References and Notes

(1) This paper has been presented at the 26th IUPAC Congress (Tokyo, Sept 4–10, 1977) [Japanese unexamined patent publication No. 118737 (1976) and 100434 (1977)].
(2) J. C. E. Simpson, C. M. Atkinson, K. Schofield, and O. Stephenson, *J. Chem. Soc.*, 646 (1945).
(3) (a) R. M. Acheson, "The Chemistry of Heterocyclic Compounds. Acridines", 2nd ed, Interscience, New York, London, Sydney, pp 46 and 188; (b) J. H. Adams, P. Gupta, M. S. Khan, J. R. Lewis, and R. A. Watt, *J. Chem. Soc., 2089 (1976).*
(4) R. N. Castle, "The Chemistry of Heterocyclic Compounds. Condensed pyridazines including Cinnolines and Phathalazines", Interscience, New York, London, Sydney, pp 20, 39, and 64.
(5) (a) W. L. F. Armarego, "The Chemistry of Heterocyclic Compounds. Fused Pyrimidines Part I. Quinazolines", Interscience, New York, London, Sydney, 1967, pp 39–67; (b) H. Kohl, N. J. Desouza, and P. D. Desai, *J. Med. Chem.*, **16,** 1045 (1973); (c) R. V. Coombs, R. P. Danna, M. Denzer, G. E. Hardtmann, B. Huegi, G. Koletar, J. Koletar, H. Otto, E. Jukniewicz, J. Perrine, E. I. Takesue, and J. H. Trapold, *ibid.*, **16,** 1237 (1973).
(6) (a) R. H. Wiley, "The Chemistry of Heterocyclic Compounds. Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings", Interscience, New York, London, Sydney, 1967, p 299; (b) E. Hannig, C. Kollmorgen, and M. Körner, *Pharmazie,* **31,** 534 (1976); (c) G. S. Zenchoff, A. Walser, and R. I. Fryer, *J. Heterocycl. Chem.*, **13,** 33 (1976).
(7) (a) R. C. Elderfield, "Heterocyclic Compounds", Vol. 4, Wiley, New York, N.Y., pp 45 and 60; (b) A. Walser, G. Zenchoff, and R. I. Fryer, *J. Heterocycl. Chem.*, **13,** 131 (1976).
(8) A. Walser and G. Silverman, *J. Heterocycl. Chem.*, **10,** 883 (1973).
(9) L. H. Sternbach, *Angew. Chem., Int. Ed. Engl.*, **10,** 34 (1971).
(10) G. A. Olah, "Friedel Crafts and Related Reactions", Vol. I, Interscience, New York, London, Sydney, 1964, p 100; Vol. III, pp 57 and 225.
(11) B. Staskun, *J. Org. Chem.*, **29,** 2856 (1964).
(12) M. W. Partridge, S. A. Slorach, and H. J. Vipond, *J. Chem. Soc.*, 3673 (1964).
(13) C. L. Hewett, L. J. Lermit, H. T. Openshaw, A. R. Todd, A. H. Williams, and F. N. Woodward, *J. Chem. Soc.*, 292 (1948).
(14) (a) K. Schofield and R. S. Theobald, *J. Chem. Soc.*, 796 (1949); (b) D. W. Ockenden and K. Schofield, *ibid.*, 3440 (1953).
(15) (a) L. H. Sternbach, E. Reeder, O. Keller, and W. Metlesics, *J. Org. Chem.*, **26,** 4488 (1961); (b) L. H. Sternbach, R. I. Fryer, W. Metlesics, G. Sach, and A. Stempel, *ibid.*, **27,** 3781 (1962).
(16) Reaction of dimethylaniline with benzophenone in the presence of *n*-butyllithium and *N,N,N',N'*-tetramethylethylenediamine gives exclusively the ortho addition product. R. E. Ludt, G. P. Crowther, and C. R. Hauser, *J. Org. Chem.*, **35,** 1288 (1970), and references cited therein.
(17) J. V. Braun, *Ber. Dtsch. Chem. Ges.*, **37,** 633 (1904).
(18) R. T. Puckowski and W. A. Ross, *J. Chem. Soc.*, 3555 (1959).
(19) (a) G. G. Ecke, J. P. Napolitano, and A. J. Koeka, *J. Org. Chem.*, **21,** 711 (1956); **22,** 639 (1957); (b) R. Stroh, J. Ebersberger, H. Haberland, and W. Hahn, *Angew. Chem.*, **68,** 387 (1956).
(20) H. Hoberg, *Justus Liebigs Ann. Chem.*, 183 (1974). Soon after our research succeeded, we found this report. Hoberg mentioned that analogous reactions with olefins or carbonyl compounds would be reported soon; to our knowledge, they have not yet been published.
(21) K. Niedenzu and J. W. Dawson, *J. Am. Chem. Soc.*, **81,** 5553 (1959).
(22) E. Testa, L. Fontanella, and M. Bovasa, *Chem. Abstr.*, **60,** 6848b (1964).
(23) H. C. Brown, *J. Chem. Soc.*, 1248 (1956).
(24) E. Testa, L. Fontanella, *Chem. Abstr.*, **66,** 28719c (1967).
(25) P. Oxley, M. W. Partridge, and W. F. Short, *J. Chem. Soc.*, 1110 (1947).
(26) R. P. Hullin, J. Miller, and W. F. Short, *J. Chem. Soc.*, 394 (1947).
(27) H. Hoberg and J. Barluenga Mur., *Justus Liebigs Ann. Chem.*, **733,** 141 (1970).
(28) (a) G. Kempter, P. Andratsche, D. Heilmann, H. Kransmann, and M. Mietasch, *Chem. Ber.*, **97,** 16 (1964); (b) H. Gevekoht, *Ber. Dtsch. Chem. Ges.*, **15,** 2086 (1882).
(29) P. Ruggli and H. Reichwein, *Helv. Chim. Acta,* **20,** 913 (1937).
(30) K. Dziewónski and L. H. Sternbach, *Chem. Abstr.*, **30,** 2972 (1936).
(31) S. J. Groszos and S. F. Stafiej, *J. Am. Chem. Soc.*, **80,** 1357 (1958).
(32) P. Oxley and W. F. Short, *J. Chem. Soc.*, 449 (1949).
(33) G. Kempter and E. Schiewald, *J. Prakt. Chem.*, **28,** 169 (1965).
(34) L. H. Sternbach, R. I. Fryer, O. Keller, W. Metlesics, G. Sach, and N. Steiger, *J. Med. Pharm. Chem.*, **6,** 261 (1963).
(35) E. Reeder, L. H. Sternbach, and R. I. Fryer, French Patent 1 493 255 [*Chem. Abstr.*, **69,** 67111e (1968)].
(36) A. Halasz, *Chem. Ind. (London)*, **47,** 1701 (1969).
(37) (a) M. A. Stahmann and A. C. Cope, *J. Am. Chem. Soc.*, **68,** 2494 (1946); (b) W. B. Wright, Jr., H. J. Brahander, and R. A. Hardy, Jr., *J. Org. Chem.*, **26,** 476 (1961).

Synthesis of Acetylenes from Carboxylic Acid Derivatives via β-Keto Sulfones

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Abstract: Mono- and disubstituted acetylenes **5** are synthesized from carboxylic acid derivatives via the readily accessible β-keto sulfones **3.** Reaction of esters, acid chlorides, and nitriles with lithiated derivatives of alkyl aryl sulfones affords the β-keto sulfones **3,** which are converted to the enol phosphates **4** via the sodium or potassium enolates (Y = OEt, NMe_2) or with catalysis by 4-dimethylaminopyridine (Y = OPh). Reductive elimination of the enol phosphates **4** with sodium in liquid ammonia or sodium amalgam in tetrahydrofuran leads to the alkynes **5.** This use of β-keto sulfones is also applied to the synthesis of cyclododecyne from cyclododecanone.

The carbonyl to olefin transformation is one of the most ubiquitous and useful carbon–carbon bond-forming methods in organic synthesis. Few direct means exist, however, for the analogous transformation of a carboxyl derivative to an acetylene. Moreover, the structural and regiochemical limitations of the common acetylene syntheses[2] via alkylation or dehydrohalogenation make a general procedure for the carboxyl to alkyne conversion highly desirable. Condensation of a carboxyl derivative with a phosphorus ylide, followed by pyrolysis of the resultant α-keto phosphorane, provides a solution to this problem.[3] However, this sequence has been restricted to the preparation of disubstituted alkynes conjugated to ester, nitrile, or aryl groups, and the pyrolysis conditions preclude its application to sensitive or highly functionalized molecules.

