New Syntheses of Some Functionalized and Acetylenic β-Keto Phosphonates

Isabelle Delamarche and Paul Mosset*

Laboratoire de Synthèses et Activations de Biomolécules, CNRS URA D 1467, ENSCR, Avenue du Général Leclerc, F-35700 Rennes, France

Received February 25, 1994[⊗]

β-Keto phosphonates ω-functionalized by an ester group **1a–f**, by a hydroxyl **5**, and with a triple bond conjugated to the carbonyl group **2a–c** were prepared by reacting dimethyl (lithiomethyl)-phosphonate (**3**) with adequate electrophiles. Cyclic anhydrides such as succinic and glutaric anhydrides were employed for the synthesis of the two first homologs **1a** and **1b**. To obtain the other longer homologs **1c–f**, 3-acylthiazolidine-2-thiones **7a–d** easily prepared using cheap 2-mercaptothiazoline proved to be the electrophiles of choice. On the other hand, the synthesis of keto phosphonates **2a–c** required the use of *N*-methoxy-*N*-methylamides.

Introduction

β-Keto phosphonates are valuable intermediates for organic synthesis, especially for the preparation of α,β-unsaturated carbonyl compounds by the Horner–Wadsworth–Emmons (HWE) reaction.[1] Various routes to β-keto phosphonates are known and could be mainly classified in four types. First, the Arbuzov reaction of trialkyl phosphites with α-halo ketones leads, however, to mixtures of keto phosphonates and enol phosphates (resulting from a Perkow reaction).[2] Formation of the latter compounds was avoided by using α-chloro epoxides[3] or by intermediate protection of the carbonyl function of α-chloro ketones[4] by a hydrazone group. A second type of reaction used masked carbonyl compounds such as enol,[5] enamine,[6] acetylenic,[7] or ene derivatives.[8] A third type refers to reactions of α-carbanionic alkylphosphonates with aldehydes followed by oxidation,[9] carboxylic acid esters,[10] carboxylic acid chlorides,[11] or *N*-methoxy-*N*-methylcarboxamides.[12] Lastly, keto phosphonates were also obtained by either base (LDA)-induced isomerization of cyclic enol phosphates[13] or reaction of ketone enolates with diethyl chlorophosphite followed by air oxidation.[14] Other miscellaneous methods include alkylation of β-keto phosphonate anions,[15] reaction of (diethylphosphono)-carboxylic acid chlorides with organometallic reagents,[16] the use of (diethoxyphosphoryl)acetonitrile oxide,[17] *via* allene oxides,[18] and reaction of silyl enol ethers with phosphite using hypervalent iodine compound.[19] In some synthetic studies, keto phosphonates functionalized by protected hydroxyl groups, acetals, thioethers, and remote unsaturations were prepared. Apart from a recent report using *N*-methoxy-*N*-methylcarboxamides[12] (Weinreb amides[20]), these routes rarely described the synthesis of β-keto phosphonates bearing a carboxylic ester func-

⊗ Abstract published in *Advance ACS Abstracts,* July 15, 1994.

(1) (a) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738. (b) Horner, L.; Hoffmann, H.; Wippel, H. G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499–2505. (c) Horner, L.; Hoffmann, H.; Klink, W.; Ertel, H.; Toscano, V. G. *Chem. Ber.* **1962**, *95*, 581–601. (d) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73–253. (e) Walker, B. J. In *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic Press: New York, 1979; pp 155–206. (f) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186. (g) Alvarez-Ibarra, C.; Arias, S.; Bañón, G.; Fernández, M. J.; Rodríguez, M.; Sinisterra, V. *J. Chem. Soc., Chem. Commun.* **1987**, 1509–1511. (h) Alvarez Ibarra, C.; Arias, S.; Fernández, M. J.; Sinisterra, J. V. *J. Chem. Soc., Perkin Trans. 2* **1989**, 503–508. (i) Koskinen, A. M. P.; Koskinen, P. M. *Synlett* **1993**, 501–502. (j) Paterson, I.; Yeung, K. S.; Smaill, J. B. *Synlett* **1993**, 774–776.

(2) (a) Lichtenthaler, F. W. *Chem. Rev.* **1961**, *61*, 607–649. (b) Baboulene, M.; Sturtz, G. *Bull. Soc. Chim. Fr.* **1974**, 1585–1590. (c) Bianchini, J.-P.; Gaydou, E. M. *C. R. Acad. Sci. Paris, Ser. C* 1975, *280*, 1521–1523. (d) Borowitz, I. J.; Anschel, M.; Firstenberg, S. *J. Org. Chem.* **1967**, *32*, 1723–1729.

(3) Gasteiger, J.; Herzig, C. *Tetrahedron Lett.* **1980**, *21*, 2687–2688.

(4) Corbel, B.; Medinger, L.; Haelters, J. P.; Sturtz, G. *Synthesis* **1985**, 1048–1051.

(5) (a) Sturtz, G. *Bull. Soc. Chim. Fr.* **1964**, 2340–2348. (b) Normant, H.; Sturtz, G. *C. R. Acad. Sci. Paris* **1965**, *260*, 1984–1987.

(6) (a) Sturtz, G. *Bull. Soc. Chim. Fr.* **1967**, 1345–1353. (b) Boeckman, R. K. Jr.; Walters, M. A.; Koyano, H. *Tetrahedron Lett.* **1989**, *30*, 4787–4790.

(7) (a) Sturtz, G.; Charrier, C.; Normant, H. *Bull. Soc. Chim. Fr.* **1966**, 1707–1713. (b) Chattha, M. S.; Aguiar, A. M. *J. Org. Chem.* **1973**, *38*, 2908–2909. (c) Poss, A. J.; Belter, R. K. *J. Org. Chem.* **1987**, *52*, 4810–4812.

(8) Sturtz, G.; Pondaven-Raphalen, A. *J. Chem. Res., Miniprint* **1980**, 2512–2523; *J. Chem. Res., Synop.* **1980**, 175.

(9) (a) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4010–4013. (b) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1981**, *103*, 1224–1226. (c) Lim, M.; Marquez, V. E. *Tetrahedron Lett.* **1983**, *24*, 4051–4054. (d) Mikolajczyk, M.; Balczewski, P. *Synthesis* **1984**, 691–694.

