Stereospecific Synthesis of Columbinic Acid

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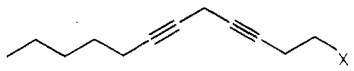
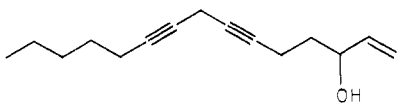
Columbinic acid (5(*E*), 9(*Z*), 12(*Z*)-octadecatrienoic acid, also known as Δ^5-*trans*-linoleic acid or ranunucleic acid[1]), has been shown to have interesting effects on essential fatty acid deficient rats[2] and is therefore theorized to have an unusual metabolic fate compared to other polyunsaturated fatty acids. Quantities of this unique fatty acid have previously been available only by extracting natural sources.[1-6] The short synthesis described below can produce both radioactively labeled and gram quantities of this fatty acid, which should aid in further understanding of its metabolism.[7]

Reaction of 1-bromo-2-octyne with the magnesium bromide salt of 2-(4-pentynyloxy)-2*H*-pyran[8] with CuCN catalysis led to the THP ether **1** in 77% yield. Removal



1, X = CH_2OTHP
2, X = CH_2OH
3, X = CHO



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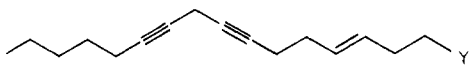
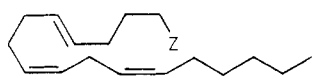


5, Y = CO_2Et
6, Y = CH_2OH



7, Z = OH
8, Z = OSO_2CH_3
9, Z = CO_2H

of the THP blocking group was carried out in acidic methanol for 16 h at 25 °C and led to the corresponding alcohol **2** in 96% yield. Oxidation by 1.5 equiv of pyridinium chlorochromate[9] in CH_2Cl_2 for 2 h proceeded in 78% yield to the aldehyde **3**, which was then dissolved in ether and 1.1 equiv of vinyl magnesium bromide were added. This led very cleanly to a 98% yield of the allylic alcohol **4**.[10] Acid-catalyzed reaction of **4** with triethyl orthoacetate and subsequent Claisen rearrangement in the manner of Johnson et al.[11] was carried out in one step with 7 equiv of triethyl orthoacetate and 0.07 equiv of propionic acid with heating to 138 °C for 1 h and resulted in ethyl 9,10,12,13-tetradehydro-1-norcolumbinate (**5**) in 91% yield. The trans nature of the newly formed double bond (evident from a consideration of the concerted mechanism involved) was confirmed by the infrared spectrum, which showed only a strong absorbance at 965 cm^{-1} and no absorbances between 675 and 700 cm^{-1}, as well as argentation thin-layer chromatography, which showed only one spot. Treatment of ester **5** with 1.5 equiv of $LiAlH_4$ in ether for 1 h afforded a 92% yield of the primary alcohol **6**, in which the triple bonds were reduced with hydrogen and Lindlar's catalyst in 94% yield. The reduced alcohol **7** was treated with methanesulfonyl chloride in pyridine to give the mesylate **8** in 97% yield, which was then converted to the title acid with KCN (or $K^{14}CN$), followed by hydrolysis with gaseous HCl in methanol and then KOH in methanol/water.[12]

Metabolic studies of this fatty acid in various biological systems will be reported in due course.

Experimental Section[13]

2-(4,7-Tridecadiynyloxy)tetrahydro-2*H*-pyran (1). A solution of ethyl magnesium bromide was prepared from 2.0 g (83 mmol) of Mg turnings and excess bromoethane in 50 mL of THF. A solution of 13.9 g (82 mmol) of 2-(4-pentynyloxy)tetrahydro-2*H*-pyran[14] in 10 mL of THF was then added dropwise with cooling over 30 min. CuCN (184 mg) was then added as catalyst and the solution refluxed for 30 min. After being cooled to 25 °C, a solution of 10.1 g (53.3 mmol) of 1-bromo-2-octyne[15] in 20 mL of THF was then added and the reaction mixture stirred for 14 h at 25 °C. The solution was then poured into 150 mL of 1 N H_2SO_4 and extracted with ether (3 × 100 mL). The combined ether layers were washed with 100 mL of saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and evaporated. The residue was distilled, giving 11.36 g (77%) of **1**: bp 140–142 °C (1.1 mmHg); IR 2940 (s), 1470 (m), 1315 (m), 1140 (s), 1120 (s), 1060 (s), 1035 (s) cm^{-1}; ^1H NMR δ 0.95 (3 H, br t), 1.2–1.8 (12 H, m), 1.9–2.3 (4 H, m), 3.05 (2 H, pentet, J = 1.5 Hz), 3.2–3.9 (4 H, m), 4.5 (1 H, br t).