The introduction of a π bond by reductive elimination is central to a variety of alkene syntheses,[4] but its utility in the formation of alkynes has been limited because the appropriate precursors (e.g., 1,2-dihaloethylenes) have generally been prepared from the alkynes themselves. The deoxygenation of benzil by reduction of a 1,3,2-dioxaphosphole with magnesium is one exception.[2k] Because the arylsulfonyl group facilitates carbanion and therefore carbon–carbon bond formation, and both the arylsulfonyl[4g,5] and phosphate[4i,6] moieties undergo reductive removal, we chose to investigate the reaction sequence of Scheme I as a new alkyne synthesis. The successful outcome of this study and the preparation of a variety of acetylenes is presented in Table I and discussed below. α-Sulfonyl ketones **3** are also available from enolate sulfenylation[7] or sulfinylation[8] and subsequent oxidation, so this procedure is useful for the conversion of ketones to alkynes as well.

Synthesis of β-Keto Sulfones. β-Keto sulfones can be prepared in good yield by the acylation of sulfonyl carbanions with carboxylic acid chlorides and esters.[9] The initial product of the

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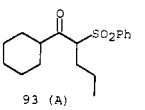
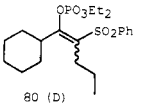
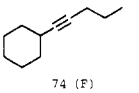
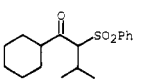
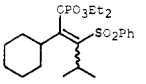
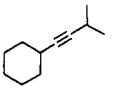
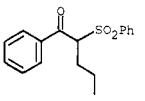
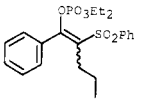
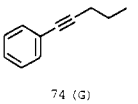
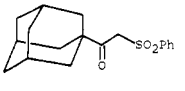
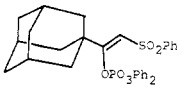
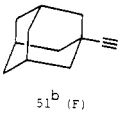
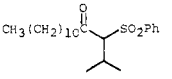
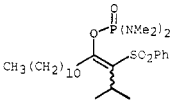
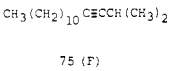
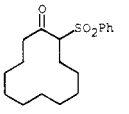
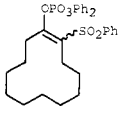
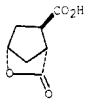
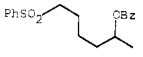
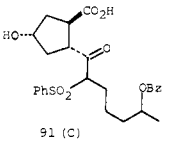
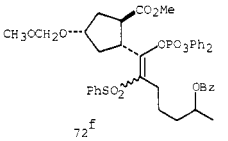
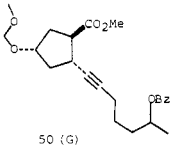
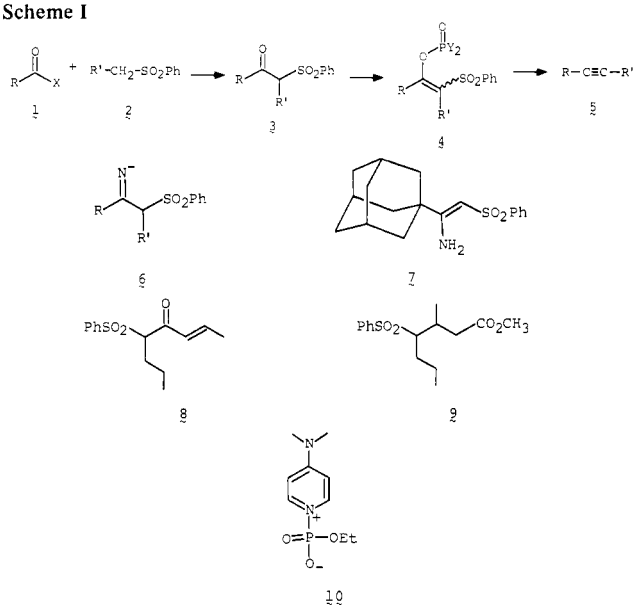
Table I. Synthesis of Alkynes via β-Keto Sulfones

entry	1	2	% yield (method)[a] 3	4	5
a	methyl cyclohexanecarboxylate	*n*-butyl phenyl sulfone	 93 (A)	 80 (D)	 74 (F)
b	methyl cyclohexanecarboxylate	*iso*-butyl phenyl sulfone	 79 (A)	 89 (D)	 78 (F)
c	methyl benzoate	*n*-butyl phenyl sulfone	 94 (A)	 93 (D)	 74 (G)
d	1-adamantanecarbonyl chloride	methyl phenyl sulfone	 70 (B)	 95 (E)	 51[b] (F)
e	undecanoyl chloride	*iso*-butyl phenyl sulfone	 71 (A)	 76 (D)	 75 (F)
f	(cyclododecanone →)		 87[c,d]	 94 (E)	 62[c,e] (F)
g			 91 (C)	 72[f]	 50 (G)

[a] A, alternating addition to **2** of *n*-butyllithium and **1**; B, one equivalent each of the sulfone dianion and **1**; C, addition of lactone **1g** to 2 equiv of LDA and the lithio derivative of **2g**; D, NaH or KH/Y_2POCl/THF-HMPA; E, 4-dimethylaminopyridine/Et_3N/$ClPO_3Ph_2$/acetonitrile; F, Na/NH_3 (l); G, 2% Na-Hg/THF. [b] 60% yield of 85% pure material. [c] Overall yield based on cyclododecanone. [d] 1, LDA/PhSSPh;[7a] 2, *m*-chloroperbenzoic acid/$CHCl_3$. [e] 74% yield of 85% pure material. [f] 1, CH_2N_2; 2, $(MeO)_2CH_2$, P_4O_{10}[10]; 3, method E above.

Scheme I



acylation, the β-keto sulfone, is more acidic than the starting sulfone, and provision for proton transfer from the product to unreacted sulfonyl carbanion must be made if the starting material is to be used efficiently.[9a] Reaction of nonenolizable esters with 1 equiv each of the sulfonyl anion and lithium diisopropylamide (LDA) affords excellent yields in appropriate cases. For example, addition of the carboxylactone **1g** to a THF solution of the anion of **2g** and 2 equiv of LDA (1 equiv is consumed by the carboxylic acid) at −78 °C affords a 91% yield of the β-keto sulfone **3g**.

The α,α-dilithio derivative of an alkyl aryl sulfone is formed on treatment with 2 equiv of butyllithium in THF in the presence of either hexamethylphosphoramide (HMPA) or *N,N,N′,N′*-tetramethylethylenediamine.[9e,f,11] This species reacts with 1 equiv of an acylating agent to form the enolate of the β-keto sulfone directly in moderate to good yield,[9e,f] without the intervention of proton-transfer reactions (Table I, entry d).

Alternatively, the problem with proton transfer may be avoided by using a nitrile as the acylating agent,[9a] because the initial condensation product **6** is not subject to proton removal, yet affords the β-keto sulfone after hydrolysis. Nitriles are

weak electrophiles, however, and deprotonation of those with α-hydrogens competes with the desired addition reaction.[9a] For instance, reaction of undecanenitrile with lithiomethyl phenyl sulfone in THF at −78 °C to room temperature provided only a 40% yield of 1-phenylsulfonyl-2-dodecanone on acidic workup. Prolonged reaction times, an excess of sulfonyl carbanion, or more vigorous conditions gave no improvement in the yield. This problem is not encountered with 1-adamantanecarbonitrile, which affords the aminovinyl sulfone **7** in 64% yield with lithiomethyl phenyl sulfone in THF/HMPA after 4 h at reflux. The β-keto sulfone **3d** is then obtained in quantitative yield with sulfuric acid in aqueous methanol. Nonetheless, reaction of the dilithio sulfone with the acid chloride **1d** is more efficient and experimentally easier in this case (Table I, entry d).

A fourth sequence involves formation of the sulfonyl carbanion with 1 equiv of butylithium and alternate addition of 0.5 equiv of acylating agent, 0.5 equiv of butyllithium, 0.25 equivalent of acylating agent, and so on. Three cycles of this procedure consume, theoretically, $\frac{7}{8}$ = 88% of the starting sulfone and in many instances is preferred over the less complicated methods above (entries a–c, e). For instance, we obtained a 75% yield of β-keto sulfone **4c** by condensation of methyl benzoate with α,α-dilithiobutyl phenyl sulfone; the alternate procedure afforded a 94% yield (82% based on starting sulfone).