(10) (a) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5654–5656. (b) Ditrich, K.; Hoffmann, R. W. *Tetrahedron Lett.* **1985**, *26*, 6325–6328. (c) For the synthesis of β-formyl and β-keto phosphonates using alkyl formates and alkanoates, see: Aboujaoude, E. E.; Collignon, N.; Savignac, P. *J. Organomet. Chem.* **1984**, *264*, 9–17.

(11) (a) Mathey, F.; Savignac, P. *Synthesis* **1976**, 766–767. (b) Savignac, P.; Mathey, F. *Tetrahedron Lett.* **1976**, 2829–2832. (c) Mathey, F.; Savignac, P. *Tetrahedron* **1978**, *34*, 649–654. (d) Varlet, J.-M.; Collignon, N.; Savignac, P. *Can. J. Chem.* **1979**, *57*, 3216–3220. (e) Hong, S.; Chang, K.; Ku, B.; Oh, D. Y. *Tetrahedron Lett.* **1989**, *30*, 3307–3308.

(12) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 2374–2378.

(13) (a) Hammond, G. B.; Calogeropoulou, T.; Wiemer, D. F. *Tetrahedron Lett.* **1986**, *27*, 4265–4268. (b) Calogeropoulou, T.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1987**, *52*, 4185–4190. (c) An, Y.-Z.; Wiemer, D. F. *J. Org. Chem.* **1992**, *57*, 317–321 and references cited therein.

(14) Lee, K.; Wiemer, D. F. *J. Org. Chem.* **1991**, *56*, 5556–5560. Similarly, the preparation of β-keto phosphonates by reaction of dialkyl chlorophosphate electrophiles with the dilithiated derivative of α-bromo ketones was previously reported: Sampson, P.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1986**, *51*, 4342–4347.

(15) (a) Grieco, P. A.; Pogonowski, C. S. *J. Am. Chem. Soc.* **1973**, *95*, 3071–3072. (b) Clark, R. D.; Kozar, L. G.; Heathcock, C. H. *Synthesis* **1975**, 635–636.

(16) Coutrot, P.; Ghribi, A. *Synthesis* **1986**, 661–664.

(17) (a) Tsuge, O.; Kanemasa, S.; Suga, H. *Chem. Lett.* **1986**, 183–186. (b) Tsuge, O.; Kanemasa, S.; Suga, H.; Nakagawa, N. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2463–2473. (c) Kanemasa, S.; Nakagawa, N.; Suga, H.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 171–179 and 180–184.

(18) Kabat, M. M. *Tetrahedron Lett.* **1993**, *34*, 8543–8544.

(19) Kim, D. Y.; Mang, J. Y.; Oh, D. Y. *Synth. Commun.* **1994**, *24*, 629–634.

(20) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818. (b) For a recent review about the chemistry of *N*-methoxy-*N*-methylamides, see: Sibi, M. P. *Org. Prep. Proc. Int.* **1993**, *25*, 15–40.

0022-3263/94/1959-5453$04.50/0

tionality that we needed in the course of other synthetic studies.[21,22] In this paper, we wish to report on the extension of the previously mentioned third type of routes for the preparation of saturated β-keto phosphonates **1** functionalized by a carboxylic ester group as well as acetylenic keto phosphonates **2** where the carbonyl group is conjugated to a triple bond.

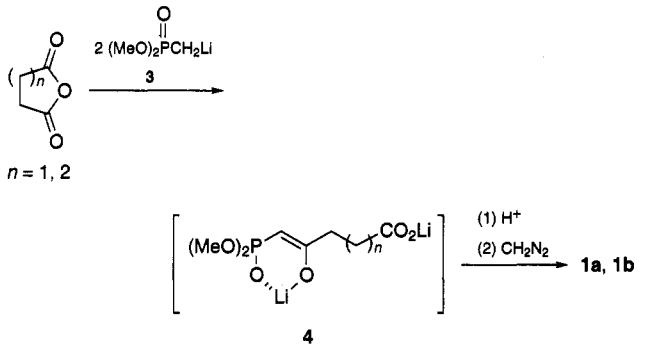
$(MeO)_2P(O)CH_2C(O)(CH_2)_nCO_2R$
1a–e: n = 2,3,4,6,7; R = Me
1f: n = 6; R = Et

$(MeO)_2P(O)CH_2C(O)C{\equiv}CR$
2a: R = $SiMe_3$
2b: R = n-Bu
2c: R = CH_2OSiPh_2-t-Bu

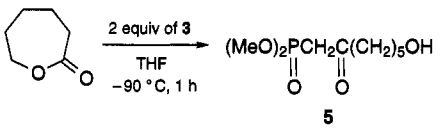
Results and Discussion

The direct introduction of a carboxylic ester group in compounds **1** is hampered by the reactivity of this functionality itself toward dimethyl (lithiomethyl)phosphonate (**3**). Two alternatives were successively employed: reactions of **3** with cyclic anhydrides and with activated carboxylic derivatives.

In the first method, we found that cyclic anhydrides such as succinic and glutaric anhydrides undergo nucleophilic opening with **3** yielding an intermediate β-keto phosphonate in its chelated enolate form **4** bearing a lithium carboxylate moiety. No further reaction could



normally occur since the carboxylate function is not reactive toward **3**. Protonation of **4** followed by subsequent esterification of the liberated carboxylic acid yielded desired **1a** and **1b**. In both cases, this process was performed in ether with good yields (76 and 78%, respectively) whereas a fair yield of **1b** (40%) was obtained in THF with glutaric anhydride. In addition, a lactone such as ε-caprolactone was also successfully opened by **3** yielding an ω-hydroxylated β-keto phosphonate **5** in 78% yield.[23] On the other hand, no reaction was observed with ε-caprolactam.



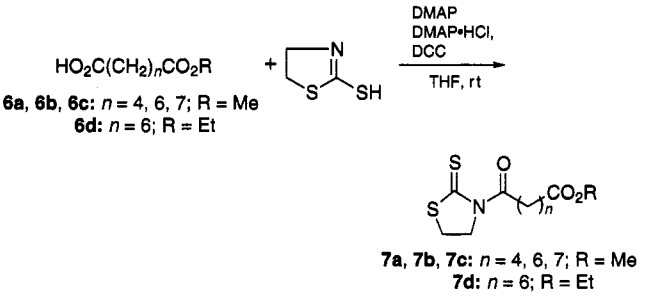
However, it should be noted that this method cannot be extended for larger homologs since larger cyclic anhydrides are either unstable[24] or unavailable. For this reason, we looked for another route involving a chemoselective reaction of **3** with a carboxylic activated group in the presence of a carboxylate ester. Among other derivatives, 3-acylthiazolidine-2-thiones **7a–d**[25] proved to be most suitable to produce saturated keto phosphonates **1c–f**.