4,7-Tridecadiyn-1-ol (2). An 11.36-g (41 mmol) sample of **1** was dissolved in a solution of 0.5 mL of concentrated H_2SO_4 in 80 mL of methanol and stirred for 16 h at 25 °C. Water (100 mL) was added and most of the methanol evaporated. The residue was extracted with ether (3 × 100 mL), and the combined ether layers were washed with 100 mL of saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and evaporated. The residue was distilled at 128–130 °C (0.9 mmHg) and weighed 7.56 g (96%): IR 3350 (br, s), 2970 (s), 1210 (s), 1050 (s) cm^{-1}; ^1H NMR δ 0.95 (3 H, br t), 1.2–1.6 (6 H, m), 1.7 (2 H, ?t or pentet), 1.9–2.2 (4 H, m), 2.25 (1 H, br s), 3.05 (2 H, pentet, J = 1.5 Hz), 3.78 (2 H, t).

4,7-Tridecadiyn-1-al (3). A solution of 9.82 g (51 mmol) of alcohol **2** in 10 mL of CH_2Cl_2 was poured into a suspension of

(1) Freiman, R. E.; Markman, A. L. *Khim. Prir. Soedin.* **1970**, *6*, 167.
(2) Houtsmuller, U. M. T. *Prog. Lipid Res.* **1981**, *20*, 889.
(3) Bagby, M. O.; Smith, C. R., Jr.; Mikolajczak, K. L.; Wolff, I. A. *Biochemistry* **1962**, *1*, 632.
(4) Kaufman, H. P.; Barve, J. *Fette, Seifen, Anstrichm.* **1965**, *67*, 14.
(5) Rankov, D.; Popov, A.; Panov, P.; Deleva, M. *J. Am. Oil Chem. Soc.* **1971**, *48*, 700.
(6) Wu, J.; Ghosh, A.; Beal, J. L. *J. Nat. Prod.* **1980**, *43*, 360.
(7) For a synthesis of a different 18-carbon polyunsaturated fatty acid containing a trans double bond (incorporated by a more routine method (e.g., Wittig reaction and Na/NH_3 reduction of an acetylene)), see: Klok, R.; Mohlmann, W. M. M.; van der Wolf, L.; Pabon, H. J. J. *Recl. Trav. Chim. Pays-Bas* **1980**, *99*, 132.
(8) Osbond, J. M.; Philpott, P. G.; Wickens, J. C. *J. Chem. Soc.* **1961**, 2779.
(9) Corey, E. J.; Suggs, E. W. *Tetrahedron Lett.* **1975**, 2647.
(10) This alcohol was also prepared in somewhat lower yield by reaction of acrolein with the Grignard derivative of 1-bromo-4,6-dodecadiyne.
(11) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Falkner, D. J.; Peterson, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.
(12) For experimental details of the conversion of alcohol **6** to acid **9**, see: Sprecher, H. *Lipids* **1971**, *6*, 889. Sprecher, H. *Prog. Chem. Fats Other Lipids* **1978**, *15*, 219.
(13) Infrared spectra were recorded on a Perkin-Elmer 710B instrument as neat films. Nuclear magnetic resonance spectra were obtained on a Varian T-60 instrument with $CDCl_3$ as solvent and Me_4Si as internal standard. Chemical shifts are given in ppm downfield from Me_4Si and relative areas, multiplicities, and coupling constants are given in parentheses. All new compounds prepared showed satisfactory IR, NMR, and mass spectra.
(14) Simply prepared in 96% yield by adding 1 drop of 12 N HCl to a cooled mixture of 4-pentyn-1-ol and dihydropyran, stirring for 4 h, adding Na_2CO_3 solid, and distilling. See also: Ward, J. P.; van Dorp, D. A. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 117.
(15) Lai, T. Y. *Bull. Soc. Chim. Fr.* **1933**, *53*, 1533.

