Synthesis of 4-Ylidenebutenolides. A Practical Route to 2-En-4-ynoic Acid Intermediates based on Conjugate Addition of Alkynyl-lithium Reagents

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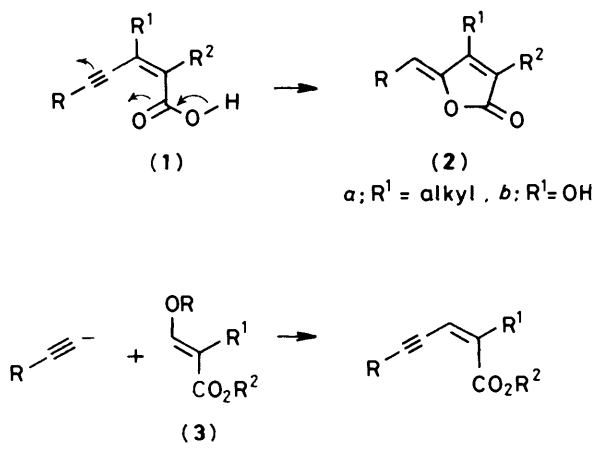
Conjugate addition of alkynyl-lithium reagents to diethyl ethoxymethylenemalonate, followed by simultaneous saponification and 1,2-elimination of ethanol from the intermediate adducts, *viz* (**18**), in the presence of ethanolic potassium hydroxide, provides a useful synthesis of substituted propargylidenemalonic acids (**19**). Cyclisation of the propargylidenemalonic acids, using known procedures then leads to the corresponding 4-ylidenebutenolides, *e.g.* (**20**) and (**21**)

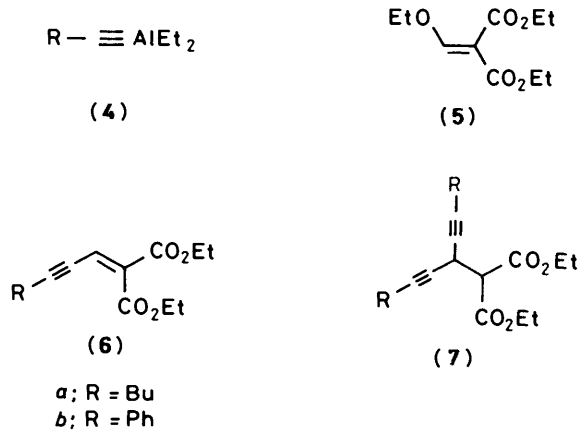
Although a number of methods for the synthesis of 4-ylidenebutenolides and 4-ylidenetetronic acids, *viz* (**2**), have been developed in the past decade,[1] their method of preparation *via* cyclisation of 2-en-4-ynoic acids (**1**) remains an attractive one, limited only by the availability of suitable routes to the precursor enynoic acids.[2] In this paper we provide a solution to this limitation with the development of a new synthesis of 2-en-4-ynoic acids based on the conjugate addition of alkynyl-lithium reagents to alkoxymethylene acrylates (**3**) and related molecules (Scheme 1).



Scheme 1.

Since copper acetylides are reported not to undergo 1,4-addition reactions with a range of Michael acceptors,[3] we were initially attracted to the use of the corresponding alkynylalanes to carry out the transformation outlined in Scheme 1.[4,5] Indeed, treatment of readily available diethy ethoxymethylenemalonate (**5**) with diethyl hex-1-ynylalane (**4a**) provided a modest 48% yield of diethyl hept-2-ynylidenemalonate (**6a**) contaminated with the product (**7a**) of further addition of (**4a**) to (**6a**). In a similar manner, diethyl (phenylethynyl)alane (**4b**) reacted with the diester (**5**) at −5 °C to give the enyne (**6b**) accompanied by less than 5% of the corresponding 2:1 adduct (**7b**).

In an attempt to expand the scope of the conjugate addition approach, particularly to precursors *e.g.* (**13**) and (**14**) to 4-ylidenetetronic acids (**2b**), and simultaneously avoid the co-formation of 2:1 adducts, we next examined the use of the substituted acrylates (**8**)—(**12**) as Michael acceptors. To our disappointment, these candidate molecules were uniformly unreactive towards the rather stable alkynylalanes (**4**). Not surprisingly however, the addition of lithium dimethylcuprate

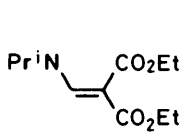


to (**5**) proceeded smoothly giving a 67% yield of diethyl isopropylmalonate, and more interesting reaction between the dithiane (**11**) and Me_2CuLi produced either (**15**) or a mixture of the malonates (**16**) and (**17**) depending on the reaction conditions.