Acylating reagents **7a–d** were conveniently prepared by condensation in THF of the methyl monoesters **6a–d** of ω,ω′-diacids with 2-mercaptothiazoline in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and catalytic amounts of 4-(dimethylamino)pyridine (DMAP) and 4-(dimethylamino)pyridine hydrochloride (DMAP·HCl). As previously reported by Boden and Keck for a macrolactonization reaction,[26] the use of a proton source such as DMAP·HCl proved very beneficial since its presence avoided the formation of more polar byproducts and enabled isolation of **7a–d** in excellent yields (see Table 1).

Table 1. Synthesis of Acylating Reagents 7 by Condensation of Methyl Monoesters 6 of ω,ω′-Diacids with 2-Mercaptothiazoline in the Presence of DCC and Catalytic Amounts of DMAP and DMAP·HCl

compd	n	yield (%)
7a	4	93
7b	6	96[a]
7c	7	92

[a] The corresponding ethyl ester **7d** was similarly prepared in 90% yield.



Addition of compounds **7a–d** to 2.5 equiv of lithium reagent **3** in THF[27] at −90/−95 °C (1 h) led to the expected functionalized keto phosphonates **1c–f**. Inspec-

(21) (a) As an intermediate for the total synthesis of a prostaglandin metabolite, dimethyl [6-(methoxycarbonyl)-2-oxohexyl]phosphonate was prepared by reaction of dimethyl (lithiomethyl)phosphonate with monomeric adipic acid anhydride[24] followed by conversion to the methyl ester with diazomethane: Taub, D.; Zelawski, Z. S.; Wendler, N. L. *Tetrahedron Lett.* **1975**, 3667–3670. The same keto phosphonate in octadeuteriated form was also prepared by reaction of 4 equiv of dimethyl (lithiomethyl)phosphonate with corresponding octadeuteriated adipic acid monomethyl ester at −78 °C for 16 h, followed by acidification with HCl and esterification of the carboxylic acid function with diazomethane: Meese, C. O.; Fürst, O.; Borstel, B. *J. Labelled Compd. Radiopharm.* **1986**, *23*, 175–185. (b) For the total synthesis of methynolide, a keto phosphonate bearing a terminal carboxylic acid was prepared: Okiawa, Y.; Yonemitsu, O. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1983**, *26*, 445–452; *Chem. Abstr.* **1984**, *100*, 209475m.

(22) Dimethyl [4-(methoxycarbonyl)-2-oxobutyl]phosphonate **1a** was synthesized by reaction of dimethyl (lithiomethyl)phosphonate with dimethyl succinate: Corey, E. J.; Shimoji, K. *J. Am. Chem. Soc.* **1983**, *105*, 1662–1664.

(23) The reaction of diethyl (lithiomethyl)phosphonate with smaller lactones followed by silylation was described: see ref 10b.

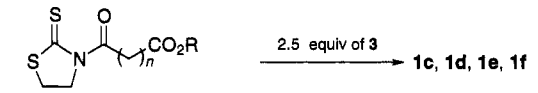
(24) Monomeric adipic acid anhydride is prepared in only modest yield from adipic acid and tends to polymerize: Hill, J. W. *J. Am. Chem. Soc.* **1930**, *52*, 4110–4114.

(25) For a first report of the acylating properties of 3-acylthiazolidine-2-thiones, see: Brown, E.; Joyeau, R.; Paterne, M. *Tetrahedron Lett.* **1977**, 2575–2578. Their amide structure instead of thioester as well as their reduction into alcohols or aldehydes were subsequently reported.[32]

(26) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394–2395.

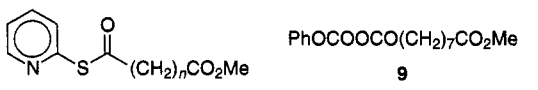
(27) Use of other solvents instead of THF gave markedly inferior yields. In the case of keto phosphonate **1e**, the use of ether or toluene gave, respectively, 48 and 20% yields.

tion of the proton NMR of the crude reaction product only showed a slight amount of attack at the ester function.[28] The small amount of symmetrical ω,ω′-bis(keto) phosphonate thus formed was easily removed after purification by chromatography on silica gel. In proton NMR, such compounds **1c–f** are essentially characterized by the methylene α to phosphorus which appeared as a doublet at *ca.* 3.1 ppm with $^1J_{PH}$ = 22.6–22.8 Hz.



7a, **7b**, **7c**: *n* = 4, 6, 7; R = Me
7d: *n* = 6; R = Et

The advantage of 3-acylthiazolidine-2-thiones as acylating reagents was more clearly evidenced by comparison with other derivatives. For instance, 2-pyridinethiol ester **8b** regioselectively reacted with **3** in THF at −90/−95 °C to afford the expected keto phosphonate **1e** in only 25% yield.[29] Compound **8a** and its homolog **8b** were prepared by reaction of **6a** and **6c** with 2,2′-dithiopyridine and triphenylphosphine in toluene. Additionally, our best result with other acylating reagents such as mixed anhydrides was obtained with **9** which even resulted in a lower yield (14%) of keto phosphonate **1e**.

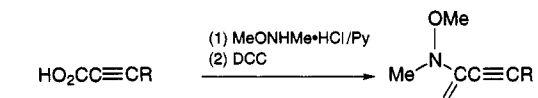


8a: *n* = 4
8b: *n* = 7

9

For synthetic purposes, it would be desirable to know how these syntheses can be extended to other types of β-keto phosphonates. For instance, we chose to investigate the influence of an unsaturation close to the carbonyl especially conjugated or separated from it by only one methylene carbon.

