Tetrahedron Letters, Vol 32, No.5, pp 635-638, 1991
Printed in Great Britain

0040-4039/91 $3 0(
Pergamon Press plc

TOTAL SYNTHESIS OF (11R,12S)-diHETE

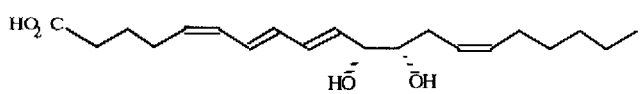
Agnès GIGOU [a], Jean-Pierre BEAUCOURT [a], Jean-Paul LELLOUCHE [a*], René GREE [b*]

a - CEN Saclay, Service des Molécules Marquées, Bât 547, 91191 Gif-sur-Yvette, France.
b - Laboratoire de Chimie Organique Biologique, associé au CNRS, ENSCR, Avenue du Général Leclerc, 35700 Rennes-Beaulieu, France

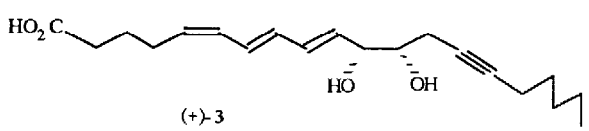
Abstract : *The first total synthesis of (11R,12S) diHETE is reported. The key step is the highly chemio- and stereoselective osmylation of a double bond in a trienyne system selectively complexed by an $Fe(CO)_3$ group.*

In the last ten years several dihydroxylated metabolites of arachidonic acid have been isolated from lipoxygenase pathways mainly via their corresponding epoxides, the LTA_4's [1]. Among them, (11,12)-diHETEs have been obtained, first from human platelets [2] and later from a partially purified 12 lipoxygenase (12 LO) from porcine leukocytes [3] It has been also established recently that an epoxide hydrolase from guinea pig liver cytosol induces the enzymatic conversion of (11,12)-LTA_4 to a single diHETE with an (11R,12S) assumed structure [4]. Since the biological importance of the 12 LO pathway has been recognized recently [5] it is of considerable interest to prepare this new diHETE not only to establish unambiguously the absolute configuration of the enzymatic metabolite but also to obtain information about its biological activitiy.

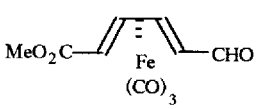
As part of our program dealing with the use of butadiene-tricarbonyliron complexes in organic synthesis [6] we have recently reported a new approach to the preparation of the (5,6)-diHETEs [7]. The purpose of this letter is to describe the first total synthesis of (11R,12S)-diHETE (+)-**2** and its (14,15) dehydroanalog (+)-**3** starting from the easily accessible complex (-)-**1** [8]. We report new results for the selective osmylation of polyunsaturated systems, *especially in the case of enynes*, a problem which has rarely been dealt with in the past [9].



