Pergamon

Tetrahedron Letters, Vol. 35, No. 7, pp. 1067-1070, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0430-6

First Total Synthesis of a Barnacle Hatching Factor 8(*R*)-Hydroxy-eicosa-5(*Z*),9(*E*),11(*Z*),14(*Z*),17(*Z*)-pentaenoic acid

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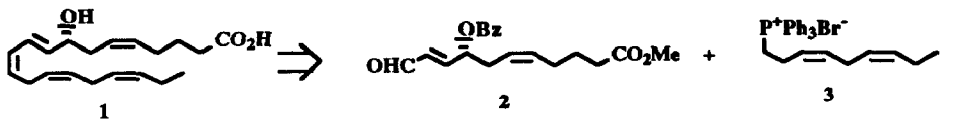
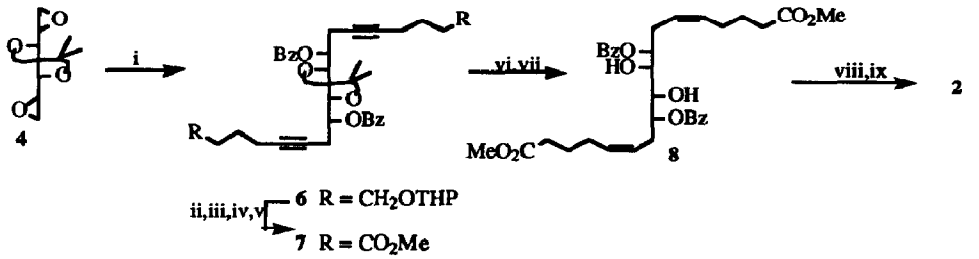
Abstract—The first total synthesis of a barnacle hatching factor (BHF) establishes its constitution and absolute stereochemistry as 8(*R*)-Hydroxy-eicosa-5(*Z*),9(*E*),11(*Z*),14(*Z*),17(*Z*)-pentaenoic acid **1**.

Recently, an eicosanoid monohydroxy fatty acid was isolated from the homogenates of *Balanus balanoides* and *Eliminus modestus* in minute quantities (10^{-9} g) and shown to induce the hatching of barnacles[1,2] (IC_{50} *ca.* 5.0×10^{-4} M).[3] The structure of the barnacle hatching factor (BHF) was suggested to be 8(*R*)-Hydroxy-eicosa-5(*Z*),9(*E*),11(*Z*),14(*Z*),17(*Z*)-pentaenoic acid **1** [8(*R*)-HEPE] on the basis of biogenetic consideration[4] and of an analysis of its mass fragmentation pattern.[1,2] Other spectroscopic studies are not possible because of the scarcity of the material which therefore warrants a total synthesis. Only the 8(*R*)-enantiomer of 8-hydroxy-eicosatetraenoic acid was active in inducing oocyte maturation in starfish.[4] Commercially available 8(*S*)-HEPE has been shown to be biologially inactive towards barnacle hatching.[5] The limited availability of 8(*S*)-HEPE in microgram quantities and the prohibitive cost render investigation of its chemistry impractical. Here we report, starting from D-mannitol and propargyl alcohol, the first total and stereoselective synthesis of **1**, which displayed a mass spectrum in accord with that of the BHF and, most importantly, exhibited bioactivity towards barnacle hatching (IC_{50} *ca.* 2.4×10^{-6} M),[3] thereby enabling the assignment of the constitution and absolute configuration **1** to the BHF.



