

SHORT, STEREOCONTROLLED SYNTHESSES OF IRREVERSIBLE EICOSANOID
 BIOSYNTHESIS INHIBITORS. 5, 6-, 8, 9-, AND 11, 12-DEHYDROARACHIDONIC ACID

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Summary: 5, 6- and 11, 12-dehydroarachidonic acids (1 and 3), which irreversibly inhibit leukotriene and prostaglandin biosynthesis, respectively, have been synthesized, along with the 8, 9-isomer (2), by novel and direct routes.

Monoacetylenic dehydroarachidonic acids (DHA's) are useful as irreversible inhibitors of the lipoxygenase enzymes involved in the first step of eicosanoid biosynthesis from arachidonic acid.^{1, 2} We describe herein especially short synthetic routes to 5, 6-, 8, 9-, and 11, 12-dehydroarachidonic acids (1, 2, and 3) which depend upon two new methods for construction of carbon carbon bonds within the unit (Z)-RC≡CCH₂CH=CHR.

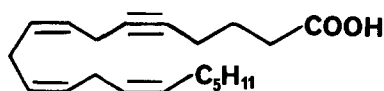
5, 6-DHA (1). 1, 1-Di-n-butyl-1-stanna-2, 5-cyclohexadiene (4),^{3, 4} in ether was allowed to react at -78° with 1 equiv of n-BuLi for 1 hr to generate (1Z, 4Z)-1-lithio-5-tributylstannyl-1, 4-pentadiene⁵ which was then treated sequentially with 1.5 equiv of CuI.Me₂S (-40°, 1 hr) and 0.76 equiv of 3-iodo-1, 2-octadiene⁶ (-45°, 16 hr; -45° to 23°, 1 hr). Extractive isolation afforded (1Z, 4Z)-1-tributylstannyltrideca-1, 4-dien-7-yne 5, R_f 0.47 (pet ether)⁷ which upon treatment with 1.5 equiv of I₂ in CH₂Cl₂ at -78° gave (1Z, 4Z)-1-iodotrideca-1, 4-dien-7-yne 6, R_f 0.24 (pet ether) (73% overall for two steps).^{8, 9} The triple bond in 6 was reduced by exposure to 1.1 equiv of disiamylborane in THF (-40°, 2 hr; -20°, 4 hr; 0°, 1 hr) followed by excess HOAc (25°, 4 hr) to give 82% yield of (1Z, 4Z, 7Z)-1-iodotridecatriene which was converted to the lithio derivative (2 equiv t-BuLi 1:3 ether - THF at -110°, 0.4 hr and -110° to -80°, 0.5 hr) and thence to the copper reagent (1.5 equiv CuI.Me₂S, -30°, 1 hr) which was coupled with methyl 5-iodo-5, 6-heptadienoate⁹ in THF-ether at -50°, 20 hr and -50° to +25° (0.5 hr) to afford after chromatography the methyl ester of 1, R_f 0.65 (1:3 ether-pet ether) which was identical with an authentic sample,¹⁰ and which was saponified to give 5, 6-DHA (1) (15 equiv LiOH in 1:1 THF-H₂O, 25°, 14 hr, 100% yield).

8, 9-DHA (2). The methyl ester of 2 was assembled from (1Z, 4Z)-1-iododeca-1, 4-diene (8) and methyl (5Z)-8-iodo-5, 8, 9-decatrienoate (9), paralleling the coupling of dihydro 6 with 7 as described above. Treatment of 8¹¹ with 2 equiv of t-BuLi at -95° for 0.5 hr followed by reaction with 1.5 equiv of CuI in Me₂S-THF and coupling with 1 equiv of iodo allene 9 in THF at -50° for 20 hr provided after chromatography on silica gel 72% of the methyl ester of 2, R_f 0.57 (3:1 pet ether-ether) as compared to R_f 0.40 for 9 with the same solvent. The allene 9 was synthesized by coupling of 5-trimethylsilyl-3-pentynylidene-triphenylphosphorane¹² and methyl 4-formylbutyrate¹³ in THF-HMPA at -78° for 0.5 hr and -78° to 40° for 2 hr to give methyl (5Z)-10-trimethylsilyldeca-5-ene-8-ynoate (85% yield, R_f 0.56 in 3:1 pet ether-ether) followed by iodination with 1 equiv of I₂ and 1 equiv of AgBF₄ in CH₂Cl₂ (70% yield).

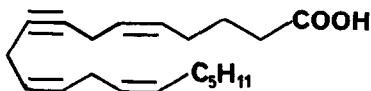
The methyl ester of 2 prepared in this way was identical with material prepared by an alternative route.² Saponification as described above for 1 gave 2 quantitatively.

11,12-DHA (3). (1Z, 4Z)-1-lithio-5-tributylstannyl-1,4-pentadiene generated from 4 as described above was treated with 3-methyl-3-methoxybutynylcopper¹⁴ in THF at -78° for 0.5 hr and then with methyl 4-iodoorthobutyrate (bp 65° at 0.4 Torr)¹⁵ in THF and the reaction was allowed to proceed at -20° for 4 hr; 4°, 2 hr; and 23°, 3 hr to afford after chromatography on basic alumina the ortho ester 10 (58%). Iodination of 10 (1 equiv I₂, 1.5 equiv of pyridine at -78° to 0° in CH₂Cl₂) gave iodo diene 11 (99%); *R_f* values (3:1 pet ether-ether using Et₃N deactivated plates) 0.6 for 10 and 0.47 for 11. Conversion of 11 to the vinylcopper reagent and coupling with (5Z)-3-iodoundeca-1,2,5-triene¹⁶ (12) in THF at -50° for 7 hr and -50° to 23° for 2 hr afforded 65% of the methyl ester of 3,² converted to 3 by saponification as above (100% yield).

