# Synthesis of α-methylene-β-lactones by nickel-catalyzed hydrocarboxylation of propargyl alcohols

## Ganit Roso-Levi, Ibrahim Amer *

*Department of Chemistry, Ben-Gurion University of the Negev, Beer Sheva 84105, Israel*

## Abstract

Substituted α-methylene-β-lactones (2) were prepared in two steps, from substituted propargyl alcohols, by hydrocarboxylation under atmospheric pressure of CO in the presence of nickel cyanide under phase-transfer conditions. The α-methylene-3-hydroxypropanoic acid derivatives so formed (12–40% yield), were cyclized with mesyl chloride (22–56% yield).

*Keywords:* Nickel; α-Methylene-β-lactones; Phase-transfer condition; Hydrocarboxylation; Propargyl alcohol

## 1. Introduction

Although a number of methods have been developed for the synthesis of α-methylene-γ-lactones 1 [1], that exhibit important fungicidal, herbicidal, antibiotic, antitumor and antihelminthic properties [2]. The synthesis of α-methylene-β-lactones 2 has hardly been reported in the literature. The first report of their preparation appeared only in 1988 [3–5]. The usefulness of these highly functionalized compounds as building blocks for a variety of organic substrates has already been demonstrated [4]. One method for the preparation of α-methylene-β-lactones starts from α,β-unsaturated acids and proceeds by photosensitized oxygenation followed by deoxygenation of the cyclic peroxides so formed (Eq. 1).



$$(1)$$
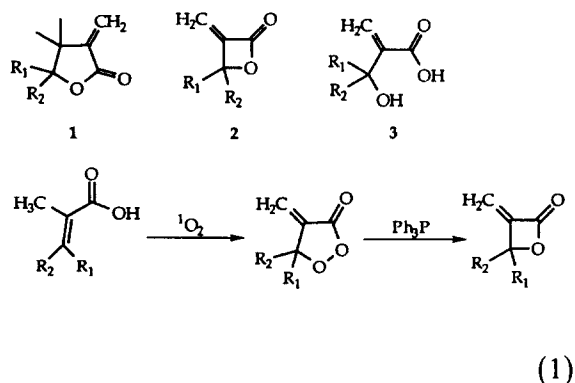
Another approach involves the preparation of α-methyl-β-lactone derivatives from thiol esters and aldehydes followed by selenation and oxidation [5] (Scheme 1). The regioisomer of α-methylene-β-lactones (e.g., β-methylene-β-lactones) are, however, well known and play an
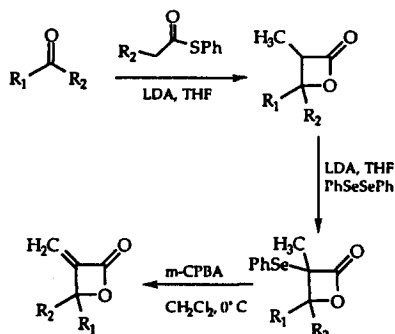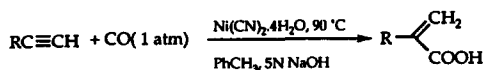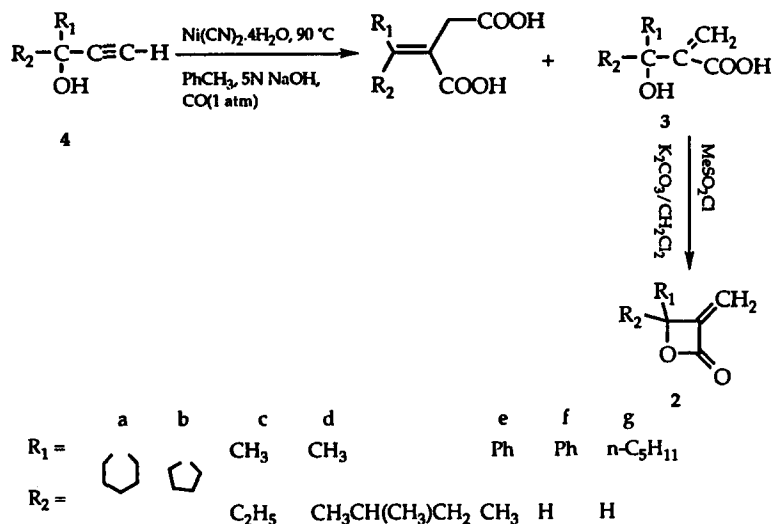
Scheme 1.