The synthesis of unsaturated β-keto sulfones such as **8** by an acylation procedure is foiled by the tendency of sulfonyl carbanions to add in a 1,4 manner to unsaturated esters. This reaction, previously reported for allylic sulfones,[12] pertains to the alkyl derivatives as well. Addition of methyl crotonate to a THF solution of α-lithiobutyl phenyl sulfone at −78 °C failed to give even a trace of β-keto sulfone **8,** affording instead the γ-sulfonyl ester **9** in quantitative yield. This potentially useful synthetic transformation[13] is all the more interesting because **9** was formed as a *single diastereomer.* ^{13}C NMR cleanly resolved the stereoisomer resonances in an epimerized mixture (2 equiv of LDA/THF at −78 °C; acetic acid quench) and showed that less than 1% of the crude addition product could have been the minor diastereomer. An attempt to obtain the β-keto sulfone **8** by acylating the sulfonyl carbanion with crotonyl chloride (0.5 equiv) also failed to give any products containing a double bond.

2-Phenylsulfonylcyclododecanone (**3f**) was prepared by oxidation of the corresponding sulfide[7] with 2 equiv of *m*-chloroperbenzoic acid. No product resulting from Baeyer–Villiger oxidation was seen, and the sulfonyl ketone was obtained in excellent yield (entry f).

Enol Phosphorylation. Direct phosphorylation of the lithium enolate of the β-keto sulfone as generated in the acylation reaction did not prove practicable for two reasons. The equivalent of alkoxide formed in the ester acylations would have consumed 1 equiv of phosphorylating agent and subsequently presented a purification problem. More importantly, these stabilized lithium enolates do not react at an appreciable rate with diethyl or diphenyl phosphorochloridate, even in the presence of HMPA, in contrast to the behavior of simple ketone enolates.[6b,d] The sodium and potassium enolates, on the other hand, are phosphorylated by these reagents in a short time at room temperature, although the reaction of the hindered enolate derived from the adamantyl ketone **3d** remains sluggish.

A milder procedure was required in the case of the complex β-keto sulfone **3g,** which was not cleanly phosphorylated using either potassium or sodium hydride. We found that 4-dimethylaminopyridine (DMAP) exerts a powerful catalytic effect in combination with triethylamine as proton acceptor and diphenyl phosphorochloridate as phosphorylating agent in acetonitrile.[14] Using 0.2 equiv of DMAP, an exothermic reaction ensues with the cyclic β-keto sulfone **3f,** and even the hindered adamantyl compound **3d** is completely phosphorylated in 15 min at 70 °C. This catalysis, which does not extend to diethyl phosphorochloridate or to reaction in THF, is probably due to the intermediacy of 4-dimethylamino-1-(diphenoxyphosphinyl)pyridinium chloride, in analogy to the mechanism of acyl transfer with DMAP catalysis.[14] Diethyl phosphorochloridate is ineffective because it reacts with DMAP in acetonitrile with precipitation of the inner salt **10.**

Phosphorylation with *N,N,N′,N′*-tetramethylphosphorodiamidic chloride was also investigated,[6d] although its poor reactivity, even in the presence of DMAP, detracts from its usefulness. An excess of reagent and prolonged reaction time are required, although in some instances it may be the derivative of choice (e.g., entry e).

Reductive Elimination. Unless precluded by another functionality in the molecule, sodium metal in liquid ammonia reduces the enol phosphates most cleanly and gives the acetylenes in the highest yield. Although alkynes can be reduced to alkenes under these conditions, for the aliphatic derivatives the reductive elimination is so much faster that this side reaction can be prevented if the blue color of the solvated electron is never allowed to persist. Small pieces of clean sodium are added to a vigorously stirred solution of the enol phosphate in liquid ammonia, with THF as cosolvent if necessary, until a blue color permeates the solution. The excess reducing agent is immediately quenched with ammonium chloride or acetic acid, and the product is isolated in the usual manner. The only significant overreduction to alkene occurs with 1-ethynyladamantane, **5d** (to the extent of 15%), as expected for the more readily reduced monosubstituted alkyne, and with cyclododecyne (**5f**) which is contaminated with about 6% of a cis/trans mixture of cyclododecene.

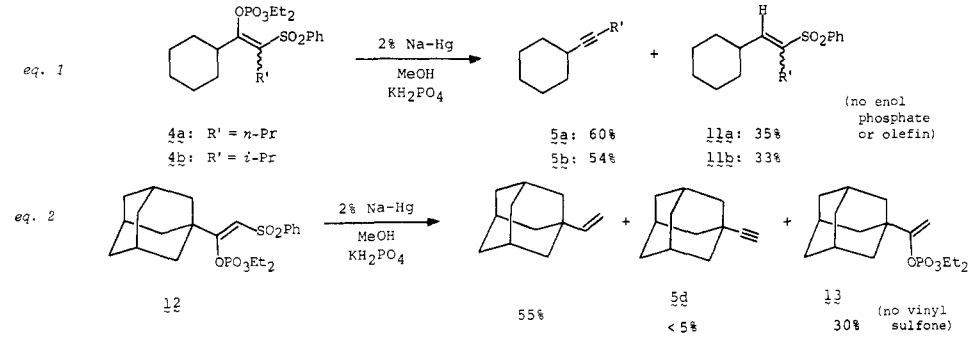
Arylacetylene **5c** is further reduced to pentylbenzene under these conditions. The benzyl ether and ester moieties of **4g** are incompatible with a dissolving metal reduction as well. The use of sodium amalgam in THF avoids overreduction in these cases, although with this reagent some P–O bond cleavage occurs, affording β-keto sulfone (**3**) as a byproduct on workup.

This cleavage is more important for less sterically encumbered enol phosphates such as **4** (R = *n*-decyl; R′ = *i*-Pr; Y = OEt) and **4f.** Even sodium/ammonia reduction results in the formation of 5–10% of 2-methyl-4-tetradecanone and cyclododecanone, respectively. On the other hand, reduction of the *N,N,N′,N′*-tetramethylphosphorodiamide derivative **4e** avoids formation of the ketone almost entirely, and the alkyne **5e** is formed cleanly.

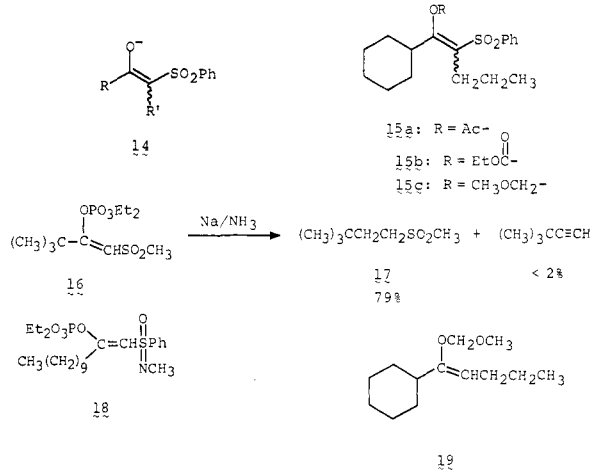
Mechanistic Implications. Both the arenesulfonyl[5] and phosphate[6] groups undergo reductive cleavage from olefinic carbon; hence, there is no a priori indication of the direction of electron flow in the reaction under consideration. Furthermore, the results outlined in Scheme II indicate that, under protic conditions, either group may be lost first. Sodium amalgam reduction of the diethyl enol phosphates in methanol occurs with a significant amount of stepwise cleavage, affording both vinyl sulfones and vinyl phosphates as products (eq 1 and 2). 1-Ethynyladamantane is stable to these conditions; 1-vinyladamantane must therefore arise from stepwise cleavage of the sulfonyl and phosphate moieties.

In a recent study on the mechanism of reductive cleavage of aryl phosphates,[15] Closson et al. showed that the preference for P–O bond cleavage or C–O bond cleavage depends upon the concentration and reducing power of the electron donor. C–O bond cleavage is favored under powerful reducing conditions; P–O cleavage arises under milder conditions. Our results are qualitatively consistent with this scheme, in that sodium amalgam leads to much more material derived from the

Scheme II



enolate **14** than sodium in ammonia does. Although this behavior implicates the phosphate moiety as the electron acceptor, the phosphate is not indispensible. Enol acetate **15a** and enol carbonate **15b** are reduced with sodium in ammonia or with sodium amalgam in buffered methanol to form 1-cyclohexyl-1-pentyne (**5a**), contaminated with comparable amounts of 1-cyclohexyl-1-pentanone.



On the other hand, reductive elimination requires the *arylsulfonyl* moiety,[5a] as shown by the fact that the methyl sulfone **16** gives the saturated sulfone **17** and only a trace of *tert*-butylacetylene with sodium in ammonia.