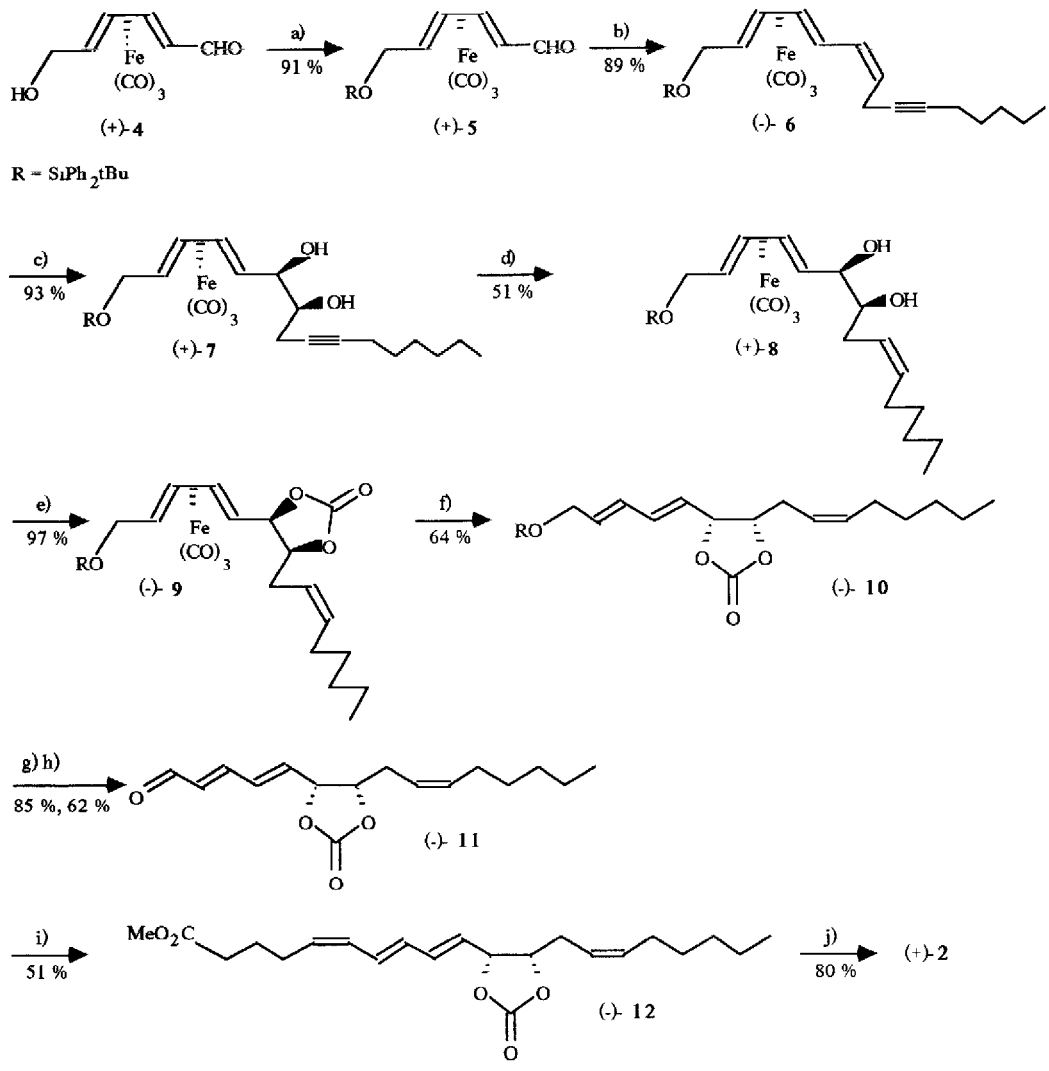
(+)-**2**



(+)-**3**



(-)- **1**



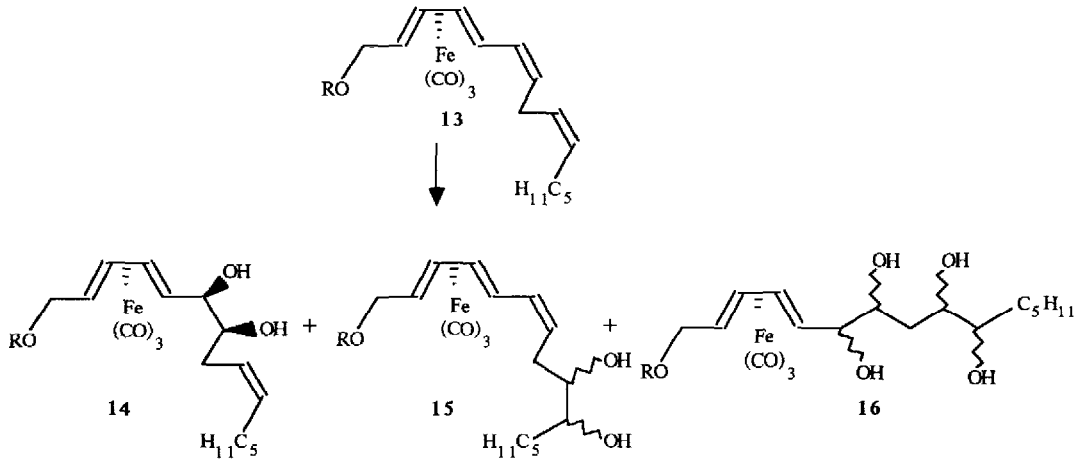
Scheme 1

a) $tBuPh_2SiCl$ (1.1 eq.), DMF, imidazole, 3 h, 20°C ; b) $Ph_3P{=}CH\text{-}CH_2\text{-}C{\equiv}C\text{-}C_5H_{11}$ (1.2 eq.), THF/DMPU, 30 min, - 78°C then 1.5 h, 0°C , c) OsO_4 (1.5 eq.), pyr, 5 h, 20°C ; d) H_2 /Pd Lindlar, MeOH, 7.5 h, 20°C ; e) Im_2CO (7.2 eq.), benzene, 2 h, 67°C ; f) $Ce(NO_3)_6(NH_4)_2$ (8.7 eq.) ; MeOH/AcOEt ; 15 min, - 20°C ; g) nBu_4NF (4.6 eq.), THF , 2 h, -5 to 0°C ; h) PDC (1.6 eq.) ; CH_2Cl_2, 24 h, 20°C ; i) $Ph_3P{=}CH\text{-}(CH_2)_3\text{-}CO_2Li$ (1.8 eq.) ; THF/HMPA ; 1 h, - 78°C then 1.5 h, - 20°C, Me_2SO_4 (2 x 4,2 eq.) ; 2 h, - 20 to 20°C ; j) 10N NaOH, MeOH, 1 h, 20°C.

