Tetrahedron Letters, Vol. 33, No. 34, pp. 4897-4900, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Total Stereospecific Synthesis of all *cis*-5,8,11,14,17-Eicosapentaenoic Acid (EPA)

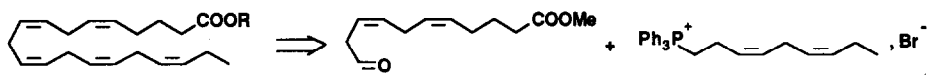
Jacques Viala and Jacqueline Sandri

Laboratoire de Synthèse Organique Associé au CNRS. Université d'Aix-Marseille III - F 13397 Marseille Cedex 13.

Key Words : All *cis*-eicosapentaenoic acid, EPA, *cis*-Wittig reaction, Ozonolysis.

Abstract : Total stereospecific synthesis of EPA has been performed by a sequence of ozonolysis, selective reduction and Wittig reactions which affords the *cis*-skipped olefinic system. Versatile Compound **4**, readily prepared from dihydro anisole, allowed us to prepare the skipped dienic synthon **2** in high yield.

EPA **1a** (all *cis*-5,8,11,14,17-eicosapentaenoic acid) is a polyunsaturated fatty acid (PUFA) of the ω-3 serie found in marine food.[1] Nutritional effects of EPA (as free acid, triglycerides or phospholipids from fish oil) are associated with lowering cardiovascular risk and arterial thrombosis.[2] More recently, studies have suggested that EPA may also have a favourable effect on other human diseases such as arthritis,[3] renal disorders,[4] asthma,[5] eczema[6] and possibly also cancer.[7] Future nutritional experiments using pure or labeled EPA will allow evaluation of its biochemical and biological role. This new interest in the ω-3 PUFA[8] prompts us to report, herein, the total stereospecific synthesis of pure natural EPA **1a**. Our strategy is convergent and is based on the Wittig reaction of the two synthons **2** and **3**.



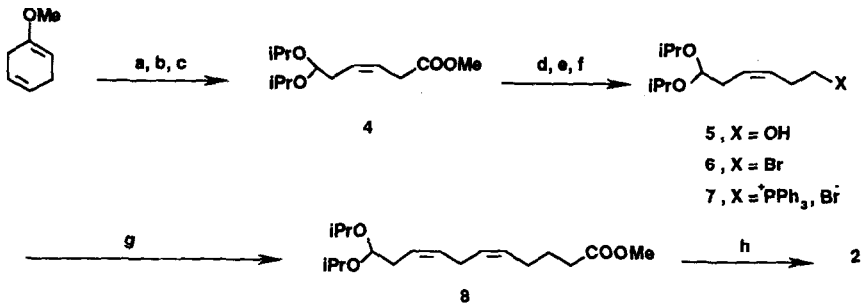
1a, R = H
1b, R = Me

2

3

Preparation of **2**, summarized in scheme **I**, starts from the commercially available 2,5-dihydroanisole. Ozonolysis[9] performed in isopropanol gave an intermediate hydroperoxyhemiacetal[10] which was reduced with dimethylsulfide and acetalized, *in situ*, into **4** in 33% yield by addition of triisopropyl orthoformate at room temperature. Incomplete reaction in isopropanol has to be tolerated because of the rapid ozonolysis of the second double bond leading to methyl 3,3-diisopropoxypropanoate and malonaldehyde bis(diisopropylacetal).[11] The versatile ester acetal **4** exhibits a *cis* double bond. Modification of either one of its functionalities would yield a powerful six-carbon-atom homologating agent. Accordingly, compound **4** was reduced with lithium aluminum hydride at low temperature into alcohol acetal **5**. Smooth conversion of **5** with Ph_3PBr_2[12] in the presence of pyridine furnished the bromide **6** in 91% yield. Displacement with triphenylphosphine in refluxing acetonitrile gave the Wittig salt **7** in 60% yield. The reaction was performed in presence of triethylamine and NaI to avoid the acid catalyzed elimination[13] of isopropanol to form an isopropyl enol ether.[14] *Cis*-Wittig reaction of the corresponding ylid with methyl 5-oxopentanoate provided the *Z,Z*-dienic ester aldehyde **8** in 80% yield. Acidic hydrolysis in the conditions already described[15] quantitatively afforded aldehyde **2**.

