Tetrahedron Vol. 48, No. 43, pp. 9531-9536, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

Homoenolic Radical Derived from Propionic Acid: A Versatile Reagent for the Radical Version of the Michael Reaction

Francisco Foubelo, Francisco Lloret and Miguel Yus*

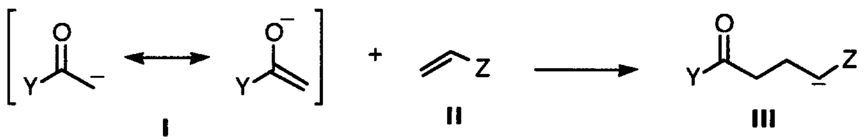
Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain

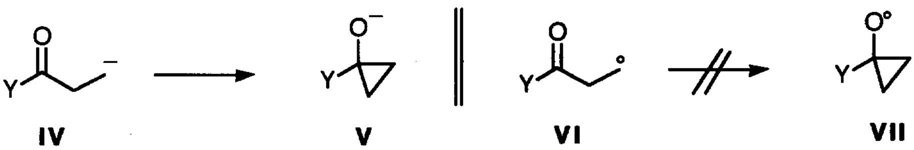
(*Received in UK* 24 *August* 1992)

Abstract: The homoenolic radical, derived from 3-iodopropionic acid (**1**) by reaction with *in situ* generated tributyltin hydride, undergoes clean carbon-carbon forming reaction with electrophilic olefins (**2**) yielding functionalized acids (**3**).

Introduction

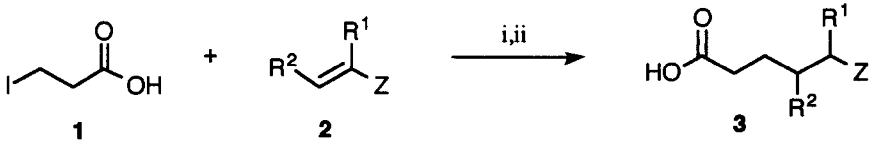
The Michael reaction, also called conjugate addition, represents one of the most important methods for creating carbon-carbon bonds giving functionalized organic compounds[1]: in a typical process an enolate **I** is added to an electrophilic olefin **II** to give the corresponding product resulting from the final hydrolysis of the carbanion **III**. However, a reaction of this type can not be carried out using the homologous β-enolate intermediate **IV**[2] because this species cyclises spontaneously, even at low temperatures, to yield irreversibly the corresponding cyclopropanolate **V**[3]. This problem could be overcome by using a homoenolic radical [4] of the type **VI**[5], since the γ-elimination to afford the radical **VII** should be an unfavourable process[8]. In this paper we report our preliminary results exploring this last possibility.





Results and Discussion

The reaction of commercially available 3-iodopropionic acid (**1**) with a mixture of tributyltin chloride (1:0.5 molar ratio) and sodium borohydride (1:4 molar ratio) in the presence of a catalytic amount (1:0.18 molar ratio) of α,α'-azobisisobutyronitrile (AIBN) followed by addition of an electrophilic olefin (**2**) yielded the corresponding products **3** (Scheme 1). As olefins **2** (see Table 1) not only α,β-unsaturated carbonyl compounds [methyl vinyl ketone or cyclohex-2-enone (entries 11 and 12, respectively); methyl acrylate, methacrylate or crotonoate (entries 1, 2 and 10, respectively); *N,N*-dimethylacrylamide (entry 5)] or nitriles [acrylonitrile or methacrylonitrile (entries 3 and 4, respectively)] can be employed, but also 1,1-dichloroethylene or 3-chloro-2-chloromethylpropene (entries 6 and 7, respectively), and styrene or 1,1-diphenylethylene (entries 8 and 9, respectively).



