DMF (5%) in buffer. Each mixture was combined in a polyethylene tube and incubated at 25 °C. The rates of inactivation were followed by removing 20-μL aliquots from the incubation mixtures at various times, diluting into excess substrate and auxiliary enzymes (final volume 1 mL), and determining the remaining enzyme activity. In addition, incubation mixture 1 was diluted 10-fold and assayed for remaining activity in an identical manner.

Assay for Inhibition by Decomposition Product of 2. The nonenzymic solution and **2** were mixed as described above for the competitive inhibition experiments. At various times, two 800-μL aliquots were removed, auxiliary enzymes (as for the competitive inhibition experiments) were added to each, and the assay was initiated by addition of PFK (20 ng) to the sample cuvette and buffer to the reference cuvette. In a separate experiment, auxiliary enzyme and dithiothreitol (final concentration 2 mM) were added to both the sample and the reference cuvette before initiation of the assay.

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Registry No. **2**, 136667-88-4; **3**, 136667-89-5; **4**, 136667-90-8; **6**, 136667-91-9; phosphofructokinase, 9001-80-3; 2-(trimethylsilyl)ethyl acetoacetate, 17165-45-6; 3-benzyl 5-[2-(trimethylsilyl)ethyl] 2-[[(phenylmethoxy)carbonyl]amino]-4-methylthiophene-3,5-dicarboxylate, 136667-92-0; 3-benzyl 2-[[(phenylmethoxy)carbonyl]amino]-4-methylthiophene-3,5-dicarboxylate, 136667-93-1; benzyl cyanoacetate, 14447-18-8.

Synthesis of Photopolymerizable Long-Chain Conjugated Diacetylenic Acids and Alcohols from Butadiyne Synthons

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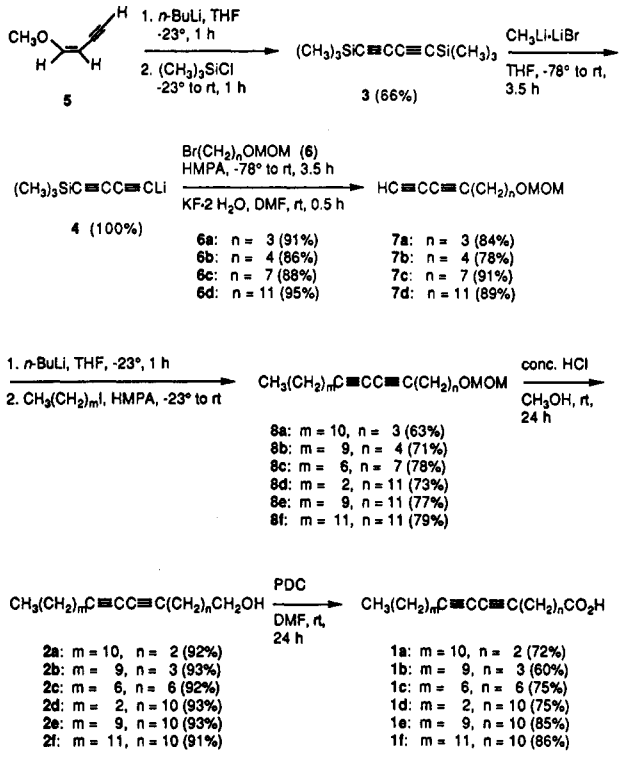
Conjugated diacetylenic chains have been incorporated into various polymerizable phospholipids for use in model membranes; ultraviolet irradiation induces cross-linking, resulting in a phospholipid polymer in the membrane bilayer.[1] In general, unsymmetrical diynoic acids **1** have been prepared by coupling of a 1-haloalkyne (usually the iodoalkyne) with a metal alkynoic acid (the Cadiot–Chodkiewicz reaction, eq 1).[2] Diynoic acids have also been

$$CH_3(CH_2)_mC{\equiv}CI + HC{\equiv}C(CH_2)_nCO_2H \xrightarrow[EtNH_2]{HONH_3^+Cl^-,\ Cu_2Cl_2} \underset{\mathbf{1}}{CH_3(CH_2)_mC{\equiv}CC{\equiv}C(CH_2)_nCO_2H} \quad (1)$$

prepared by the Cu_2Cl_2-catalyzed oxidative coupling of

Scheme I. Syntheses of Diacetylenic Alcohols 2a–f and Diacetylenic Acids 1a–f



ω-alkynoic acids with terminal alkynes.[3]