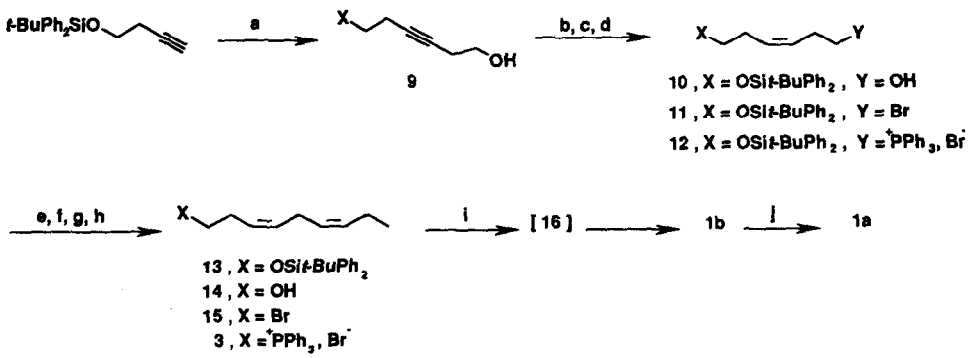
Scheme I



a : O_3, iPrOH, -80°C; b : Me_2S, -80°C to rt; c : $HC(iOPr)_3$, H^+, **4** (33%); d : $LiAlH_4$, THF, -70°C to -30°C, **5** (73%); e : Ph_3PBr_2, pyridine, CH_3CN, 0°C to rt, 1 h, **6** (91%); f : Ph_3P, Et_3N, NaI, CH_3CN, 85°C, 15 h, **7** (60%); g : $NaN(SiMe_3)_2$, THF, + $OHC(CH_2)_3COOMe$, -100°C to rt, **8** (80%); h : TsOH (0,05 equiv), THF/H_2O, 10 min, **2** (quant).

In scheme **II**, the *t*-butyldiphenylsilyl ether of 3-butynol was homologated with ethylene oxide to monoprotected diol **9** in 70% yield.[16] Selective reduction of the triple bond over P-2 nickel[17] quantitatively provided the *cis* ethylenic monoprotected diol **10** which was converted into the phosphonium salt **12** in 89% yield. The corresponding ylid was condensed under *cis*-Wittig reaction conditions with propanal leading to the silyl ether of *Z,Z*-3,6-nonadienol **13** in 65% yield. Fluoride deprotection[18] furnished alcohol **14** followed by successive conversion under mild conditions to the bromide **15** (96%) and to phosphonium salt **16** (92%). Wittig reaction of the corresponding ylid of **3** at low temperature with aldehyde **2**, thoroughly dried by azeotropic distillation of benzene, afforded the methyl ester of EPA **1b**. Saponification with LiOH gave the pure natural EPA **1a**.[19]

Scheme II



a : BuLi, ethylene oxide, -70°C, Et_2O/THF/HMPA, **9** (70%); b : $Ni(OAc)_2$, $NaBH_4$, H_2, ethanol, **10** (100%); c : Ph_3P/CBr_4, CH_2Cl_2, 0°C to rt, **11** (94%); d : Ph_3P, CH_3CN, 85°C, 15 h, **12** (95%); e : $NaN(SiMe_3)_2$, THF, + propanal, -100°C to rt, **13** (65%); f: NBu_4F, THF, **14** (70%); g : Ph_3PBr_2, pyridine, CH_3CN, 0°C to rt, 1 h, **15** (96%); h : Ph_3P, CH_3CN, 85°C, 15 h, **3** (92%); i : $NaN(SiMe_3)_2$, THF, +**2**, -100°C to rt, **1b** (50%); j : LiOH, THF, rt, 15 h, **1a** (92 %).

NMR data of methyl EPA **1b** and EPA **1a**[20] are in agreement with those reported[21] for natural EPA isolated from cod fish oil.

This total synthesis of EPA by sequential elaboration of double bonds will allow the synthseses of other kinds of PUFA like docosahexaenoic acid (DHA). A strategy based on the versatile ester acetal **4** should give both lipophilic and carboxylic parts of the PUFA's.

References and notes

1. Weaver, B.J.; Holob, B.J. *Progress in Food and Nutrition Science* **1988**, *12*, 111.

2. (a) Fincham, J.E.; Gouws, E.; Woodroof, C.W.; Van Wyk, M.J.; Kruger, M.; Smuts, C.M.; Van Jaarsveld, P.J.; Taljaard, J.J.F.; Schall, R.; Strauss, J.A. de W.; Benadé, A.J.S. *Arteriosclerosis and Thrombosis* **1991**, *11*, 719.
   (b) Dyerberg, J.; Bang, H.O.; Stoffersen, E.; Moncada, S.; Vane, J.R. *The Lancet* **1978**, *80*, 117.
   (c) Dyerberg, J. *Nutrition Reviews* **1986**, *44*, 125.

3. Kremer, J.M.; Lawrence, D.A.; Jubiz, W.; Digiacomo, R.; Rynes, R.; Bartholomew, L.E.; Sherman, M. *Arthritis and Rheumatism* **1990**, *33*, 810.

4. Kher, V.; Barcelli, U.; Weiss, M.; Gallon, L.; Pajel, P.; Laskarzewski, P.; Pollak, V.E. *Prostaglandins Leukotrienes Med.* **1986**, *22*, 323.