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16.8 g (78 mmol) of pyridinium chlorochromate in 100 mL of CH_2Cl_2, and the mixture was stirred at 25 °C for 2 h. Ether (3 × 75 mL) was added and removed from the black residue and then filtered through a small column of Florosil. The filtrate was then washed with 100 mL of 0.1 N NaOH, dried over $MgSO_4$, filtered, evaporated, and distilled at 128–130 °C (0.8 mmHg), giving 7.67 g (79%) of **3**: IR 2940 (s), 1735 (s), 1320 (m), 1120 (m) cm^{-1}; ^1H NMR δ 0.95 (3 H, br t), 1.2–1.6 (6 H, m), 2.2–2.4 (4 H, m), 2.6 (2 H, br t), 3.05 (2 H, pentet, J = 1.5 Hz), 9.8 (1 H, br t).

6,9-Pentadecadiyn-1-en-3-ol (4). A solution of vinyl magnesium bromide (30 mL, 1 M in THF) was added with cooling to a solution of 4.68 g (24.6 mmol) of **3** in 20 mL of dry ether and the solution refluxed for 30 min. It was then poured into 80 mL of 1 N HCl and extracted with ether (3 × 100 mL), and the combined ether layers were washed with 100 mL of saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and evaporated, leaving 5.33 g (98%) of **4** (after drying at 1 mmHg for 1 h). This was used in the next reaction without further purification: IR 3400 (br s), 2940 (s), 1430 (m), 1310 (s), 1050 (m) cm^{-1}; ^1H NMR δ 0.90 (3 H, br t), 1.2–1.6 (6 H, m), 2.2–2.4 (6 H, m), 3.05 (2 H, pentet, J = 1.5 Hz), 4.25 (1 H, q), 5.0–6.2 (3 H, m, typical of vinyl group).

Ethyl 8,11-Heptadecadiyn-4(*E*)-enoate (5). A solution of 5.33 g (24.4 mmol) of **4** and 0.13 mL of propionic acid (1.74 mmol) in 30 mL of triethyl orthoacetate (164 mmol) was heated to 138 °C for 1 h with distillative removal of ethanol. The solution was poured into 100 mL of ether, washed with 100 mL of saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and evaporated. The excess triethyl orthoacetate was removed by distillation at 1 mmHg, and the residue was passed through a short column of silica gel. After removal of the solvent, the residue weighed 6.40 g (91%): IR 3050 (m), 2940 (s), 1740 (s), 1050 (s), 964 (s) cm^{-1}; ^1H NMR δ 0.97 (3 H, br t), 1.30 (3 H, t), 1.3–1.5 (6 H, m), 2.0–2.4 (8 H, m), 3.05 (2 H, pentet, J = 1.5 Hz), 4.15 (2 H, q), 5.46 (2 H, br s).

8,11-Heptadecadiyn-4(*E*)-en-1-ol (6). To a cooled solution of 6.40 g (22.2 mmol) of **5** in 50 mL of ether was added 1.01 g (26.6 mmol) of $LiAlH_4$ suspended in 20 mL of ether. The suspension was refluxed for 1 h and then the following were added in succession: 6 mL of ethyl acetate, 1 mL of methanol, and 100 mL of cold 1 N HCl. The material was extracted with ether (3 × 100 mL), and the combined ether layers were washed with 100 mL of saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and evaporated. The crude product was filtered through a small column of silica gel and activated charcoal, leaving 5.03 g of **6** (92%): IR 3400 (br s), 2940 (s), 1050 (s), 965 (s) cm^{-1}; ^1H NMR δ 0.93 (3 H, br t), 1.2–1.8 (8 H, m), 2.0–2.4 (8 H, m), 3.05 (2 H, pentet, J = 1.5 Hz), 3.68 (2 H, t), 5.50 (2 H, br s).

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Registry No. **1**, 87681-28-5; **2**, 87681-29-6; **3**, 87681-30-9; **4**, 87681-31-0; **5**, 87681-32-1; **6**, 87681-33-2; **7**, 87681-34-3; **8**, 87681-35-4; **9**, 2441-53-4; 2-(4-pentynyloxy)tetrahydro-2*H*-pyran, 62992-46-5; 1-bromo-2-octyne, 18495-27-7; vinyl bromide, 593-60-2; triethyl orthoacetate, 78-39-7.

Thermal Reactions of Stereoisomeric 1-Phenyl-1,3,5-heptatrienes

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An electrocyclic reaction potentially can give two stereoisomeric products, one via an orbital symmetry allowed route and a second via either a forbidden route or a symmetry-independent route. The allowed route is well established, and the $\Delta\Delta H^{\ddagger}$ between it and the other routes has been estimated for the cyclobutene–butadiene[2] and octatetraene–cyclooctatriene[3] cases. No example of a suitable hexatriene–cyclohexadiene case giving sufficient nonallowed product has been found as yet, so no estimate of $\Delta\Delta H^{\ddagger}$ for this system is available. We have prepared and studied three hexatrienes with substitution intended to enhance the visibility of the nonallowed reaction.