This acetylenic-coupling reaction has also been used to prepare long-chain conjugated (enyne[4] and diyne[5]) alcohols **2**. Disadvantages of this method of preparation of **1** and **2** are as follows: (a) higher ω-alkynoic acids are obtained in low yields (generally <50%),[2,3] (b) preparation of 1-haloalkynes is required in the Cadiot–Chodkiewicz reaction, and (c) unsymmetrical ω-diynoic acids are frequently contaminated by symmetrical diynoic acids.[3] The report by Zweifel and Rajagopalan[6] that the nucleophilic butadiyne synthons 1,4-bis(trimethylsilyl)-1,3-butadiyne (**3**) and 4-lithio-1-(trimethylsilyl)butadiyne (**4**) can be prepared from (*Z*)-1-methoxybut-1-en-3-yne[7] (**5**) via a series of metalation–elimination–metalation reactions suggested to us that **5** would be useful for the preparation of diacetylenic acids and alcohols **1** and **2**.

Membranes stabilized by photopolymerization have a wide range of potential applications.[8] Because of the current interest in the behavior of poly(diacetylene) chains in long-chain phospholipids as stabilizing units in membranes,[1] we have focused our attention on the efficient preparation of long-chain conjugated diacetylenic alcohols and acids. The position of the diacetylene along the hydrocarbon chain has been varied, making possible a future study of the structural requirements for efficient polymerization of lipid diacetylenes in multilayer films.

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Results and Discussion

Scheme I shows our application of the butadiyne synthon methodology to the synthesis of conjugated long-chain diacetylenic acids 1 and alcohols 2. Lithium (trimethylsilyl)butadiyne 4 was obtained from 3 by monodesilylation with methyllithium–lithium bromide complex in THF[6] and then was coupled with the MOM-protected ω-bromoalkan-1-ol 6,[9] giving ω-(methoxymethoxy)-1,3-alkadiynes 7. Since it was expected that the product of the first coupling reaction would be 4-alkyl-1-(trimethylsilyl)buta-1,3-diyne,[10] which then can be converted to terminal diyne by using potassium fluoride dihydrate,[11] we combined these two reaction steps in situ and directly prepared 7 in 78–91% yields. Coupling of the lithium salt of 7 with alkyl iodide gives unsymmetrical diynes 8 in good yields. The use of HMPA as cosolvent to promote alkylation has been reported previously,[12] and we also found that HMPA gives higher yields than without HMPA. As expected, alkyl iodides give higher yields than the corresponding bromides. Conjugated diacetylenic alcohols 2 can be easily prepared in 91–93% yields by deprotection of MOM-protected alcohols 8 using concentrated HCl in methanol at room temperature. Conjugated diacetylenic acids 1 were obtained in 60–86% by oxidation of the alcohols 2 by using pyridinium dichromate in dimethylformamide.

The above results demonstrate that (*Z*)-1-methoxybut-1-en-3-yne (5) serves as a useful synthon, via butadiyne derivatives 3 and 4, for the synthesis of the positional isomers and homologues of conjugated diacetylenic alcohols and acids. This method provides a more direct access to conjugated diacetylenic compounds than does the Cadiot–Chodkiewicz heterocoupling reaction. The conjugated diacetylenic acids and alcohols 1 and 2 can be used in the preparation of identical-acid and mixed-acid, mixed-ether, and ether/ester phosphatidylcholines by reactions with glycidyl and glycerol derivatives in the presence of catalysts.[1d-f,13]

Experimental Section

The solvents used were dried as follows: tetrahydrofuran was refluxed over sodium benzophenone ketyl for several hours immediately prior to use, and hexamethylphosphoramide and dimethylformamide were distilled from calcium hydride and stored over type 3A molecular sieves. ω-Bromoalkan-1-ol, 1-iodopropane, 1-iodoheptane, 1-iodoundecane, butyllithium, methyllithium–lithium bromide complex, methyllithium, and chlorotrimethylsilane were purchased from Aldrich. Potassium fluoride dihydrate was from Mallinckrodt Chemical Works. 1-Iododecane and 1-iodododecane were prepared by the reaction of the corresponding *n*-alkyl bromides with sodium iodide in acetone at room temperature for 24 h, followed by vacuum distillation. Pyridinium dichromate (PDC) was prepared according to a previous procedure.[14]

Melting points are uncorrected. Silica gel G TLC plates of 0.25-mm thickness (Analtech, Newark, DE) were used to monitor reactions, with 10% sulfuric acid in ethanol and/or short-wavelength ultraviolet light to visualize the spots. Flash chromatography was carried out with silica gel 60 (230–400 ASTM mesh) of E. Merck, purchased from Aldrich. ^{1}H NMR spectra were recorded at 200 MHz, and chemical shifts are given in parts per million from tetramethylsilane as internal standard. Elemental analyses were performed by Desert Analytics, Tucson, AZ, and by Oneida Research Services, Inc., Whitesboro, NY.