Other Routes Investigated. We studied a variety of reducing agents in an attempt to uncover milder conditions for the elimination. Chromous ion is very effective in the reductive elimination of vicinal dihalides;[16] however, enol phosphate **4c** is unaffected by chromous acetate in DMF or chromous chloride in aqueous DMF. Aluminum amalgam reduces aryl arylvinyl sulfones to the olefins in aqueous THF,[5b] but it does not react with the enol phosphate derivatives (**4**) under either aprotic or protic conditions. *S*-Arylsulfoximines are more susceptible to reductive cleavage than are the corresponding sulfones,[17] and reaction of the β-keto sulfoximine enol phosphate **18** with aluminum amalgam in aqueous THF affords a small amount of the primary acetylene, but the procedure is not synthetically practical. Reduction of the enol ether **15c** with sodium in ammonia does not give any acetylene, only enol ether **19.** The vinyl carbanion, generated directly in the cleavage of the sulfonyl moiety or by further reduction of a radical intermediate, undergoes protonation by ammonia faster than expulsion of the alkoxide ion. In the absence of any proton source, using sodium naphthalenide in THF,[4c] alkynes are formed from the enol ethers of β-keto sulfones, but these strongly basic conditions cause alkyne-allene isomerization as well and we did not pursue this lead further.

Experimental Section

Melting points were determined with a Büchi or Meltemp melting-point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 710 spectrophotometer.

^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian Associates Model T-60 or Hitachi-Perkin-Elmer Model R-24B spectrometer. Chemical shifts are reported in parts per million on the δ scale relative to tetramethylsilane as internal standard. Data are presented as follows: chemical shift (multiplicity, integrated intensity, coupling constants, assignment).

^{13}C NMR spectra were recorded in $CDCl_3$ on a Nicolet Model TT23 spectrometer (25.14 MHz). Chemical shifts are reported in parts per million on the δ scale, referenced to $CDCl_3$ as 77.0-ppm relative to tetramethylsilane. Data are presented as follows: chemical shift (multiplicity in off-resonance decoupled spectrum, assignment).

Tetrahydrofuran (THF) was dried by distillation from sodium benzophenone ketyl, hexamethylphosphoric triamide (HMPA) by fractional distillation from sodium at reduced pressure, and ammonia by distillation from sodium. Unless otherwise specified, reaction workups culminated in drying the solvent over anhydrous $MgSO_4$ and removing the solvent by evaporation at reduced pressure, distillations involved bulb to bulb distillation using a Kugelrohr oven, at the oven temperature and pressure indicated, and the chromatographic adsorbant was Davison Grade 923 silica gel, 100-200 mesh, eluted with the indicated solvent.

β-Keto Sulfones. 1-Cyclohexyl-2-phenylsulfonyl-1-pentanone (3a). A solution of 10.0 g (50.5 mmol) of butyl phenyl sulfone[18] in 60 mL of THF was stirred under nitrogen at −78 °C and 51.7 mmol of an *n*-butyllithium–hexane solution was added via syringe. After 15 min, 3.60 mL (25.2 mmol) of methyl cyclohexanecarboxylate was added, resulting in gradual dissipation of the yellow color of the α-lithio sulfone and precipitation of the gummy enolate over a 30-min period. The mixture became homogeneous upon the addition of 70 mL of THF and 5 mL of HMPA. A second portion of butyllithium (25.8 mmol) was added, followed in 15 min by 1.80 mL (12.6 mmol) of the ester. After 30 min, this procedure was repeated with 13 mmol of butyllithium and 6.3 mmol of ester. The reaction mixture was brought to room temperature and washed with aqueous NH_4Cl, water, and brine, dried, and concentrated. The crude product was crystallized from 60 mL of hexane and 5 mL of diisopropyl ether to give 12.71 g (93%) of the β-keto sulfone **3a:** mp 74–76 °C; ^{1}H NMR δ 2.7 (m, 1, >CHCO), 4.28 (t, 1, SO_2CHCO); IR ($CHCl_3$) 1150, 1310 (SO_2), 1715 (C=O) cm^{-1}. Recrystallization from hexane afforded a sample for analysis: mp 75–75.5 °C.

Anal. ($C_{17}H_{24}O_3S$) C, H, S.

The following β-keto sulfones were prepared in a similar manner. All gave satisfactory combustion analyses (C, H, S).

1-Cyclohexyl-3-methyl-2-phenylsulfonyl-1-butanone (3b).[19] Acylation step performed at 25 °C (79% yield): mp 108–109 °C (diisopropyl ether); ^{1}H NMR δ 0.92 (d, 3, CH_3), 1.20 (d, 3 CH_3), 4.15 (d, 1, J = 9 Hz, SO_2CHCO); IR ($CHCl_3$) 1150, 1310 (SO_2), 1715 (C=O) cm^{-1}.

1-Phenyl-2-phenylsulfonyl-1-pentanone (3c): 94% yield; mp 79–82 °C (diisopropyl ether); ^{1}H NMR δ 5.13 (t, 1, J = 7 Hz, SO_2CHCO); IR ($CDCl_3$) 1140, 1310 (SO_2), 1680 (C=O) cm^{-1}.

2-Methyl-3-phenylsulfonyl-4-tetradecanone (3e). Acylation with the acid chloride (71% yield after chromatography): ^{1}H NMR δ 3.9 (d, 1, J = 9 Hz, SO_2CHCO); IR (film) 1160, 1320 (SO_2), 1710 (C=O) cm^{-1}.

3,3-Dimethyl-1-methylsulfonyl-2-butanone. Reaction of dimethyl sulfone with pivaloyl chloride (94% yield): mp 61–62 °C (diisopropyl

ether); ^{1}H NMR δ 1.25 (s, 9), 3.17 (s, 3), 4.25 (s, 2); IR ($CDCl_3$) 1140, 1330 (SO_2), 1710 (C=O) cm^{-1}.

1-(1-Adamantyl)-2-phenylsulfonylethanone (3d). (A) Reaction of Dilithiomethyl Phenyl Sulfone with 1-Adamantanecarbonyl Chloride. A mixture of 15.6 g (0.10 mmol) of methyl phenyl sulfone, 150 mL of THF, 100 mL of HMPA, and 0.21 mmol of an *n*-butyllithium–hexane solution was stirred at 0 °C under nitrogen for 20 min. To the resulting brown suspension was added a solution of 19.9 g (0.10 mmol) of 1-adamantanecarbonyl chloride in 30 mL of THF. Stirring was continued at 0 °C for 20 min before the enolate was quenched with aqueous H_2SO_4. The mixture was extracted three times with ethyl acetate, and the combined organic layer was washed three times with water and with brine, dried, and concentrated to a moist solid. Direct recrystallization from diisopropyl ether gave 18.4 g of pure product, mp 109–111 °C, and chromatography (1:1 ether/petroleum ether) of the mother liquor provided more, for a combined yield of 70%. Recrystallization from 1:1 diisopropyl ether/ethyl acetate afforded a sample for analysis: mp 112–113 °C; ^{1}H NMR δ 4.30 (s, 2, $COCH_2SO_2$); IR ($CHCl_3$) 1155, 1220 (SO_2), 1707 (C=O) cm^{-1}.

Anal. ($C_{18}H_{22}O_3S$) C, H, S.

(B) Reaction of Lithiomethyl Phenyl Sulfone with 1-Adamantanecarbonitrile. 1-Amino-1-(1-adamantyl)-2-phenylsulfonylethene (7). To a stirred solution of 1.56 g (10 mmol) of methyl phenyl sulfone in 5 mL of THF and 5 mL of HMPA under nitrogen was added 10.5 mmol of an *n*-butyllithium–hexane solution and, 10 min later, 1.61 g (10 mmol) of 1-adamantanecarbonitrile. The deep-burgundy solution was kept at 75 °C for 4 h and at 25 °C for 12 h before it was quenched with aqueous NH_4Cl and extracted twice with ethyl acetate. The organic layer was washed twice with water and with brine, dried, and concentrated to a thick gum consisting of a 5:1 ratio of enamine **7** and starting sulfone. Crystallization from CCl_4 afforded 1.97 g (62%) of pure material: mp 127–130 °C; ^{1}H NMR δ 4.77 (s, 1, =CH-), 6.0 (br s, 2, NH_2); IR ($CDCl_3$) 1075 (CN), 1130, 1280 (SO_2), 1545 (NH), 1615 (C=C), 3380, 3525 (NH) cm^{-1}. An analytical sample was purified by recrystallization from diisopropyl ether: mp 138–140 °C.

Anal. ($C_{18}H_{23}NO_2S$) C, H, N, S.

The enamine **7** was converted in quantitative yield to the β-keto sulfone **3d** on standing in equal parts of methanol and 2 N H_2SO_4 for 30 min at 25 °C.