The basis for this rests on the following facts: (a) this electrocyclization is essentially irreversible, (b) the allowed reaction rate is virtually independent of trans substituents on terminal carbons,[4] and (c) a phenyl group in that position should enhance the forbidden reaction rate,[5] and also any diradical process.[6] A rough calculation for the $\Delta H^{\ddagger}$ for formation of a pentadienyl–benzyl orthogonal diradical gives a value of 125–130 kJ/mol (263 − 84 for the pentadienyl radical[6] and −52 for the benzyl radical[6]). This suggests the diradical should be competitive with the allowed ring closure which has $\Delta H^{\ddagger} \approx 121$ kJ/mol. Since a phenyl in a cis rather than a trans position raises $\Delta H^{\ddagger}$ for the allowed reaction by ~20 kJ/mol, the diradical should be readily observed with that isomer.

Results and Discussion

Several attempts were made to prepare (*E*,*Z*,*E*)-1-phenyl-1,3,5-heptatriene (**2**) by semihydrogenation of (*E*)-1-phenyl-1-hepten-3-yn-6-ol or (*E*)-1-phenyl-5-hepten-3-yn-1-ol followed by an elimination. This basic scheme, used in many cases previously,[7] failed in this case. An alternative route to such stereoisomeric trienes was developed (Scheme I), and three isomeric 1-phenyl-1,3,5-

Scheme I

$$\mathrm{PhCH{=}CHBr + MeCH{=}CHC{\equiv}CH} \xrightarrow[\mathrm{CuI,\ Et_2NH}]{\mathrm{Pd(PPh_3)_2Cl_2}} \mathrm{PhCH{=}CHC{\equiv}CCH{=}CHMe} \xrightarrow{\mathrm{H_2/Pd}}$$

(1-*E*,5-*E*)-**1**
(1-*E*,5-*Z*)-**3**
(1-*Z*,5-*E*)-**5**

$$\mathrm{PhCH{=}CHCH{=}CHCH{=}CHMe}$$

(*E*,*Z*,*E*)-**2**
(*E*,*Z*,*E*)-**4**
(*Z*,*Z*,*E*)-**6**

heptatrienes were successfully prepared via this method. All the dienynes, **1**, **3**, and **5**, are stable compounds, unequivocally identifiable by NMR. As such, each represents a key point in the synthetic scheme since each was obtained in pure form, free from any isomeric impurity.

Semihydrogenation of such dienynes is not generally a clean reaction,[8] normally leading to mixtures including trienes whose central double bond can be of either *E* or *Z* configuration, overhydrogenation products, and possibly unreacted dienyne. No evidence for geometric isomerization of the initial double bonds has been noted. The pattern was followed in the present examples. Semihydrogenation of 1 gave 80% trienes and 20% overhy-

(1) Woodward, R. B.; Hoffman, R. "Conservation of Orbital Symmetry"; Verlag Chemie: Weinheim/Bergstr., Germany, 1970.
(2) Stephenson, L. M.; Brauman, J. I. *Acc. Chem. Res.* **1974**, *7*, 65.
(3) (a) Dahmen, A.; Huisgen, R. *Tetrahedron Lett.* **1969**, 1465. (b) Staley, S. W.; Henny, T. J. *J. Am. Chem. Soc.* **1971**, *93*, 1292.
(4) Marvell, E. N.; Caple, G.; Delphey, C.; Platt, J.; Polston, N.; Tashiro, J. *Tetrahedron* **1973**, *29*, 3797.
(5) Epiotis, N. D. *J. Am. Chem Soc.* **1973**, *95*, 1200, 1214. Baldwin, J. E. "Pericyclic Reactions"; Marchand, A. P., Lehr, R. E., Eds.; Academic Press: New York, 1977; Vol. II, p 272.
(6) For a summary of stabilization energies for a series of radical see: Egger, K. W.; Cocks, A. T. *Helv. Chim. Acta* **1973**, *56*, 1537.
(7) Marvell, E. N.; Caple, G.; Schatz, B.; Pippin, W. *Tetrahedron* **1973**, *24*, 3781.
(8) Marvell, E. N.; Li, T. H. *Synthesis* **1973**, 457.

0022-3263/83/1948-5379$01.50/0