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A NEW ROUTE TO Z-DISUBSTITUTED OLEFINS. A SIMPLE SYNTHESIS OF POLYUNSATURATED FATTY ACIDS BY REITERATIVE COUPLING

E. J. Corey and Thomas M. Eckrich
Department of Chemistry, Harvard University, Cambridge, MA 02138

Summary: A new synthesis of 5,6-dehydroarachidonic acid **(8)** is described which illustrates the first stereospecific, iterative and non-acetylenic route to this type of polyunsaturated fatty acid.

The foregoing letter describes a general and stereospecific synthetic route to a wide variety of *cis*-1,2-disubstituted cyclopropanes which takes advantage of the ready availabiity of the versatile *Z*-vinylstannane **1**, prepared in a single step by sequential reaction of propargyl alcohol with lithium tetrahydroaluminate and tri-*n*-butyltin triflate.[1] The intermediate **1** is also very useful for the synthesis of a wide range of *Z*-olefins and polyolefins. In this paper that utility is illustrated by application to the synthesis of 5,6-dehydroarachidonic acid **(8)**, a useful irreversible inhibitor of leukotriene biosynthesis.[2] The synthesis documents the effectiveness of two new synthetic tactics for the synthesis of important *Z*-polyolefins: (1) *cis* carbostannylation using tributyltin triflate and (2) iterative coupling based on the difunctional intermediate **1**.

Reaction of di-*n*-pentylcopper lithium with 2.2 equiv of acetylene in ether at -30° for 20 min generated bis[*Z*-1-heptenyl]copper lithium[3] which upon reaction *in situ* with tri-*n*-butyltin triflate (1 equiv per heptenyl group) afforded *Z*-1-heptenyltri-*n*-butylstannane **(2)** in 90% yield after quenching and extractive isolation.[4] The tri-*n*-butyltin group of **2** was cleanly replaced by lithium (1 equiv of *n*-butyllithium in tetrahydrofuran (THF) at -40° for 1 hr, yellow solution); and the resulting vinyllithium reagent was treated successively with 1 equiv of anhydrous magnesium bromide (in dry ether at -40° with stirring for 1 hr), 0.005 equiv of Li_2CuCl_4 at -78°,[5] and then at -78° with 1.1 equiv of the *Z*-acetate **3** (b.p. 124° at 0.25 mm, obtained in 95% yield from 1 and 2 equiv of acetic anhydride - 8 equiv of pyridine at 23° for 4 hr). After 6 hr at -35° the reaction mixture was quenched with NH_3-NH_4Cl-H_2O (pH 8) to afford after extractive isolation, filtration through a plug of basic alumina with 2% triethylamine in hexane as solvent, and concentration *in vacuo* the desired coupling product **4** in 89% yield.[6,7] The *Z*-vinylstannane **4** was then coupled to acetate **2** by an identical procedure to give after isolation as above the *Z*,*Z*,*Z*-triene **5** in 84% yield. Lithium-tin exchange of **5** with *n*-butyllithium in THF (2 hr at -40°) and successive reaction with 1.1 equiv of cuprous cyanide (-40°, 1 hr) and 1 equiv of bromo allene **6**[2b,8] (-35°, 10 hr) afforded after extractive isolation and chromatography on silica gel in the presence of triethylamine the bicyclic ortho ester **7** in 84% yield. Exposure of **7** to 1.1 equiv of sodium bisulfate in dimethoxyethane-water at 0° for 5 min followed by lithium hydroxide for 30 min at 23° provided 5,6-dehydroarachidonic acid (**8**)[2] in 98% yield, and after esterification with diazomethane the corresponding methyl ester,[2] each of which was identical with an authentic sample.

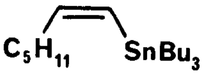
The procedures which follow provide details for the syntheses of tri-*n*-butyltin triflate, *Z*-vinylstannane **1**, and coupling product **4**.

Tri-n-butyltin Triflate. Trifluoromethanesulfonic anhydride (7.34 g, 26 mmol) was added over 15 min with stirring to bis(tri-*n*-butyltin) oxide (14.9 g, 25 mmol; exothermic reaction, red color develops). After 1 hr the mixture was distilled (155-167° at 0.08 mm) to afford 20.43 g (93%) of hygroscopic solid, mp 41-43°.