5. Salmon, J.A.; Terano, T.; *NATO ASI Ser., Ser. A* **1987**, *131*, 131.

6. Rhodes, E.L.; *Br. J. Clin. Pract.* **1984**, *38*, 115.

7. (a) Dinarello, C.A.; Endres, S. *UCLA Symp. Mol. Cell. Biol., New Ser.* **1989**, *100*, 201.
   (b) Das, U.N. *Nutrition* **1990**, *6*, 429.

8. (a) Sanders, T.A.B. : The Importance of Eicosapentaenoic and Docosahexaenoic Acids. In *Role Fats Hum. Nutr.*; Padley, F.B.; Podmore, J.H. Eds.: Chichester , UK; **1985**, 101-16.
   (b) Beloludtsev Y.Y.; Demin, PM.; Myyagkova, G.I.; Zabolotskii, D.A.; Evstigneeva, R.P. *Bioorg. Khim.* **1988**, *14*, 100. *Chem. Abs.* **1989**, *109*, 110069f.

9. Carvalho, J.F.; Prestwich, G.D. *J. Org. Chem.* **1984**, *49*, 1251.

10. Pierrot, M.; El Idrissi, M.; Santelli, M. *Tetrahedron Lett.* **1989**, *30*, 461.

11. Methyl 3,3-diisopropoxypropanoate : ^{1}H NMR δ 4.99 (1H, t, *J* = 6.0 Hz), 3.80 (2H, sept, *J* = 6.1 Hz), 3.65 (3H,s), 2.62 (2H, d, *J* = 6.0 Hz), 1.13 (6H, d, *J* = 6.1 Hz), 1.08 (6H, d, *J* = 6.01 Hz); ^{13}C NMR δ 170.1 (C), 97.1 (CH), 68.5 (2CH), 51.4 (CH_3), 41.3 (CH_2), 23.2 ($2CH_3$), 22.2 ($2CH_3$). Malonaldehyde bis(diisopropylacetal) has not been identified.

12. Sandri, J.; Viala, J. *Synthetic Communications* (submitted for publication).

13. (a) Miller, R.D.; Mckean, D.R. *Tetrahedron Lett.* **1982**, *23*, 323.
   (b) Wohl, R.A. *Synthesis* **1974**, 38.

14. (6-isopropoxy-3,5-hexadienyl)triphenylphosphonium bromide : ^{1}H NMR δ 7.85-7.60 (15H, m), 6.31-4.70 (4H, m), 3.88 (1H, sept, *J* = 6.1 Hz), 3.70-3.57 (2H, m), 2.48-2.39 (2H, m), 1.12 (6H, d, *J* = 6.1 Hz); ^{13}C NMR δ 146.3 (CH), 134.8-130.0 (15C arom), 127.8 (CH), 123.3 (CH), 122.5 (CH, d, J_{cccp} = 15 Hz), 117.5 (CH_2, d, J_{cp} = 85 Hz), 74.7 (CH), 22.5 (CH_2, d, J_{ccp} = 48 Hz), 21.0 ($2CH_3$).

15. Viala, J.; Munier, P.; Santelli, M. *Tetrahedron* **1991**, *47*, 3347.

16. Delorme, D.; Girard, Y.; Rokach, J. *J. Org. Chem.* **1989**, *54*, 3635.

17. Brown, C.A.; Ahuja, V.K. *J. Chem. Soc.; Chem. Commun.* **1973**, 553.

18. Labelle, M.; Falgueyret, J.P.; Riendeau, D.; Rokach, J. *Tetrahedron* **1990**, *46*, 6301.

19. All compounds show correct mass spectra or elemental anlyses. NMR ^{1}H and ^{13}C are respectively recorded at 200 and 50.312 MHz in $CDCl_3$. Key compounds are described below.

4 : ^{1}H NMR δ 5.61-5.54 (2H, m), 4.51 (1H, t, J = 5.5 Hz), 3.80 (2H, sept, J = 6.1 Hz), 3.62 (3H, s), 3.07 (2H, d, J = 5.3 Hz), 2.29 (2H, dd, J = 5.5, 5.2 Hz), 1.13 (6H, d, J = 6.1 Hz), 1.08 (6H, d, J = 6.1 Hz) ; ^{13}C NMR δ 172.1 (C), 127.7 (CH), 123.0 (CH), 99.4 (CH), 67.9 (2CH), 51.6 (CH_3), 33.9 (CH_2), 32.9 (CH_2), 23.2 ($2CH_3$), 22.4 ($2CH_3$).