1,4-Bis(trimethylsilyl)-1,3-butadiyne (3). This compound was prepared in 66% yield as described previously.[6]

General Procedure for the Preparation of 1-Bromo-ω-(methoxymethoxy)alkane 6. To a stirred suspension of 5.0 g (35.2 mmol) of phosphorus pentoxide in 40 mL of methylene chloride and 70 mL (60.2 g, 791 mmol) of dimethoxymethane was added dropwise a solution of 10.0 mmol of ω-bromoalkan-1-ol in 10 mL of methylene chloride. After the reaction mixture was stirred overnight at room temperature, the solution was decanted to leave a residue that was dissolved in water and extracted with methylene chloride. After the combined organic layer was washed with saturated sodium bicarbonate solution and dried over sodium sulfate, the solvents were removed to give a residue that was purified by flash chromatography (elution with 15:1 hexane/EtOAc) to yield 1-bromo-ω-(methoxymethoxy)alkane 6 as a colorless liquid.

1-Bromo-3-(methoxymethoxy)propane (6a): 91% yield; ^{1}H NMR ($CDCl_3$) δ 4.63 (s, 2 H, OCH_2O), 3.66 (t, J = 5.86 Hz, 2 H, CH_2O), 3.53 (t, J = 6.50 Hz, 2 H, CH_2Br), 3.37 (s, 3 H, OCH_3), 2.12 (m, 2 H, $CH_2CH_2CH_2$). Anal. Calcd for $C_5H_{11}O_2Br$: C, 32.81; H, 6.06. Found: C, 33.15; H, 5.94.

1-Bromo-4-(methoxymethoxy)butane (6b): 86% yield; ^{1}H NMR ($CDCl_3$) δ 4.61 (s, 2 H, OCH_2O), 3.56 (t, J = 6.13 Hz, 2 H, CH_2O), 3.45 (t, J = 6.62 Hz, 2 H, CH_2Br), 3.36 (s, 3 H, OCH_3), 1.68–2.10 (m, 4 H, $(CH_2)_2$). Anal. Calcd for $C_6H_{13}O_2Br$: C, 36.57; H, 6.65. Found: C, 36.21; H, 6.37.

1-Bromo-7-(methoxymethoxy)heptane (6c): 88% yield; ^{1}H NMR ($CDCl_3$) δ 4.62 (s, 2 H, OCH_2O), 3.52 (t, J = 6.45 Hz, 2 H, CH_2O), 3.41 (t, J = 6.80 Hz, 2 H, CH_2Br), 3.36 (s, 3 H, OCH_3), 1.38–1.90 (m, 10 H, $(CH_2)_5$). Anal. Calcd for $C_9H_{19}O_2Br$: C, 45.20; H, 8.01. Found: C, 44.96; H, 7.84.

1-Bromo-11-(methoxymethoxy)undecane (6d): 95% yield; ^{1}H NMR ($CDCl_3$) δ 4.62 (s, 2 H, OCH_2O), 3.51 (t, J = 6.48 Hz, 2 H, CH_2O), 3.40 (t, J = 6.99 Hz, 2 H, CH_2Br), 3.36 (s, 3 H, OCH_3), 1.29–1.89 (m, 18 H, $(CH_2)_9$). Anal. Calcd for $C_{13}H_{27}O_2Br$: C, 52.88; H, 9.22. Found: C, 52.38; H, 9.06.

