An Efficient Synthesis of 4-Oxo-2,5-hexadienoates via Δ^2-Isoxazoline Intermediates

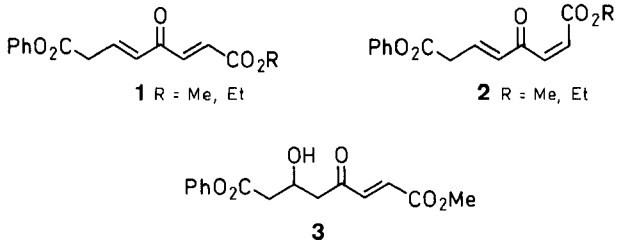
Pier Giovanni Baraldi, Rita Bazzanini, Angelica Bigoni, Stefano Manfredini, Daniele Simoni,* Giampiero Spalluto

Dipartimento di Scienze Farmaceutiche, Università di Ferrara, via Fossato di Mortara 17–19, I-44100 Ferrara, Italy

Received 2 March 1993; revised 7 June 1993

An efficient method for the preparation of 4-oxo-2,5-hexadienoates starting from 3,5-disubstituted Δ^2-isoxazolines is described. The N–O bond cleavage of the isoxazoline ring, promoted by molybdenum hexacarbonyl, afforded the β-hydroxy ketone intermediates **9a–d** which were smoothly dehydrated to the expected 4-oxo-2,5-hexadienoates **10a–d** in about 40% yield starting from **6a,b**.

The 4-oxo-2,5-hexadienoate moiety has recently attracted increasing attention due its presence in natural antitumor agents such as melodienone (**1**) and homoisomelodienone (**2**), two cytotoxic compounds isolated together with the hydroxyl derivative **3** from *Melodorum fruticosum* Lour (Anonaceae).[1,2] The interesting antibacterial activity of 6-substituted 4-oxo-2,5-hexadienoic acids has also been the object of a study in the past.[3] Moreover, in view of the importance of divinyl ketones in organic synthesis the parent 4-oxo-2,5-hexadienoate moiety could be of interest as an intermediate in cyclopentenone synthesis.[4]