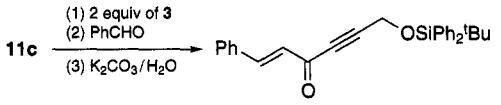
Unfortunately, we observed that by contrast to saturated analogs, 3-acylthiazolidine-2-thiones could not be suitably prepared either from 2-alkenoic or 3-alkenoic acids. The same problem arose with 2-alkynoic and 3-alkynoic acids. On the other hand, *N*-methoxy-*N*-methylamides proved to be the derivatives of choice for the preparation of γ,δ-acetylenic β-keto phosphonates **2**. First, 2-alkynoic acids **10a–c** are treated in acetonitrile with *N*,*O*-dimethylhydroxylamine hydrochloride and pyridine followed by DCC to afford the corresponding *N*-methoxy-*N*-methylamides **11a–c** in 63, 95, and 76% yield, respectively.



10a: R = $SiMe_3$
10b: R = *n*-Bu
10c: R = $CH_2OSiPh_2{}^tBu$

11a
11b
11c

Uneventfully, amides **11a** and **11b** reacted with 2 equiv of lithium reagent **3** in THF at −50 °C (0.5 h) to afford after acidification and purification, acetylenic β-keto phosphonates **2a** and **2b** in, respectively, 78 and 80% yield. With the amide **11c** functionalized by a *tert*-butyldiphenylsilyl ether, the acylation proceeded rapidly (20 min at −80 °C) but the expected β-keto phosphonate **2c** proved to be too unstable for its isolation. However, in that case, it is possible to use it *in situ* since after addition of benzaldehyde to the cooled reaction mixture, followed by potassium carbonate and water, then reaction at room temperature, the expected doubly α,β-unsaturated ketone **12** was isolated in 50% (unoptimized) yield.



12

Conclusion. We have described efficient syntheses of β-keto phosphonates bearing an ester functionality or a triple bond conjugated to the carbonyl group. They involved the use of adequately activated carboxylic electrophiles with dimethyl(lithiomethyl)phosphonate **3**. In particular, easily prepared saturated 3-acylthiazolidine-2-thiones were shown to react efficiently and with a high chemoselectivity with **3** in the presence of an ester group. On the other hand, *N*-methoxy-*N*-methylamides appeared to be the electrophiles of choice for the synthesis of conjugated acetylenic β-keto phosphonates **2**. Furthermore, such phosphonates which are accessible by these methodologies would also constitue useful intermediates in organic synthesis.[30]

Experimental Section

General. Nuclear magnetic resonance spectra were obtained in $CDCl_3$ solution using Me_4Si as an internal standard for ^1H and ^{13}C and external H_3PO_4 for ^{31}P.

Dimethyl [4-(Methoxycarbonyl)-2-oxobutyl]phosphonate (1a).[22] To a solution of dimethyl methylphosphonate (1.1 mL, 10 mmol, 2.0 equiv) in anhydrous ether (80 mL) was added dropwise while stirring (−90 °C, nitrogen) a 1.6 M solution of *n*-BuLi in hexanes (6.9 mL, 11 mmol, 2.2 equiv). After 60 min reaction at −90 °C, a solution of succinic anhydride (0.5 g, 5.0 mmol) in anhydrous THF (5 mL) was added. Transfer of the anhydride was completed by THF (2 × 1 mL). The reaction mixture was allowed to warm slowly to −5 °C, and a solution of oxalic acid (1.04 g, 11.5 mmol) in methanol (5 mL) was

(28) A reaction of an optically active 4-isopropyl-substituted 3-acylthiazolidine-2-thione with dimethyl (lithiomethyl)phosphonate, however, in the absence of any other electrophilic functionality has been reported: Astles, P. C.; Thomas, E. J. *Synlett* **1989**, 42–45.

(29) An efficient chemoselective reaction of a Grignard reagent with a 2-pyridinethiol ester in the presence of a methyl ester leading to the corresponding keto methyl ester was reported in the synthesis of (±)-pyrenophorine: Gerlach, H.; Oertle, K.; Thalmann, A. *Helv. Chim. Acta* **1977**, *60*, 2860–2865.

(30) β-Keto phosphonates were used as intermediates in total syntheses of the following compounds. Prostanoids: see refs 21a and 22. Polyether natural products: see ref 1j and references cited therein; see also: Oikawa, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1985**, *26*, 1541–1544. An inophore antibiotic: Boons, G.-J.; Lennon, I. C.; Ley, S. V.; Owen, E. S. E.; Staunton, J.; Wadsworth, D. J. *Tetrahedron Lett.* **1994**, *35*, 323–326. Macrocyclic compounds: see ref 1j and references cited therein and refs 21b and 28. Hydroxylated C-18 fatty acids metabolites: Suemune, H.; Hayashi, N.; Funakoshi, K.; Akita, H.; Oishi, T.; Sakai, K. *Chem. Pharm. Bull.* **1985**, *33*, 2168–2170. Suemune, H.; Harabe, T.; Sakai, K. *Chem. Pharm. Bull.* **1988**, *36*, 3632–3637. Eicosanoid derivatives: Nakamura, T.; Namiki, M.; Ono, K. *Chem. Pharm. Bull.* **1987**, *35*, 2635–2645. Durand, T.; Savignac, P.; Girard, J.-P.; Escale, R.; Rossi, J.-C. *Tetrahedron Lett.* **1990**, *31*, 4131–4134. Nunn, K.; Mosset, P.; Grée, R.; Saalfrank, R. W. *J. Org. Chem.* **1992**, *57*, 3359–3364. Mevinic acids and analogues: Rosen, T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 3731–3733. Heathcock, C. H.; Hadley, C. R.; Rosen, T.; Theisen, P. D.; Hecker, S. J. *J. Med. Chem.* **1987**, *30*, 1858–1873. Karanewsky, D. S.; Malley, M. F.; Gougoutas, J. Z. *J. Org. Chem.* **1991**, *56*, 3744–3747. Blackwell, C. M.; Davidson, A. H.; Launchbury, S. B.; Lewis, C. N.; Morrice, E. M.; Reeve, M. M.; Roffey, J. A. R.; Tipping, A. S.; Todd, R. S. *J. Org. Chem.* **1992**, *57*, 1935–1937. Methylenomycin B: Mikolajczyk, M.; Zurawinski, R. *Synlett* **1991**, 575–576. A taxane derivative: Pettersson, L.; Frejd, T. *J. Chem. Soc., Chem. Commun.* **1993**, 1823–1825.