General Procedure for the Preparation of ω-(Methoxymethoxy)-1,3-alkadiyne (7). To a solution of 10.0 mmol of 1,4-bis(trimethylsilyl)-1,3-butadiyne (3) in 20 mL of THF was added dropwise 6.7 mL (10.0 mmol) of methyllithium–lithium bromide complex (a 1.5 M solution in ether) at −78 °C. After the reaction mixture was stirred for 3.5 h at room temperature under nitrogen, a solution of 12.0 mmol of 1-bromo-ω-(methoxymethoxy)alkane 6 in 20 mL of HMPA was added dropwise at −78 °C. After the mixture was stirred for 30 min at room temperature, the pH was adjusted to 7.0 by addition of 3 N HCl at 0 °C. The layers were separated, and the aqueous layer was extracted three times with hexane. The combined organic layer was evaporated to a residue. A slurry of 1.88 g (20 mmol) of potassium fluoride dihydrate in 20 mL of DMF was added, and the mixture was stirred for 30 min at room temperature. The reaction mixture was poured into 15 mL of 3 N HCl solution with stirring at 0 °C. The layers were separated, and the aqueous layer was extracted three times with hexane. The combined organic layer was washed with 3 N HCl, saturated sodium bicarbonate solution, brine, and dried over sodium sulfate. Removal of the solvents gave a residue that was purified by flash chromatography (elution with 20:1 hexane/EtOAc) to yield ω-(methoxymethoxy)-1,3-alkadiyne 7 as a light yellow liquid.[15]

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(15) In order to avoid polymerization of the generated terminal diynes and other conjugated diacetylenes, the conjugated alkynes should be stored at low temperature in the dark. Compounds containing the MOM protecting group generally did not give satisfactory combustion analyses despite repeated reanalysis; however, they had appropriate spectral characteristics and were converted into products (2 and 1) that gave analyses that were within 0.4% of the theoretical values.

7-(Methoxymethoxy)-1,3-heptadiyne (7a): 84% yield; ^{1}H NMR ($CDCl_3$) δ 4.58 (s, 2 H, OCH_2O), 3.57 (t, J = 6.05 Hz, 2 H, CH_2O), 3.32 (s, 3 H, OCH_3), 2.36 (t, J = 6.99 Hz, 2 H, $CH_2C{\equiv}C$), 1.95 (s, 1 H, $C{\equiv}CH$), 1.75–1.82 (m, 2 H, $CH_2CH_2CH_2$).

8-(Methoxymethoxy)-1,3-octadiyne (7b): 78% yield; ^{1}H NMR ($CDCl_3$) δ 4.60 (s, 2 H, OCH_2O), 3.54 (t, J = 5.91 Hz, 2 H, CH_2O), 3.35 (s, 3 H, OCH_3), 2.32 (t, J = 6.20 Hz, 2 H, $CH_2C{\equiv}C$), 2.01 (s, 1 H, $C{\equiv}CH$), 1.65 (m, 4 H, $(CH_2)_2$).

11-(Methoxymethoxy)-1,3-undecadiyne (7c): 91% yield; ^{1}H NMR ($CDCl_3$) δ 4.61 (s, 2 H, OCH_2O), 3.52 (t, J = 6.49 Hz, 2 H, CH_2O), 3.36 (s, 3 H, OCH_3), 2.26 (t, J = 6.81 Hz, 2 H, $CH_2C{\equiv}C$), 1.98 (s, 1 H, $C{\equiv}CH$), 1.35–1.62 (m, 10 H, $(CH_2)_5$). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 73.95; H, 9.41.

15-(Methoxymethoxy)-1,3-pentadecadiyne (7d): 89% yield; ^{1}H NMR ($CDCl_3$) δ 4.62 (s, 2 H, OCH_2O), 3.52 (t, J = 6.52 Hz, 2 H, CH_2O), 3.36 (s, 3 H, OCH_3), 2.26 (t, J = 6.68 Hz, 2 H, $CH_2C{\equiv}C$), 1.97 (s, 1 H, $C{\equiv}CH$), 1.28–1.58 (m, 18 H, $(CH_2)_9$). Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.01; H, 10.60.

General Procedure for the Preparation of 1-(Methoxymethoxy)alkadiyne (8). To a solution of 2.0 mmol of ω-(methoxymethoxy)-1,3-alkadiyne **7** in 8 mL of THF was added dropwise 1.5 mL (2.4 mmol) of *n*-butyllithium (a 1.6 M solution in hexane) at −23 °C. The reaction mixture was stirred for 1 h at −23 °C under nitrogen, and then a solution of 2.4 mmol of 1-iodoalkane in 8 mL of HMPA was added dropwise. The mixture was stirred for 30 min at −23 °C and for 1.5 h at room temperature. The pH was adjusted to 6.0 with 3 N HCl. The reaction mixture was extracted three times with hexane. The combined organic layer was washed with saturated sodium bicarbonate solution, brine, and dried over sodium sulfate. Removal of the solvents gave a residue that was purified by flash chromatography (elution with 25:1 hexane/EtOAc) to yield 1-(methoxymethoxy)alkadiyne **8** as a colorless liquid.

