JOURNAL OF MASS SPECTROMETRY
J. Mass Spectrom. 2007; **42**: 1287–1293
Published online in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/jms.1173

JMS

Probing the mechanism of direct Mannich-type α-methylenation of ketoesters via electrospray ionization mass spectrometry

Cíntia D. F. Milagre,[1] Humberto M. S. Milagre,[1] Leonardo S. Santos,[2] Marcelo L. A. Lopes,[1] Paulo J. S. Moran,[1] Marcos N. Eberlin[1] and J. Augusto R. Rodrigues[1]*

[1] Institute of Chemistry, State University of Campinas, 13084-971, Campinas, SP, Brazil
[2] Instituto de Química de Recursos Naturales, Universidad de Talca, Talca, Chile

Received 20 October 2006; Accepted 5 December 2006

Reactions promoting direct Mannich-type α-methylenation of α, β and γ-ketoesters have been monitored via electrospray ionization mass and tandem mass spectrometric experiments. Key intermediates of the catalytical cycle of this synthetically useful reaction have been intercepted and characterized. The mechanistic information provided by electrospray ionization mass spectrometry/mass spectrometry (ESI-MS/MS) guided the optimization of reaction conditions, allowing α-methyleneketoesters to be prepared in high yields (80–95%) and in high-enough purity for immediate further manipulation. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: ketoesters; α-methylenation; electrospray ionization mass spectrometry; reaction mechanisms

INTRODUCTION

α,β-Unsaturated carbonyl compounds are of great importance in organic synthesis. One of their most pronounced characteristics is high reactivity towards various nucleophiles[1–6] in reactions that can form two or more chiral centers. These versatile reagents are also used as building blocks in many asymmetric transformations, including Diels-Alder cycloadditions,[7–9] Michael addition,[10] 1,3-dipolar cycloaddition reactions[11,12] and bioreductions.[13–18] Owing to this wide range of applications, many efforts have been made trying to find optimal synthetic routes of α-methylene carbonyl compounds[6,19–36] for their use as synthetic intermediates,[37–40] to mimic biologically active natural products[41–46] and as potential antitumor drugs.[47–51] Recently, we reported several methods to directly prepare α-methylene carbonyl compounds.[29] Several of these methods were successful for ketones, but unfortunately they failed for ketoesters. The synthesis and further transformations of α-methyleneketoesters have been explored to a limited extent,[30–32,52–57] which encouraged us to develop efficient methods to prepare these somewhat overlooked but important molecules. Herein we report a mechanistic study by direct infusion electrospray ionization mass spectrometry (ESI-MS) of Mannich-type α-methylenation of α, β and γ-ketoesters, which helped us to develop a convenient one-pot method for the efficient preparation of their α-methylene derivatives (Scheme 1).

*Correspondence to: J. Augusto R. Rodrigues, Institute of Chemistry, State University of Campinas, 13084-971, Campinas, SP, Brazil. E-mail: jaugusto@iqm.unicamp.br

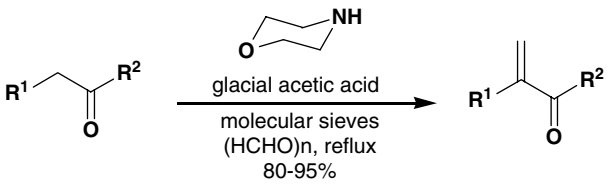
RESULTS AND DISCUSSION

In our first attempt to prepare α-methyleneketoesters, the most straightforward conditions were tested: ketoesters **1**, **3** and **9** (Table 1, entries 1–3) were treated with a 37% aqueous formaldehyde/acetic acid solution in the presence of catalytic amounts of morpholine under reflux. However, no products arising from α-methylenation were obtained using these experimental conditions. Ketoesters **3** and **9** formed a black product with a polymeric aspect, whereas **1** furnished **2,** but in a very low yield, together with a black polymeric product similar to that formed by **3** and **9**. Since preparation of the Mannich bases often requires anhydrous conditions, we replaced the 37% aqueous formaldehyde solution by solid paraformaldehyde and the acetic acid by glacial acetic acid while performing the reaction under a dry nitrogen atmosphere. Under these nearly moisture-free conditions, portions of the starting materials were recovered and the desired products were formed in 46–75% yield (Table 1, entries 4–6). Thus, water plays an important role in the α-methylenation of ketoesters; as the Mannich base is formed, water is released and de-amination occurs to form the desired α-methylene ketoester.

We then monitored the reaction via ESI-MS(/MS) experiments, trying to intercept ionic intermediates and thereby collect mechanistic information that could guide the optimization of reaction conditions. Via ESI(+)-MS, we monitored the reaction of **1** with paraformaldehyde catalyzed by morpholine in an acetic acid/acetonitrile solution, a reaction that was expected to form the α-methyleneketoesters **2** (Scheme 2). ESI-MS has been shown to constitute a proper technique for mechanistic studies[58]

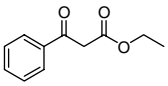
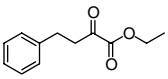
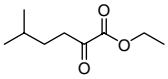
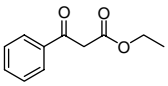
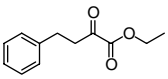
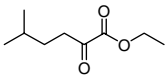
Copyright © 2007 John Wiley & Sons, Ltd.

JMS



Scheme 1. Direct Mannich-type α-methylenation of carbonyl compounds.