added. After 30 min of further stirring at room temperature, the resulting mixture was cooled at 0 °C and an ethereal diazomethane solution [prepared, for instance, from *N*-nitroso-*N*-methylurea (2.3 g), 50% aqueous KOH (4.5 mL) in ether (60 mL)] was added until persistence of a yellow color. Enough drops of acetic acid were added to discharge the yellow color of excess diazomethane. The white precipitate of lithium oxalate was filtered off over Celite. After concentration of the filtrate, the residue was subjected either to flash chromatography on silica gel (11 g) using ethyl acetate/petroleum ether (1:1 and then 3:1) as eluent or to Kugelrohr distillation. In the latter case, dimethyl methylphosphonate was distilled off at 100 °C using a water pump and then β-keto phosphonate **1a** at 100 °C under 4−5 × 10^{-2} mbar. **1a** was obtained (0.96 g, 73%, R_f = 0.54 with CH_2Cl_2/MeOH 9:1, iodine visualization): colorless oil; IR (neat, KBr) ν 1737 (C=O ester), 1720 (C=O ketone) cm^{-1}; ^1H NMR (90 MHz) δ 3.80 (d, 6H, J_{PH} = 11.2 Hz), 3.68 (s, 3H), 3.15 (d, 2H, J_{PH} = 22.6 Hz), 2.95 (part A of an AA'BB' system, 2H, J = 6.1 Hz, J' = 6.9 Hz), 2.60 (part B of an AA'BB' system, 2H); ^{13}C NMR (22.5 MHz) δ 200.20 (J_{CP} = 6.1 Hz), 172.80, 53.05 (J_{CP} = 6.5 Hz), 51.70, 41.16 (J_{CP} = 128.4 Hz), 38.62 (J_{CP} = 1.8 Hz), 27.75; ^{31}P NMR (32.4 MHz) δ 22.25. Anal. Calcd for $C_8H_{15}O_6P$: C, 40.34; H, 6.35. Found: C, 40.37; H, 6.52.

Dimethyl [5-(Methoxycarbonyl)-2-oxopentyl]phosphonate (1b). The same procedure as described for **1a** was used with glutaric anhydride (0.57 g, 5.0 mmol) to give **1b** (0.99 g, 78%, R_f = 0.56 with CH_2Cl_2/MeOH 9:1): colorless oil; IR (neat, KBr) ν 1734 (C=O ester), 1718 (C=O ketone) cm^{-1}; ^1H NMR (90 MHz) δ 3.79 (d, 6H, J_{PH} = 11.2 Hz), 3.67 (s, 3H), 3.10 (d, 2H, J_{PH} = 22.7 Hz), 2.71 (t, 2H, J = 6.9 Hz), 2.51−2.23 (m, 2H), 2.12−1.77 (m, 2H); ^{13}C NMR (22.5 MHz) δ 201.09 (J_{CP} = 6.3 Hz), 173.39, 53.02 (J_{CP} = 6.5 Hz), 51.47, 42.87 (J_{CP} = 1.5 Hz), 41.30 (J_{CP} = 127.9 Hz), 32.72, 18.70; ^{31}P NMR (32.4 MHz) δ 22.55. Anal. Calcd for $C_9H_{17}O_6P$: C, 42.86; H, 6.79. Found: C, 42.87; H, 7.10.

Dimethyl [6-(Methoxycarbonyl)-2-oxohexyl]phosphonate (1c). To a solution of dimethyl methylphosphonate (0.66 mL, 6.0 mmol, 2.5 equiv) in anhydrous THF (48 mL) was added dropwise while stirring (−60 °C, nitrogen) a 1.6 M solution of *n*-BuLi in hexanes (3.75 mL, 6.0 mmol, 2.5 equiv). After 30 min reaction at −60 °C, the reaction mixture was cooled at −90/−95 °C and a solution of 3-acylthiazolidine-2-thione **7a** (0.63 g, 2.4 mmol) in anhydrous THF (2 mL) was added. Transfer of **7a** was completed by THF (2 × 0.5 mL). After 60 min of further reaction at −90/−95 °C, a solution of oxalic acid (0.6 g, 6.6 mmol) in THF (6 mL) was added. Stirring was continued for 30 min while the cooling bath was maintained. Precipitated lithium oxalate was filtered over Celite. The filtrate was concentrated, and the residue was subjected to flash chromatography on silica gel (12 g). First, elution with ethyl acetate/petroleum ether (1:4 and then 1:1) removed less polar byproducts including 2-mercaptothiazoline. Then, elution with ethyl acetate/petroleum ether (3:1) and ethyl acetate afforded keto phosphonate **1c** (0.39 g, 61%, R_f = 0.59 with CH_2Cl_2/MeOH (9:1)); colorless oil: IR (neat, NaCl) ν 1732 (C=O ester), 1717 (C=O ketone) cm^{-1}; ^1H NMR (90 MHz) δ 3.79 (d, 6H, J_{PH} = 11.2 Hz), 3.66 (s, 3H), 3.10 (d, 2H, J_{PH} = 22.7 Hz), 2.65 (t, 2H, J = 6.7 Hz), 2.33 (t, 2H, J = 6.6 Hz), 1.69−1.55 (m, 4H); ^{13}C NMR (22.5 MHz) δ 201.43 (J_{CP} = 6.2 Hz), 173.67, 52.99 (J_{CP} = 6.5 Hz), 51.42, 43.53 (J_{CP} = 1.5 Hz), 41.25 (J_{CP} = 128.0 Hz), 33.71, 24.17, 22.80; ^{31}P NMR (32.4 MHz) δ 22.67. Anal. Calcd for $C_{10}H_{19}O_6P$: C, 45.12; H, 7.19. Found: C, 45.11; H, 7.35.

Dimethyl [8-(Methoxycarbonyl)-2-oxooctyl]phosphonate (1d), Dimethyl [9-(Methoxycarbonyl)-2-oxononyl]-phosphonate (1e), and Dimethyl [8-(Ethoxycarbonyl)-2-oxooctyl]phosphonate (1f). The same procedure as described for **1c** was used with 3-acylthiazolidine-2-thiones **7b**, **7c**, and **7d** to give β-keto phosphonates **1d**, **1e**, and **1f** as colorless oils in 69, 65, and 70% yield, respectively. **1e** solidified on storage in freezer yielding a white solid melting at −2 to −1 °C.