1-(Methoxymethoxy)-4,6-octadecadiyne (8a): 63% yield; ^{1}H NMR ($CDCl_3$) δ 4.62 (s, 2 H, OCH_2O), 3.61 (t, J = 6.14 Hz, 2 H, CH_2O), 3.36 (s, 3 H, OCH_3), 2.38 (t, J = 7.01 Hz, 2 H, $C{\equiv}CCH_2(CH_2)_2O$), 2.24 (t, J = 6.83 Hz, 2 H, $CH_2C{\equiv}C$), 1.80 (m, 2 H, CH_2CH_2O), 1.26–1.55 (m, 18 H, $(CH_2)_9$), 0.88 (t, J = 6.40 Hz, 3 H, ω-CH_3).

1-(Methoxymethoxy)-5,7-octadecadiyne (8b): 71% yield; ^{1}H NMR ($CDCl_3$) δ 4.59 (s, 2 H, OCH_2O), 3.51 (t, J = 6.05 Hz, 2 H, CH_2O), 3.33 (s, 3 H, OCH_3), 2.18–2.31 (m, 4 H, $(CH_2C{\equiv}C)_2$), 1.23–1.68 (m, 20 H, $(CH_2)_{10}$), 0.85 (t, J = 6.37 Hz, 3 H, ω-CH_3).

1-(Methoxymethoxy)-8,10-octadecadiyne (8c): 78% yield; ^{1}H NMR ($CDCl_3$) δ 4.61 (s, 2 H, OCH_2O), 3.51 (t, J = 6.47 Hz, 2 H, CH_2O), 3.36 (s, 3 H, OCH_3), 2.24 (t, J = 6.64 Hz, 4 H, $(CH_2C{\equiv}C)_2$), 1.27–1.62 (m, 20 H, $(CH_2)_{10}$), 0.88 (t, J = 6.43 Hz, 3 H, ω-CH_3).

1-(Methoxymethoxy)-12,14-octadecadiyne (8d): 73% yield; ^{1}H NMR ($CDCl_3$) δ 4.62 (s, 2 H, OCH_2O), 3.52 (t, J = 6.51 Hz, 2 H, CH_2O), 3.36 (s, 3 H, OCH_3), 2.19–2.26 (m, 4 H, $(CH_2C{\equiv}C)_2$), 1.26–1.69 (m, 20 H, $(CH_2)_{10}$), 0.98 (t, J = 7.33 Hz, 3 H, ω-CH_3).

1-(Methoxymethoxy)-12,14-pentacosadiyne (8e): 77% yield; ^{1}H NMR ($CDCl_3$) δ 4.62 (s, 2 H, OCH_2O), 3.52 (t, J = 6.55 Hz, 2 H, CH_2O), 3.36 (s, 3 H, OCH_3), 2.24 (t, J = 6.77 Hz, 4 H, $(CH_2C{\equiv}C)_2$), 1.26–1.62 (m, 34 H, $(CH_2)_{17}$), 0.88 (t, J = 6.39 Hz, 3 H, ω-CH_3).

1-(Methoxymethoxy)-12,14-heptacosadiyne (8f): 79% yield; ^{1}H NMR ($CDCl_3$) δ 4.62 (s, 2 H, OCH_2O), 3.52 (t, J = 6.56 Hz, 2 H, CH_2O), 3.36 (s, 3 H, OCH_3), 2.24 (t, J = 6.79 Hz, 4 H, $(CH_2C{\equiv}C)_2$), 1.26–1.63 (m, 38 H, $(CH_2)_{19}$), 0.88 (t, J = 6.41 Hz, 3 H, ω-CH_3).

General Procedure for the Preparation of Alkadiyn-1-ol 2. To a solution of 1.0 mmol of 1-(methoxymethoxy)alkadiyne **8** in 25 mL of methanol was added 3 mL of 37% hydrochloric acid. The reaction mixture was stirred overnight at room temperature. After removal of methanol, water and chloroform were added and the organic layer was separated. The aqueous layer was extracted three times with chloroform. The combined organic layer was washed with saturated sodium bicarbonate solution and brine and dried over sodium sulfate. Removal of the solvents gave a residue that was purified by flash chromatography (elution with 6:1 hexane/EtOAc) to yield alkadiyn-1-ol **2** as a light yellow liquid or white solid.