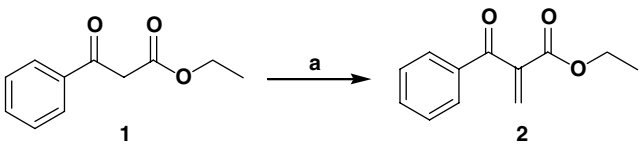
Table 1. Direct α-methylenation of ketoesters under nonoptimized conditions

Entry	Substrate	Conditions[a]	Time (h)	Yield (%)
1	 **1**	1	48	5
2	 **3**	1	48	–
3	 **9**	1	48	–
4	 **1**	2	10	75
5	 **3**	2	10	60
6	 **9**	2	10	46

[a] Conditions: 1 (1.0 mmol), morpholine (0.3 mmol), 37% aqueous solid paraformaldehyde solution (9.0 mmol) and acetic acid (5.0 ml); 2 (1.0 mmol), morpholine (0.3 mmol), paraformaldehyde solid (9.0 mmol) and glacial acetic acid (5.0 ml) under reflux and a dry nitrogen atmosphere.

since it transfers ions directly from the solution to the gas phase with efficiency and gentleness (no or little dissociation), thereby providing proper snapshots of the ion composition of the reaction solutions. We have been using this technique extensively to investigate the mechanisms of major reactions.[59–64]

The ESI(+)-MS collected for the reaction solution was clean and mechanistically enlightening (Fig. 1). As soon as the reaction mixture was formed and electrosprayed, ESI(+)-MS detected both reactants: morpholine in its protonated form $[\mathbf{5}+\mathrm{H}]^+$ of m/z 88 and ethyl benzoylacetate **1** in its protonated and sodiated forms, that is, $[\mathbf{1}+\mathrm{H}]^+$ of m/z 193 and $[\mathbf{1}+\mathrm{Na}]^+$ of m/z 215, as well as its proton dimer form



Scheme 2. Direct Mannich-type α-methylenation of ethyl benzoylacetate **1**. Optimized conditions: **1** (1.0 mmol), morpholine (0.3 mmol), solid paraformaldehyde (9.0 mmol) and glacial acetic acid (5.0 ml) under reflux, dry nitrogen atmosphere and addition of molecular sieves.

$[(\mathbf{1})_2+\mathrm{H}]^+$ of m/z 280. Both reactants were also detected in the form of a proton bound adduct, that is, $[\mathbf{1}+\mathbf{5}+\mathrm{H}]^+$ of m/z 280. Besides the reactants, two key cationic intermediates were also detected as major ions: **7** of m/z 118 and **6** of m/z 100 (Scheme 3). It appears that only kinetic evidence was previously available for the intermediacy of iminium ions such as **6** in the Mannich reactions.[65]

Continuous ESI(+)-MS monitoring showed that the composition of the reaction solution changes considerably with time. After 12 min, ESI(+)-MS mainly detected another key intermediate: the aldol **8** in its protonated form of m/z 292 (Fig. 1(b)) whereas the abundance of the starting reagents $[\mathbf{1}+\mathrm{H}]^+$ of m/z 193 and $[\mathbf{5}+\mathrm{H}]^+$ of m/z 88 as well as intermediates **6** of m/z 100 and **7** of m/z 118 decreased accordingly.

As Figure 2 exemplifies, ESI(+)-MS was able to continuously monitor the α-methylenation reaction of **1** via the consumption of **1** ($[\mathbf{1}+\mathrm{H}]^+$ of m/z 193) and the formation of the final product **2** via its preceding aldol precursor $[\mathbf{8}+\mathrm{H}]^+$ of m/z 292.

For further characterization, the gaseous cationic intermediates detected by ESI(+)-MS were subject to collision-induced dissociation (CID) via ESI(+)-MS/MS experiments. The iminium ion **6** of m/z 100 was found to lose a neutral molecule of 30 Da (most likely formaldehyde) to form a fragment ion of m/z 70 (Fig. 3(a)). Intermediate **7** of m/z 118 (Fig. 3(b)) was found to undergo retro-addition to form protonated morpholine $[\mathbf{5}+\mathrm{H}]^+$ of m/z 88. Intermediate **8** of m/z 292 was found to dissociate mainly by a retro-aldol reaction to form intermediate **6** of m/z 100 as well as by the loss of neutral morpholine (**5**) to form a minor fragment ion of m/z 205, that is, most likely $[\mathbf{2}+\mathrm{H}]^+$. Note that this gas-phase process induced by collisions is analogous to that occurring in solution for **8** in the last reaction step forming the final α-methyleneketoester product **2**.

Scheme 3 presents a catalytical cycle for direct Mannich-type α-methylenation of ketoester **1** that forms the α-methylene ketoester **2** in the presence of **5**. This cycle is based on previous mechanistic interpretations[66] but now shows *authentic* cationic intermediates (**6**, **7** and **8**) that have been properly detected and characterized by ESI(+)-MS(/MS).

On the basis of the ESI(+)-MS(/MS) data and hoping to favor the formation of intermediates **7** and **6**, we repeated the reaction for **1** using a 9 : 1 excess of paraformaldehyde as well as molecular sieves to remove, with high efficiency, the water liberated from **7**. These new reaction conditions promoted a total conversion of **1** to **2** in 2 h, with product yields as high as 90%. The crude material was of sufficient

Copyright © 2007 John Wiley & Sons, Ltd.