important role in organic synthesis [6,7]. The difference between the two regioisomers is rationalized by the lack of synthetic methods for α-methylene-β-lactones, whereas the β-methylene-β-lactones can be easily synthesized by dimerization of aldehydic ketenes [7].

We recently reported the regiospecific hydrocarboxylation of terminal alkynes to α-methylene carboxylic acids (Eq. 2) [8].



It thus seemed conceivable that propargyl alcohols could be converted to α-methylene-β-hydroxy acids 3 by hydrocarboxylation of the

alkyne unit and cyclization of 3 would produce α-methylene-β-lactones 2 (Scheme 2).

## 2. Experimental

Solvents were purified according to standard procedures. Proton and carbon NMR were performed on a Varian XL-200 spectrometer. Infrared spectra were recorded on a Nicolet 5ZDX FT-IR spectrometer. Mass spectra were obtained on a GC–MS spectrometer, with a mass selective detector HP 5971A.

$Ni(CN)_2 \cdot 4H_2O$ was purchased from Strem Chemical Co. Some of the alkynols used in this study were purchased from commercial suppliers and others were prepared from sodium acetylide and the appropriate carbonyl compounds.

### 2.1. General procedure for the carbonylation of alkynols in the presence of $Ni(CN)_2 \cdot 4H_2O$ under phase-transfer conditions

A 100-ml triple-necked flask equipped with a neoprene seal and a small magnetic bar was charged with a mixture of 1 mmol of $Ni(CN)_2 \cdot 4H_2O$, 20 ml of 5 N NaOH, 20 ml of toluene and 0.22 mmol of tetradecyltrimethylammo-



Scheme 2.

nium bromide. The mixture was stirred at 90°C under carbon monoxide. After 1 h, the temperature was lowered (see Tables 1 and 2 for reaction temperatures), and 10 mmol of alkynol in 5–10 ml of toluene was added in small portions. Stirring was continued for 16 h. The reaction mixture was cooled and separated. The aqueous phase was neutralized with 10% hydrochloric acid. The products were isolated by extraction with methylene chloride, dried on magnesium sulfate, and the solvent removed under reduced pressure. The mono carboxylation **3** and the dicarboxylation product and 2-alkylidene-1,4-butanedioic acid [9], respectively, were separated by addition of a 4:1 mixture of ether:hexane (the diacids were isolated in 10–20% yield).

When the hydrocarboxylation reaction was performed in 40 mmol alkynol, a 40% isolated yield of $\alpha$-methylene-$\beta$-lactone was obtained in the case of **3a**.

### 2.1.1. 2-(1-Hydroxycyclohexyl)-2-propenoic acid (3a)

$^1$H NMR (CDCl$_3$) $\delta$ 1.56–1.67 (m, 6H), 1.78–1.90 (m, 4H), 5.86 (s, 1H), 6.35 (s, 1H), 6.90 (b, COOH + OH); $^{13}$C NMR (CDCl$_3$) $\delta$ 21.63 (1C), 25.55 (2C), 36.00 (2C), 72.38 (C–OH), 125.78 (=CH$_2$), 145.60 (C–COOH), 171.85 (COOH); IR (Nujol) $\nu$ 1686 cm$^{-1}$; MS ($m/z^+$, rel. int.) 152 (M – H$_2$O$^{+}$, 42), 109 (C$_6$H$_{13}$, 100), 55 (C$_4$H$_7^+$, 50).