1α,2β,4β-2-(6-Benzyloxy-1-oxo-2-phenylsulfonylheptyl)-4-hydroxycyclopentanecarboxylic acid (3g). To a solution of 4.82 g (14.5 mmol) of 5-benzyloxyhexyl phenyl sulfone[21] (**2g**) and 4.7 mL (33.4 mmol) of diisopropylamine in 90 mL of THF stirred under nitrogen at −78 °C was added 45.7 mmol of an *n*-butyllithium–hexane solution. After stirring the yellow solution for 10 min, 2.22 g (14.2 mmol) of *exo*-3-oxo-2-oxabicyclo[2.2.1]heptane-5-carboxylic acid[21] (**1g**) in 90 mL of THF was added over a 5-min period. The mixture was stirred at −78 °C for 15 min, warmed gradually to 25 °C, and partitioned between ether and ice water. The organic layer was extracted with 5% $NaCO_3$, and the combined aqeuous phase was washed with ether, acidified (pH 2), and extracted with ether. The ether layer was washed with water and brine, dried, and concentrated to give 6.32 g (91% yield) of analytically pure β-keto sulfone **3g** as a thick syrup: ^{1}H NMR δ 1.10 (d, 3, J = 6 Hz, CH_3), 0.95–2.28 (m, 10), 2.78–4.00 (m, 4), 4.32–4.42 (m, 4, >CHO), 7.25 (s, 5, Ph), 7.4–7.9 (m, 5, $PhSO_2$); IR (film) 1150, 1315 (SO_2), 1450 (CH_2), 1710 (C=O), 3400 (OH) cm^{-1}.

Anal. ($C_{26}H_{32}O_7S$) C, H, S.

2-Phenylsulfonylcyclododecanone (3f). The procedure of Trost, Salzmann, and Hiroi[7a] was used to prepare 2-phenylthiocyclododecanone from 4.73 g (26.0 mmol) of cyclododecanone. The crude product of this reaction was oxidized to the sulfone with 2.2 equiv of *m*-chloroperbenzoic acid in $CHCl_3$ (20 mL/g of keto sulfide) at 0 °C for 30 min. The reaction mixture was washed with 2 N NaOH, dried, and concentrated, and the crude product was crystallized from diisopropyl ether to give the β-keto sulfone **3f** in 87% yield (based on cyclododecanone); ^{1}H NMR δ 2.80 (t, 2, CH_2CO), 4.25 (dd, J = 4, 10 Hz, $COCHSO_2$); IR ($CHCl_3$) 1150, 1310 (SO_2), 1712 (C=O) cm^{-1}. Recrystallization from diisopropyl ether provided a sample for analysis: mp 113–114 °C.

Anal. ($C_{18}H_{26}O_3S$) C, H, S.

Enol Phosphates. 1-Cyclohexyl-1-(diethoxyphosphinyl)oxy-2-phenylsulfonyl-1-pentene (4a). A 33-mmol sample of sodium hydride was suspended in 40 mL of THF and 10 mL of HMPA at 25 °C, and 8.13 g (26.4 mmol) of β-keto sulfone **3a** was added. When hydrogen evolution ceased, the mixture was cooled in an ice bath while 4.4 mL (30.4 mmol) of diethyl phosphorochloridate was added. Stirring was continued at 25 °C for 18 h before the mixture was partitioned between ethyl acetate and aqueous NH_4Cl. The organic layer was washed with water and brine, dried, and concentrated to give a crude product which was purified by chromatography (15% ether in $CHCl_3$), giving 4.17 g (80%) of the oily enol phosphate **4a**, as a mixture of stereoisomers. An analytical sample was prepared by distillation [150 °C (0.025 Torr)]: IR (film) 1030 (P=O), 1160, 1300 (SO_2), 1605 (C=C) cm^{-1}. The stereoisomers could be resolved chromatographically; the less polar isomer was assigned the E configuration by comparison of the ^{1}H-NMR spectra of the two compounds[22]: ^{1}H NMR (less polar isomer) δ 2.46 [t, 2, J = 7.5 Hz, [-$CH_2C(SO_2)$=], 3.33 [m, 1, >CHC(O)=]; (more polar isomer) δ 2.3 (t, 2, J = 8 Hz, -$CH_2C(SO_2)$=], 2.3 [m, 1, >CHC(O)=].

Anal. ($C_{21}H_{33}O_6PS$) C, H, P, S.

The following enol phosphates were prepared in a similar manner. All gave satisfactory combustion analyses (C, H, P, S).

1-Cyclohexyl-1-(diethoxyphosphinyl)oxy-3-methyl-2-phenylsulfonyl-1-butene (4b): 89% yield after chromatography; ^{1}H NMR δ 1.1 (t, 6, J = 7 Hz, CH_3CO), 3.97 and 3.93 (two dq, 4, J = 7 Hz, -CH_2O of two stereoisomers); IR (film) 1050 (P=O), 1150, 1300 (SO_2), 1607 (C=C) cm^{-1}.

1-(Diethoxyphosphinyl)oxy-1-phenyl-2-phenylsulfonyl-1-pentene (4c). Using potassium hydride (93% yield): mp 72–73 °C (diisopropyl ether); ^{1}H NMR δ 0.75 (t, 3, J = 7 Hz), 1.0 (t, 6, J = 7 Hz), 1.5 (m, 2), 2.3 (t, 2, J = 7 Hz), 3.42 (dq, J = 7 Hz), 7.3–8.2 (m, 5); IR (film) 1040 (P=O), 1150, 1300 (SO_2), 1630 (C=C) cm^{-1}.

1-(1-Adamantyl)-1-(diethoxyphosphinyl)oxy-2-phenylsulfonylethene (12): 69% yield based on unrecovered starting material; ^{1}H NMR δ 1.35 (dt, 6, J = 1.5, 7 Hz, CH_3), 4.27 (dq, 4, J = 7 Hz, OCH_2), 5.79 (d, 1, J = 1.7 Hz, -OCH=); IR (film) 960, 1030 (P=O), 1150, 1290 (SO_2), 1620 (C=C) cm^{-1}.

2-(Diethoxyphosphinyl)oxy-3,3-dimethyl-1-methylsulfonyl-1-butene (16). Reaction run at 55 °C (88% yield after chromatography): mp 61–65 °C (diisopropyl ether); ^{1}H NMR δ 1.27 (s, 9), 1.37 (dt, 6, J = 2, 7 Hz), 3.20 (s, 3), 4.28 (dq, 4, J = 7 Hz), 6.0 (d, 1, J = 2 Hz); IR (film) 1040 (P=O), 1140, 1300 (SO_2), 1625 (C=C) cm^{-1}.

1-(1-Adamantyl)-1-(diphenoxyphosphinyl)oxy-2-phenylsulfonylethene (4d). A mixture of 4.5 g (14.15 mmol) of β-keto sulfone **3d**, 15 mL of dry CH_3CN, 3.52 mL (17.0 mmol) of diphenyl phosphorochloridate, 2.8 mL (20 mmol) of triethylamine, and 0.35 g (2.8 mmol) of 4-dimethylaminopyridine was stirred at 70 °C for 30 min. The mixture was cooled and partitioned between $CHCl_3$ and water, and the organic layer was washed with 2 N H_2SO_4, saturated $NaHCO_3$, and brine, dried, and concentrated to a semisolid, which was triturated with ether to give 7.37 g (95%) of the enol phosphate **4d** as colorless crystals, mp 138–139 °C. Recrystallization from ethyl acetate provided an analytical sample: mp 140–141 °C; ^{1}H NMR δ 6.02 (d, 1, J = 2 Hz, =CH-), 7.25 (s, 10), 7.4–8.2 (m, 5); IR ($CHCl_3$) 960 (P=O), 1170, 1310 (SO_2), 1600, 1630 (C=C) cm^{-1}.

Anal. ($C_{30}H_{31}O_6PS$) C, H, P, S.

The following enol phosphates were prepared in a similar manner. Both gave satisfactory combustion analyses (C, H, P, S) after chromatographic purification.

1-(Diphenoxyphosphinyl)oxy-2-phenylsulfonylcyclododecene (4f): 94% yield; ^{1}H NMR δ 1.0–2.8 (m, 20), 7.0–8.2 (m, 15); IR ($CHCl_3$) 960 (P=O), 1150, 1300 (SO_2), 1595, 1630 (C=C) cm^{-1}.