DOI: 10.1002/jms

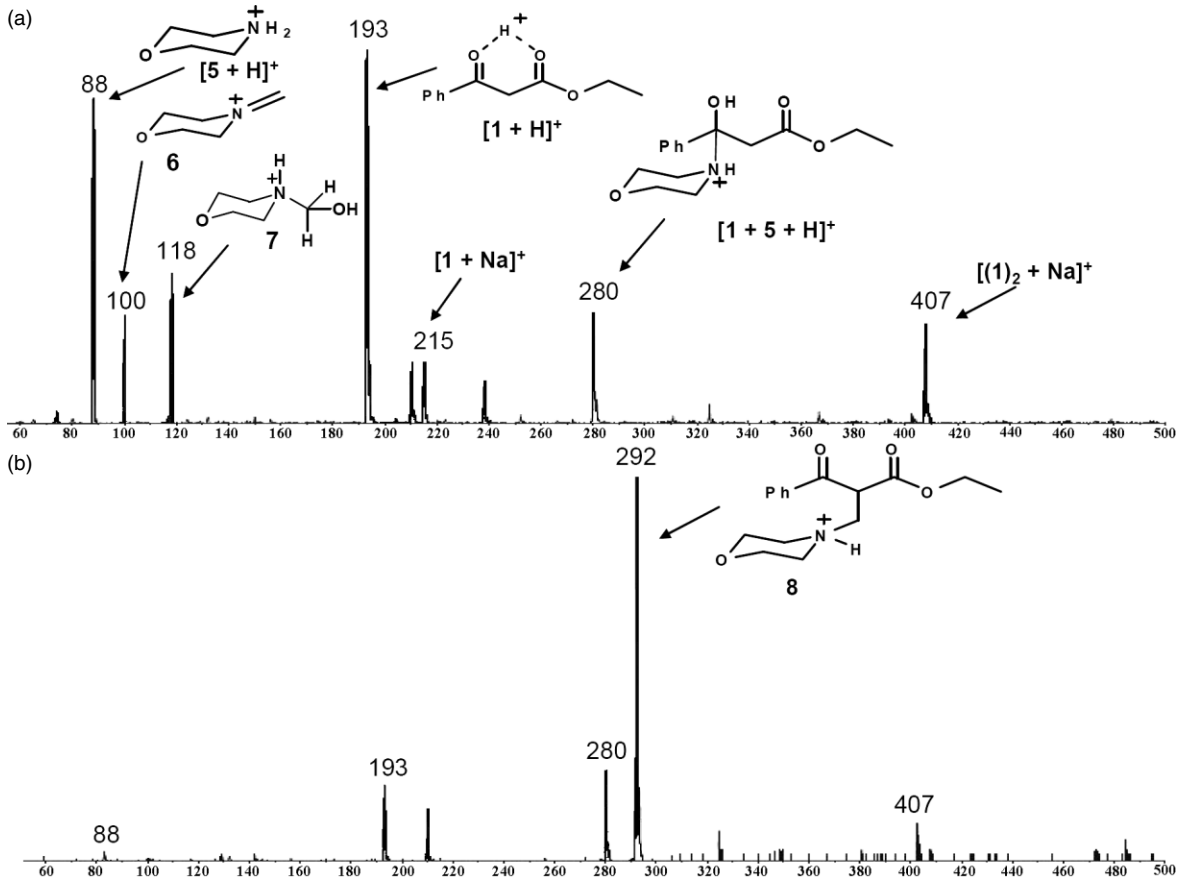
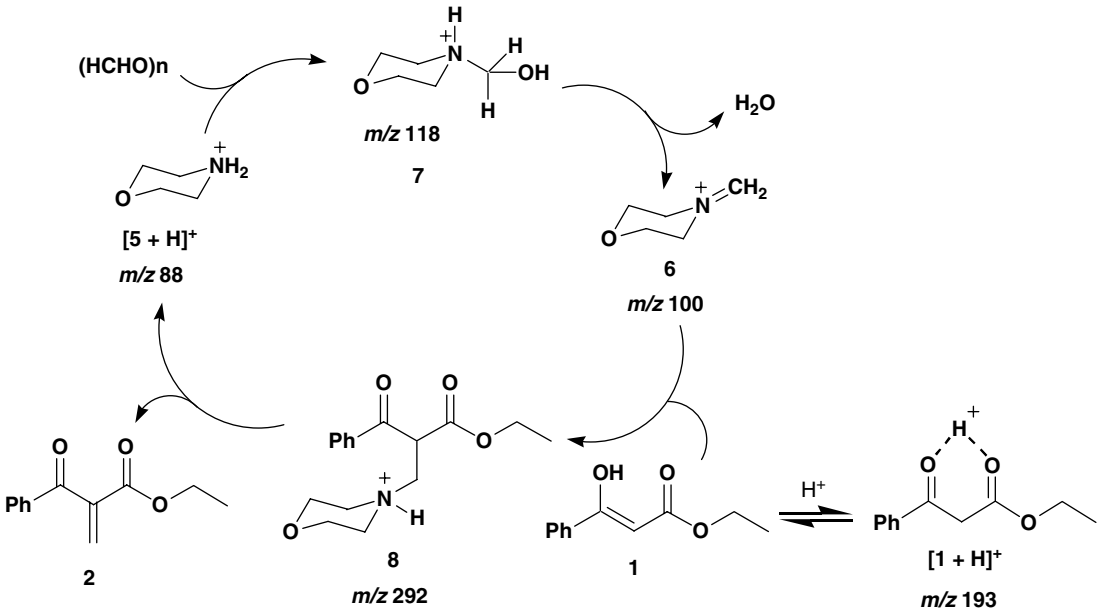


Figure 1. ESI(+)-MS for the α-methylenation reaction of **1** after (a) $t_R = 0.1$ min and (b) $t_R = 12$ min.



Scheme 3. Catalytic cycle for α-methylenation of β-ketoesters in glacial acetic acid medium as probed by ESI-MS monitoring.

purity for immediate further manipulation. As Table 2 summarizes, these optimal reaction conditions were also successfully applied to the α, β or γ-ketoesters **3**, **9**, **11** and **13,** providing yields of the respective α-methylene products as high as 85–95%. All the crude products were formed in pure enough forms for immediate further manipulation.

EXPERIMENTAL

Materials

The starting esters **9**,[67–69] **11**[70] and **13**[71] were prepared according to reported procedures. Ethyl benzoylacetate **1** (97% from Acros) and ethyl 2-oxo-4-phenylbutyrate **3** (97% from Aldrich) were commercially available and used as

Copyright © 2007 John Wiley & Sons, Ltd.

DOI: 10.1002/jms

provided. The purity of all other chemicals used was at least laboratory grade.

General procedure for the methylenation of ketoesters

The reaction was carried out under a nitrogen atmosphere. The ketoester (1.0 mmol) and a freshly prepared solution of morpholine (0.3 mmol) in glacial acetic acid (5.0 ml) were mixed in a 25 ml double-necked round flask with a coiled reflux condenser. Molecular sieves (4Å) and solid paraformaldehyde (9.0 mmol) were then added and the mixture was stirred and heated (Table 2). The reaction mixture was cooled to room temperature and quenched with solid $NaHCO_3$ followed by repeated (3 times) extractions with an equal volume of ethyl acetate. The combined organic extracts were washed with brine and water and dried with anhydrous $MgSO_4$, followed by evaporation of the solvent under reduced pressure.