1d: IR (neat, KBr) ν 1736 (C=O ester), 1716 (C=O ketone) cm^{-1}; ^1H NMR (90 MHz) δ 3.79 (d, 6H, J_{PH} = 11.2 Hz), 3.66 (s, 3H), 3.08 (d, 2H, J_{PH} = 22.8 Hz), 2.61 (t, 2H, J = 6.9 Hz), 2.30 (t, 2H, J = 7.3 Hz), 1.81−1.09 (m, 8H); ^{13}C NMR (22.5 MHz) δ 201.8 (J_{CP} = 6.1 Hz), 174.02, 53.06 (J_{CP} = 6.2 Hz), 51.38, 43.96 (J_{CP} = 1.5 Hz), 41.16 (J_{CP} = 128.3 Hz), 33.90, 28.80, 28.49, 24.71, 23.12. Anal. Calcd for $C_{12}H_{23}O_6P$: C, 48.98; H, 7.88. Found: C, 49.12; H, 8.06.

1e: IR (neat, KBr) ν 1733 (C=O ester), 1719 (C=O ketone) cm^{-1}; ^1H NMR (90 MHz) δ 3.80 (d, 6H, J_{PH} = 11.2 Hz), 3.66 (s, 3H), 3.12 (d, 2H, J_{PH} = 22.8 Hz), 2.60 (t, 2H, J = 6.9 Hz), 2.31 (t, 2H, J = 7.1 Hz), 1.72−1.25 (m, 10H); ^{13}C NMR (22.5 MHz) δ 201.81 (J_{CP} = 6.1 Hz), 174.07, 52.97 (J_{CP} = 6.5 Hz), 51.35, 44.04 (J_{CP} = 1.5 Hz), 41.30 (J_{CP} = 128.2 Hz), 34.02, 28.98, 28.92, 28.73, 24.87, 23.32. Anal. Calcd for $C_{13}H_{25}O_6P$: C, 50.64; H, 8.17. Found: C, 50.12; H, 8.28.

1f: IR (neat, KBr) ν 1731 (C=O ester), 1716 (C=O ketone) cm^{-1}; ^1H NMR (90 MHz) δ 4.12 (q, 2H, J = 7.1 Hz), 3.79 (d, 6H, J_{PH} = 11.2 Hz), 3.09 (d, 2H, J_{PH} = 22.8 Hz), 2.61 (t, 2H, J = 6.9 Hz), 2.29 (t, 2H, J = 7.1 Hz), 1.88−1.07 (11H: m, 8H and CH_3 t at 1.25 ppm, J = 7.1 Hz); ^{13}C NMR (22.5 MHz) δ 201.75 (J_{CP} = 6.3 Hz), 173.58, 60.11, 53.00 (J_{CP} = 6.5 Hz), 43.99 (J_{CP} = 1.6 Hz), 41.28 (J_{CP} = 128.4 Hz), 34.23, 28.85, 28.56, 24.78, 23.20, 14.27; ^{31}P NMR (32.4 MHz) δ 22.70. Anal. Calcd for $C_{13}H_{25}O_6P$: C, 50.64; H, 8.17. Found: C, 50.53; H, 8.49.

Dimethyl (7-Hydroxy-5-oxoheptyl)phosphonate (5). To a solution of dimethyl methylphosphonate (0.88 mL, 8 mmol, 2.0 equiv) in anhydrous THF (65 mL) was added dropwise while stirring (−90 °C, nitrogen) a 1.6 M solution of *n*-BuLi in hexanes (5.6 mL, 8.9 mmol, 2.2 equiv). After 60 min reaction at −90 °C, ε-caprolactone (0.45 mL, 4.0 mmol) was added. After 60 min further at −90 °C, a solution of oxalic acid (0.48 g, 5.3 mmol) in THF (4 mL) was added. The resulting mixture was allowed to warm to room temperature in 30 min and filtered over Celite. Concentration of the filtrate and Kugelrohr distillation of the residue afforded phosphonate **5** (0.74 g, 78%, R_f = 0.45 with CH_2Cl_2/MeOH 9:1): colorless oil; IR (neat, KBr) ν 3415 (O-H), 1714 (C=O) cm^{-1}; ^1H NMR (90 MHz) δ 3.79 (d, 6H, J_{PH} = 11.2 Hz), 3.64 (t, 2H, J = 6.1 Hz), 3.08 (d, 2H, J_{PH} = 22.7 Hz), 2.64 (t, 2H, J = 6.7 Hz), 1.85−1.13 (m, 6H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 201.90 (J_{CP} = 6.1 Hz), 61.93, 53.02 (J_{CP} = 6.5 Hz), 44.04 (J_{CP} = 1.6 Hz), 41.10 (J_{CP} = 128.6 Hz), 32.44, 25.23, 23.20; ^{31}P NMR (32.4 MHz) δ 23.15. Due to the hygroscopicity of this compound, combustion analysis was performed on its benzoate. It was prepared by reaction with benzoyl chloride in the presence of pyridine in dichloromethane. After recrystallization from an ether/petroleum ether mixture, it was obtained as white crystals melting at 45 °C. Anal. Calcd for $C_{16}H_{23}O_6P$: C, 56.14; H, 6.77. Found: C, 55.86; H, 6.66.