Methyl 1α,2β,4β-2-(6-Benzyloxy-1-[diphenoxyphosphinyl]oxy-2-phenylsulfonyl-1-heptenyl)-4-methoxymethoxycyclopentanecarboxylate (4g). Reaction of the methyl ester methoxymethyl ether, prepared in 80% yield from the hydroxy acid **3g** with CH_2N_2 and $CH_3OCH_2OCH_3/P_4O_{10}$[10] (91% yield): ^{1}H NMR δ 1.0 (d, 3, J = 6 Hz, CH_3), 3.25 (s, 3), 3.55 (s, 3), 4.73 [m, 1, H (4)], 4.33 (br s, 2, $PhCH_2O$), 4.45 (s, 2, OCH_2O), 7.15 (s, 5, Ph), 7.20 (s, 10, PhO), 7.4–8.0 (m, 5, $PhSO_2$); IR (film) 1030 (P=O), 1155, 1305 (SO_2), 1595, 1635 (C=C), 1735 (C=O) cm^{-1}.

4-(Bis[dimethylamino]phosphinyl)oxy-2-methyl-3-phenylsulfonyl-3-tetradecene (4e). To a 3.28-mmol sample of potassium hydride was added a solution of 1.0 g (2.74 mmol) of β-keto sulfone **3e** in 15 mL of THF. Two milliliters (13.5 mmol) of *N,N,N',N'*-tetramethylphosphorodiamidic chloride was introduced, and the reaction was allowed to proceed at 25 °C for 20 h. The mixture was partitioned between ether and water, and the organic layer was washed with aqueous $NaHCO_3$ and brine, dried, and concentrated to give 1.05 g (76%) of the oily enol phosphorodiamidate **4e.** Chromatography (ethyl

acetate) provided an analytical sample and separated the stereoisomers; the less polar fraction was assigned the *E* configuration based on comparison of the ^{1}H NMR spectra:[22] ^{1}H NMR (less polar isomer) δ 1.43 [d, 6, J = 7.5 Hz, -CH(C**H**$_3$)$_2$], 2.58 (d, 12, J = 10.5 Hz, NC**H**$_3$); IR (film) 1000 (P=O), 1150, 1310 (SO_2), 1617 (C=C); (more polar isomer) δ 1.21 [d, 6, J = 7.5 Hz, -CH(C**H**$_3$)$_2$], 2.72 (d, 12, J = 10.5 Hz, NC**H**$_3$); IR (film) 990 (P=O), 1155, 1310 (SO_2), 1620 (C=C).

Anal. ($C_{25}H_{45}O_4N_2PS$) C, H, N, P, S.

Reductions. General Procedure for Sodium–Ammonia Reductions. In an oven-dried, three-neck round-bottom flask equipped with nitrogen inlet, dry ice condenser, and magnetic stir bar is placed a THF solution of the substrate. Ammonia is distilled from a blue sodium solution and condensed into the flask, and small, clean pieces of sodium metal are introduced slowly to the vigorously stirring solution until a dark blue color persists throughout the mixture. Solid NH_4Cl or acetic acid is added to quench the excess reductant, and the ammonia is allowed to evaporate without external heating. The residue is partitioned between water and pentane or ether, and the organic layer is washed twice with 2 N NaOH and with brine, and dried. The solvents are removed by distillation through a Vigreux column at atmospheric pressure, and the alkyne is finally distilled (bulb to bulb) with a Kugelrohr oven.

The following alkynes were prepared in this manner. Satisfactory combustion analyses were obtained for all new compounds after purification by preparative VPC (SE-30).

1-Cyclohexyl-1-pentyne (5a): 74% yield after distillation [140 °C (35 Torr)]; VPC analysis indicated less than 2% contamination by other materials; ^{13}C NMR δ 84.4 and 79.6 (s, C≡C), 33.1, 25.9, 24.8, 22.5, 20.6 (t, CH_2), 29.1 (d, CH), 13.1 (q, CH_3); ^{1}H NMR δ 0.97 (t, 3), 2.14 (t, 2, ≡CC**H**$_2$–); IR (film) 1453 (CH_2), 2875, 2950 (CH) cm^{-1}.

1-Cyclohexyl-3-methyl-1-butyne (5b): 78% yield after distillation [150 °C (35 Torr)]; ^{13}C NMR δ 85.7 and 83.4 (s, C≡C), 33.2, 26.0, and 24.8 (t, $-CH_2-$), 29.0 and 23.4 (d, >CH–), 20.4 (q, $-CH_3$); ^{1}H NMR δ 1.13 [d, 6, J = 7 Hz, -CH(C**H**$_3$)$_2$]; IR (film) 1450 (CH_2), 2875, 2950 (CH) cm^{-1}.

2-Methyl-3-tetradecyne (5e). Reduction of the phosphorodiamidate **4e** [75% yield after distillation; 100 °C (0.1 Torr)]. VPC analysis indicated less than 2% contamination by other materials: ^{13}C NMR δ 85.6 and 79.3 (s, C≡C); ^{1}H NMR δ 0.87 (br t, 3, CH_3), 1.13 (d, 6, J = 7 Hz), 1.30 (br s, 18, CH_2); IR (film) 1460 (CH_2), 2870, 2940 (CH) cm^{-1}.

Cyclododecyne (5f).[2f,23] Reduction performed at −78 °C, acetic acid quench [74% overall yield based on cyclododecanone, after distillation; 150 °C (20 Torr)]. This material was shown by NMR to contain about 6% cyclododecene and 8% cyclododecanone: ^{13}C NMR δ 81.1 (s, C≡C), 25.6, 25.4, 24.8, 24.5, 18.3 (t, $-CH_2-$); ^{1}H NMR δ 1.3–1.8 (m, 16, CH_2), 2.2 (br, 4, $-CH_2C$), 2.5 [t, CH_2C(=O) contaminant], 5.3 (t, olefin contaminant); IR (film) 1450, 1460 (CH_2), 2870, 2930 (CH) cm^{-1}.

1-Ethynyladamantane (5d). A suspension of 3.0 g (5.45 mmol) of enol phosphate **4d** in 20 mL of THF and 100 mL of ammonia was stirred rapidly and treated with small pieces of clean sodium at such a rate that the enol phosphate was able to dissolve before the blue color of excess sodium appeared, at which point NH_4Cl was added. The reaction mixture was worked up as described above to give 522 mg (60%) of a semisolid after distillation [150 °C (25 Torr)]. The ^{1}H NMR spectrum revealed the presence of 15% 1-vinyladamantane; the acetylene could be purified by recrystallization from methanol: mp 80–81 °C (lit.[24] 83 °C); ^{13}C NMR δ 92.3 (≡C–), 66.5 (≡CH), 42.5, 36.1, 27.7; ^{1}H NMR δ 2.03 (s, 1, ≡C–H); IR (film) 2120 (C≡C), 3320 (≡C–H) cm^{-1}.

3,3-Dimethylbutyl Methyl Sulfone (17). The enol phosphate **16** (3.0 g, 9.6 mmol) was dissolved in 60 mL of ammonia and reduced according to the general procedure. After evaporation of the ammonia, the mixture was partitioned between ether and water, and the organic layer was washed with brine, dried, and concentrated to afford 1.23 g (79%) of crystalline sulfone **17:** ^{13}C NMR δ 42.3 (t, CH_2SO_2), 39.7 (q, CH_3SO_2), 34.7 (t, CCH_2C), 29.4 (s, >C<), 28.4 [q, $(CH_3)_3C$]; ^{1}H NMR δ 1.1 (s, 9), 1.8 (m, 2), 3.0 (s, 3), 3.1 (m, 2); IR (film) 1140, 1300 (SO_2). Recrystallization from diisopropyl ether provided an analytical sample, mp 61–62.5 °C.

Anal. ($C_7H_{16}O_2S$) C, H, S.

1-Phenyl-1-pentyne (5c). A mixture of 2.1 g (4.8 mmol) of the enol phosphate **4c** and 25 g of 2% sodium amalgam in 10 mL of dry THF was stirred without external cooling for 20 min. The mixture was diluted with ether, washed twice with 2 N NaOH and with brine, dried (K_2CO_3), concentrated, and distilled [140 °C (35 Torr)] to give 513 mg (74%) of 1-phenyl-1-pentyne[25] **5c.** VPC analysis showed less than 4% contamination by other material: ^{13}C NMR δ 131.3, 127.8, and 127.1 (d, aryl CH), 124.1 (s, aryl C), 89.8 and 80.7 (s, C≡C), 22.0 and 21.1 (t, CH_2), 13.2 (q, CH_3); ^{1}H NMR δ 1.03 (t, 3), 1.60 (sextet, 2), 2.37 (t, 2), 7.1–7.4 (m, 5); IR (film) 2260 (w, C≡C) cm^{-1}.