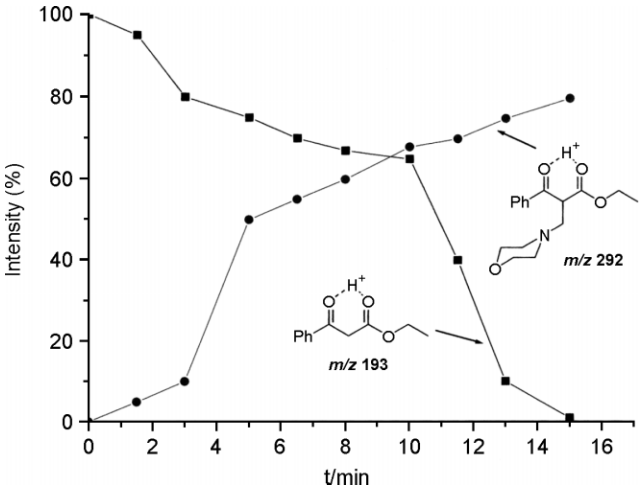


Figure 2. ESI(+)-MS monitoring of α-methylenation of **1** via the abundances of the protonated reagent [**1** + H]$^+$ of *m/z* 193 and the intermediate of the last reaction step, that is, **8** of *m/z* 292.

Product analysis

NMR spectra were recorded on a Gemini 300P spectrometer using standard pulse sequences. Chemical shifts (δ) are given in ppm and coupling constants (J) in Hz. Deuterated solvents were used as lock and reference [^{1}H NMR relative to the proton resonance resulting from incomplete deuteration of the $CDCl_3$ (δ 7.27) and ^{13}C NMR relative to the carbon of the $CDCl_3$ (δ 77.0)]. Infrared spectra were recorded on a Bomen (FT-IR Michelson) spectrometer scanning between 4000 and 400 cm^{-1} (ν_{CO}) using a NaCl cell. Gas chromatographic analyses were performed on a Shimadzu GC-MS QP5000 with a DB-5 (5% phenylmethylsiloxane) 25 m × 0.25 mm × 0.25 µm column. Helium was used as the carrier gas at a pressure of 100 kPa. Samples (1.0 µl) were injected with a split injection ratio of 1 : 100. The temperature of the injector and detector were 250 and 270 °C, respectively. The temperature program was 80 °C for 3 min, 20 °C min^{-1},

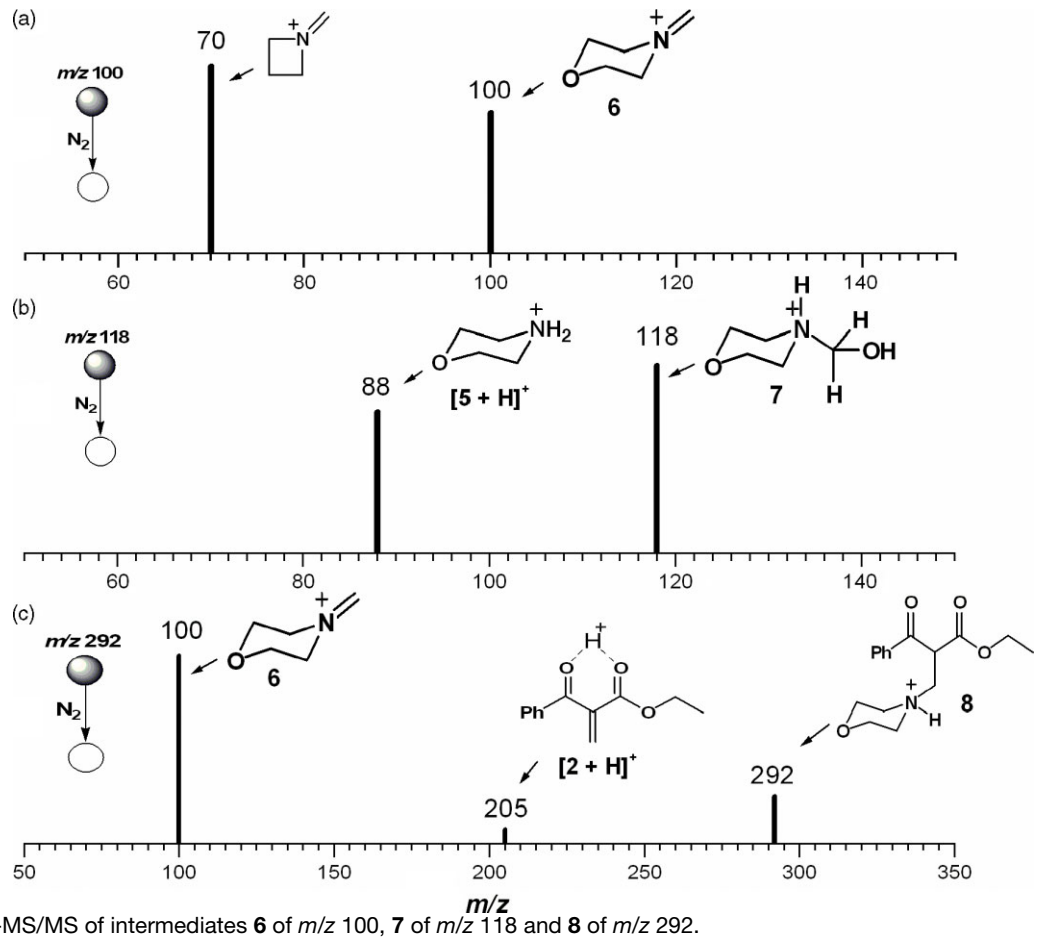
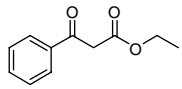
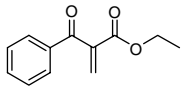
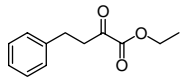
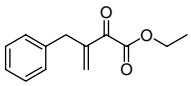
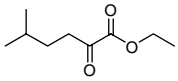
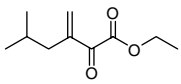
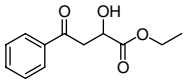
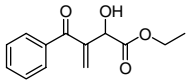
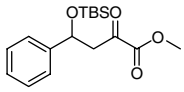
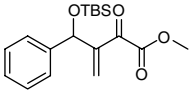


Figure 3. ESI(+)-MS/MS of intermediates **6** of *m/z* 100, **7** of *m/z* 118 and **8** of *m/z* 292.