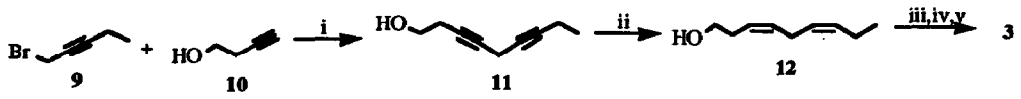
1 **2** **3**

Retrosynthetic analysis of **1** shows that dissection of the strategic 11-alkene gives the upper half aldehyde **2** and the bottom half phosphonium salt **3** which can be assembled *via* a *Z*-selective Wittig reaction to yield the target molecule. The construction of **2** is illustrated in Scheme 1. Oxirane opening reaction[6] of the known diepoxide **4**,[7] readily accessible from D-mannitol in four steps, with the lithium salt of the alkyne **5**[8] followed by *in situ* benzoylation afforded the benzoate **6** as a viscous oil, $[\alpha]_D^{24}$ + 10.1° (*c* 1.0, $CHCl_3$).[9] Selective methanolysis of the tetrahydropyranyl ether in **6** gave the corresponding primary alcohol which then was subjected to an oxidation-esterification sequence to form the methyl ester **7**, $[\alpha]_D^{24}$ + 9.0° (*c* 1.3, $CHCl_3$). Stereoselective hydrogenation of the triple bond in **7** with Lindlar's catalyst followed by deacetonation gave the ene-diol **8**, $[\alpha]_D^{24}$ + 51.2° (*c* 6.5, $CHCl_3$).[10] Glycol cleavage oxidation[11] of the diol moiety in **8** with sodium metaperiodate followed by Wittig reaction with formylmethylenetriphenylphosphorane in CH_2Cl_2 furnished the *Z,E*-dienal **2**, $[\alpha]_D^{24}$ - 108.2° (*c* 0.9, $CHCl_3$).[12] The stereochemistry of the two double bonds in **2** was indicated from the ^{1}NMR spectrum ($J_{5,6}$ = 10.2 Hz and $J_{9,10}$ = 15.6 Hz).



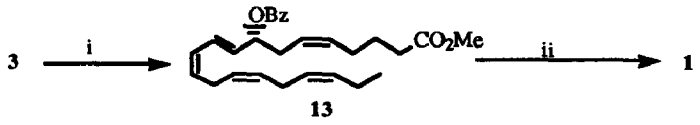
Scheme 1 *Reagents and conditions*: i, $HC{\equiv}C(CH_2)_3CH_2OTHP$ **5**, *n*-BuLi, THF/DMPU, Δ, then PhCOCl, 0 °C (79%); ii, TsOH, MeOH, Δ (74%); iii, $(COCl)_2$, DMSO, Et_3N, (78%); iv, $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O (94%); v, MeOH, HCl (93%); vi, H_2, Lindlar's catalyst, benzene (98%); vii, 80% aqueous TFA, 0 °C (84%); viii, $NaIO_4$, MeOH/H_2O, 0 °C (97%); ix, $Ph_3P{=}CHCHO$, CH_2Cl_2 (85%).

On the other hand, the synthesis of the phosphonium salt is depicted in Scheme 2. Coupling reaction of 1-bromo-pent-2-yne **9**[13] with the commercially available but-3-yn-1-ol **10** under copper (I) catalysed phase transfer conditions[14] gave the skipped diyne **11** in 73% yield. Stereoselective hydrogenation of **11** over nickel boride[15] with a catalyst modifier ethylenediamine[16] afforded the *Z,Z*-diene **12**[17] in 79% yield. The *Z,Z*-geometry of the diene moiety in **12** was evident from the ^{1}NMR spectrum ($J_{3,4}$ = 10.6 Hz and $J_{6,7}$ = 10.9 Hz). The alcohol **12** was then transformed into the phosphonium salt **3** in the conventional way.



Scheme 2 *Reagents and conditions*: i, K_2CO_3, CuI, *t*-Bu_4NI, DMF (73%); ii, H_2, $Ni(OAc)_2$, $NaBH_4$, EtOH, $H_2N(CH_2)_2NH_2$ (79%); iii, MsCl, Et_3N, Et_2O (87%); iv, NaI, acetone (88%); v, PPh_3, MeCN, Δ (98%).