Methyl 1α,2β,4β-2-(6-Benzyloxy-1-heptynyl)-4-methoxymethoxycyclopentanecarboxylate (5g). In a similar manner, the enol phosphate **4g** was reduced with sodium amalgam in THF to afford a 50% yield of the alkyne **5g** after chromatographic purification: ^{13}C NMR δ 81.3 and 80.7 (s, C≡C); ^{1}H NMR δ 1.18 (d, 3, J = 6 Hz), 3.35 (s, 3), 3.68 (s, 3), 4.47 (AB q, 2, PhC**H**$_2$), 4.62 (s, 2, OCH_2O), 7.28 (s, 5, Ph); IR (film) 1735 (C=O), 2970 (CH) cm^{-1}.

Anal. ($C_{22}H_{30}O_5$) C, H.

1-Cyclohexyl-2-phenylsulfonyl-1-pentene (11a). A suspension of 1.56 g (3.5 mmol) of enol phosphate **4a,** 13 mL of methanol, 130 mg of powdered KH_2PO_4, and 13 g of 2% sodium amalgam was stirred at 0 °C for 20 min. The mixture was diluted with 2 N NaOH and extracted twice with pentane, and the organic layer was washed twice with 2 N NaOH, dried (K_2CO_3), and concentrated. The residue was subjected to bulb to bulb distillation [140 °C (35 Torr)], affording 315 mg (60%) of 1-cyclohexyl-1-pentyne **5a** as the distillate and 360 mg (35%) of the vinyl sulfone **11a** as the pot residue: ^{1}H NMR δ 6.64 (d, 1, J = 10 Hz, C=CH–); IR (film) 1140, 1300 (SO_2), 1650 (w, C=C) cm^{-1}. An analytical sample of **11a** was obtained by chromatography (25% ether in petroleum ether) and distillation [160 °C (0.05 Torr)].

Anal. ($C_{17}H_{24}O_2S$) C, H, S.

1-Cyclohexyl-3-methyl-2-phenylsulfonyl-1-butene (11b). In a similar reaction, the enol phosphate **4b** gave a 54% yield of the alkyne **5b** and a 33% yield of the vinyl sulfone **11b:** ^{1}H NMR δ 1.03 [d, 6, J = 7 Hz, -CH(C**H**$_3$)$_2$], 6.76 (d, 1, J = 11 Hz, =CH–); IR (film) 1050, 1310 (SO_2), 1647 (w, C=C) cm^{-1}. Chromatography (25% ether in petroleum ether) and distillation [130 °C (0.1 Torr)] provided a sample of **11b** for analysis.

Anal. ($C_{17}H_{24}O_2S$) C, H, S.

1-(1-Adamantyl)-1-(diethoxyphosphinyl)oxyethene (13). By a similar procedure, the enol phosphate **12** afforded, after distillation [150 °C (40 Torr)], a 55% yield of 1-vinyladamantane (identified by ^{1}H NMR) and a 30% yield of the enol phosphate **13** as the pot residue. ^{1}H NMR δ 1.34 (t, 6), 4.17 (dq, 4, J = 7.5 Hz), 4.43 and 4.83 (ABX, 2, =C**H**$_2$); IR (film) 1000 (P=O), 1230, 1280 (CO), 1640 (C=C) cm^{-1}.

Exact mass ($C_{16}H_{27}O_4P$): calcd, 314.1645; found, 314.1639.

Methyl 3-Methyl-4-phenylsulfonylheptanoate (9). A solution of 1.0 g (5.1 mmol) of butyl phenyl sulfone in 5 mL of THF was stirred under ntirogen at −78 °C and treated with 5.1 mmol of an *N*-butyllithium–hexane solution and, 10 min later, with 0.54 mL (5.1 mmol) of methyl crotonate. After 15 min, the mixture was neutralized with 2 N H_2SO_4 and extracted with ether, and the ether layer was washed with dilute K_2CO_3 and brine, dried (K_2CO_3), and concentrated to give 1.48 g (98%) of the conjugate addition product **9:** ^{13}C NMR δ 172.5 (s, C=O), 139.1 (s, aryl C), 133.2, 128.8 and 128.1 (d, aryl CH), 66.9 (d, C**H**SO_2), 51.1 (q, OCH_3), 36.7 (t, C**H**$_2CO_2$), 29.5 (d, C**H**–CH_3), 27.0 and 21.1 (t, CH_2CH_2), 17.3 (q, C**H**$_3$CH), 13.3 (q, C**H**$_3CH_2$); in an epimerized mixture, new resonances are seen at δ 66.3, 39.0, 29.1, 25.8, 21.5, and 15.1. ^{1}H NMR δ 0.82 (t, 3), 1.12 (d, 3, J = 7 Hz), 3.67 (s, 3, CH_3O); in the epimerized mixture, a new methoxy resonance is visible at δ 3.57; IR (film) 1150, 1300 (SO_2), 1735 (C=O) cm^{-1}. An analytical sample was obtained by chromatography (1:1 ether/petroleum ether) and distillation [150 °C (0.05 Torr)].

Anal. ($C_{15}H_{22}O_4S$) C, H, S.

4-Dimethylamino-1-(ethoxyhydroxyphosphinyl)pyridinium Hydroxide Inner Salt (10). In an attempt to prepare the enol phosphate **4a,** 308 mg (1.0 mmol) of β-keto sulfone **3a,** 1 mL of dry CH_3CN, 0.175 mL (1.2 mmol) of diethyl phosphorochloridate, 146 mg (1.2 mmol) of 4-dimethylaminopyridine, and 0.15 mL (1.1 mmol) of triethylamine was stirred at 70 °C for 5 h and a day at 25 °C. TLC analysis showed that none of the desired enol phosphate was present, so the precipitate was filtered, washed with CH_3CN, and dried to give 118 mg (43%) of the hygroscopic inner salt **10.** An analytically pure sample was obtained by recrystallization from CH_3CN: mp 133–135 °C; ^{1}H NMR δ 1.20 (t, 3, J = 7 Hz, CCH_3), 1.70 (s, 6, NCH_3), 3.93 (dq, 4, J = 7.25 Hz, OCH_2), 6.90 (dd, 2, J = 1, 7.5 Hz, β-H), 8.48 (dd,

2, J = 6.0, 7.5 Hz, α-H); IR ($CHCl_3$) 1040, 1080, 1110, 1310, 1560, 1635 cm^{-1}.

Anal. ($C_9H_{15}N_2O_3P$) C, H, N, P.