With the failure of the alanes (**4a**) and (**4b**) to react with the Michael acceptors (**8**)—(**12**), and prompted by a brief report by Kraus and Pezzanito[6] of the addition of *alkyl-lithium* reagents to (**5**) we next examined the use of *alkynyl-lithium* reagents in reactions with (**5**). In the event, both phenylethynyl-lithium and hexylethynyl-lithium were found to add smoothly in a Michael fashion to (**5**) leading to compounds (**18a** and **b**) in 76% and 85% yield respectively. In contemporaneous studies Seebach *et al*[7] have also highlighted the use of *alkynyl-lithium* reagents in Michael addition reactions.

Treatment of the diester (**18b**) with hot ethanolic potassium hydroxide resulted in simultaneous 1,2-elimination of ethanol, and saponification producing the ylidenemalonic acid (**19b**). Thermal cyclisation of (**19b**), which has already been reported,[8] then gave the 4-benzylidenebut-2-enolide (**20**). In a similar manner, the ylidenemalonic acid (**19a**) was produced from (**18a**) in the presence of ethanolic potassium hydroxide. This acid failed to cyclise after several hours in refluxing chloroform in the presence of mercuric oxide.[8,9] Dissolution in methanol containing 1% aqueous silver nitrate[10] for 1 h however, followed by crystallisation gave the required ylidenebutenolide (**21**) whose formation was accompanied by the isomeric pyrone (**22**).

We were less successful in our attempts to extend the general methodology described above to the synthesis of the corresponding ylidenetetronic acid ring system (**2b**). These attempts were frustrated by the failure of alkynyl-lithium reagents to add in a Michael fashion to molecules like the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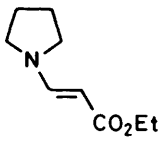
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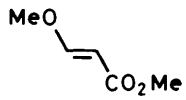
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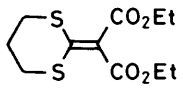
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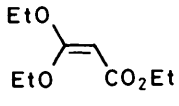
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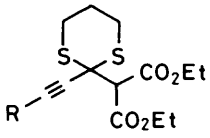
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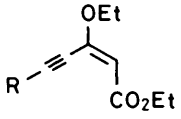
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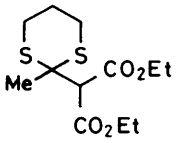
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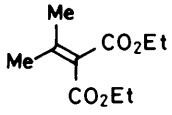
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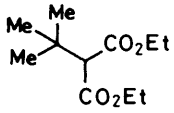
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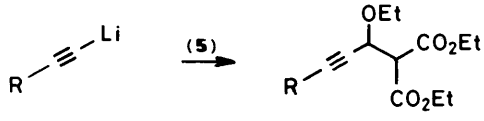
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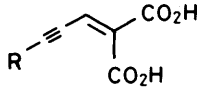
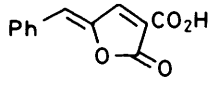
a ; R = Bu
b ; R = Ph


(19)
a ; R = Bu
b ; R = Ph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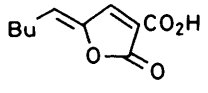
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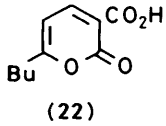
(22)

dithiane (**11**), which instead led to products resulting from 1,2-addition to their ester functions.

Experimental

For general experimental details see ref. 11.

Diethyl Hept-2-ynylidenemalonate (**6a**).—Butyl-lithium (1.4M; 8 cm^3) in hexane was added to a solution of hex-1-yne (0.82 g) in dry ether (30 cm^3) at 5 °C under nitrogen, and then a solution of diethylaluminium chloride (2.07M; 4.8 cm^3) in hexane was introduced. The mixture was stirred at 5 °C for 0.5 h and then a solution of diethyl ethoxymethylene-malonate (2.16 g) in dry ether (5 cm^3) was added. The resulting mixture was stirred at 5—20 °C for 0.5 h, then quenched with ammonium hydroxide solution and extracted with ether. Evaporation of the dried ether extracts left an oil which was distilled to give the malonate (1.2 g, 48%) as a pale yellow oil, b.p. 110—130 °C at 0.05 mmHg, $\lambda_{max.}$ (EtOH) 266 and 332 nm; $\nu_{max.}$(film) 2 240, 1 730, and 1 610 cm^{-1}; δ 0.95 (t, *J* 7, CH_2*Me*), 1.4 (m, 10 H), 2.42 (m, 2 H), 4.24 (q, *J* 7, CO_2CH_2Me), 4.32 (q, *J* 7, CO_2CH_2Me), and 6.86 (t, *J* 2, $CH_2C{=}CCH$:).