### 2.1.2. 2-(1-Hydroxycyclopentyl)-2-propenoic acid (3b)

$^1$H NMR (CDCl$_3$) $\delta$ 1.71–1.90 (m, 8H), 5.88 (s, 1H), 6.30 (s, 1H), 7.80 (b, COOH + OH); $^{13}$C NMR (CDCl$_3$) $\delta$ 23.23 (2C), 38.67 (2C), 81.90 (C–OH), 125.41 (=CH$_2$), 143.32 (C–COOH), 172.20 (COOH), IR (Nujol) $\nu$ 1688 cm$^{-1}$.

### 2.1.3. 3-Hydroxy-3-methyl-2-methylen-epentanoic acid (3c)

$^1$H NMR (CDCl$_3$) $\delta$ 1.18 (t, $J = 7.2$ Hz, 3H), 1.34 (s, 3H), 1.85 (q, $J = 7.2$ Hz, 2H),

5.87 (s, 1H), 6.41 (s, 1H), 7.10 (b, COOH + OH): $^{13}$C NMR (CDCl$_3$) $\delta$ 8.41 (1C), 25.60 (1C), 33.64 (1C), 74.75 (C–OH), 126.78 (=CH$_2$), 143.72 (C–COOH), 171.51 (COOH); IR (Nujol) $\nu$ 1691 cm$^{-1}$; MS ($m/z^+$, rel. int.) 129 (M – CH$_3^+$, 9), 115 (M – CH$_5^+$, 57), 97 (M – C$_2$H$_7$O$^+$, 100).

### 2.1.4. 3-Hydroxy-3,5-dimethyl-2-methylen-ehexanoic acid (3d)

$^1$H NMR (CDCl$_3$) $\delta$ 0.91 (d, $J = 5.7$ Hz, 6H), 1.50 (s, 3H), 1.61–1.85 (m, 3H), 5.92 (s, 1H), 6.39 (s, 1H); IR (Nujol) $\nu$ 1691, cm$^{-1}$; MS ($m/z^+$, rel. int.), 157 (M – CH$_3^+$, 9), 139 (M – CH$_5$O$^+$, 11), 115 (M – C$_4$H$_9^+$, 98), 97 (M – C$_4$H$_{11}$O$^+$, 100).

### 2.1.5. 3-Hydroxy-2-methylene-3-phenylbutanoic acid (3e)

$^1$H NMR (CDCl$_3$) $\delta$ 1.654 (s, CH$_3$), 6.04(s, 1H), 6.54 (s, 1H), 7.14–7.41 (m, 5H), 8.10 (bs, COO*H* + O*H*); MS ($m/z^+$, rel. int.), 174 (M – H$_2$O$^{+}$, 50), 129 (M – C$_{10}$H$_9^+$, 100), 115 (C$_9$H$_7^+$, 48); IR (Nujol) $\nu$ 1694 cm$^{-1}$.

### 2.1.6. 3-Hydroxy-2-methylene-3-phenylpropanoic acid (3f)

$^1$H NMR (CDCl$_3$) $\delta$ 5.59 (s, C*H*OH), 5.98 (s, 1H), 6.51 (s, 1H), 7.19–7.41 (m, 5H), $^{13}$C NMR (CDCl$_3$) $\delta$ 72.74 (C–OH), 126.63 (=CH$_2$), 141.23 (=C–COOH), 172.30 (COOH), 127.39–128.70 (6C, aromatic); MS ($m/z^+$, rel. int.), 178 (M$^{+}$, 39), 177 (M – H$^+$), 160 (M – H$_2$O$^{+}$, 18), 132 (M – C$_9$H$_8$O$^+$, 54), 105 (C$_7$H$_5$O$^+$, 100), 77 (C$_6$H$_5^+$, 78); IR (Nujol) $\nu$ 1694 cm$^{-1}$.