Synthesis of 1 and 3. To a stirred mixture of lithium tetrahydroaluminate (28.45 g, 0.75 mol) and 2.5 l of THF (dried over 4Å molecular sieves) under N_2 at 0° was added over 1.5 hr propargyl alcohol (84.1 g, 1.5 mol). After an additional 30 min at 0° the solution was warmed to 23° and stirred for 23 hr. The resulting slurry was cooled to -70° and a solution of tri-*n*-butyltin triflate (0.43 mol) in 500 ml of ether was added over 45 min. After 4.5 hr at -70°, the mixture was treated sequentially with gaseous ammonia (5 l.), 400 ml of methanol, 250 ml of saturated aqueous NH_3-NH_4Cl (pH 8), and 500 ml of hexane. The product was obtained from the hexane-THF by filtration through Celite, extractive isolation (hexane), drying and concentration under reduced

1 R = H

3 R = $COCH_3$



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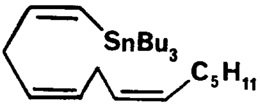

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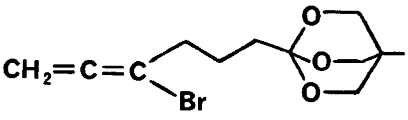

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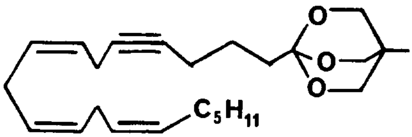

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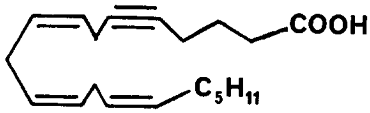

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pressure. The oil thus obtained was dissolved in 1 l. of hexane and the solution was saturated with gaseous NH_3, filtered and concentrated to yield 118.5 g (80%) of 1 as a colorless oil.

Acetylation of 1 (118.5 g, 0.34 mol) in 220 ml of dry pyridine at 0° with acetic anhydride (65 ml, 0.68 mol) at 0° for 30 min and 23° for 4-5 hr, pouring the resulting mixture into 2 l. of 1:1 water-hexane and extractive isolation (hexane) gave 126.0 g(95%) of acetate 3 as a colorless oil; IR (film) 1744, 1603 cm.$^{-1}$; pmr ($CDCl_3$) (δ): 6.63 (dt, J = 12.9, 6.3Hz, 1H); 6.19 (d, J = 12.9Hz, 1H); 4.50 (d, J = 6.3Hz, 1H); 2.06 (s, 3H); 0.75-1.75 (m, 27H).

Synthesis of **4**. A solution of 2 (10.71 g, 27.7 mmol) in 30 ml of THF was treated at -70° over 5 min with *n*-butyllithium (27.7 mmol, hexane solution). The green solution was stirred for 1 hr at -40° and then treated over 5 min at -70° with 30 mmol of ethereal magnesium bromide (from dibromoethane and magnesium turnings in 25 ml of ether). The slurry was stirred at -40 to -30° for 1 hr and then treated successively at -70° with 3 (30.5 mmol, 11.85 g in 30 ml of THF) over

15 min and Li_2CuCl_4[5] (0.15 mmol in 3.0 ml of THF). The bright yellow slurry was stirred at -40 to -30° for 6 hr, then warmed to -15° and poured into 150 ml of aqueous NH_4Cl-NH_3 buffer (pH 8). The crude product (23.62 g) was isolated by extractive workup followed by filtration through a plug of basic alumina (2% NEt_3 in hexane as eluant). Distillation (129-136°/0.08 mm Hg) gave 10.45 g (89%) of **4** as a colorless liquid, homogeneous by tlc (R_f = 0.67, pet. ether). IR (film) 1618, 1596 cm.$^{-1}$; pmr ($CDCl_3$) (δ): 6.45 (dt, J = 12.19, 6.29Hz, 1H); 5.83 (d, J = 12.19Hz, 1H); 5.44 (m, 1H); 5.33 (m, 1H); 2.79 (dd, 6.29, 6.59Hz, 2H); 2.05 (m, 2H); 0.75-1.72 (m, 27H).[9]

References and Notes

1. E. J. Corey and T. M. Eckrich, Tetrahedron Letters, preceding paper.

2. (a) E. J. Corey and J. E. Munroe, J. Am. Chem. Soc, 104, 1752 (1982);
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3. A. Alexakis, G. Cahiez and J. F. Normant, Tetrahedron, 36, 1961 (1980) and refs. therein cited.

4. The corresponding reaction of n-$C_5H_{11}Cu \bullet MgBr_2$ with acetylene, followed by stannylation afforded 2 in slightly lower yield (80%). H. Westmijze, J. Meijer, H. J. T. Bos, and P. Vermeer, Rec. Trav. Chim., 95, 299, 304 (1976). Z-1-Butenyltri-n-butylstannane was similarly prepared in 79% yield.

5. A red solution of Li_2CuCl_4 in dry THF was prepared from 2 LiCl and 1 $CuCl_2$.

6. Satisfactory spectroscopic data (pmr, ir, mass) were obtained using chromatographically purified samples of each reaction product. All organometallic reactions were conducted in an atmosphere of nitrogen or argon.

7. For Li_2CuCl_4-catalyzed coupling reactions see G. Fouquet and M. Schlosser, Angew. Chem. Int. Ed., 13, 82 (1974).

8. (a) E. J. Corey and N. Raju, Tetrahedron Letters, 24, 5571 (1983);
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