Copyright © 2007 John Wiley & Sons, Ltd.

DOI: 10.1002/jms

Table 2. Direct α-methylenation of ketoesters under optimized conditions

Entry	Substrate	Product	Temperature and time[a]	Yield (%)
1	 **1**	 **2**	70 °C 2.0 h	90
2	 **3**	 **4**	70 °C 1.5 h	95
3	 **9**	 **10**	55 °C 2.0 h	85
4	 **11**	 **12**	70 °C 4.0 h	85
5	 **13**	 **14**	70 °C 2.0 h	85

[a] Reaction conditions: substrate (1.0 mmol), morpholine (0.3 mmol), solid paraformaldehyde (9.0 mmol) and glacial acetic acid (5.0 ml) under reflux, dry nitrogen atmosphere and addition of molecular sieves.

and 280 °C for 5 min. High resolution (and high accuracy) 70 eV EI-MS were obtained on a Micromass Autospec mass spectrometer using a solid probe to introduce the samples.

ESI(+)-MS analysis

ESI(+)-MS and ESI(+)-MS/MS experiments in the positive ion mode were performed in a QTrap (Applied Biosystem) mass spectrometer. The tandem mass spectrometric experiments were performed via Q1 mass selection of the desirable product ion, Q2 CID with N_2, and linear ion-trap mass analysis of the CID ionic fragments. Main conditions were curtain gas nitrogen flow of 20 ml min^{-1}, ion spray voltage of 4500 eV, declustering potential of 21 eV, entrance potential of 10 eV and collision cell exit potential of 12 eV. A microsyringe pump was used to infuse the reaction solution directly to the ESI source at flow rates of 10 µl min^{-1}. CID was performed with N_2 at energies ranging from 20 to 35 eV.

Characterization data

Ethyl 2-methylene-3-oxo-3-phenylpropionate (**2**). (0.194 g, 90%); colorless oil; IR ν_{max} cm^{-1} 1730, 1680, 1597, 1450, 1367, 1229, 1041, 968 (film); ^{1}H NMR ($CDCl_3$, 300.1 MHz) δ 7.35–7.90 (m, 5H), 6.66 (s, 1H), 6.10 (s, 1H), 4.19 (q, *J* 7.3 Hz, 2H), 1.10 (t, *J* 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.0 MHz) δ 196.8, 170.9, 133.2, 128.5, 128.3, 65.9, 64.1, 62.0, 13.9; GC-MS (EI) m/z 204 ($M^{+\bullet}$), 175 (7%), 158 (7), 105 (100), 77 (44); HRMS (EI) Found: 204.07860. Calcd for $C_{12}H_{12}O_3$: 204.07851.

Ethyl 3-methylene-2-oxo-4-phenylbutanoate (**4**). (0.207 g, 95%); colorless oil; IR ν_{max} cm^{-1} 2983, 1744, 1283 (film); ^{1}H NMR ($CDCl_3$, 300.1 MHz) δ 7.24 (m, 5H), 6.21 (s, 1H), 5.96 (s, 1H), 4.35 (q, *J* 7.3 Hz, 2H), 3.64 (s, 2H), 1.36 (t, *J* 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.0 MHz) δ 187.8, 163.7, 144.3, 137.5, 132.9, 129.1, 128.5, 113.7, 62.2, 35.8, 14.1; GC-MS (EI) m/z 218 ($M^{+\bullet}$), 189 (6%), 145 (41), 117 (100), 115 (82), 91 (42); HRMS (EI) Found: 218.08228. Calcd for $C_{13}H_{14}O_3$: 218.09430.

Ethyl 5-methyl-3-methylene-2-oxohexanoate (**10**). (0.156 g, 85%); colorless oil; IR ν_{max} cm^{-1} 2963, 2924, 2871, 1742, 1683, 1460, 1362, 1255, 1216, 1099, 1036 (film); ^{1}H NMR ($CDCl_3$, 300.1 MHz) δ 6.12 (s, 1H), 5.95 (s, 1H), 4.37 (q, *J* 7.3 Hz, 2H), 2.22 (d, *J* 7.3 Hz, 2H), 1.75 (m, 1H), 1.34 (t, *J* 7.3 Hz, 3H), 0.88 (d, *J* 3.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.0 MHz) δ 188.7, 164.2, 143.8, 132.5, 61.2, 38.5, 28.2, 22.4, 14.4; GC-MS (EI) m/z 184 ($M^{+\bullet}$), 141 (12%), 111 (24), 93 (22), 55 (100); HRMS (EI) Found: 184.10994. Calcd for $C_{10}H_{16}O_3$: 184.10995.

Ethyl 2-hydroxy-3-methylene-4-oxo-4-phenylbutanoate (**12**). (0.199 g, 85%); pale yellow oil; ^{1}H NMR ($CDCl_3$, 300.1 MHz) δ 7.79 (d, *J* 7.0 Hz, 2H), 7.40–7.60 (m, 3H), 6.19 (s, 1H), 5.82 (s, 1H), 5.34 (s, 1H), 4.18 (q, *J* 7.9 Hz, 2H), 1.26 (t, *J* 7.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.0 MHz) δ 197.2, 172.5, 144.9, 132.9, 129.6, 128.5, 127.3, 71.7, 62.3, 15.3; GC-MS (EI) m/z 234 ($M^{+\bullet}$), 205 (5%), 161(80) 132 (15), 115 (10), 105 (100), 83 (25), 77 (55); HRMS (EI) Found: 234.07671. Calcd for $C_{13}H_{14}O_4$: 234.08921.