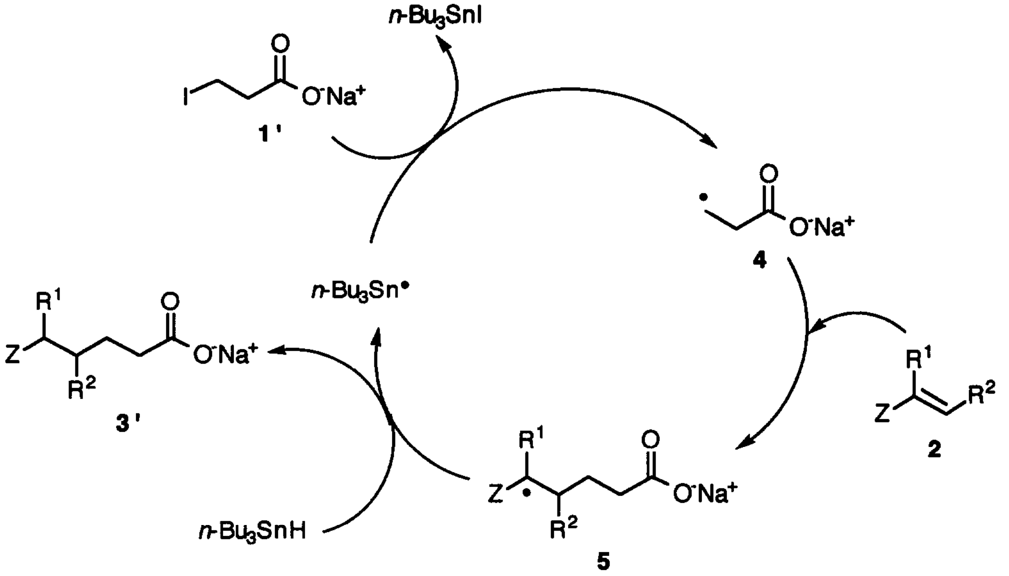
Scheme 1. *Reagents and conditions*: i, *n*-Bu_3SnCl, $NaBH_4$, AIBN, EtOH, 20°C, 4h; ii, NaF, H_2O.

Since the reaction does not work in the absence of AIBN the mechanism involved in the process should be of the free radical type. The *in situ* generated tributyltin hydride[9] -by reaction of tributyltin chloride and sodium borohydride- reacts with the sodium salt **1'** of the acid **1**[10] -initially formed by reaction of the acid with sodium borohydride- to give the corresponding radical **4**, which is added to the olefin **2** yielding a second radical **5**; this last species takes a hydrogen from the tributyltin hydride to afford the corresponding salt of the reaction product **3'**, which after final hydrolysis gives the acid **3** (Scheme 2). As it can be seen in Scheme 3, one of the reaction products is tributyltin iodide, which in the presence of sodium borohydride is also a source ot the radical *n*-Bu_3Sn°, through the corresponding hydride, so the reaction is catalytic with respect to the tin compound. However, we found that the best results are obtained working with a 1:0.5 molar ratio of **1**:*n*-Bu_3SnCl (see general procedure).

From the results described here we conclude that this methodology represents a practical alternative to the use of homoenolate anions in Michael-type reactions. Other advantage of the procedure is that it is not necessary to use a stoichiometric amount of tributyltin hydride[9]: a catalytic amount of tributyltin chloride is sufficient.

Experimental

General.- Mp's are uncorrected and were measured on a Reichert thermovar apparatus. IR spectra were determined with a Pye Unicam SP3-200 spectrometer. ^1H and ^{13}C NMR spectra were recorded in a Bruker AC-300 using $CDCl_3$ as solvent and $SiMe_4$ as internal standard; chemical shifts are given in δ (ppm) and the coupling constants (*J*) are measured in Hz. MS (EI) were recorded with a Hewlett Packard EM/CG HP-5988A



Scheme 2.

spectrometer. The purity of volatile distilled products and the chromatographic analysis (GLC) were determined with a flame ionization detector and a 12m HP-1 capillary column (0.2 m diam., 0.33 μm film thickness), using nitrogen (2 ml/min) as the carrier gas, $T_{injector}$ = 270°C, T_{column} = 60°C (3 min) and 60-270°C (15°C/min). Thin layer chromatography (TLC) was carried out on Scheleicher & Schnell F1500/LS 254 plates coated with a 0.2 mm layer of silica gel, using a mixture of hexane/ethyl acetate as eluant; R_f values (see Table 1) are given under these conditions. Microanalyses were performed by the Microanalyses Service of the University of Alicante. All reagents were commercially availabe (Aldrich) and were of the best grade. Ethanol was carefully dried with sodium followed by refluxing (2h) and distilled under argon.