With the upper and lower half of the target molecule readily at hand, we set to complete the synthesis of **1** (Scheme 3). Thus the phosphonium salt **3** was deprotonated (*n*-BuLi, THF, -78 °C) and the aldehyde **2** added followed by 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU). HPLC analysis of the mixture isolated by flash chromatography showed that the *Z* : *E* ratio of the newly formed 11-alkene was 12 : 1. Fractionation by preparative HPLC then gave the pentaene **13** as a clear oil, $[\alpha]_D^{24}$ - 75.7° (*c* 2.7, $CHCl_3$). Saponification of the two ester groups in **13** followed by acidification with formic acid furnished the target molecule 8(*R*)-HEPE **1** as a colourless oil, $[\alpha]_D^{24}$ + 33.4° (*c* 2.1, $CHCl_3$), with 86% e.e.[18] Since derivatised[19] **1** showed a mass fragmentation pattern similar with that of the BHF and exhibited bioactivity towards barnacle hatching (IC_{50} *ca.* 2.4×10^{-6} M),[20] the structure and stereochemistry of the BHF is confirmed as 8(*R*)-Hydroxy-eicosa-5(*Z*),9(*E*),11(*Z*),14(*Z*),17(*Z*)-pentaenoic acid **1**.



Scheme 3 *Reagents and conditions*: i, *n*-BuLi, THF, -78 °C, then **2**, DMPU, -78 to -25 °C (87%); ii, K_2CO_3, MeOH, H_2O (85%).

In conclusion, we have developed a convergent and enantioselective synthesis of **1** using tafftmannitol as the source of chirality and using Wittig reactions and catalytic hydrogenation of alkynes to introduce stereoselectively the five double bonds. The convergent strategy employed allows facile syntheses of acetylenic analogues and geometric isomers. Research in this direction is in progress.

Acknowledgment. We thank the S.E.R.C. for financial support and Dr. D. L. Holland for discussion and performing the bioassay.

References and notes

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(3) IC_{50} is defined as the concentration of the material to cause a 50% hatch.

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(8) Reaction of the commercially available hex-5-yn-1-ol with 2,3-dihydropyran (CH_2Cl_2, TsOH) gave **5** in 98% yield.
(9) All new compounds gave satisfactory spectral and HMRS or analytical data.
(10) Reversed phase HPLC analysis showed that **8** was > 95% one isomer.
(11) For a recent review, see Shing, T. K. M. *Comprehensive Organic Synthesis*, eds. Trost, B. M. and Fleming, I., Pergamon Press, Oxford, **1991**, vol. 7, p. 703.
(12) There was no indication of the undesired *Z,Z*- isomer by TLC and ^{1}NMR spectral analysis.
(13) Bromide **9** was prepared from propargyl alcohol in four steps, see: Kajiwara, T.; Odake, Y.; Hatanaka, A. *Agr. Biol. Chem.*, **1975**, *39*, 1617.
(14) These conditions were used previously for the substitution of allyl halides with terminal alkynes, see: Jeffery, T. *Tetrahedron Lett.*. 1989, 225.
(15) Brown, H. C.; Brown, C. A. *J. Am. Chem. Soc.*, **1963**, *85*, 1005.
(16) Brown, C. A.; Ahuja, V. *J. Chem. Soc., Chem. Commun.*, **1973**, 553. Stereoselectivity for the hydrogenation was significantly poorer without the ethylenediamine.
(17) GC analysis showed that **12** was > 95% one isomer.
(18) **1** was derivatised with ethereal diazomethane into the corresponding methyl ester whose e.e. was determined by the Mosher's protocol.[21] The aldehyde **2** is believed to undergo a little racemization.
(19) **1** was treated with ethereal diazomethane followed by silylation with bis-trimethylsily-trifluoroacetamide.
(20) The bioassay was carried out by Dr. D. L. Holland at the Marine Science Laboratories, Menai Bridge, Anglesey, U.K. The IC_{50} (5.0×10^{-4} M) of the natural material is higher than that of the synthetic 8(*R*)-HEPE **1**. The likely explanation of this discrepancy is the error in the determination of the molarity of the test solution of the natural material since only small quantities (10^{-9} g) of the BHF was isolated from crushed barnacles.
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(*Received in China* 20 *March* 1993; *accepted* 29 *November* 1993)