Tetrahedron Letters,Vol.30,No.19,pp 2545-2548,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

SYNTHESIS OF (±)-HEPOXILIN A_3 UTILIZING ARSONIUM YLIDES

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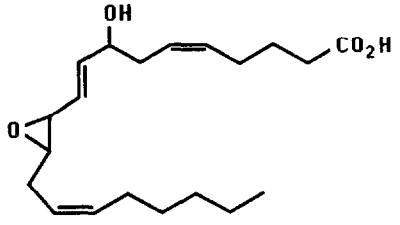
Summary : (±)-Hepoxilin A_3, a biologically active metabolite of arachidonic acid, was prepared from 1-heptyne and δ-valerolactone by a simple, convergent strategy that exploits arsonium ylides for homologation/functionalization.

Hepoxilin A_3, **1** was initially isolated[1] in 1982 from incubations of arachidonic acid with rat lung homogenate and subsequantly characterized[2] as 8-hydroxy-11,12-epoxyeicosa-5,9,14-trienoic acid, epimeric at C(8). Previously, **1** had been proposed as the pivotal intermediate leading to the 8,9,12- and 8,11,12-triols (trioxilins) produced by blood platelets and other tissues via the 12-lipoxygenase pathway[3-5]. Pace-Asciak reported that **1** is an endogenous product of pancreatic islets[6] where it displays insulin secretagogue activity[7] and that it potentiates calcium transport across membranes[8]. Furthermore, hepoxilin A_3 concentrations in the circulation have been correlated with plasma insulin levels[9]. More recent studies[10] suggest **1** acts as a second messenger for presynaptic inhibition in Aplysia sensory cells. In the rat, a hepoxilin A_3 pathway has been demonstrated in several parts of the central nervous system[11], although its functional significance remains obscure.



1

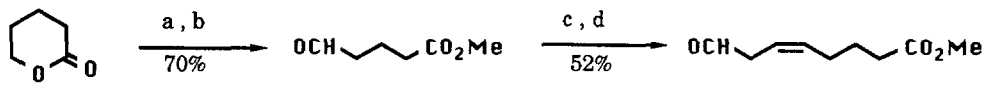
Hepoxilin A_3

Continuing efforts to elucidate the occurrence and physiological role(s) of hepoxilin A_3 are trammeled by the limited availability of natural material and would be greatly expedited by the development of an inexpensive and pratical synthetic route to **1**.

Herein, we report an efficient total synthesis of (±)-hepoxilin A_3 by a convergent strategy that exploits the unique properties of arsonium ylides. Corey and Su[12] have described a synthesis of 11,12(S,S)-**1** using an epoxyaldehyde and a stabilized phosphonium ylide.

The C(1)-C(8) moiety **4** was prepared as outlined in Scheme I. δ-Valerolactone **2** was subjected to acidic methanolysis followed by pyridinium chlorochromate oxidation to give aldehyde **3**[13] which was homologated using (3,3-diisopropoxypropylidene)triphenylphosphorane[14] **5**. Mild acetal hydrolysis with trifluoroacetic acid in chloroform[15] afforded the somewhat labile β,γ-unsaturated aldehyde **4**.

Scheme I

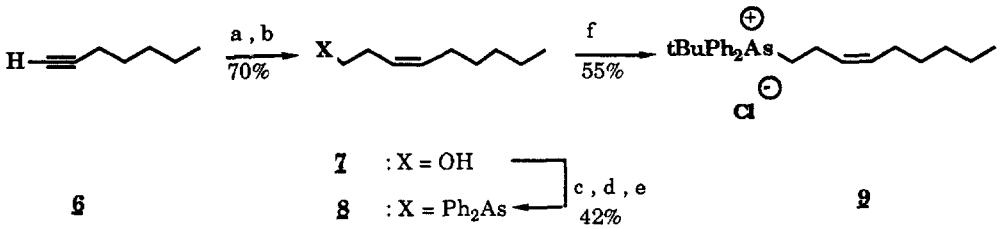


2 **3** **4**

[a] H^+, MeOH. [b] PCC,CH_2Cl_2. [c] **5**,THF, -78 to 23°C,6h. [d] CF_3CO_2H,$CHCl_3$.