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References and Notes

(1) National Science Foundation Predoctoral Fellow, 1973–1976.
(2) (a) T. L. Jacobs, *Org. React.*, **5**, 1 (1949); (b) R. J. Bushby, *Q. Rev., Chem. Soc.*, **24**, 585 (1970); (c) L. Brandsma, "Preparative Acetylenic Chemistry", Elsevier, New York, N.Y., 1971; for recently introduced synthetic methods see, inter alia: (d) P. Wieland, *Helv. Chim. Acta*, **53**, 171 (1970); (e) I. Lalezari, A. Shafiee, and M. Yalpani, *Angew. Chem., Int. Ed. Engl.*, **9**, 464 (1970); (f) E. Wenkert and C. A. McPherson, *Synth. Commun.*, **2**, 331 (1972); (g) H. Maier and I. Manzal, *Synthesis*, 215 (1971); (h) E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, 3769 (1972); (i) E. C. Taylor, R. L. Robey, and A. McKillop, *Angew. Chem., Int. Ed. Engl.*, **11**, 48 (1972); (j) E. W. Colvin and B. J. Hamill, *J. Chem. Soc., Chem. Commun.*, 151 (1973); (k) S. Nakayama, M. Yoshifuji, R. Okazaki, and N. Inamoto, *J. Chem. Soc., Perkin Trans. 1*, 2069 (1973); (l) K. Sonogashira, Y. Tohda, and N. Hagihara, *Tetrahedron Lett.*, 4467 (1975) and references therein; (m) J. Villievas, P. Perriot, and J. F. Normant, *Synthesis*, 458 (1975); (n) J. Weill-Raynal, *ibid.*, 633 (1976) reviews syntheses via organoboranes; (o) D. P. Bauer and R. S. Macomber, *J. Org. Chem.*, **41**, 2640 (1976); (p) P. J. Kocienski, J. M. Ansell, and B. E. Norcross, *ibid.*, **41**, 3650 (1976).
(3) G. Märkl, *Chem. Ber.*, **94**, 3005 (1961); S. T. D. Gough and S. Tripett, *J. Chem. Soc.*, 2333 (1962); see also G. Märkl, *Angew. Chem., Int. Ed. Engl.*, **1**, 160 (1962).
(4) (a) H. B. Dykstra, J. F. Lewis, and C. E. Boord, *J. Am. Chem. Soc.*, **52**, 3396 (1930); (b) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 112 (1959); (c) J. C. Carnahan, Jr., and W. D. Closson, *J. Chem. Soc.*, 112 (1959); (c) J. C. Carnahan, Jr., and W. D. Closson, *Tetrahedron Lett.*, 3447 (1972); (d) K. B. Sharpless and T. C. Flood, *J. Chem. Soc., Chem. Commun.*, 370 (1972); (e) R. L. Sowerby and R. M. Coates, *J. Am. Chem. Soc.*, **94**, 4758 (1972); (f) C. R. Johnson, J. R. Shanklin, and R. A. Kirchhoff, *ibid.*, **95**, 6462 (1973); (g) M. Julia and J.-M. Paris, *Tetrahedron Lett.*, 4833 (1973); (h) J. E. McMurry, *Acc. Chem. Res.*, **7**, 281 (1974); (i) J. A. Marshall and M. E. Llewellyn, *Synth. Commun.*, **5**, 293 (1975); (j) J. E. McMurry and T. Hoz, *J. Org. Chem.*, **40**, 3797 (1975); (k) Y. Watanabe, M. Shiono, and T. Mukaiyama, *Chem. Lett.*, 871 (1975).
(5) (a) R. E. Dabby, J. Kenyon, and R. F. Mason, *J. Chem. Soc.*, 4881 (1952); (b) V. Pascali and A. Umani-Ronchi, *J. Chem. Soc., Chem. Commun.*, 351 (1973); (c) B. M. Trost, H. C. Arndt, P. E. Strege, and T. R. Verhoeven, *Tetrahedron Lett.*, 3477 (1976).
(6) (a) G. W. Kenner and N. R. Williams, *J. Chem. Soc.*, 522 (1955); (b) R. E. Ireland and G. Pfister, *Tetrahedron Lett.*, 2145 (1969); (c) M. Fetizon, M. Jurion, and N. Trong-Anh, *J. Chem. Soc., Chem. Commun.*, 112 (1969); (d) R. E. Ireland, D. C. Muchmore, and U. Hengartner, *J. Am. Chem. Soc.*, **94**, 5098 (1972).
(7) (a) B. M. Trost, T. N. Salzmann, and K. Hiroi, *J. Am. Chem. Soc.*, **98**, 4887 (1976), and references therein; (b) D. Seebach and M. Teschner, *Tetrahedron Lett.*, 5113 (1973).
(8) R. M. Coates and H. D. Pigott, *Synthesis*, 319 (1975); H. J. Monteiro and J. P. de Souza, *Tetrahedron Lett.*, 921 (1975).
(9) (a) L. Field, J. E. Lawson, and J. W. McFarland, *J. Am. Chem. Soc.*, **78**, 4389 (1956); (b) H.-D. Becker and G. A. Russell, *J. Org. Chem.*, **28**, 1896 (1963); (c) H. Stetter and R. Hesse, *Monatschefte*, **98**, 755 (1967); (d) H. O. House and J. K. Larson, *J. Org. Chem.*, **33**, 61 (1968); (e) E. M. Kaiser, L. E. Solter, R. A. Schwartz, R. D. Beard, and C. R. Hauser, *J. Am. Chem. Soc.*, **93**, 4237 (1971); (f) K. Kondo and D. Tunemoto, *Tetrahedron Lett.*, 1397 (1975).
(10) K. Fuji, S. Nakano, and F. Fujite, *Synthesis*, 276 (1975).
(11) V. Pascali, N. Tangari, and A. Umani-Ronchi, *J. Chem. Soc., Perkin Trans. 1*, 1166 (1973); N. Bosworth and P. Magnus, *ibid.*, 2319 (1973).
(12) J. Martel, C. Huynh, E. Toromanoff, and G. Nominé, *Bull Soc. Chim. Fr.*, 982 (1967); J. Martel and C. Huynh, *ibid.*, 985 (1967); M. Julia and A. Guy-Rouault, *ibid.*, 1411 (1967); R. V. M. Campbell, L. Crombie, D. A. R. Findley, R. N. King, G. Pattenden, and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 897 (1975).
(13) J. B. Hendrickson, A. Giga, and J. Waring, *J. Am. Chem. Soc.*, **96**, 2275 (1974); J. L. Herrmann, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Lett.*, 3271 (1973).
(14) G. Hofle and W. Steglich, *Synthesis*, 619 (1972); *Angew. Chem., Int. Ed. Engl.*, **8**, 981 (1969).
(15) S. J. Shafer, W. D. Closson, J. M. F. van Dijk, O. Piepers, and H. M. Buck, *J. Am. Chem. Soc.*, **99**, 5118 (1977).
(16) J. R. Hanson, *Synthesis*, 1 (1974).
(17) C. W. Schroeck and C. R. Johnson, *J. Am. Chem. Soc.*, **93**, 5305 (1971); C. R. Johnson, *Acc. Chem. Res.*, **6**, 341 (1973).
(18) W. A. Baldwin and R. Robinson, *J. Chem. Soc.*, 1445 (1932).
(19) We prepared isobutyl phenyl sulfone[20] from the reaction of sodium benzenesulfinate with isobutyl iodide in DMF at 90 °C.
(20) E. Gipstein, E. Wellisch, and O. J. Sweeting, *J. Org. Chem.*, **29**, 207 (1964).
(21) P. A. Bartlett and F. R. Green III, *J. Am. Chem. Soc.*, following paper in this issue.
(22) I. J. Borowitz, S. Firstenberg, E. W. R. Casper, and R. K. Crouch, *J. Org. Chem.*, **36**, 3282 (1971).
(23) H. Nozaki and R. Noyori, *J. Org. Chem.*, **30**, 1652 (1965); W. Ziegenbein and W. M. Schneider, *Chem. Ber.*, **98**, 824 (1965).
(24) H. Setter and P. Goebel, *Chem. Ber.*, **95**, 1039 (1962).
(25) B. S. Kupin and A. A. Petrov, *J. Gen. Chem. USSR (Engl. Transl.)*, **31**, 2958 (1961); R. Truchat, *Ann. Chim.*, **16**, 398 (1931).

Total Synthesis of Brefeldin A

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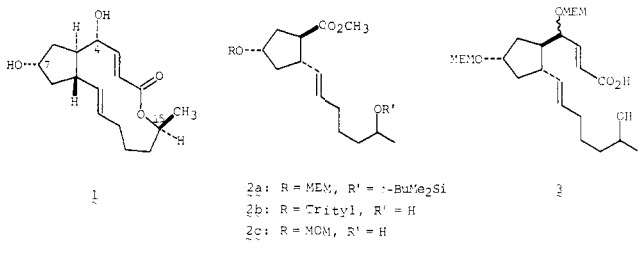
Abstract: A total synthesis of (±)-brefeldin A has been achieved in 15 steps from *trans*-4-oxo-1,2-cyclopentanedicarboxylic acid via the key intermediate **2c**. Two distinct syntheses of **2** have been developed, leading to the trityl ether **2b** and the methoxymethyl ether **2c**. The former involves stereoselective conjugate addition of vinylalane **16** to hydroxy enone **4** and a surprisingly regioselective trityl ether isomerization. The latter synthesis employs the bicyclic lactone **21** to establish the stereochemistry around the five-membered ring and incorporates a new carboxyl to acetylene conversion. The ester **2c** is further elaborated via a β-keto sulfoxide alkylation–elimination sequence to the γ-ketoacrylic acid **34**, which is lactonized using Mukaiyama's procedure. Selective reduction and deprotection provide racemic brefeldin A.

Brefeldin A (**1**) possesses a diverse spectrum of antifungal,[2] antiviral,[3] antimitotic,[4] and antitumor[2a] activity in addition to the synthetic attractions of its macrocyclic framework. This fungal metabolite has been isolated from a variety of organisms,[2a,5] and was known variously as ascotoxin,[5f] cyanein,[5b] and decumbin,[5a] before the identity of these materials with brefeldin A was established.[5f,6] The complete structure was revealed by X-ray diffraction,[7] after chemical and spectroscopic studies had elucidated all features except the configuration at C-4.[5f,8] Biosynthetic studies[5j,9] have established that the molecule is derived entirely from acetate and have ruled out a number of more detailed postulates. In 1976, Corey and Wollenberg reported the first total synthesis of racemic bre-



1 2a: R = MEM, R' = t-BuMe2Si 2b: R = Trityl, R' = H 2c: R = MOM, R' = H 3

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