### 2.1.7. 3-Hydroxy-2-methylenoctanoic acid (3g)

$^1$H NMR (CDCl$_3$) $\delta$ 0.89 (t, $J = 6.0$ Hz, 3H), 1.31 (m, 6H), 1.63 (m, 2H), 4.42 (t, $J = 6.3$ Hz, O–C–H), 5.91 (s, 1H), 6.39 (s, 1H), 6.00 (b, COOH + OH); IR (Nujol) $\nu$ 1699 cm$^{-1}$; MS ($m/z^+$, rel. int.) 101 (M – C$_3$H$_{11}^+$, 100), 83 (M$^+$ – C$_5$H$_{13}$O$^+$, 78), 55 (C$_4$H$_7^+$, 13).

## 2.2. General procedure for the cyclization of α-methylene-β-hydroxy acids 3 to α-methylene-β-lactone 2

A mixture of the appropriate α-methylene-β-hydroxy acid 3 (1.1 mmol) in 10 ml of methylene chloride, 10 mmol of sodium carbonate and 5 mmol of mesyl chloride was stirred vigorously at 20°C for 2 h. Water was then added, and the layers separated. The aqueous layer was extracted with methylene chloride (3 × 20 ml), and the combined organic layers were dried (MgSO$_4$) followed by rotary evaporation.

In the case of cyclization products of α-methylene-β-hydroxy acids 3e, 3f and 3g unstable and polymerized very easily.

### 2.2.1. 3-Methylene-4-spirocyclohexyl-2-oxetanone (2a)

$^1$H NMR (200 MH$_z$, CDCl$_3$) δ 1.46–1.68 (m, 10H), 5.42 (d, $J = 1.8$ Hz, 1H), 5.80 (d, $J = 1.8$ Hz, 1H); IR (Nujol) ν 1812 cm$^{-1}$; MS ($m/z^+$, rel. int.), 152 (M$^{+\cdot}$, 2), 108 (M $-$ CO$_2^{+\cdot}$, 58), 96 (C$_7$H$_{12}^+$, 50).

### 2.2.2. 3-Methylene-4-spirocyclopentyl-2-oxetanone (2b)

$^1$H NMR (200 MH$_z$, CDCl$_3$) δ 1.76–1.90 (m, 8H), 5.38 (d, $J = 2.0$ Hz, 1H), 5.85 (d, $J = 2.0$ Hz, 1H); IR (Nujol) ν 1814 cm$^{-1}$; MS ($m/z^+$, rel. int.) 138 (M$^{+\cdot}$, 81), 93 (C$_7$H$_9^+$, 100).

### 2.2.3. 4-Ethyl-4-methyl-3-methylene-2-oxetanone (2c)

$^1$H NMR (200 MHz, CDCl$_3$) δ 0.954 (t, $J = 7.5$ Hz, 3H), 1.54 (s, 3H), 1.85 (q, $J = 7.5$ Hz, 2H), 5.27 (d, $J = 1.8$ Hz 1H), 5.78 (d, $J = 1.8$ Hz, 1H); IR (Nujol) ν 1812 cm$^{-1}$; MS ($m/z^+$, rel. int.), 97 (M $-$ C$_2$H$_5^+$, 99), 82 (M$^-$C$_3$H$_8^+$, 21), 67 (C$_5$H$_7^+$, 82), 55 (C$_4$H$_7^+$, 100).

### 2.2.4. 4-Isobutyl-4-methyl-3-methylene-2-oxetanone (2d)

$^1$H NMR (200 MHz, CDCl$_3$) δ 0.93 (d, $J = 6.3$ Hz, 6H), 1.25 (m, 1H), 1.61 (s, 3H),

1.79 (d, $J = 4.5$ Hz, 2H), 5.32 (d, $J = 1.8$ Hz, 1H), 5.82 (d, $J = 1.8$ Hz, 1H): IR (Nujol) ν 1813 cm$^{-1}$; MS ($m/z^+$, rel. int.) 139 (M $-$ CH$_3^+$, 99), 97 (M $-$ C$_4$H$_9^+$, 100), 67 (C$_5$H$_7^+$, 20), 55 (C$_4$H$_7^+$, 45).