Repetition of the reaction by the addition of diethyl ethoxymethylene-malonate to the alane at −40 °C (14 h), followed by extraction gave the same heptynylidenemalonate contaminated by the product (**7a**), δ 1—1.5 resulting from further addition of the alane (**4a**) to the initially formed product (**6a**).

Diethyl 3-Phenyl-2-propynylidenemalonate (**6b**).—A solution of butyl-lithium (1.5M; 6.7 cm^3) in hexane was added over 2 min to a stirred solution of phenylacetylene (1.02 g) in dry ether (40 cm^3) under nitrogen at −3 °C. The solution was stirred at −3 °C for 0.25 h and then a solution of diethylaluminium chloride (1.8M; 6.7 cm^3) in hexane was added, followed after a further 0.25 h by a solution of diethyl ethoxymethylenemalonate (2.16 g) in dry ether (10 cm^3). The resulting mixture was stirred at −5 °C for 2 h and then at 25 °C for 48 h, after which it was diluted with dilute hydrochloric acid and extracted with ether. Evaporation of the dried ether extracts left an oil which on distillation gave the malonate (1.31 g, 48%) as a colourless liquid, b.p. 147—149 °C at 0.02 mmHg, $\lambda_{max.}$(EtOH) 310 and 318.5 nm; $\nu_{max.}$(film) 2 240, 1 730, 1 615, and 1 595 cm^{-1}; δ 1.31 (t, *J* 7, CO_2CH_2*Me*), 1.36 (t, *J* 7, CO_2CH_2*Me*), 4.25 (q, *J* 7, CO_2CH_2Me), 4.34 (q, *J* 7, CO_2CH_2Me), 7.04 (=CH), and 7.35 (br, 5 H) (Found: C, 70.7; H, 6.1. $C_{16}H_{16}O_4$ requires C, 70.6, H, 5.9%).

Michael Acceptors.—The Michael acceptors used in the investigation were prepared by literature procedures:

(E)-*Ethyl 3-methoxyacrylate* (**10**)[12] showed $\lambda_{max.}$(EtOH) 228 nm; $\nu_{max.}$(film) 1 710 and 1 630 cm^{-1}; δ 1.2 (t, *J* 7, CH_2*Me*), 3.63 (OMe), 4.12 (q, *J* 7, CH_2Me), 5.13 (d, *J* 12.5, =$CH$$CO_2$Et), and 7.57 (d, *J* 12.5, =CHOMe) (Found: M^+, 130.0636. Calc. for $C_6H_{10}O_3$: *M*, 130.0630).

Diethyl N,N-*di-isopropylaminomethylenemalonate* (**8**)[13] showed b.p. 114—116 °C at 0.01 mmHg, $\lambda_{max.}$(EtOH) 286 nm; $\nu_{max.}$(film) 1 710, 16 85, and 1 595 cm^{-1}; δ 1.14 (d, *J* 6.5, 2 × $CHMe_2$), 1.27 (t, *J* 7, 2 × OCH_2*Me*), 3.68 (septet, *J* 6.5, 2 × CHMe$_2$), 4.16 (q, *J* 7, 2 × OCH_2Me), and 7.46 (=CH).

Diethyl 1,3-*dithian-2-ylidenemalonate* (**11**)[14] showed m.p. 60—61 °C (ether–pentane), $\lambda_{max.}$(EtOH) 251 and 313 nm; $\nu_{max.}$(KBr) 1 690 cm^{-1}; δ 1.28 (t, *J* 7, 2 × OCH_2*Me*), 2.17 (pentuplet, *J* 6.5, 2 H), 2.94 (t, *J* 6.5, 4 H), and 4.18 (q, *J* 7, 2 × OCH_2Me).

Ethyl 3,3-*diethoxyacrylate* (**12**)[15] showed b.p. 122 °C at 10 mmHg, $\lambda_{max.}$(EtOH) 245 nm; $\nu_{max.}$(film) 1 717, 1 675, and 1 615 cm^{-1}; δ 1.28 (t, *J* 7, OCH_2*Me*), 1.41 (t, *J* 7, 2 × OCH_2*Me*), 4.0

(q, *J* 7, OCH_2Me), 4.16 (q, *J* 7, OCH_2Me), 4.26 (=CH), and 4.27 (q, *J* 7, CO_2CH_2Me).