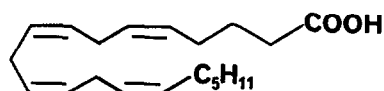
The syntheses of 1, 2, and 3 described here demonstrate the power of the two new methods which are used to form the key carbon carbon bonds: (1) the use of 3-iodo allenes and (Z)-vinyl Cu(I) reagents to form (Z)-CH=CH-CH₂C≡C- units with position and stereospecificity, and (2) the use of stannacyclohexadiene 4 as an equivalent of (Z,Z)-LiCH=CHCH₂CH=CHLi.¹⁷



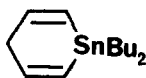
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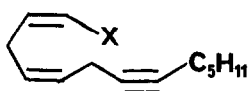
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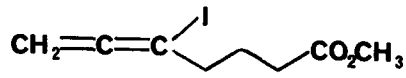
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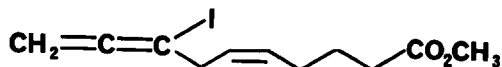
5, X = SnBu₃
6, X = I



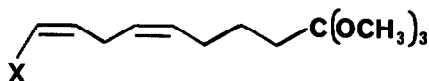
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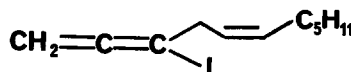
8



9

10, X = SnBu₃

11, X = I



12

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- Corey, E. J.; Park, H.; *J. Am. Chem. Soc.*, 1982, **104**, 000.
- Corey, E. J.; Munroe, J. E.; *J. Am. Chem. Soc.*, 1982, **104**, 000.
- Ash, A. J. III; Shu, P.; *J. Am. Chem. Soc.*, 1971, **93**, 1804.
- Jutzi, P.; Baumgartner, J.; *J. Organomet. Chem.*, 1978, **148**, 257.
- Reactions reported herein were conducted under an atmosphere of argon. Satisfactory infrared, proton magnetic resonance and mass spectral data were obtained using chromatographically purified and homogeneous samples of each synthetic intermediate. Unless otherwise indicated, products were isolated as colorless oils. All reaction temperatures are in °C.
- 3-Iodo-1,2-octadiene (*R_f* 0.60, pet ether) was prepared from 1-lithiohept-1-yne by the sequence (1) alkylation in THF containing 1 equiv of HMPA⁸ with trimethylsilylmethyl chloride and (2) reaction with iodine - silver trifluoroacetate in CH₂Cl₂ at -78° followed by filtration and passage through silica gel.
- All *R_f* values were obtained by thin layer chromatography on silica gel using the solvent indicated.
- Solvent abbreviations: THF, tetrahydrofuran; HMPA, hexamethylphosphorictriamide.
- Corey, E. J.; Kang, J.; *J. Am. Chem. Soc.*, 1981, **103**, 4618. Methyl 5-iodo-5,6-heptadienoate was synthesized in 80% yield by treatment of methyl 7-trimethylsilyl-5-heptynoate with 1 equiv of iodine and 1 equiv of silver trifluoroacetate in CH₂Cl₂ at -78° followed by filtration and passage through silica gel, *R_f* 0.41 (3:1 ether-pet ether).

10. Corey, E. J.; Park, H.; Barton, A.; Nil, Y.; Tetrahedron Lett., 1980, 21, 4243.
11. The iodide 8 was synthesized from 1,4-decadiyne [Rachlin, A. I.; Wasylw, N.; Goldberg, M. W.; J. Org. Chem., 1961, 26, 2688] by terminal iodination (98% yield) (1 equiv ethylmagnesium bromide in ether at -30° followed by 1.2 equiv of I_2) and cis reduction (2.3 equiv of disiamylborane in THF at 0° for 4 hr and 23° for 1.5 hr followed by treatment with 20 equiv of HOAC at 23° for 12 hr) (80% yield).
12. This ylide was generated from the corresponding phosphonium salt which was prepared by the sequence (1) $Me_3SiCH_2C\equiv CH + Me_3SiCH_2C\equiv CCH_2CH_2OH$ (1 equiv n-BuLi, THF, -45°; 1 equiv Me_3Al ; 2 equiv of ethylene oxide at 4° for 16 hr (56%)); (2) alcohol to bromide (1.1 equiv of triphenylphosphone, 1.5 equiv CBr_4 , 2 equiv pyridine in CH_2Cl_2 (86%)); (3) bromide to triphenylphosphonium salt (1.5 equiv triphenylphosphine, acetonitrile at reflux for 24 hr in the presence of 1 equiv of powdered $CaCO_3$ (88%)).
13. Prepared by ozonolysis of 1-methoxycyclopentene at -78° in CH_3OH using Me_2S reduction, aqueous extractive isolation and distillation; see also Corey, E. J.; Niwa, H.; Knolle, J.; J. Am. Chem. Soc., 1978, 100, 1942.
14. Corey, E. J.; Floyd, D.; Lipshutz, B.; J. Org. Chem., 1978, 43, 3418.
15. Prepared in 80% yield from 4-iodobutyronitrile (bp 72-75° at 8 Torr) by reaction with 1.15 equiv of acetyl chloride in methanol at 4° for 24 hr to form the crystalline imido ester hydrochloride and further reaction with 1:1 methanol-ether at 23° and distillation.
16. The iodo allene 12 was synthesized from 5-trimethylsilyl-3-pentynylidinetriphenylphosphorane (made as described above) by the sequence: (1) reaction with 1.25 equiv of 1-hexanal in THF-HMPA at -78° in 0.5 hr and -78° to 23° for 3 hr to form (5Z)-1-trimethylsilylundeca-2-yn-5-ene; and (2) iodination as described for 7 and 9.
17. This research was assisted financially by a grant from the National Science Foundation.

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