The synthesis of (+)-2 is described in scheme 1. The optically pure complex (-)-1 [8], of known (2R,5S) absolute configuration, is transformed into alcohol (+)-4 and then into its silyl ether (+)-5 [10]. Using a THF/DMPU mixture as solvent, the Wittig reaction of 5 is highly stereoselective (E/Z = 97/3) giving the key intermediate (-)-6 in 89 % yield after purification by chromatography. The Z geometry of the double bond is established by ^1H NMR (300 MHz, C_6D_6, ^3J = 10.7 Hz).

The osmylation of (-)-6, under stoichiometric conditions, occurs very smoothly giving glycol (+)-7 in 93 % yield. Several aspects of this reaction are worthy of note :

- First the addition is completely chemioselective for the double bond and no product resulting from a reaction at the triple bond could be isolated even in the presence of excess OsO_4. This result is not due to an electronic effect of the organometallic moiety since, under the same conditions, the reaction of complex 13 is not selective and a mixture of 14 (24 %), 15 (16 %) and 16 (39 %) is obtained (scheme 2) [11].



Scheme 2

- Second, the osmylation of 6 is completely stereoselective, giving 7 as the only isolated diol as determined by HPLC, ^1H and ^{13}C NMR. The absolute configuration of 7, resulting from an addition of OsO_4 anti to the $Fe(CO)_3$ group, is attributed by analogy to the results obtained previously during the synthesis of (5R,6S)-diHETE [7].

The next steps in the synthesis of (11R,12S)-diHETE proved to be more straigthforward. Semi-reduction of (+)-7 gives (+)-8 (51 % ; non optimized yield) which is transformed into the carbonate (-)-9. Decomplexation leads to (-)-10 which is desilylated and oxidised to give the dienal (-)-11 (34 % overall yield from 9). A final Wittig reaction, followed by *in situ* esterification, affords (-)-12 (51 % after chromatography) which, after complete saponification, yields (+)-2. The physical data (including high field ^1H NMR) of our synthetic (11R,12S)-diHETE are in excellent agreement with those reported for the natural product [4].

The same sequence of reactions has been performed, starting from (+)-7 but without the semi-reduction step, for the preparation of the (14,15)-dehydro derivative (+)-3 (18 % non optimized overall yield from 7). This compound is of interest as a possible precursor for deuterium or tritium labelled (+)-2.

In conclusion, this first total synthesis of (11R,12S)-diHETE confirms that diene-tricarbonyliron complexes are useful intermediates for the regio- and stereocontrolled osmylation of double bonds in polyenic systems even in the presence of remote triple bonds. This approach could be extended to the synthesis of other diHETEs and may also be useful in the preparation of other natural products.

References and Notes

1 "Leukotriene Syntheses : A new class of biologically active compounds including SRS-A". Scheinmann F., Ackroyd J. Ed., Raven Press N.Y., 1984 ; "The Leukotrienes, Chemistry and Biology" Chakrin L.W., Bailey D.M. Ed , Acad. Press, Orlando, 1984 ; "Leukotriene and Lipoxygenases" Rokach J. Ed., Elsevier N.Y., 1989.

2 Westlund P., Adv. Prostaglandin Thromboxane Leukotriene Res., 1987, 17, 99.

3 Kitamura S, Shimizu T., Miki I., Izumi T., Kasama T., Sato A., Sano H., Seyama Y., Eur. J. Biochem., 1988, 176, 725.

4 Miki I., Shimizu T., Seyama Y., Kitamura S., Yamaguchi K , Sano H., Ueno H., Hiratsuka A., Watabe T., J. Biol. Chem., 1989, 264, 5799.

5 See for instance : Spector A.A., Gordon J.A., Moore S.A., Prog. Lipid Res., 1988, 27, 271 , Shimizu T., Wolfe S., J. Neurochem., 1990, 55, 1 ; Piomelli D., Greengard P , Trends Pharmacol. Sciences, 1990, 11, 367 and references therein.

6 Grée R., Synthesis, 1989, 341.

7 Gigou A., Lellouche J.P., Beaucourt J.P., Toupet L., Angew. Chem. Int. Ed., 1989, 28, 755.

8 Monpert A., Martelli J., Grée R., Carrié R., Tetrahedron Lett., 1981, 22, 1961.

9 Few studies have dealt with the chemioselectivity in the osmylation reaction of molecules bearing both double and triple bonds ; see for instance : Kende A.S., Smith C.A., Tetrahedron Lett., 1988, 29, 4217.

10 Djedaini F., Grée D., Martelli J., Grée R., Leroy L., Bolard J., Toupet L., Tetrahedron Lett., 1989, 30, 3781.

11 Only one diastereoisomer is obtained in the case of 15 and 16 but the stereochemistry has not been established yet.

(Received in France 6 November 1990)