(E)-*Ethyl 3-pyrrolidinoacrylate* (**9**) showed m.p. 38—39 °C (light petroleum), $\lambda_{max.}$(EtOH) 285.5 nm; $\nu_{max.}$(KBr) 1 690 and 1 610 cm^{-1}, δ 1.14 (t, *J* 7, OCH_2Me), 1.95 (m, 4 H), 3.15—3.55 (m, 4 H), 4.08 (q, *J* 7, OCH_2Me), 4.42 (d, *J* 12.5, $=CHCO_2Et$), and 7.59 (d, *J* 12.5, $=CHNR_2$) (Found: C, 63.9; H, 8.9; N, 8.3. Calc. for $C_9H_{15}NO_2$: C, 63.7; H, 8.8; N, 8.1%).

Diethyl Isopropylmalonate.—Diethyl ethoxymethylenemalonate (0.85 g) in dry ether (20 cm^3) was added over 5 min to a stirred solution of lithium dimethylcuprate [prepared from MeLi (1.4M; 8.5 cm^3) and CuI (1.3 g)] in dry ether (100 cm^3) under nitrogen at 0 °C, and the resulting yellow mixture was stirred at 0 °C for 0.25 h and then at 23 °C for 0.5 h. The mixture was poured onto cold dilute hydrochloric acid and then extracted with diethyl ether. Evaporation of the dried ether extracts left an oil which on chromatography (silica gel; diethyl ether) followed by distillation gave the malonate (0.55 g, 67%) as a colourless oil b.p. 85—90 °C at 0.9 mmHg (lit.,[16] b.p. 107—109 °C at 18 mmHg), $\lambda_{max.}$(EtOH) 214 nm; $\nu_{max.}$(film) 1 750 and 1 730 cm^{-1}; δ 0.99 (d, *J* 7, $CHMe_2$) 1.25 (t, *J* 7, OCH_2Me), 2.35 (m, $CHMe_2$), 3.07 (d, *J* 8, $CHCO_2Et$), and 4.14 (q, *J* 7, CO_2CH_2Me).

Diethyl t-Butylmalonate (**17**).—Addition of lithium dimethylcuprate to diethyl 1,3-dithian-2-ylidenemalonate, according to the procedure described above, followed by chromatography [silica gel; ether–hexane (4:1)] gave the malonate (15%), $\nu_{max.}$ 1 750 and 1 725 cm^{-1}; 1.12 (CMe_3), 1.26 (t, *J* 7, 2 × CO_2CH_2Me), 3.15 ($CHCO_2Et$), and 4.1 (q, *J* 7, 2 × CO_2CH_2Me),[17] and also diethyl isopropylidenemalonate (*ca* 5%). Inverse addition of lithium dimethylcuprate to the dithiane (**37**) at −70 °C followed by distillation led largely to diethyl 1-(1,3-dithian-2-yl)-ethylmalonate (**15**) (41%), b.p. 110 °C (oven temp) at 0.06 mmHg, δ 1.28 (t, *J* 7, CO_2CH_2Me), 1.89 (Me), 1.6—2.3 (m, 2 H), 2.6—3.3 (m, 4 H), 4.19 (q, *J* 7, CO_2CH_2Me), and 4.42 ($CHCO_2Et$) Found: M^+, 292.0818. $C_{12}H_{20}O_4S_2$ requires *M*, 292.0803).

Diethyl (1-Ethoxy-3-phenylprop-2-ynyl)malonate (**18b**).—Repetition of the procedure used for the synthesis of diethyl 3-phenylprop-2-ynylmalonate, but excluding the addition of diethylaluminium dichloride, gave, after distillation, the 1-ethoxymalonate (76%), b.p. 135—140 °C at 0.015 mmHg, $\nu_{max.}$(film) 2 210 and 1 755 cm^{-1}; δ 1.3 (m, 9 H), 3.85 (d, *J* 9.5, $CHCO_2Et$), 3.53—4.35 (m, 6 H), 4.97 (d, *J* 9.5, CHOEt), and 7.4 (br, 5 H), contaminated by *ca.* 12% of the enynoate (**6b**).