Preparation of Compounds **3**. *General Procedure*.- A solution of tributyltin chloride (0.16 g, 0.5 mmol) in dry ethanol (2 ml) was added dropwise over a period of 10 min to a mixture of 3-iodopropionic acid (**1**, 0.20 g, 1.0 mmol), sodium borohydride (0.15 g, 4.0 mmol), AIBN (0.03 g, 0.18 mmol), the corresponding olefin (**2**, 10.0 mmol) and dry ethanol (8 ml) at 0°C. The reaction mixture was allowed to warm to room temperature and stirring was continued for 4 h at this temperature. A saturated aqueous sodium fluoride solution (5 ml) was then added. The precipitated tributyltin fluoride was removed by filtration and the filtrate was evaporated (15 torr). The resulting residue was successively extracted with dichloromethane and sodium carbonate and 3 N hydrochloric acid. The organic layer was dried over sodium sulfate and evaporated (15 torr). The resulting residue was purified by flash chromatography (hexane/ethyl acetate) and/or recrystallized (see Table 1) to yield pure products **3**. Yields, mp's and R_f values are given in Table 1. Spectral and analytical data follow. In the case of known compounds, their data are in agreement with those in the literature.

5-Methoxycarbonylpentanoic acid (**3a**)[11]: ν_{max} (film) 3500-2700 (OH), 1700 cm^{-1} (C=O); δ_H 1.67-1.73 [4H, m, $CH_2(CH_2)_2CH_2$], 2.33-2.40 (4H, m, $CH_2CO_2CH_3$ and CH_2CO_2H), 3.67 (3H, s, CH_3), 10.36 (1H, s, OH); δ_C 23.9, 24.1 [$CH_2(CH_2)_2CH_2$], 33.5 (CH_2CO_2H and $CH_2CO_2CH_3$), 51.5 (CH_3), 173.8(CO_2CH_3), 179.4 (CO_2H); *m/z* 142 (M^+-H_2O, 9%), 129 (46), 114 (100), 111 (39), 101 (55), 100 (48), 87 (22), 83 (36), 82 (16), 74 (83), 59 (97), 55 (98), 45 (32), 43 (49), 42 (21), 41 (32).

5-Methoxycarbonylhexanoic acid (**3b**)[12]: ν_{max} (film) 3640-3050 (OH), 1700 cm^{-1} (C=O); δ_H 1.17 (3H, d, *J* = 7.1, $CHCH_3$), 1.66-1.72 (4H, m, $CH_2CH_2CO_2H$ and CH_2CH), 2.36 (2H, t, *J* = 7.1, CH_2CO_2H), 2.42-2.50 (1H, m, CH), 3.68 (3H, s, OCH_3), 9.50 (1H, s, OH); δ_C 16.9 (CH_3CH), 22.3 ($CH_2CH_2CO_2H$), 32.9,

Table 1. Reaction of 3-iodopropionic acid (**1**) with olefins **2** under radical conditions. Isolation of products **3**.

Entry	Starting olefin	Product 3					
		No.	R^1	R^2	Z	Yield (%)[a]	R_f[b] or mp (°C)[c]
1	**2a**	**3a**	H	H	CO_2Me	76	0.47 (1/1)
2	**2b**	**3b**	Me	H	CO_2Me	72	0.49 (1/1)
3	**2c**	**3c**	H	H	CN	80	0.35 (1/1)
4	**2d**	**3d**	Me	H	CN	93	0.44 (1/1)
5	**2e**	**3e**	H	H	$CONMe_2$	65	0.43 (1/1)
6	**2f**	**3f**	Cl	H	Cl	58	0.48 (2/1)
7	**2g**	**3g**	CH_2Cl	H	CH_2Cl	58	0.31 (2/1))
8	**2h**	**3h**	Ph	H	Ph	50	85-86
9	**2i**	**3i**	H	H	Ph	43	56-57
10	**2j**	**3j**	H	Me	CO_2Me	56	0.48 (1/1)
11	**2k**	**3k**	H	H	COMe	54	0.49 (1/2)
12	**2l**[d]	**3l**	H	$-(CH_2)_2CO-$		63	0.22 (2/1)