Methyl 4-(*t*-butyldimethylsilyl)oxy-2-oxo-3-methylene-4-phenylbutanoate (**14**). (0.283 g, 85%); pale yellow oil; IR

Copyright © 2007 John Wiley & Sons, Ltd.

DOI: 10.1002/jms

ν_{max} cm^{-1} 2955, 2929, 2889, 2857, 1742, 1684, 1472, 1255, 1100 (film); ^{1}H NMR ($CDCl_3$, 300.1 MHz) δ 7.49 (m, 5H), 6.61 (s, 1H), 6.39 (s, 1H), 5.70 (s, 1H), 3.98 (s, 3H), 0.98 (s, 9H), 0.03 (s, 3H), −0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.0 MHz) δ 186.7, 163.7, 148.3, 142.3, 131.5, 128.0, 127.1, 126.1, 71.5, 52.8, 25.9, 18.4, −4.9, −4.6; GC-MS (EI) m/z 334 ($M^{+\bullet}$), 277 (17%), 171 (100), 143 (24), 115 (59), 89 (76), 75 (79), 73 (80); HRMS (EI) Found: 334.18115. Calcd for $C_{18}H_{26}O_4Si$: 334.16004.

Acknowledgements

The authors thank the Brazilian science foundations FAPESP, CAPES, CNPq, FUNCAMP and SAE-UNICAMP, and LSS thanks Utalca, for financial support.

REFERENCES

1. Mathieu J, Raynal JN. *Formation of C–C Bonds*, Vol II. Georg Thieme Verlag: Stuttgart, 1975.
2. Stewart JM, Chang CH. Addition reactions of atroponitrile (α-Cyanostyrene). *J. Org. Chem.* 1956; **21**: 635.
3. Hellmann H, Teichmann K, Lingens F. Alpha-acylaminoacrylester aus acylaminomalonestern. *Chem. Ber.* 1958; **91**: 2427.
4. Burn D, Butcher FK, Cole A, Coombs RA, Davies MT, Green MJ, Petrow V. Modified steroid hormones – XLIX: 7-Substituted 6-oxo-3α,5α-cyclosteroids-1. The preparation of 7-methyl-6-oxo-3α,5α-cyclosteroids. *Tetrahedron* 1968; **24**: 4033.
5. Lunn WHW. Steroids. CCLXXVI.[1] the acid-catalyzed reaction between ketones and formaldehyde in dimethyl sulfoxide. *J. Org. Chem.* 1965; **30**: 2925.
6. Gras JL. A direct synthesis of α-methylene ketones. *Tetrahedron Lett.* 1978; **19**: 2111.
7. Yamauchi M, Aoki T, Li MZ, Honda Y. Reactivity of 2-methylene-1,3-dicarbonyl compounds: catalytic enantioselective Diels–Alder reaction. *Tetrahedron: Asymmetry* 2001; **12**: 3113.
8. Yamauchi M, Honda Y, Matsuki N, Watanabe T, Date K, Hiramatsu H. Reactivity of 2-methylene-1,3-dicarbonyl compounds. Stereoselective and asymmetric diels-alder reactions. *J. Org. Chem.* 1996; **61**: 2719.
9. Yamauchi M, Watanabe T. High asymmetric induction in the diels-alder reactions of 1-benzoyl-1-phenyl-menthyloxycarbonylethene. *J. Chem. Soc., Chem. Commun.* 1988; **1**: 27.
10. Huang CG, Chang BR, Chang NC. An efficient synthesis of γ-substituted α,β-unsaturated-δ -lactams. Formal synthesis of (±)-protoemetinol. *Tetrahedron Lett.* 2002; **43**: 2721.
11. Yamauchi M. Reactivity of 2-methylene-1,3-dicarbonyl compounds. 1,3-dipolar cycloaddition reaction with nitrile oxide. *J. Heterocycl. Chem.* 2002; **39**: 1013.
12. Yamauchi M, Yajima M. Reactivity of 2-methylene-1,3-dicarbonyl compounds. 1,3-dipolar cycloaddition reaction with ethyl diazoacetate. *Chem. Pharm. Bull.* 2001; **49**: 1638.
13. Conceição GJA, Moran PJS, Rodrigues JAR. Highly efficient extractive biocatalysis in the asymmetric reduction of an acyclic enone by the yeast *Pichia stipitis*. *Tetrahedron: Asymmetry* 2003; **14**: 43.
14. Siqueira EP, Rodrigues JAR, Moran PJS. Baker's yeast reduction of α-methyleneketones. *Tetrahedron: Asymmetry* 2001; **12**: 847.
15. Dumanski PG, Florey P, Knettig M, Smallridge AJ, Trewhella MA. The baker's yeast-mediated reduction of conjugated methylene groups in an organic solvent. *J. Mol. Catal., B Enzym.* 2001; **11**: 905.
16. Kawai Y, Hayashi M, Inaba Y, Saitou K, Ohno A. Asymmetric reduction of α,β-unsaturated ketones with a carbon-carbon double-bond reductase from baker's yeast. *Tetrahedron Lett.* 1998; **39**: 5225.
17. Kawai Y, Saitou K, Hida K, Ohno A. Asymmetric reduction of α,β-unsaturated ketones with a carbon-carbon double-bond reductase from baker's yeast. *Tetrahedron: Asymmetry* 1995; **6**: 2143.