4,6-Octadecadiyn-1-ol (2a): 92% yield; mp 37–39 °C; ^{1}H NMR ($CDCl_3$) δ 3.74 (t, J = 6.16 Hz, 2 H, CH_2OH), 2.38 (t, J = 6.95 Hz, 2 H, $C{\equiv}CCH_2(CH_2)_2O$), 2.24 (t, J = 6.85 Hz, 2 H, $CH_2C{\equiv}C$), 1.70–1.83 (m, 3 H, CH_2CH_2O and OH), 1.23–1.55 (m, 18 H, $(CH_2)_9$), 0.88 (t, J = 6.39 Hz, 3 H, ω-CH_3). Anal. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52. Found: C, 82.00; H, 11.56.

5,7-Octadecadiyn-1-ol (2b): 93% yield; light yellow liquid; ^{1}H NMR ($CDCl_3$) δ 3.67 (t, J = 5.84 Hz, 2 H, CH_2OH), 2.21–2.34 (m, 4 H, $(CH_2C{\equiv}C)_2$), 1.26–1.66 (m, 21 H, $(CH_2)_{10}$ and OH), 0.88 (t, J = 5.83 Hz, 3 H, ω-CH_3). Anal. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52. Found: C, 82.36; H, 11.58.

8,10-Octadecadiyn-1-ol (2c): 92% yield; mp 23–24 °C; ^{1}H NMR ($CDCl_3$) δ 3.63 (t, J = 6.48 Hz, 2 H, CH_2OH), 2.25 (t, J = 6.59 Hz, 4 H, $(CH_2C{\equiv}C)_2$), 1.27–1.56 (m, 21 H, $(CH_2)_{10}$ and OH), 0.88 (t, J = 6.36 Hz, 3 H, ω-CH_3). Anal. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52. Found: C, 82.56; H, 11.76.

12,14-Octadecadiyn-1-ol (2d): 93% yield; mp 33–34 °C; ^{1}H NMR ($CDCl_3$) δ 3.63 (t, J = 6.55 Hz, 2 H, CH_2OH), 2.19–2.26 (m, 4 H, $(CH_2C{\equiv}C)_2$), 1.27–1.64 (m, 20 H, $(CH_2)_{10}$), 0.98 (t, J = 7.33 Hz, 3 H, ω-CH_3). Anal. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52. Found: C, 81.45; H, 11.39.

12,14-Pentacosadiyn-1-ol (2e): 93% yield; mp 58–59 °C; ^{1}H NMR ($CDCl_3$) δ 3.64 (t, J = 6.34 Hz, 2 H, CH_2OH), 2.24 (t, J = 6.61 Hz, 4 H, $(CH_2C{\equiv}C)_2$), 1.26–1.51 (m, 35 H, $(CH_2)_{17}$ and OH), 0.88 (t, J = 6.01 Hz, 3 H, ω-CH_3). Anal. Calcd for $C_{25}H_{44}O$: C, 83.27; H, 12.30. Found: C, 83.22; H, 12.16.

12,14-Heptacosadiyn-1-ol (2f): 91% yield; mp 58–59 °C; ^{1}H NMR ($CDCl_3$) δ 3.64 (t, J = 6.34 Hz, 2 H, CH_2OH), 2.24 (t, J = 6.73 Hz, 4 H, $(CH_2C{\equiv}C)_2$), 1.26–1.55 (m, 39 H, $(CH_2)_{19}$ and OH), 0.88 (t, J = 6.06 Hz, 3 H, ω-CH_3). Anal. Calcd for $C_{27}H_{48}O$: C, 83.44; H, 12.45. Found: C, 83.22; H, 12.64.

General Procedure for the Preparation of Alkadiynoic Acid 1. To 0.5 mmol of alkadiyn-1-ol **2** was added a solution of 1.5 g (4.0 mmol) of pyridinium dichromate in 3 mL of dimethylformamide. The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into 10 volumes of water, acidified with 3 N HCl, and extracted with ether. Removal of the solvents gave a residue that was purified by flash chromatography (elution with 500:100:5 hexane/EtOAc/85% formic acid) to yield alkadiynoic acid **1** as a white solid.

4,6-Octadecadiynoic acid (1a): 72% yield; mp 74–75 °C; ^{1}H NMR ($CDCl_3$) δ 9.20 (br s, 1 H, CO_2H), 2.59 (br s, 4 H, $C{\equiv}CCH_2CH_2CO_2$), 2.24 (t, J = 6.82 Hz, 2 H, $CH_2C{\equiv}C$), 1.26–1.55 (m, 18 H, $(CH_2)_9$), 0.89 (t, J = 6.38 Hz, 3 H, ω-CH_3). Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.17; H, 10.34.