Dimethyl [2-Oxo-4-(trimethylsilyl)but-3-ynyl]phosphonate (2a). To a solution of dimethyl methylphosphonate (0.076 mL, 0.7 mmol, 1.3 equiv) in anhydrous THF (6 mL) was added dropwise while stirring (−60 °C, nitrogen) a 1.6 M solution of *n*-BuLi in hexanes (0.435 mL, 0.7 mmol, 1.3 equiv). After 60 min reaction at −60 °C, a solution of *N*-methoxy-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide[31] (**11a**) (100 mg, 0.54 mmol) in anhydrous THF (0.5 mL) was added. Transfer of amide was completed by THF (2 × 0.2 mL). After 30 min further reaction at −50 °C, a solution of oxalic acid (70 mg, 0.77 mmol) in THF (0.7 mL) was added. Precipitated lithium oxalate was immediately filtered over Celite. Concentration of the filtrate and removal of dimethyl methylphosphonate under vacuum afforded crude keto phosphonate **2a** (105 mg) as a yellow oil. Attempted purifications for analytical purposes either by Kugelrohr distillation or by flash chromatography on Florisil completely degraded the product: IR (neat, NaCl) ν 2091 (C≡C), 1677 (C=O) cm^{-1}; ^1H NMR (90 MHz) δ 3.83 (d, 6H, J_{PH} = 11.3 Hz), 3.32 (d, 2H, J_{PH} = 21.9 Hz), 0.17 (s, 9H); ^{13}C NMR (22.5 MHz) δ 176.97 (J_{CP} = 7.1 Hz), 101.79 (J_{CP} = 2.8 Hz), 100.23, 53.29 (J_{CP} = 6.4 Hz), 43.38 (J_{CP} = 130.3 Hz), −0.92.

Dimethyl (2-Oxooct-3-ynyl)phosphonate (2b). To a solution of dimethyl methylphosphonate (0.217 mL, 2.0 mmol, 2.4 equiv) in anhydrous THF (16 mL) was added dropwise while

(31) For the preparation of this compound, see the supplementary material.

(32) Nagao, Y.; Kawabata, K.; Seno, K.; Fujita, E. *J. Chem. Soc., Perkin. Trans. 1* **1980**, 2470−2473.

stirring (−50 °C, nitrogen) a 1.6 M solution of *n*-BuLi in hexanes (1.25 mL, 2.0 mmol, 2.4 equiv). After 30 min reaction at −50 °C, a solution of *N*-methoxy-*N*-methylhept-2-ynamide[31] (**11b**) (143 mg, 0.84 mmol) in anhydrous THF (1 mL) was added. Transfer of amide was completed by THF (2 × 0.3 mL). After 30 min further reaction at −50 °C, a solution of oxalic acid (100 mg, 1.1 mmol) in THF (1 mL) was added. Precipitated lithium oxalate was immediately filtered over Celite. Concentration of the filtrate and removal of dimethyl methylphosphonate at 80 °C under vacuum (7 mm Hg) afforded crude ketophosphonate **2b** (185 mg, 80%) as a yellow oil which appeared to be clean according to ^{13}C NMR: IR (neat, KBr) ν 2211 (C≡C), 1672 (C=O) cm^{-1}; ^1H NMR (300 MHz) δ 3.82 (d, 6H, J_{PH} = 11.2 Hz), 3.27 (d, 2H, J_{PH} = 22.1 Hz), 2.41 (t, 2H, J = 7.0 Hz), 1.67−1.51 (m, 2H), 1.52−1.36 (m, 2H), 0.93 (t, 2H, J = 7.2 Hz); ^{13}C NMR (22.5 MHz) δ 177.44 (J_{CP} = 6.9 Hz), 96.67, 81.32 (J_{CP} = 2.8 Hz), 53.10 (J_{CP} = 6.4 Hz), 43.72 (J_{CP} = 129.4 Hz), 29.63, 21.95, 18.72, 13.49.

3-[5-(Methoxycarbonyl)-1-oxopentyl]-2-thiazolidinethione (7a). To a solution of adipic acid monomethyl ester (0.40 g, 2.5 mmol) in anhydrous THF (30 mL) was added 4-(dimethylamino)pyridine (61 mg, 0.5 mmol, 0.2 equiv), 4-(dimethylamino)pyridine hydrochloride (80 mg, 0.5 mmol, 0.2 equiv), and 2-mercaptothiazoline (298 mg, 2.5 mmol, 1.0 equiv). After 5 min of stirring at room temperature, *N,N'*-dicyclohexylcarbodiimide (0.775 g, 3.75 mmol, 1.5 equiv) was added. After 8 h of further stirring at room temperature, dicyclohexylurea was removed by filtration of the reaction mixture over a small plug of silica gel using petroleum ether/CH_2Cl_2 (3:1) plus 2% Et_3N as eluent. The filtrate was concentrated, and the residue was taken up with ether (50 mL). This ethereal solution was washed twice with 0.5 M hydrochloric acid (30 mL) and then with 5% aqueous $NaHCO_3$. Drying (Na_2SO_4) and concentration afforded 3-acylthiazolidine-2-thione **7a** as a yellow oil which solidified on prolonged storage in the freezer yielding a yellow solid melting at 13 °C (0.61 g, 93%, R_f = 0.29, ether/petroleum ether (7:3)): IR (neat, KBr) ν 1735 (C=O of ester), 1700 (C=O of CON), 1367 (C=S) cm^{-1}; ^1H NMR (90 MHz) δ 4.58 (t, 2H, J = 7.5 Hz), 3.67 (s, 3H), 3.29 (t, 2H, J = 7.5 Hz), 3.27 (t, 2H, J = 7.0 Hz), 2.35 (t, 2H, J = 6.7 Hz), 1.79−1.62 (m, 4H); ^{13}C NMR (22.5 MHz) δ 201.61, 174.21, 173.67, 56.08, 51.48, 38.05, 33.72, 28.36, 24.23, 24.16. Anal. Calcd for $C_{10}H_{15}NO_3S_2$: C, 45.96; H, 5.78; N, 5.36. Found: C, 46.68; H, 5.84; N, 5.42.

3-[7-(Methoxycarbonyl)-1-oxoheptyl]-2-thiazolidinethione (7b), 3-[8-(methoxycarbonyl)-1-oxooctyl]-2-thiazolidinethione (7c), and 3-[7-(ethoxycarbonyl)-1-oxoheptyl]-2-thiazolidinethione (7d). The same procedure as described for **7a** was used with suberic acid monomethyl ester, azelaic acid monomethyl ester, and suberic acid monoethyl ester to give 3-acylthiazolidine-2-thiones **7b**, **7c**, and **7d** in, respectively, 96, 92, and 75% yield.