18. Utaka M, Onoue S, Takeda A. Asymmetric reduction of alpha-methylene ketones by using fermenting baker yeast – preparation of optically-active beta-hydroxy alpha-methyl ketones. *Chem. Lett.* 1987; **5**: 971.
19. Nakahira H, Ryu I, Ikebe M, Oku Y, Ogawa A, Kambe N, Sonoda N, Murai S. Beta-Trichlorostannyl ketones and aldehydes. Preparation and facile amine-induced dehydrostannation leading to alpha-methylene ketones and aldehydes. *J. Org. Chem.* 1992; **57**: 17.
20. Paterson I. α-Alkylation and α-alkylidenation of carbonyl compounds by *o*-silylated enolate phenylthioalkylation. *Tetrahedron* 1988; **44**: 4207.
21. Reich HJ, Jasperse CP, Renga JM. Organoselenium chemistry. Alkylation of acid, ester, amide, and ketone enolates with bromomethyl benzyl selenide and sulfide. Preparation of selenocysteine derivatives. *J. Org. Chem.* 1986; **51**: 2981.
22. Tamura R, Watabe K, Katayama H, Suzuki H, Yamamoto Y. Asymmetric synthesis of 3-substituted-2-exo-methylenecyclohexanones via 1,5-diastereoselection by using a chiral amine. *J. Org. Chem.* 1990; **55**: 408.
23. Gras JL. A facile entry to vinyl ketones. *Tetrahedron Lett.* 1978; **32**: 2955.
24. Kim MY, Lim GJ, Lim JI, Kim DS, Kim IY, Yang JS. An efficient process of ondansetron synthesis. *Heterocycles* 1997; **45**: 2041.
25. Bhattacharya A, Segmuller B, Ybarra A. Preparation of acrylophenones and 2-alkyl indanones utilizing hexamethylenetetramine as an inexpensive mannich reagent. *Synth. Commun.* 1996; **26**: 1775.
26. Hon YS, Hsu TR, Chen CY, Lin YH, Chang FJ, Hsieh CH, Szu PH. Dibromomethane as one-carbon source in organic synthesis: microwave-accelerated α-methylenation of ketones with dibromomethane and diethylamine. *Tetrahedron* 2003; **59**: 1509.
27. Hannaby M, Warren S. Dehydration of alcohols with an adjacent phenylthio (PhS) group. *Tetrahedron Lett.* 1985; **26**: 3133.
28. Toshimitsu A, Owada H, Terao K, Uemura S, Okano MJ. Pyridylseleno group in organic synthesis. Preparation and oxidation of alpha-(2-pyridylseleno) carbonyl compounds leading to alpha,beta-unsaturated ketones and aldehydes. *J. Org. Chem.* 1984; **49**: 3796.
29. Rodrigues JAR, Siqueira EP, Mancilha M, Moran PJS. Preparation of alpha-methylene ketones by direct methylene transfer. *Synth. Commun.* 2003; **33**: 331.
30. Hon YS, Liu YW, Hsieh CH. Dibromomethane as one-carbon source in organic synthesis: a versatile methodology to prepare the cyclic and acyclic α-methylene or α-keto acid derivatives from the corresponding terminal alkenes. *Tetrahedron* 2004; **60**: 4837.
31. Kummer DA, Brenneman JB, Martin SF. An efficient synthesis of alpha-branched enones. *Synlett* 2004; **8**: 1431.
32. Ksander GM, McMurry JE, Johnson M. A method for the synthesis of unsaturated carbonyl compounds. *J. Org. Chem.* 1977; **42**: 1180.
33. Biswas K, Borner C, Gimeno J, Goldsmith PJ, Ramazzotti D, So ALK, Woodward S. Expedient synthesis of β,β-disubstituted α-methylenepropionates. *Tetrahedron* 2005; **61**: 1433.
34. Tramontini M. Advances in chemistry of mannich bases. *Synthesis* 1973; **12**: 703.
35. Kleinman EF. In *Comprehensive Organic Synthesis*, vol. 2, Trost BM, Fleming I (eds). Pergamon: New York, 1991; 893.
36. Tramontini M, Angiolini L. *Mannich Bases, Chemistry and Uses*. CRC Press: Boca Raton, FL, 1994.
37. Cormier RA, Schreiber WL, Agosta WC. Photochemical rearrangements of alpha-methylene ketones. *J. Am. Chem. Soc.* 1973; **95**: 4873.
38. Shono T, Nishiguchi I, Komamura T, Sasaki M. Hydrogen bonding in N-substituted amino acids. Crystal structure of the N,N-diethyl-beta-alanine-benzene inclusion compound. *J. Am. Chem. Soc.* 1979; **101**: 984.
39. Tye H. Catalytic asymmetric processes. *J. Chem. Soc., Perkin Trans. 1* 2000; 275.