5,7-Octadecadiynoic acid (1b): 60% yield; mp 47–49 °C; ^{1}H NMR ($CDCl_3$) δ 10.21 (br s, 1 H, CO_2H), 2.51 (t, J = 7.35 Hz, 2 H, CH_2CO_2), 2.36 (t, J = 6.79 Hz, 2 H, $C{\equiv}CCH_2(CH_2)_2CO_2$), 2.24 (t, J = 6.83 Hz, 2 H, $CH_2C{\equiv}C$), 1.85 (m, 2 H, $CH_2CH_2CO_2$), 1.26–1.56 (m, 16 H, $(CH_2)_8$), 0.88 (t, J = 6.40 Hz, 3 H, ω-CH_3). Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 77.91; H, 10.31.

8,10-Octadecadiynoic acid (1c): 75% yield; mp 42–43 °C (lit.[3] mp 41.5–42 °C); ^{1}H NMR ($CDCl_3$) δ 11.23 (br s, 1 H, CO_2H), 2.36 (t, J = 7.38 Hz, 2 H, CH_2CO_2), 2.25 (t, J = 6.55 Hz, 4 H, $(CH_2C{\equiv}C)_2$), 1.27–1.71 (m, 18 H, $(CH_2)_9$), 0.88 (t, J = 6.34 Hz, 3 H, ω-CH_3). Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.36; H, 10.26.

12,14-Octadecadiynoic acid (1d): 75% yield; mp 58–59 °C; ^{1}H NMR ($CDCl_3$) δ 10.62 (br s, 1 H, CO_2H), 2.35 (t, J = 7.44 Hz, 2 H, CH_2CO_2), 2.23 (m, 4 H, $(CH_2C{\equiv}C)_2$), 1.28–1.67 (m, 18 H, $(CH_2)_9$), 0.99 (t, J = 7.33 Hz, 3 H, ω-CH_3). Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 77.34; H, 10.36.

12,14-Pentacosadiynoic acid (1e): 85% yield; mp 57–59 °C (lit.[2c] mp 52–54 °C); ^{1}H NMR ($CDCl_3$) δ 10.72 (br s, 1 H, CO_2H), 2.35 (t, J = 7.43 Hz, 2 H, CH_2CO_2), 2.24 (t, J = 6.77 Hz, 4 H, $(CH_2C{\equiv}C)_2$), 1.26–1.67 (m, 32 H, $(CH_2)_{16}$), 0.88 (t, J = 6.40 Hz, 3 H, ω-CH_3).

12,14-Heptacosadiynoic acid (1f): 86% yield; mp 62–63 °C (lit.[2c] mp 38–40 °C); ^{1}H NMR ($CDCl_3$) δ 10.81 (br s, 1 H, CO_2H), 2.35 (t, J = 7.45 Hz, 2 H, CH_2CO_2), 2.24 (t, J = 6.77 Hz, 4 H, $(CH_2C{\equiv}C)_2$), 1.26–1.67 (m, 36 H, $(CH_2)_{18}$), 0.88 (t, J = 6.36 Hz, 3 H, ω-CH_3).

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Registry No. **1a**, 136667-35-1; **1b**, 136667-54-4; **1c**, 33128-26-6; **1d**, 136667-55-5; **1e**, 101216-59-5; **1f**, 106510-41-2; **2a**, 136667-36-2; **2b**, 136667-49-7; **2c**, 136667-50-0; **2d**, 136667-51-1; **2e**, 136667-52-2; **2f**, 136667-53-3; **3**, 4526-07-2; **4**, 73084-25-0; **6a**, 78365-43-2; **6b**, 34508-57-1; **6c**, 136667-39-5; **6d**, 136667-40-8; **7a**, 136667-37-3; **7b**, 136667-41-9; **7c**, 136667-42-0; **7d**, 136667-43-1; **8a**, 136667-38-4; **8b**, 136667-44-2; **8c**, 136667-45-3; **8d**, 136667-46-4; **8e**, 136667-47-5; **8f**, 136667-48-6; 3-bromo-1-propanol, 627-18-9; 4-bromo-1-butanol, 33036-62-3; 7-bromo-1-heptanol, 10160-24-4; 11-bromo-1-undecanol, 1611-56-9; 1-iodoundecane, 4282-44-4; 1-iododecane, 2050-77-3; 1-iodoheptane, 4282-40-0; 1-iodopropane, 107-08-4; 1-iododecane, 4292-19-7.

