generation of 1,4(Z)-1-lithio-5-tributylstannyl-1,4-pentadiene (2) was carried out by reaction of 1,1-di-n-butyl-1-stanna-2,5-cyclohexadiene and n-butyllithium in ether at -40° for 0.5 hr, see E. J. Corey and J. Kang, Tetrahedron Letters, 23, 1651 (1982).

11. Satisfactory infrared, proton magnetic resonance and mass spectral data were obtained using chromatographically purified and homogeneous samples of each synthetic intermediate.

12. B. H. Lipshutz, J. A. Kozlowski, and R. S. Wilhelm, J. Org. Chem., 48, 546 (1983) and previous papers of the series.

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15. The complex n-$Bu_4NCu(CN)_2$ was prepared as a colorless solid by treatment of a slurry of CuCN in methanol with a solution of 1 equiv of tetra-n-butylammonium cyanide in methanol at 25° under N_2, evaporation of the resulting solution to dryness in vacuo and azeotropic drying (3 times) with toluene in vacuo.

16. E. J. Corey and J. E. Munroe, J. Am. Chem. Soc., 104, 1752 (1982).

17. See E. J. Corey and J. A. Katzenellenbogen, J. Am. Chem. Soc., 91, 1851 (1969).

18. This compound, which is of biogenetic interest, [see E. J. Corey, B. De, J. W. Ponder, and J. M. Berg, Tetrahedron Letters, 25, 1015 (1984)] has been synthesized by us using the approach outlined herein for 7.

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