## 3. Results and discussion

Hydrocarboxylation of 1-ethynylcyclohexanol (4a) (10 mmol) at 80°C with carbon monoxide (1 atm) and nickel cyanide (1 mmol), took place under phase transfer conditions using toluene as the organic phase, 5N NaOH as the aqueous phase, and tetradecyltrimethylammonium bromide as the phase-transfer catalyst. After 19 h α-methylene β-acid 3a and 2-cyclohexylidene-1,4-butanedioic acid were obtained in 40% and 14% isolated yields, respectively [9] (Table 1, Scheme 2). Only 7% of 3a was formed when the reaction was performed in the absence of the phase-transfer catalyst. The yields of 3a also diminished when the concentrations of the base reduced (e.g. 3 N NaOH gave only 27% yield of 3a). The nature of the organic phase significantly affected the yield of 3a. The results summarized in Table 1 indicate that the polar solvents (e.g., 4-methylpentane-2-one and chlorobenzene) were less effective for the hydrocarboxylation reaction than the non polar solvents (i.e., toluene and cyclohexane). Moreover, the application of polar solvents led

Table 1
Nickel–cyanide-catalyzed hydrocarboxylation of 1-ethynylcyclohexanol (4a) under phase-transfer conditions [a]

| Solvent | Base (N) | Temp. (°C) | Yield of 3a (%) |
| --- | --- | --- | --- |
| Toluene | 5 | 50 | 7 |
| Toluene | 5 | 80 | 40 |
| Toluene | 4 | 80 | 36 |
| Toluene | 3 | 80 | 27 |
| Chlorobenzene | 5 | 80 | 26 |
| Cyclohexane | 5 | 70 | 44 |
| 4-Methylpentane-2-one | 5 | 80 | 11 |

[a] Reaction conditions: 10 mmol 4a; 1 mmol Ni(CN)$_2$·4H$_2$O, 0.22 mmol tetradecyltrimethylammonium bromide, 20 ml solvent, 20 ml aqueous phase, 1 atm of CO; stirring speed 1000 rpm.

Table 2
Hydrocarboxylation of alkynols (4) Catalyzed by nickel cyanide under phase-transfer conditions [a] and cyclization of 2-methylene-3-hydroxy acids 3 to α-methylene-β-lactones 2 [b]

| Substrate | Temp. (°C) | Time (h) | Yield of 3 (%) | Yield of 2 (%) |
|---|---|---|---|---|
| a | 80 | 16 | 40 | 33 |
| b | 65 | 19 | 26 | 30 |
| c | 80 | 20 | 30 | 56 |
| d | 80 | 20 | 24 | 22 |
| e | 90 | 19 | 26 | |
| f | 65 | 22 | 35 | - [c] |
| g | 80 | 20 | 12 | - [c] |

[a] Reaction conditions: 10 mmol alkynol; 1 mmol $Ni(CN)_2 \cdot 4H_2O$; 0.22 mmol tetradecyltrimethylammonium bromide; 20 ml toluene; 20 ml aqueous phase 5 N NaOH; 1 atm CO; stirring speed 1000 rpm.
[b] Reaction conditions: 1.1 mmol 3, 10 ml $CH_2Cl_2$, 10 mmol $Na_2CO_3$, 5 mmol mesyl chloride, 2-3 h, 25°C.
[c] Polymerization took place.

to extensive polymerization of the alkynol. Temperature had a significant influence on the hydrocarboxylation reaction. For the synthesis of 2-(1-hydroxycyclohexyl)-2-propenoic acid (3a) the range of 70-80°C was found to be better. Lower temperatures gave very low yield of 3a. While higher temperatures were found to promote the formation of significant amounts of the dicarboxylation product 2-cyclohexylidene-1,4-butanedioic acid. Table 2 summarizes the hydrocarboxylation of various ethynylalkanols.

Cyclization of the α-methylene acid 3 with mesyl chloride and sodium carbonate in dichloromethane [10] gave the corresponding α-methylene β-lactones 2 in 22-56% isolated yield (Table 2).