Diethyl (1-Ethoxyhept-2-ynyl)malonate (**18a**).—By the procedure described above, reaction between 1-lithiohex-1-yne and diethyl ethoxymethylenemalonate gave the ethoxymalonate (**18a**) (85%) as a liquid, $\nu_{max.}$(film) 1 760, 1 740, and 1 602 cm^{-1}; δ 0.9 (m, 3 H), 1.1—1.5 (m, 6 H), 2.2 (m, CH_2C=), 3.7 (d, *J* 10.3, $CHCO_2Et$), 3.3—4.0 (m, 2 H), 4.25 (q, *J* 7, 2 H), and 4.71 (dt, *J* 10.3 and 1.6, =CCHOEt), contaminated by *ca* 6% of the corresponding enynoate (**6a**) (δ 6.91, t, *J* 2, =CH).

5-Benzylidene-2-oxo-2,5-dihydrofuran-3-carboxylic Acid (**20**).—Saponification of diethyl (1-ethoxy-3-phenylprop-2-ynyl)malonate (**18b**) according to the procedure described for the analogue (**18a**)[8] gave the diacid (**19b**) (95%) as a pale yellow powder, $\nu_{max.}$(KBr) 3 200—2 300, 2 190, 1 720, 1 685, and 750 cm^{-1}, which was used without further purification. A suspension of the diacid (**19b**) (0.2 g) in 1,2-dichlorobenzene (15 cm^3) was heated under reflux until all the diacid had dissolved (0.3 h), and was then cooled. The mixture was treated with light petroleum (b.p. 40—60 °C) whereupon the furancarboxylic acid (**20**) separated as a yellow powder. Recrystallisation from dioxane gave the furancarboxylic acid as yellow crystals, m.p. 215—218 °C (decomp.) (lit.,[8] m.p. 218 °C), $\lambda_{max.}$(EtOH) 358 nm; $\nu_{max.}$ (KBr) 3 100—3 000, 1 775, 1 675, 1 615, and 1 560 cm^{-1}; δ (CD_6SO) 6.7 (PhCH=), 7.2—7.65 m (3 H), 7.7—7.9 m (2 H), and 8.5 [HC=C(CO_2H)].

2-Oxo-5-pentylidene-2,5-dihydrofuran-3-carboxylic Acid (**21**).—A solution of diethyl (1-ethoxyhept-2-ynyl)malonate (**18a**) (2 g) in ethanol (35 cm^3) was heated under reflux in the presence of 10% aqueous potassium hydroxide (25 cm^3) for 1 h. The mixture was evaporated under reduced pressure, then diluted with water and acidified with dilute hydrochloric acid. The oil which separated was extracted with ethyl acetate. Evaporation of the ethyl acetate extracts left hept-2-ynylidenemalonic acid (**19a**) (1.08 g, 79%) as a viscous oil, $\lambda_{max.}$(EtOH) 266 nm, $\nu_{max.}$(film) 3 400—2 400, 2 200, and 1 715 cm^{-1}; δ 0.88 (t, *J* 7, CH_2Me), 115 (m, 4 H), 2.53 (m, CH_2C=), 7.55 (t, *J* 2, =CCH), and 10.8 (CO_2H).[10]

Aqueous silver nitrate solution (1%; 5 drops) was added to a solution of the diacid (**19a**) (0.4 g) in methanol (15 cm^3), and the solution was left at 25 °C for 1 h and then evaporated to dryness under reduced pressure, to leave a 3:2 mixture (by inspection of the ^1H n.m.r. spectrum) of the furancarboxylic acid (**21**) and the pyrone (**22**).[10] Crystallisation from aqueous methanol gave fine white needles m.p. 110—123 °C of largely the furancarboxylic acid, $\nu_{max.}$($CHCl_3$) 1 764 cm^{-1}; δ 0.9 (t, *J* 7, CH_2Me), 1.4 (m, 4 H), 2.53 (m, CH_2C=), 5.84 (t, *J* 8, CH_2CH=), 7.85 (br, CO_2H), and 8.04 [HC=C(CO_2H)], [*cf.* δ 6.38 (d, *J* 7, BuC=CH) 8.44 [d, *J* 7, HC=C(CO_2)] for the pyrone (**22**)] (Found: C, 61.3; H, 6.4. Calc. for $C_{10}H_{12}O_4$ C, 61.2; H, 6.2%).