[a] Isolated not optimized yield based on the starting acid **1**; all compounds were>95% pure (GLC and/or 300MHz ^1H NMR. [b] Hexane/ethyl acetate; the corresponding ratios are given in parenthesis. [c] From hexane/chloroform. [d] **2l** refers to cyclopent-2-enone.

33.7 ($\mathit{C}H_2CH$ and $\mathit{C}H_2CO_2H$), 39.1 (CH), 51.6 (OCH_3), 176.9 ($\mathit{C}O_2CH_3$), 179.6 (CO_2H); *m/z* 156 (M^+-H_2O, 2%), 143 (17), 128 (19), 115 (32), 114 (28), 97 (22), 88 (100), 73 (22), 59 (33), 57 (19), 55 (33).

5-Cyanopentanoic acid (**3c**)[13]: ν_{max} (film) 3500-2700 (OH), 2240 (CN), 1700 cm^{-1} (C=O); δ_H 1.70-1.80 [4H, m, $CH_2(C\mathit{H}_2)_2CH_2$], 2.37-2.45 (4H, m, $C\mathit{H}_2CO_2H$ and $C\mathit{H}_2CN$), 10.06 (1H, s, OH); δ_C 16.8 ($\mathit{C}H_2CN$), 23.4, 24.5 [$CH_2(\mathit{C}H_2)_2CH_2$], 32.9 ($\mathit{C}H_2CO_2H$), 119.2 (CN), 178.8 (CO_2H); *m/z* 109 (M^+-H_2O, 28%), 87 (14), 82 (18), 81 (62), 69 (14), 68 (83), 55 (66), 54 (100), 45 (62), 43 (42), 42 (35), 41 (93).

5-Cyanohexanoic acid (**3d**)[14]: ν_{max} (film) 3640-2815 (OH), 2240 (CN), 1700 cm^{-1} (C=O); δ_H 1.34 (3H, d, J = 7.0, CH_3), 1.58-1.94 (4H, m, $C\mathit{H}_2CH_2CO_2H$ and $C\mathit{H}_2CH$), 2.42 (2H, t, J = 7.0, $C\mathit{H}_2CO_2H$), 2.65 (1H, sextet, J = 7.0, CH), 9.60 (1H, s, OH); δ_C 17.7 (CH_3), 21.9 ($\mathit{C}H_2CH_2CO_2H$), 25.2 (CH), 33.0, 33.1 ($\mathit{C}H_2CH$ and $\mathit{C}H_2CO_2H$), 122.4 (CN), 178.9 (CO_2H); *m/z* 123 (M^+-H_2O, 25%), 114 (30), 96 (30), 95 (38), 87 (33), 73 (18), 68 (61), 55 (100), 54 (55), 43 (38), 42 (24), 41 (55).

6-Dimethylamino-6-oxohexanoic acid (**3e**)[15]: ν_{max} (film) 3620-2800 (OH), 1710 (HOC=O), 1610 cm^{-1} (N-C=O); δ_H 1.67-1.68 [4H, m, $CH_2(C\mathit{H}_2)_2CH_2$], 2.33-2.40 (4H, m, $C\mathit{H}_2CO_2H$ and $C\mathit{H}_2CON$), 2.95 (3H, s, $NC\mathit{H}_3CH_3$), 3.02 (3H, s, $NCH_3C\mathit{H}_3$), 9.65 (1H, s, OH); δ_C 24.3, 24.4 [$CH_2(\mathit{C}H_2)_2CH_2$], 32.8, 33.7 ($\mathit{C}H_2CO_2H$ and $\mathit{C}H_2CON$), 35.5, 37.3 (2xCH_3), 173.3 (CON), 178.1 (CO_2H); *m/z* 173 (M^+, 6%), 114 (14), 87 (100), 72 (66), 55 (33), 45 (56), 44 (34), 42 (16).