The unit containing C(12)-C(20) was obtained by adding the magnesium salt of 1-heptyne **6** to ethylene oxide[16] at -20°C and partial hydrogenation of the resultant acetylenic alcohol to *cis*-olefin **7**[17] using Lindlar catalyst in ethyl acetate (Scheme II). The iodide derived from **7** by sequential tosylation and sodium iodide exchange generated arsine **8** upon lithiodiphenylarsine[18] displacement. Aluminum chloride mediated addition of t-butyl chloride to **8** furnished crystalline arsonium salt **9** (dichlroromethane /ether)

Scheme II

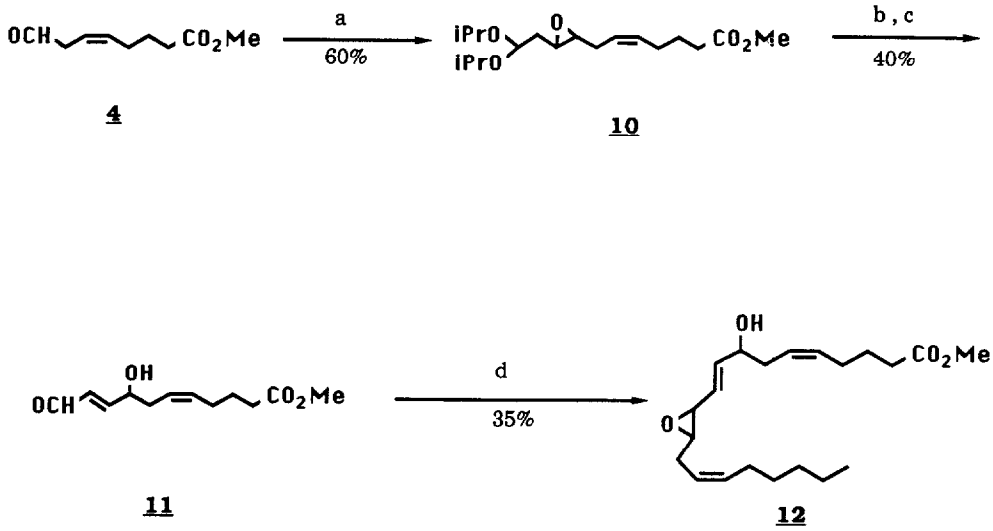


6 **9**

[a] EtMgBr (1.0 equiv), Et_2O, reflux, 2 h ; oxirane (2.0 equiv), -20°C, 2 h. [b] Pd/$CaCO_3$/Pb (10 % w/w), H_2, AcOEt, 25°C, 3 h. [c] TsCl, C_5H_5N, 0°C, 3 h. [d] NaI, CH_3COCH_3, 25°C, 2 h. [e] Ph_2AsLi, THF, -78° to 25°C, 1 h. [f] t-BuCl (1.2 equiv), $AlCl_3$, CH_2Cl_2, 25°C, 24 h.

Conversion of **4** to γ-hydroxy-enal **11** was realized utilizing the newly developed[19] β-formyl vinyl anion equivalent (3,3-diisopropoxypropyl) triphenylarsonium chloride[20] **13** (Scheme III). The ylide of **13** (generated with 0.3 M LDA in THF at -40°C) was condensed with **4** to give selectively[18a] *trans*-epoxide **10** which was purified over silica gel (hexane/ether/triethylamine 89:10:1). The epoxyaldehyde obtained from **10** by acetal hydrolysis using Conia's method[21] was smoothly isomerized to *trans*-enal **11** by stirring with an ethereal suspension of silica gel, filtration and chromatographic purification. Coupling of **11** with the ylide of **9** (generated as above) yielded **12**, the methyl-ester of hepoxilin A_3[22].

Scheme III



[a] **13**, LDA, THF, -40°C. [b] SiO_2, H_2SO_4. [c] SiO_2, Et_2O. [d] **9**, LDA, THF/HMPA (90-10), -40°C.

Prior to biological evaluation, the sodium salt of **1** is prepared by dissolving 100 mg of **12** in 100 ml of ethanol and 100 ml of 1M aqueous sodium carbonate under an argon atmosphere. After standing at ambient for 4 h and at 0°C overnight, the solvent is removed under an argon stream and the residue re-dissolved in an appropriate vehicle.

Acknowledgement : This work was supported by the CNRS, and NATO Grant 26/85.

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22. Spectral data were identical with those in ref. 12. TLC: SiO_2, C_6H_6/Et_2O 85:15, R_f 0.38 and 0.33 for the two C(8)-epimeric alcohols of **12**. Ester **12** was further characterized as its TMS ether and as the TMS ether of the triol obtained after reduction with lithium aluminum hydride.

(Received in France 7 March 1989)