Acknowledgements

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References

1 For review see: G. Pattenden, *Fortschr. Chem. Org. Naturst.*, 1978, **35**, 133; see also: T. Kitamura, Y. Kawakami, T. Imagawa, and M. Kawanisi, *Tetrahedron Lett.*, 1978, 4297; G. A. Kraus and H. Sugimoto, *J. Chem. Soc., Chem. Commun.*, 1978, 30; J. Weinstock, J. E. Blank, H.-J. Oh, and B. M. Sutton, *J. Org. Chem.*, 1979, **44**, 673; P. J. Jerris, P. M. Wovkulich, and A. B. Smith, *Tetrahedron Lett.*, 1979, 4517; D. W. Knight and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 1979, 62, 70, and 84; M. J. Begley, D. R. Gedge, D. W. Knight, and G. Pattenden, *ibid.*, 1979, 77; D. R. Gedge and G. Pattenden, *ibid.*, 1979, 89; S. C. M. Fell, J. Heaps, and J. S. E. Holker, *J. Chem. Soc., Chem. Commun.*, 1979, 81; M. D'Auria, G. Piancatelli, and A. Scettri, *Tetrahedron*, 1980, **36**, 3071; R. A. Massy-Westropp and M. F. Price, *Aust. J. Chem.*, 1980, **33**, 333; T. Yamada, H. Hagiwara, and H. Uda, *J. Chem. Soc., Chem. Commun.*, 1980, 838; K. Tanaka, M. Terauchi, and A. Kaji, *Bull. Chem. Soc. Jpn*, 1982, **55**, 3935; D. R. Gedge, G. Pattenden, and A. G. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1986, preceding paper and refs therein.

2 P. K. Christensen, N. A. Sörensen; I. Bell, E. R. H. Jones, and M. C. Whiting, *Festschr. Arthur Stoll*, 1957, 545 (*Chem. Abstr.*, 1959, **53**, 346e); F. Bohlmann and R. Reinecke, *Chem. Ber.*, 1966, **99**, 3437. See also: F. Serratosa, *Tetrahedron*, 1961, **16**, 185; C. Behil, J. Castellá, J. Castells, R. Mestres, J. Pascal, and F. Serratosa, *An. R. Soc., Esp. Fis. Quim., Ser. B*, 1961, **57**, 617; I. Fleming and J. Harley-Mason, *J. Chem. Soc.*, 1963, 4778; M. Yamamoto, *J. Chem. Soc., Chem. Commun.*, 1978, 649.

3 See: G. H. Posner, *Org. React.*, 1972, **19**, 1; E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, 1972, **94**, 7210; R. F. Newton and S. M. Roberts, *Tetrahedron*, 1980, **36**, 2163.

4 *cf.* J. Hooz and R. B. Layton, *J. Am. Chem. Soc.*, 1971, **93**, 7320; J. Schwartz, D. B. Carr, R. T. Hansen, and F. M. Dayrit, *J. Org. Chem.*, 1980, **45**, 3053; R. F. Newton, D. P. Reynolds, J. Greenwood, and F. Scheinmann, *J. Chem. Soc., Perkin Trans 1*, 1980, 2346.

5 For use of alkynylboranes see: G. A. Molander and H. C. Brown, *J. Org. Chem.*, 1977, **42**, 3106.
6 G. A. Kraus and J. O. Pezzanite, *J. Org. Chem.*, 1979, **44**, 2480.
7 R. Locher and D. Seebach, *Angew. Chem., Int. Ed. Eng.*, 1981, **20**, 569.
8 J. Castañer and J. Pascual, *J. Chem. Soc.*, 1958, 3962.
9 M. Yamamoto, *J. Chem. Soc., Perkin Trans. 1*, 1981, 582.
10 C. Belil, J. Pascual, and F. Serratosa, *Tetrahedron*, 1964, **20**, 2701.
11 M. J. Begley, N. G. Clemo, and G. Pattenden, *J. Chem. Soc., Perkin Trans 1*, 1985, 2393.
12 E. Winterfeldt and H. Preuss, *Chem. Ber.*, 1966, **99**, 450.
13 R. Osman and Y. Shvo, *Tetrahedron*, 1978, **34**. 2321.
14 K. A. Jensen and L. Henriksen, *Acta Chem. Scand.*, 1968, **22**, 1107.
15 S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.*, 1945, **67**, 1017.
16 C. R. C. Handbook of Chemistry and Physics, 59th Edition.
17 E. L. Eliel Hutchins and M. Knoeber, *Org. Synth.*, 1970, **50**, 38; C. Holmberg, *Liebigs Ann. Chem.*, 1981, 748.

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