5,5-Dichloropentanoic acid (**3f**) : ν_{max} (film) 3610-2470 (OH), 1700 cm^{-1} (C=O); δ_H 1.86-1.96 (2H, m, $C\mathit{H}_2CH_2CO_2H$), 2.23-2.30 (2H, m, $C\mathit{H}_2CH$), 2.44 (2H, t, J = 7.2, $C\mathit{H}_2CO_2H$), 5.78 (1H, t, J = 5.9, CH), 9.56 (1H, s, OH); δ_C 20.9 ($CH_2CH_2CO_2H$), 42.4 (CH_2CO_2H and CH_2CH), 72.7 (CH), 179.3 (CO_2H); *m/z* 137 (M^+-Cl^{35}, 1.5%), 99 (100), 88 (9), 87 (16), 75 (10), 73 (21), 62 (11), 55 (8), 53 (10), 45 (15), 43 (11).

6-Chloro-5-chloromethylhexanoic acid (**3g**) : ν_{max} (film) 3620-3120 (OH), 1720 cm^{-1} (C=O); δ_H 1.45-1.73 [4H, m, $(CH_2)_2CH$], 2.02-2.10 (1H, m, CH), 2.34 (2H, t, *J* = 7.3, CH_2CO_2H), 3.55-3.77 (4H, m, 2xCH_2Cl), 10.05 (1H, s, OH); δ_C 22.0 ($CH_2CH_2CO_2H$), 29.0 (CH_2CH), 33.8 (CH_2CO_2H), 45.1 (2xCH_2Cl), 51.6 (CH), 173.5 (CO_2H); *m/z* 181 (M^+-H_2O, 2.2%), 101 (6), 87 (7), 75 (7), 73 (100), 59 (17), 55 (10).

5,5-Diphenylpentanoic acid (**3h**) : ν_{max} (KBr) 3600-2800 (OH), 1690 cm^{-1} (C=O); δ_H 1.54-1.64 (2H, m, $CH_2CH_2CO_2H$), 2.04-2.12 (2H, m, CH_2CH), 2.35 (2H, t, *J* = 7.4, CH_2CO_2H), 3.89 (1H, t, *J* = 7.8, CH), 7.12-7.32 (10H, m, 2xArH), 10.41 (1H, s, OH); δ_C 23.1 ($CH_2CH_2CO_2H$), 33.9, 34.9 (CH_2CO_2H and CH_2CH), 51.1 (CH), 126.2, 127.7, 128.4, 144.6 (2xArC), 179.9 (CO_2H); *m/z* 181 [M^+-$(CH_2)_2CO_2H$, 13%], 180 (100), 179 (54), 178 (52), 165 (80), 89 (25), 77 (18), 76 (18), 51 (14). Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found : C, 80.42; H, 7.09.

5-Phenylpentanoic acid (**3i**)[16]: ν_{max} (KBr) 3650-2810 (OH), 1690 cm^{-1} (C=O); δ_H 1.65-1.70 [4H, m, $CH_2(CH_2)_2CH_2$], 2.35-2.39 (2H, m, CH_2CO_2H), 2.60-2.63 (2H, m, CH_2Ph), 7.15-7.29 (5H, m, ArH), 10.45 (1H, s, OH); δ_C 24.5 , 30.7 [$CH_2(CH_2)_2CH_2$], 33.9 (CH_2CO_2H), 35.5 (CH_2Ph), 125.8, 128.3, 128.4, 142.0 (ArC), 179.8 (CO_2H); *m/z* 178 (M^+, 15%), 160 (12), 104 (24), 92 (21), 91 (100), 65 (15).