The sequence of reaction 4 → 3 → 2 (Scheme 2) represents an effective and general method for the preparation of α-methylene-β-lactones 2, all in moderate yields. The α-methylene acids 3 were characterized by IR and NMR and mass spectrometry. The carbonyl frequencies (1686-1699 $cm^{-1}$) are characteristic for such acids. The proton chemical shifts at 5.86-5.98 and 6.30-6.51 and the carbon resonances at 125.41-145.60 of the carbon-carbon double bond support the proposed structure.

The hydrocarboxylation of ethynylalkanols to α-methylene-ω-hydroxy acids offers a convenient general preparation of α-methylene acids. Hydrocarboxylation of 3-butyne-1-ol and 4-pentyne-1-ol produced, after acidification, a mixture of α-methylene acids and α-methylene-γ-lactone (50% yield) and α-methylene-δ-lactone (86% yield) respectively. The α-methylene-β-lactones 2 were characterized by their IR, NMR spectral data and mass spectrometry. The carbonyl frequencies at 1695-1773 $cm^{-1}$ are characteristic of β-lactones, with ring strain caused by the exomethylene substituent. The proton chemical shifts of the vinylic hydrogens were at 5.27-5.42 and 5.85-5.78.

Difficulties were encountered in the cyclization of 3e, 3f and 3g by mesyl chloride at 25°C and at 0°C, it appears that their α-methylene-β-lactones 2e, 2f and 2g were much more sensitive to these conditions than the other compounds (e.g., 2a-2d). In the case of 3e and 3f, we performed the cyclization by an alternative route, in which tosyl chloride and pyridine [11] were used instead of mesyl chloride and sodium carbonate without success.

Our new route to α-methylene-β-lactones provides thus an easier synthesis than published methods [3-5]. The starting propargyl alcohol derivatives are easy to prepare in one step from inexpensive commercial compounds.

## Acknowledgements

## References

[1] F.T. Murray, E.G. Samsel, V. Varma and J.R. Norton, J. Am. Chem. Soc., 103 (1981) 7520 and references therein.
[2] G.N. Perkins and G.P. Belikov, Zh. Mikrobiol. Epidemiol. Immunobiol., 41 (1964) 109; A. Dal Pozzo, A. Danzi, V.

Mariotti and E. Meneghini, Bull. Chim. Farm., 111 (1972) 342, 113 (1974) 280; V.J. Afanasen and V.S. Suleimyin, Veterinariya (Moscow), 4 (1977) 68; D. Dzegunge, Vzaimodeistvie Virusov Kletki, (1977) 130.

[3] W. Adam, L. Hasemann and F. Prechtl, Angew. Chem. Int. Ed. Engl., 27 (1988) 1536; W. Adam, L. Hasemann, F. Prechtl, R. Albert, N.D. Grau, B. Nestler, E.-M. Peters, K. Peters and H.G. Schnering, J. Org. Chem., 56 (1991) 5778.

[4] W. Adam, L. Hasemann, F. Prechtl, V.O.N. Salgado, B. Nestler, E.-M. Peters, K. Peters and H. G.Schnering, J. Org. Chem., 56 (1991) 5782.

[5] R.L. Danheiser, Y. M. Choi, M. Menichincheri and E.J. Stoner, J. Org. Chem. 58 (1993) 322.

[6] S. Searles in A.R. Katritzky and C.W. Rees (eds.), Comprehensive Heterocyclic Chemistry, Vol. 7, Part 5.13, Pergamon Press, New York, 1984, p. 363.

[7] Y. Etienne and N. Fischer in A. Weissberger (Ed.), The Chemistry of Heterocyclic Compounds, Vol. 19, Part II, Wiley, New York, 1964, p. 729.

[8] I. Amer and H. Alper, J. Organomet. Chem., 383 (1990) 573.

[9] N. Satyanarayana and H. Alper, Organometallics, 10 (1991) 804.

[10] A.J. Mageswaram and M.U.S. Sultanbawa, J. Chem. Soc., Perkin Trans. I, (1976) 884.

[11] W. Adam, J. Baeza and J.-C. Liu, J. Am. Chem. Soc., 94 (1972) 2000.