7 : ^{1}H NMR δ 7.85-7.66 (15H, m), 5.80-5.36 (2H, m), 4.42 (1H, t, J = 5.4 Hz), 3.76-3.59 (4H, m), 2.43-2.27 (2H, m), 2.06 (2H, m), 1.10 (6H, d, J = 6.1 Hz), 1.03 (6H, d, J = 6.1 Hz) ; ^{13}C NMR δ 135.2 (3CH, d, J = 3 Hz), 133.6 (6CH, d, J = 10 Hz), 130.6 (6CH, d, j = 13 Hz), 128.3 (CH, d, J_{cccp} = 16 Hz), 127.1 (CH, d, J_{ccccp} = 1 Hz), 117.9 (CH_2, d, J_{cp} = 93 Hz), 99.2 (CH), 68.4 (2CH), 34.2 (CH_2), 23.2 (2 CH_3), 23.0 (CH_2, d, J_{ccp} = 49 Hz), 22.5 (2 CH_3).

8 ^{1}H NMR δ 5.41-5.30 (4H, m), 4.51 (1H, t, J = 5.5 Hz), 3.83 (2H, sept, J = 6.1 Hz), 3.62 (3H, s), 2.74 (2H, br t, J = 5.1 Hz), 2.32 (2H, dd, J = 4.9, 5.5 Hz), 2.28 (2H, t, J = 7.5 Hz), 2.06 (2H, td, J = 7.1, 6.1 Hz), 1.66 (2H, tt, J = 7.1, 7.5 Hz), 1.15 (6H, d, J = 6.1 Hz), 1.10 (6H, d, J = 6.1 Hz) ; ^{13}C NMR δ 173.2 (C1), 129.9 (C9), 128.9 (C5 and C6), 124.6 (C8), 99.9 (C11), 67.9 (2C isopropyl), 51.5 (OCH_3), 33.8 (C10), 33.4 (C2), 26.6 (C4), 25.9 (C7), 24.8 (C3), 23.4 (2C isopropyl), 22.5 (2C isopropyl).

9 See ref. 14.

10 ^{1}H NMR δ 7.64-7.27 (10H, m), 5.65-5.25 (2H, m), 3.60 (2H, t, J = 6.7 Hz), 3.50 (2H, t, J = 6.3 Hz), 2.39-2.07 (4H, m), 0.98 (9H, s) ; ^{13}C NMR δ 135.6 (4CH arom), 133.9 (2C arom), 129.6 (2CH arom), 129.3 (CH), 127.7 (4CH arom), 127.2 (CH), 63.6 (CH_2), 62.2 (CH_2), 30.9 ($2CH_2$), 26.7 ($3CH_3$), 19.22 (C).

14 ^{1}H NMR δ 5.58-5.20 (4H, m), 3.61 (2H, t, J = 6.5 Hz), 2.77 (2H, Br t, J = 6.6 Hz), 2.31 (2H, td, J = 6.5, 6.9 Hz), 2.03 (2H, td, J = 7.5, 6.7 Hz), 0.93 (3H, t, J = 7.5 Hz) ; ^{13}C NMR δ 132.0 (CH), 131.0 (CH), 126.8 (CH), 125.4 (CH), 62.0 (CH_2), 30.6 (CH_2), 25.5 (CH_2), 20.5 (CH_2),14.2 (CH_3).

20. **1b** ^{1}H NMR δ 5.44-5.22 (10H, br s), 3.64 (3H,s), 2.88-2.68 (8H, m), 2.30 (2H, t, J = 7.5 Hz), 2.10-2.02 (4H, m), 1.76-1.60 (2H, m), 0.95 (3H, t, J = 7.5 Hz); ^{13}C NMR δ 173.9 (C) , 132.0 (CH), 128.9 (CH), 128.6 (CH), 128.3 (CH), 128.2 (2CH), 128.1 (2CH), 127.7 (CH), 127.0 (CH), 51.4 (CH_3), 33.40 (CH_2), 26.5 (CH_2), 25.6 (CH_2), 25.5 (CH_2), 24.8 (CH_2), 20.6 (CH_2), 14.3 (CH_3).

1a ^{1}H NMR δ 5.46-5.28 (10H, br s), 2.89-2.72 (8H, m) 2.34 (2H, t, J = 7.5 Hz) 2.17-1.99 (4H, m), 1.77-1.62 (2H, m), 0.96(3H, t, J = 7.5 Hz); ^{13}C NMR δ 180.4 (C), 132.0 (CH), 129.0 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 128.2 (2CH), 128.1 (CH), 127.7 (CH), 127.0 (CH), 33.5 (CH_2), 26.5 (CH_2), 25.6 ($3CH_2$), 25.5 (CH_2), 24.5 (CH_2), 20.6 (CH_2), 14.3 (CH_3).

21. Corey, E.J. ; Wright, S.W. *J. Org. Chem.*, **1988**, *53*, 5980.

(Received in France 27 April 1992)