4-Methyl-5-methoxycarbonylpentanoic acid (**3j**)[17]: ν_{max} (film) 3600-3150 (OH), 1700 cm^{-1} (C=O); δ_H 0.96 (3H, d, *J* = 6.6, $CHCH_3$), 1.52-1.75 (2H, m, $CH_2CH_2CO_2H$), 2.00-2.04 (1H, m, CH), 2.17 (1H, dd, *J* = 14.9, 7.8, $CHHCO_2CH_3$), 2.32 (1H, dd, *J* = 14.9, 7.8, $CHHCO_2CH_3$), 2.34-2.41 (2H, m, CH_2CO_2H), 3.67 (3H, s, OCH_3), 9.57 (1H, s, OH); δ_C 19.3 (CH_3CH), 29.8 (CH), 31.3, 31.5 ($CH_2CH_2CO_2H$), 41.2 ($CH_2CO_2CH_3$), 51.5 (OCH_3), 173.2 (CO_2CH_3), 179.5 (CO_2H); *m/z* 143 (M^+-CH_3O, 38%), 128 (52), 125 (37), 115 (62), 114 (43), 101 (41), 83 (44), 74 (100), 73 (72), 59 (63), 55 (84), 43 (36).

6-Oxoheptanoic acid (**3k**)[18]: ν_{max} (film) 3600-2800 (OH), 1700 cm^{-1} (C=O); δ_H 1.62-1.68 [4H, m, $CH_2(CH_2)_2CH_2$], 2.14 (3H, s, CH_3), 2.21-2.46 (4H, m, CH_2CO_2H and CH_2COCH_3), 9.48 (1H, s, OH); δ_C 23.0, 24.1 [$CH_2(CH_2)_2CH_2$], 29.8 (CH_3), 33.8 (CH_2CO_2H), 43.2 (CH_2COCH_3), 179.4 (CO_2H), 208.7 ($COCH_3$); *m/z* 126 (M^+-H_2O, 11%), 98 (10), 84 (11), 58 (37), 55 (34), 45 (11), 43 (100).

3,(3-Oxocyclopentanyl)propanoic acid (**3l**)[19]: ν_{max}(film) 3460-2700 (OH), 1700 cm^{-1} (C=O); δ_H 1.77-1.88 (4H, m, $CH_2CH_2CO_2H$ and CH_2CH_2CO), 2.16-2.46 (7H, m, CH_2CO_2H, *CH*, CH_2COCH_2), 9.42 (1 H, s, OH); δ_C 29.2, 30.3, 32.3 ($CH_2CH_2CO_2H$ and CH_2CH_2CO), 36.5 (CH), 38.4, 44.7 (CH_2COCH_2), 179.4 (CO_2H), 209.1 (CO); *m/z* 156 (M^+, 6%), 97 (11), 96 (61), 83 (100), 82 (12), 69 (11), 60 (11), 56 (13), 55 (55), 54 (11), 41 (22).

Acknowledgement. This work was supported by the DGICYT (no. PB88-0287). F.F. thanks the Ministerio de Educación y Ciencia of Spain for a fellowship.

References and Notes

1. Carey, F. A.; Sundberg, R.-J. *Advanced Organic Chemistry*; Part A, 3rd Edn.; Plenum Press: New York, 1990; p. 39.
2. For reviews on homoenolate intermediates see: (a) Werstiuk, N. H. *Tetrahedron* **1983**, *39*, 205. (b) Stowell, J. C. *Chem. Rev.* **1984**, *84*, 409. (c) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932. (d) Hase, T. A. Ed. *Umpoled Synthons*; J. Wiley & Sons: New York, 1987.
3. Alternatives to homoenolates **V** involve: (a) the use of homoenolates derived from low electropositive metals such as tin (Nakahira, H.; Ryu, I.; Ogawa, A.; Kambe, N.; Sonoda, N. *Organometallics* **1990**,