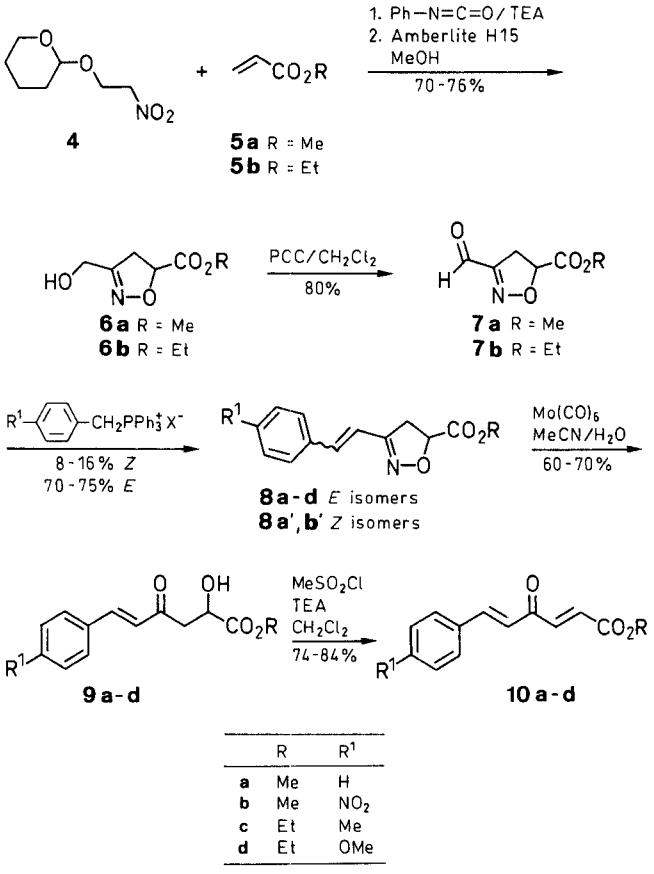


Scheme 1

As a part of an ongoing project centered on the development of [3 + 2] nitrile oxide cycloaddition strategies for the construction of natural compounds we have reported the transformation of the isoxazole and the isoxazoline rings into the γ-oxoacrylate function.[5] More recently, we also reported the preparation of this moiety starting from simple 2,4-dioxoalkanoates.[6] In continuation of this program, we were attracted by the possibility of synthesizing the title derivatives, 4-oxo-2,5-hexadienoates, a class of compounds strictly related to the γ-oxoacrylate moiety. In this paper, we describe a mild and very effective procedure for the preparation of 4-oxo-2,5-hexadienoates having the general structures **10a–d**, starting from the unreported, readily available, 3-formyl-Δ^2-isoxazoline-5-carboxylates **7a,b**. Surprisingly, only a few reports dealing with the preparation of 4-oxo-2,5-hexadienoates are reported in patent literature.[7,8]

Our approach starts from the pyranyl derivative **4**, easily prepared from commercially available 2-nitroethanol as described in literature.[9] This was transformed through a [3 + 2] cycloaddition reaction into the acrylate **5a,b**, under Mukaiyama conditions,[10] to afford in a regioselective manner and good yield the corresponding isoxazoline; removal of the protective group by the use of Amberlite H-15[11] in methanol at 50 °C, led to the primary alcohol **6a,b** in 70–75% yield, calculated from the tetrahydropyranyl derivative **4**. Oxidation of the primary alcohols **6a,b** to the aldehydes **7a, b** was easily performed by pyridinium chlorochromate (PCC) in methylene chloride solution in 85% yield. All compounds **8a–d** were constructed through a Wittig reaction between the aldehydes **7a,b** and the appropriate phosphonium salts which were commercially available or prepared with standard procedures.

The *E* configuration of the newly generated double bond was unambiguously determined by NMR spectroscopy by the presence of an AB system with doublets centered at about $\delta = 6.8$ and 7.1 and with a coupling constant of 16.4–16.2 Hz. In two cases it was possible to isolate the *Z* isomers (compounds **8a',b'**) with $J = 12.1$–11.8 Hz.



	R	R¹
a	Me	H
b	Me	NO_2
c	Et	Me
d	Et	OMe

Scheme 2

The next step involved the reductive N–O cleavage[12] of the isoxazolines **8a–d** with $Mo(CO)_6$ in wet acetonitrile to give the β-hydroxy ketones **9a–d** in 60–70% yield. The

Analytical Data for Compounds **8a–d, 9a–d, 10a–d**[a]