Facile Chloride Substitution of Activated Alcohols by Triphosgene: Application to Cephalosporin Chemistry

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Functionalization of cephalosporins at C-3 has been instrumental in the development of a series of clinically useful β-lactam antibacterials.[1] Such structural manipulations are often carried out on halogenated intermediates; therefore, there exists a need for new and mild synthetic routes to these compounds. Whereas a number of reagents are available for halogenation of hydroxyl compounds, the vast majority are not useful for chemical conversions on cephalosporins. The primary problem is the lability of the β-lactam ring of cephalosporins to both acidic and basic conditions. Furthermore, the ability of ceph-3-ems to isomerize to the undesired ceph-2-ems, under even mildly basic conditions, complicates the problem.

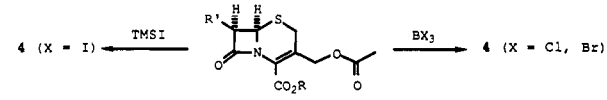
Bromination of 3-methylcephem sulfoxides with *N*-bromosuccinimide (NBS) in the absence[2] or presence[3] of photoinitiation has been reported (**1** → **2**). A complicating factor noted with the use of NBS is the possibility of overreaction at C-2 or at the C-7 substituent to give dibromo derivatives. It is significant that the reaction failed when applied to 1-oxocephems.[4]

1 **2**

A practical route to halogenated cephems is provided by the conversion of 3-*exo*-methylenecephams to ceph-3-em halides (**3** → **4**).[5] Compound **3** undergoes reaction with *tert*-butyl hypochlorite, bromine, or iodine under basic conditions to afford the chloro-, bromo- and iodocephems, respectively.

3 **4** (X = Cl, Br, I)

Reactions of boron trihalide[6] and iodotrimethylsilane[7] with cephems possessing ester functionalities at C-3 (**5**) provide additional entries into the corresponding halocephem derivatives. A principal drawback to this chemistry is the fact that acid labile protective groups such as the *tert*-butyl, benzhydryl, and *p*-methoxybenzyl functions, which are used widely in β-lactam chemistry, cannot be used with these reagents. Deacetylcephalosporins have been reported to undergo reaction in the presence of phosphorus pentachloride and pyridine to give the corresponding chloro analogues.[8] However, protection of the amide group typically found at C-7 of cephalosporins is required in this reaction, since the reagent (PCl_5/pyridine) facilitates the cleavage of this function in a competing reaction with chlorination at C-3.[8,9]



5

We report here on the chlorination of the cephem nucleus at the C-3 position using triphosgene (bis(trichloromethyl)carbonate). Deacetylcephalothin (**6**), a semisynthetic cephalosporin, and triphosgene undergo an exothermic reaction in the presence of pyridine at room temperature to give compound **4**. Two such cephalosporins, one with the *p*-methoxybenzyl and the other with the benzhydryl groups at the C-4 carboxylate, were prepared in 60–80% yields. Whereas some $\Delta^3 \rightarrow \Delta^2$ isomerization was noted when triethylamine was used in this reaction, no such undesired side reaction was detected in the presence of equimolar amounts of pyridine. The lactone **8** was the only other observed product. However **8** was readily separated from the cephem chloride by chromatography. In order to minimize the lactonization problem a 6-fold excess of triphosgene was used to speed up the chlorination reaction; however, the yield of the cephem chlorides improved only by 4–5%. The reaction is thought to proceed through an unstable cephem chloroformate (**7**); formation of chloroformates in reactions of hydroxy compounds with triphosgene is precedented.[10] In a typical reaction, we allow a solution of the alcohol and triphosgene (3:1 molar ratio) to stir in a minimum amount of THF or CH_2Cl_2. The progress of the reaction can be conveniently monitored by measuring CO_2 evolution by a manometer connected to the vessel. As shown in Table I, the reaction is applicable to benzylic, allylic and propargylic alcohols. The chlorides listed in Table I were each made from the corresponding alcohol in less than 15 min at room temperature, with the exception of propargyl chloride. Whereas the chloroformate of propargyl alcohol formed in less than 1 min, gentle warming was necessary to drive the reaction to completion to give propargyl chloride. It is significant that under these conditions with unactivated alcohols chloroformates are isolated readily without a trace

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