9, 277), zinc (Ochiai, H.; Nishihara, T.; Tamura, Y.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 1343) or zinc-copper (Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1988**, *29*, 2395), manganese (DeShong, P.; Sidler, D. R.; Rybczynski, P.-J.; Slough, G. A.; Rheingold, A. L. *J. Am. Chem. Soc.* **1988**, *110*, 2575), niquel (Schönecker, B.; Walther, D.; Fischer, R.; Nestler, B.; Bräumlich, G.; Eibisch, H.; Droescher, P. *Tetrahedron Lett.* **1990**, *31*, 1257), palladium (Osakada, K.; Doh, M.-K.; Ozagua, F.; Yamamoto, A. *Organometallics* **1990**, *9*, 2197), platinum (Ikura, K.; Ryu, I.; Ogawa, A.; Sonoda, N.; Harada, S.; Kasai, N. *Organometallics* **1991**, *10*, 528), gold (Ito, Y.; Inouye, M.; Suhinome, M.; Murakami, M. *J. Organomet. Chem.* **1988**, *342*, C41), antimony, gallium, tellurium, cadmium, mercury or germanium (Nakamura, E.; Shimada, J.; Kuwajima, I. *Organometallics* **1985**, *4*, 641) and lanthanoid metals (Fukuzawa, S.; Sumimoto, N.; Fujinami, T.; Shizuyoshi, S. *J. Org. Chem.* **1990**, *55*, 1628). (b) The use of masked enolates derived from more electronegative metals such as lithium (Barluenga, J.; Fernández, J. R.; Rubiera, C.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3113) or magnesium (Greiner, A. *Tetrahedron Lett.* **1989**, *30*, 3547).

4. For general information about radicals in synthetic organic chemistry see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, 1986. (b) Curran, D. P. 'Radical Addition Reactions'. In *Comprehensive Organic Synthesis*; Vol. 4; Trost, B. M.; Fleming, I. Eds.; Pergamon Press: Oxford, 1991; Cap. 4.1.
5. Species of this type have been rarely proposed as intermediates, following the 'mercury route'[6,7] (Giese, B.; Horler, H. *Tetrahedron* **1985**, *41*, 4025), the 'tin route'[7] (Ryu, I.; Kujano, K.; Yamazoki, H.; Sonoda, N. *J. Org. Chem.* **1991**, *56*, 5003) or by means of manganese(III) salts (Iwasawa, N.; Hayakawa, S.; Isobe, K.; Narasaka, K. *Chem. Lett.* **1991**, 1193).
6. Barluenga, J.; Yus, M. *Chem. Rev.* **1988**, *88*, 487.
7. Giese, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 553.
8. Adlington, R. M.; Baldwin, J. E.; Basak, A.; Kozyrod, R. P. *J. Chem. Soc., Chem. Commun.* **1983**, 944.
9. The reaction can be carried out using stoichiometric amounts of tributyltin hydride (see, for instance: Brandi, A.; Cicchi, S.; Goti, A. *Tetrahedron Lett.* **1991**, *32*, 3265).
10. The same reaction starting from lithio 3-iodopropionate (prepared from the acid **1** and *n*-butyllithium) gives the same result.
11. Morgan G. T.; Walton E. *J. Chem. Soc.* **1933**, 91.
12. Reinheckel H. *Monatsh. Chem.* **1967**, *98*, 1437.
13. Feldhues U.; Schäfer H. J. *Synthesis* **1982**, 145.
14. Nikishin G. I.; Troyanski E. I.; Misintsev V. V.; Molokanov A. N.; Ogibin Y. N. *Tetrahedron Lett.* **1986**, *27*, 4215.
15. Moldenhauer O.; Irion W.; Mastaglio D.; Pfluger R.; Döser H. *Liebigs Ann. Chem.* **1953**, *583*, 50.
16. Walter M.; Besendorf H.; Schnider O. *Helv. Chim. Acta* **1961**, *44*, 1546.
17. Takahashi J.; Mori K.; Matsui M. *Agric. Biol. Chem.* **1979**, *47*, 1605.
18. Sevrin M.; Dumont W.; Krief A. *Tetrahedron Lett.* **1977**, *18*, 3835.
19. Suemune H.; Oda K.; Sakai K. *Tetrahedron Lett.* **1987**, *28*, 3373.