Compound	m.p. (°C)	Yield (%)	IR ν (cm^{-1})	^{1}H NMR ($CDCl_3$) δ, J (Hz)
8a	oil[b]	72	1740[e]	3.48 (m, 2H), 3.82 (s, 3H), 5.14 (dd, 1H, J = 7.2, 10.8) 6.78 (d, 1H, J = 16.4), 7.08 (d, 1H, J = 16.4), 7.34–7.45 (m, 5H)
8b	oil[b]	75	1740[e]	2.95 (m, 2H), 3.77 (s, 3H), 4.95 (dd, 1H, J = 7.3, 10.5), 6.61 (d, 1H, J = 16.3), 6.96 (d, 1H, J = 16.3), 7.47 (d, 2H, J = 8.6 Hz), 8.24 (d, 2H, J = 8.6 Hz)
8c	oil[b]	72	1745[e]	1.33 (t, 3H, J = 7.2), 2.36 (s, 3H), 3.49 (m, 2H), 4.27 (d, 2H, J = 7.2), 5.12 (dd, 1H, J = 8.2, 10.0), 6.74 (d, 1H, J = 16.4), 7.03 (d, 1H, J = 16.4), 7.23 (d, 2H, J = 6.4), 7.36 (d, 2H, J = 6.4)
8d	oil[b]	70	1740[e]	1.31 (t, 3H, J = 7.2), 3.41 (m, 2H), 3.83 (s, 3H), 4.31 (d, 2H, J = 7.2), 5.15 (dd, 1H, J = 8.6, 10.3), 6.69 (d, 1H, J = 16.4), 7.0 (d, 1H, J = 16.4), 7.23–7.35 (m, 4H)
9a	oil[c]	60	3500, 1745, 1690, 1660, 1610[e]	3.23 (m, 2H), 3.35 (br, 1H), 3.81 (s, 3H), 4.60 (m, 1H), 6.74 (d, 1H, J = 16.4), 7.37–7.57 (m, 5H), 7.58 (d, 1H, J = 16.4)
9b	oil[c]	70	3450, 1740, 1680, 1650, 1600, 1580[e]	3.18 (m, 2H), 3.46 (br, 1H), 3.83 (s, 3H), 4.64 (m, 1H), 6.85 (d, 1H, J = 16.2), 7.61 (d, 1H, J = 16.2), 7.72 (d, 2H, J = 8.8), 8.27 (d, 2H, J = 8.8)
9c	oil[c]	70	3450, 1740, 1680, 1660, 1600[e]	1.32 (t, 3H, J = 7.1), 2.37 (s, 3H), 3.18 (m, 2H), 3.51 (br, 1H), 4.26 (q, 2H, J = 7.1), 4.62 (m, 1H), 6.69 (d, 1H, J = 16.2), 7.19 (d, 2H, J = 8.0), 7.43 (d, 2H, J = 8.0), 7.58 (d, 1H, J = 16.2)
9d	oil[c]	65	3450, 1740, 1680, 1650, 1600[e]	1.32 (t, 3H, J = 7.2), 3.22 (m, 2H), 3.48 (br, 1H), 3.79 (s, 3H), 4.26 (q, 2H, J = 7.2), 4.57 (m, 1H), 6.64 (d, 1H, J = 16.2), 6.90 (d, 2H, J = 8.6), 7.41 (d, 2H, J = 8.6), 7.55 (d, 1H, J = 16.2)
10a	75[d]	84	1715, 1660, 1600[f]	3.83 (s, 3H), 6.82 (d, 1H, J = 15.6), 6.96 (d, 1H, J = 16.2), 7.42 (m, 3H), 7.51 (d, 1H, J = 15.6), 7.58 (m, 2H), 7.72 (d, 1H, J = 16.2)
10b	84–86[d]	74	1720, 1640, 1600[f]	3.77 (s, 3H), 6.85 (d, 1H, J = 16.2), 6.95 (d, 1H, J = 16.2), 7.61 (d, 1H, J = 16.2), 7.70 (d, 1H, J = 16.2), 7.72 (d, 2H, J = 8.8), 8.27 (d, 2H, J = 8.8)
10c	78[d]	80	1710, 1660, 1600[f]	1.34 (t, 3H, J = 7.3), 2.39 (s, 3H), 4.27 (d, 2H, J = 7.3), 6.81 (d, 1H, J = 15.9), 6.93 (d, 1H, J = 16.3), 7.2 (d, 2H, J = 8.3), 7.48 (d, 2H, J = 8.3), 7.62 (d, 1H, J = 15.9), 7.72 (d, 1H, J = 16.3)
10d	80–81[d]	80	1710, 1660, 1590[f]	1.25 (t, 3H, J = 7.1), 3.72 (s, 3H), 4.27 (d, 2H, J = 7.1), 6.85 (d, 1H, J = 16.0), 6.91 (d, 1H, J = 16.4), 6.95 (d, 2H, J = 8.6), 7.31 (d, 2H, J = 8.6), 7.62 (d, 1H, J = 16.0), 7.73 (d, 1H, J = 16.4)

[a] All final compounds, including **6a,b** and **7a,b**, gave satisfactory microanalyses: C ± 0.35, H ± 0.19, N ± 0,27%.
[b] Eluent: EtOAc/petroleum ether, 1 : 1.
[c] Eluent: EtOAc/petroleum ether, 6 : 5.
[d] Crystallization solvents: Et_2O/hexane.
[e] Neat.
[f] KBr.

latter compounds were smoothly dehydrated by the action of methanesulfonyl chloride and triethylamine, affording in appreciable yield the expected divinyl ketones **10a–d**.

The ^{1}H NMR spectrum of compounds **10a–d** includes an additional characteristic AB system (centered at about δ = 7 and 7.7, J = 16.2–16.4 Hz) for the COCH=CHCO$_2$R absorptions: these values are fully consistent with an *E, E* stereochemistry of the two double bonds present in the final compounds.

In conclusion, this new method gives an easy and productive access to the 4-oxo-2,5-hexadienoate moiety. Our current efforts in this area are directed toward the extention of this strategy to the synthesis of the natural melodienone **(1)** and of structurally related analogs, which have potential antitumor activity.