7b: yellow oil which solidified on storage in freezer yielding yellow crystals melting at 29−30 °C; IR (Nujol, KBr) ν 1733 (C=O of ester), 1687 (C=O of CON) cm^{-1}; ^1H NMR (90 MHz) δ 4.58 (t, 2H, J = 7.5 Hz), 3.66 (s, 3H), 3.28 (t, 2H, J = 7.5 Hz), 3.24 (pseudo dd, 2H, J = 7.6, 6.9 Hz), 2.31 (pseudo t, 2H, J = 7.2 Hz), 1.93−1.50 (m, 4H), 1.50−1.07 (m, 4H); ^{13}C NMR (22.5 MHz) δ 201.52, 174.57, 173.97, 56.11, 51.36, 38.29, 33.93, 28.82, 28.63, 28.34, 24.74, 24.50. Anal. Calcd for $C_{12}H_{19}NO_3S_2$: C, 49.80; H, 6.62; N, 4.84. Found: C, 49.79; H, 6.67; N, 4.78.

7c: yellow oil which crystallized at room temperature to afford yellow crystals melting at 40 °C (lit.[30] mp 39.5−40 °C); IR (Nujol, KBr) ν 1723 (C=O of ester), 1706 (C=O of CON), 1367 (C=S) cm^{-1}; ^1H NMR (90 MHz) δ 4.58 (t, 2H, J = 7.5 Hz), 3.66 (s, 3H), 3.30 (t, 2H, J = 7.5 Hz), 3.23 (t, 2H, J = 7.2 Hz), 2.31 (t, 2H, J = 7.2 Hz), 1.92−1.48 (m, 4H), 1.48−1.05 (m, 6H); ^{13}C NMR (22.5 MHz) δ 201.49, 174.57, 173.94, 56.13, 51.31, 38.31, 33.95, 28.94, 28.90, 28.81, 28.35, 24.81, 24.61.

7d: yellow oil which solidified on storage in freezer yielding a yellow solid melting at 18 °C; IR (neat, KBr) ν 1732 (C=O of ester), 1702 (C=O of CON), 1369 (C=S) cm^{-1}; ^1H NMR (90 MHz) δ 4.58 (t, 2H, J = 7.4 Hz), 4.13 (q, 2H, J = 7.1 Hz), 3.29 (t, 2H, J = 7.5 Hz), 3.25 (t, 2H, J = 7.2 Hz), 2.31 (t, 2H, J = 7.0 Hz), 1.76−1.31 (m, 8H), 1.26 (t, 3H, J = 7.2 Hz); ^{13}C NMR (22.5 MHz) δ 201.53, 174.68, 173.64, 60.13, 56.06, 38.32, 34.24, 28.82, 28.65, 28.30, 24.78, 24.51, 14.27. Anal. Calcd for $C_{13}H_{21}NO_3S_2$: C, 51.46; H, 6.98; N, 4.62. Found: C, 51.68; H, 7.10; N, 4.91.

(5*E*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-4-oxo-6-phenylhex-5-en-2-yne (12). To a solution of dimethyl methylphosphonate (0.080 mL, 0.74 mmol, 2.1 equiv) in anhydrous THF (5 mL) was added dropwise while stirring (−80 °C, nitrogen) a 1.6 M solution of *n*-BuLi in hexanes (0.445 mL, 0.71 mmol, 2.0 equiv). After 15 min reaction at −80 °C, a solution of *N*-methoxy-*N*-methyl-4-[(*tert* -butyldiphenylsilyl)oxy]but-2-ynamide[31] (**11c**) (135 mg, 0.35 mmol) in THF (0.5 mL) was added. Transfer of amide was completed by THF (2 × 0.2 mL). After 20 min further reaction at −80 °C, TLC monitoring showed a complete transformation of amide into keto phosphonate (R_f = 0.05, ether). Benzaldehyde (0.054 mL, 0.53 mmol, 1.5 equiv) was consequently added, and the resulting mixture was allowed to warm to −40 °C in 1 h and then to room temperature in 2.5 h. As TLC showed a partial formation of **12**, an aqueous solution (10 mL) of potassium carbonate (147 mg, 1.06 mmol, 3.0 equiv) was subsequently added. After stirring overnight at room temperature, the resulting red mixture was diluted with brine and extracted with ether. Drying ($MgSO_4$), concentration, and flash chromatography on silica gel using ether/petroleum ether (1:19) as eluent afforded acetylenic enone **12** as a yellow oil (75 mg, 50%, R_f = 0.49 with ether/petroleum ether 1:1): IR (neat, KBr) ν 2219 (C≡C), 1634 (C=O), 1598 (aromatic C=C) cm^{-1}; ^1H NMR (300 MHz) δ 7.76 (d, 1H, J = 16.1 Hz), 7.77−7.67 (m, 4H), 7.54−7.48 (m, 2H), 7.48−7.34 (m, 9H), 6.74 (d, 1H, J = 16.1 Hz), 4.57 (s, 2H), 1.11 (s, 9H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 177.73, 148.72, 135.56 (4C), 134.02, 132.53 (2C), 131.08, 130.05 (2C), 129.02 (2C), 128.62 (2C), 127.90 (4C), 127.65, 90.85, 82.45, 52.59, 26.66, 19.24.

Acknowledgment. I.D. thanks "Région Bretagne" for a doctoral fellowship.

Supplementary Material Available: Detailed characterizations of all compounds; additional procedures for 3-(trimethylsilyl)prop-2-ynoic acid (**10a**), *N*-methoxy-*N*-methyl-3-(trimethylsilyl)prop-2-ynamide (**11a**), *N*-methoxy-*N*-methylhept-2-ynamide (**11b**), **8a**, **8b**, 4-[(*tert*-butyldiphenylsilyl)oxy]but-2-yn-1-ol, 4-[(*tert*-butyldiphenylsilyl)oxy]but-2-ynoic acid (**10c**), and *N*-methoxy-*N*-methyl-4-[(*tert* -butyldiphenylsilyl)oxy]but-2-ynamide (**11c**) (11 pages). This material is contained in librairies on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Registry nos. supplied by author: 1a, 71235-01-3; **1b**, 104227-38-5; **1e**, 98442-93-4; adipic acid monomethyl ester **6a**, 627-91-8; suberic acid monomethyl ester **6b**, 3946-32-5; azelaic acid monomethyl ester **6c**, 2104-19-0; suberic acid monoethyl ester **6d**, 14113-01-0; **7c**, 74058-66-5; 3-(trimethylsilyl)prop-2-ynoic acid **10a** , 5683-31-8; 4-*tert* -butyldiphenylsilyloxybut-2-yn-1-ol, 92808-80-5.