Melting points were obtained in open capillary tubes and are uncorrected. Reaction courses and product mixtures were routinely monitored by thin layer chromatography (TLC) on silica gel precoated F254 Merck plates. Infrared sprectra (IR) were measured on a Perkin-Elmer 257 instrument. ^{1}H NMR spectra were determined for solutions in $CDCl_3$ with a Bruker AC-200 spectrometer and peak positions are given in parts per million downfield from tetramethylsilane as internal standard. All drying operations were performed over anhydrous $MgSO_4$. Column chromatography (medium pressure) was carried out by using the "flash" technique.[13] Petroleum ether refers to the fraction with boiling range 40–60 °C.

Alkyl 3-Hydroxymethyl-4,5-dihydroisoxazole-5-carboxylates 6a,b; General Procedure:

To a solution of the tetrahydropyranyl derivative **4** (3.60 g, 19.4 mmol) and the acrylate **5a,b** (194 mmol) in dry benzene (10 mL) containing Et_3N (0.3 mL, 2.1 mmol), phenylisocyanate (5.1 mL, 47.1 mmol) in benzene (10 mL) was added dropwise at r.t., and the mixture was allowed to stand overnight at r.t. The cooled mixture (5 °C) was filtered, the filtrate was washed with 2% aq NH_3 (2 × 50 mL) and brine (3 × 50 mL), dried and concentrated in vacuo. The residual oil was dissolved in MeOH (50 mL) and stirred in the presence of Amberlite H-15 (300 mg) at 50 °C for 3 h. Filtration and removal of the solvent in vacuo left a crude oil which was flash chromatographed on silica gel (eluent: petroleum ether/EtOAc, 1:1).

6a: oil; yield: 2.34 g (76%).

IR (neat): ν = 3400 (br), 1740, 1630 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.37 (m, 2H), 3.41 (br 1H), 3.72 (s, 3H), 4.41 (s, 2H), 5.06 (dd, 1H, J = 7.38, 10.8 Hz).

6b: oil; yield: 2.35 g (70%).

IR (neat): ν = 3400 (br), 1740, 1630 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.26 (t, 3 H, J = 7.1 Hz), 3.33 (m, 2 H), 3.52 (br, 1 H), 4.15 (q, 2 H, J = 7.1 Hz), 4.36 (s, 2 H), 5.1 (dd, 1 H, J = 7.61, 10.6 Hz).

Alkyl 3-Formyl-4,5-dihydroisoxazole-5-carboxylates 7a,b; General Procedure:

To a well-stirred suspension of pyridinium chlorochromate (2.70 g, 12.5 mmol) in dry CH_2Cl_2 (30 mL), a solution of the appropriate alcohol **6a,b** (6.28 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The resulting mixture was stirred at r.t. for 3 h. Addition of Et_2O (50 mL) followed by filtration through a pad of Celite and concentration in vacuo afforded a residue which was flash chromatographed on silica gel (eluent: petroleum ether/EtOAc, 7:3).

7a: oil; yield: 1.57 g (80%).

IR (neat): ν = 1740, 1690 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.35 (m, 2 H), 3.82 (s, 3 H); 4.41 (s, 2 H); 5.26 (dd, 1 H, J = 8.9, 10.3 Hz), 9.95 (s, 1 H).

7b: oil; yield: 1.71 g (80%).

IR (neat): ν = 1740, 1690 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.26 (t, 3 H, J = 7.1 Hz), 3.38 (m, 2 H), 4.25 (q, 2 H, J = 7.1 Hz), 5.26 (dd, 1 H, J = 9.0, 10.3 Hz), 9.93 (s, 1 H).

Alkyl (*E*)-3-(2-Arylvinyl)-4,5-dihydroisoxazole-5-carboxylates 8a–d; General Procedure:

To a solution of potassium *tert*-butoxide (0.90 g, 7.9 mmol) in dry DMSO (5 mL) at r.t. was added the triphenylphosphonium salt (7.9 mmol). The mixture was stirred for 1 h until dissolution of the salt was complete. The aldehyde **7a,b** (3.18 mmol) dissolved in DMSO (5 mL) was then added dropwise to the ylide solution. The mixture was stirred for 1 h at 25°C and then quenched with cold water (15 mL) and extracted with Et_2O (2 × 50 mL). The organic extracts were washed with brine, dried, and evaporated under reduced pressure. The residue was flash chromatographed on silica gel (eluent: petroleum ether/Et_2O) (Table).

8a': *Z* isomer, oil; yield: 0.107 g (16%).

IR (neat): ν = 1740 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.87 (m, 2 H), 3.74 (s, 3 H), 4.90 (dd, 1 H, J = 6.9, 10.3 Hz), 6.52 (d, 1 H, J = 12.1 Hz), 7.05 (d, 1 H, J = 12.1 Hz), 7.19–7.36 (m, 5 H).

8b': *Z* isomer, oil; yield: 0.07 g (8%).

IR (neat): ν = 1740 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.92 (m, 2 H), 3.77 (s, 3 H), 5.0 (dd, 1 H, J = 7.2, 10.2 Hz), 6.65 (d, 1 H, J = 11.8 Hz), 6.97 (d, 1 H, J = 11.8 Hz), 7.46 (d, 2 H, J = 8.3 Hz), 8.22 (d, 2 H, J = 8.3 Hz).

Alkyl (*E*)-6-Aryl-2-hydroxy-4-oxo-5-hexenoates 9a–d; General Procedure:

To a mixture of the isoxazoline **8a–d** (2.36 mmol) in MeCN containing water (5 drops), molybdenum hexacarbonyl (0.312 g, 1.18 mmol) was added and the well-stirred suspension heated at reflux. After 1 h, to complete the reaction, an additional amount molybdenum hexacarbonyl (0.15 g) was added and reflux continued until disappearance of starting material (TLC analyses). The mixture was cooled to r.t., silica gel (3 g) was added, the solvent evaporated in vacuo and the residue was flash chromatographed on a silical gel column eluting with petroleum ether/EtOAc (Table).

Alkyl (*E,E*)-6-Aryl-4-oxo-2,5-hexadienoates 10a–d; General Procedure:

An ice-cooled solution of **9a–d** (1.06 mmol) in CH_2Cl_2 (5 mL) was treated with methanesulfonyl chloride (0.165 mL, 2.13 mmol) and Et_3N (0.59 mL, 2.13 mmol). After 10 min at 0°C, an additional amount of Et_3N (0.59 mL, 2.13 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 30 min. The reaction was stirred at r.t. for 1 h and the mixture was then washed with 10% aq citric acid, brine, dried and concentrated in vacuo.

The residue was flash chromatographed on silica gel (eluent: petroleum ether/EtOAc) (Table).

This work was supported by Consiglio Nazionale delle Ricerche (CNR), Ministero della Ricerca Scientifica e Tecnologica (MURST, grant 40 and 60%).

(1) Jung, J.H.; Pummangura, S.; Chaichantipyuth, C.; Patarapanich, C.; Fanwick, P.E.; Chang, C.-J.; McLaughlin, J.L. *Tetrahedron* **1990**, *46*, 5043.
(2) Jung, J.H.; Chang, C.-J.; Smith, D.L.; McLaughlin, J.L.; Pummangura, S.; Chaichantipyuth, C.; Patarapanich, C. *J. Nat. Prod.* **1991**, 500.
(3) Klotmann, G.; Mueller, H.; Ger. Offen. 1,955,375, 1971; *Chem. Abstr.* **1972**, *76*, 3552.
(4) Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429.
(5) Baraldi, P.G.; Barco, A.; Benetti, S.; Moroder, F.; Pollini, G.P.; Simoni, D. *J. Org. Chem.* **1983**, *48*, 1297.
(6) Manfredini, S.; Simoni, S.; Zanirato, V.; Casolari, A. *Tetrahedron Lett.* **1988**, *29*, 3997.
(7) Geisen, J.; Deiters, W. U.S. Patent 2,967,874, 1961; *Chem. Abstr.* **1961**, *55*, 13317.
(8) Kazutaka, T. *Hakko Kogaku Zasshi* **1960**, *38*, 106; *Chem. Abstr.* **1961**, *55*, 2971.
(9) Kozikowski, A.P.; Adamczyk, M. *J. Org. Chem.* **1983**, *48*, 366.
(10) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.
(11) Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S. *Synthesis* **1979**, 618.
(12) Baraldi, P.G.; Barco, A.; Benetti, S.; Manfredini, S.; Simoni, D. *Synthesis* **1987**, 276.
(13) Still, W.C.; Kahan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2932.