Copyright © 2007 John Wiley & Sons, Ltd.

40. Conceição GJA, Moran PJS, Rodrigues JAR. Regio- and enantioselective reduction of a α-methyleneketone by *Rhodotorula glutinis*. *ARKIVOC* 2003; **x**: 500.
41. Stiger KD, Mar-Tang R, Bartlet PA. Synthesis of two potential inhibitors of *para*-aminobenzoic acid synthase. *J. Org. Chem.* 1999; **64**: 8409.
42. Mori K, Harashima S. Assignment of (6*R*,10*R*)-relative stereochemistry to the major component of the sex pheromone of the maritime pine scale, *matsucoccus feytaudi*. *Tetrahedron Lett.* 1991; **32**: 5995.
43. Cywin CL, Kallmerten J. Enantioselective synthesis of a sex attractant pheromone of the pine scale *Matsucoccus feytaudi*. *J. Nat. Prod.* 1991; **54**: 1664.
44. Mori K, Furuuchi T, Kiyota H. Pheromone synthesis. 165. a new synthesis of (3s,7r,8e,10e)-3,7,9-trimethyl-8,10-dodecadien-6-one, the major component of the sex-pheromone of the maritime pine scale. *Liebigs Ann. Chem.* 1994; **10**: 971.
45. Einhorn J, Menassieu P, Malosse C, Ducrot PH. Identification of the sex pheromone of the maritime pine scale *matsucoccus feytaudi*. *Tetrahedron Lett.* 1990; **31**: 6633.
46. Shimizu I, Hayashi K, Ide N, Oshima M. Facile synthesis of (−) -serricornin by means of palladium-catalyzed hydrogenolysis of alkenyloxiranes. *Tetrahedron* 1991; **47**: 2991.
47. Grieco PA. Methods for synthesis of alpha-methylene lactones. *Synthesis (Stuttg)* 1975; 67.
48. Lawrence NJ, McGown AT, Nduka J, Hadfield JA, Pritchard RG. Cytotoxic michael-type amine adducts of α-methylene lactones alantolactone and isoalantolactone. *Bioorg. Med. Chem. Lett.* 2001; **11**: 429.
49. Beekman AC, Woerdenbag HJ, van Uden W, Pras N, Konings AWT, Wikström HV, Schmit TJ. Structure-cytotoxicity relationships of some helenanolide-type sesquiterpene lactones. *J. Nat. Prod.* 1997; **60**: 252.
50. Picman AK. Biological-activities of sesquiterpene lactones. *Biochem. Syst. Ecol.* 1986; **14**: 255.
51. Schmidt TJ. Toxic activities of sesquiterpene lactones: Structural and biochemical aspects. *Curr. Org. Chem.* 1999; **3**: 577.
52. Lawrence NJ, Crump JP, McGown AT, Hadfield JA. Reaction of Baylis–Hillman products with Swern and Dess–Martin oxidants. *Tetrahedron Lett.* 2001; **42**: 3939.
53. Queignec R, Kirschleger B, Lambert F, Aboutaj M. High-yield synthesis of alpha-propargylic acrylic ester – a general access to alpha-substituted acrylic esters. *Synth. Commun.* 1988; **18**: 1213.
54. Yamauchi M, Katayama S, Watanabe T. 2-methylthiomethylation of 1,3-dicarbonyl compounds and synthesis of 2-methylene-1,3-dicarbonyl compounds. *Synthesis* 1982; **11**: 935.
55. Takeda T, Watanabe M, Rahim MA, Fujiwara T. Deacylative condensation I. A new facile method for the direct α-methylenation of ester or lactone starting from monosubstituted active methylene compounds. *Tetrahedron Lett.* 1978; **39**: 3753.
56. Kirschleger B, Queignec R. Heterogeneous mediated alkylation of ethyl diethylphosphonoacetate – a one pot access to alpha-alkylated acrylic esters. *Synthesis (Stuttg)* 1986; **11**: 926.
57. Amri H, Rambaud M, Villieras J. Esters α-méthyléniques et α-hydroxyméthylés par addition d'organolithiens ou magnésiens sur l' α-(hydroxymethyl) acrylate d'éthyle et ses dérivés en présence de cuivre(I). *J. Org. Chem.* 1986; **308**: C27.
58. Santos LS, Knaack L, Metzger JO. Investigation of chemical reactions in solution using API-MS. *Int. J. Mass Spectrom.* 2005; **246**: 84.
59. Santos LS, Pavam CH, Almeida WP, Coelho F, Eberlin MN. Probing the mechanism of the baylis-hillman reaction by electrospray ionization mass and tandem mass spectrometry. *Angew. Chem., Int. Ed. Engl.* 2004; **43**: 4330.
60. Raminelli C, Prechtl MHG, Santos LS, Eberlin MN, Comasseto JV. Coupling of vinylic tellurides with alkynes catalyzed by palladium dichloride: evaluation of synthetic and mechanistic details. *Organometallics* 2004; **23**: 3990.
61. Domingos JB, Longhinotti E, Brandão TAS, Bunton CA, Santos LS, Eberlin MN, Nome F. Mechanisms of nucleophilic substitution reactions of methylated hydroxylamines with Bis(2,4-dinitrophenyl)phosphate. Mass spectrometric identification of key intermediates. *J. Org. Chem.* 2004; **69**: 6024.
62. Meurer EC, Santos LS, Pilli RA, Eberlin MN. Probing the mechanism of the petasis olefination reaction by atmospheric pressure chemical ionization mass and tandem mass spectrometry. *Org. Lett.* 2003; **5**: 1391.
63. Ferraz HMC, Pereira FLC, Gonçalo ERS, Santos LS, Eberlin MN. Unexpected synthesis of conformationally restricted analogues of γ-amino butyric acid (GABA): mechanism elucidation by electrospray ionization mass spectrometry. *J. Org. Chem.* 2005; **70**: 110.
64. Domingos JB, Longhinotti E, Brandão TAS, Santos LS, Eberlin MN, Bunton CA, Nome F. Reaction of Bis(2,4-dinitrophenyl) phosphate with hydrazine and hydrogen peroxide. Comparison of *O*- and *N*-Phosphorylation. *J. Org. Chem.* 2004; **69**: 7898.
65. Benkovic SJ, Benkovic PA, Comfort DR. Kinetic detection of the imminium cation in formaldehyde-amine condensations in neutral aqueous solution. *J. Am. Chem. Soc.* 1969; **91**: 1860.
66. Clayden J, Greeves N, Warren S, Wothers P. *Organic Chemistry*. Oxford University Press Inc.: New York, 2001.
67. Okonya JF, Hoffman RV, Johnson MC. Synthesis of 2-oxazolone-4-carboxylates from 3-nosyloxy- and 3-bromo-2-ketoesters. *J. Org. Chem.* 2002; **67**: 1102.
68. Tsuboi S, Furutani H, Ansari MH, Sakai T, Utaka M, Takeda A. Highly enantioselective reduction of 3-chloro-2-oxoalkanoates with fermenting bakers' yeast. A new synthesis of optically active 3-chloro-2-hydroxyalkanoates and glycidic esters. *J. Org. Chem.* 1993; **58**: 486.
69. Weinstock LM, Currie RB, Lovell AVA. A general, one-step synthesis of α-ketoesters. *Synth. Commun.* 1981; **11**: 943.
70. Fadnavis NW, Radhika KR. Enantio- and regiospecific reduction of ethyl 4-phenyl-2,4-dioxobutyrate with baker's yeast: preparation of (*R*)-HPB ester. *Tetrahedron: Asymmetry* 2004; **15**: 3443.
71. Rodrigues JAR, Moran PJS, Milagre CDF, Ursini CV. Diastereo- and enantioselective synthesis of a conagenin skeletal amide moiety. *Tetrahedron Lett.* 2004; **45**: 3579.

Copyright © 2007 John Wiley & Sons, Ltd.

DOI: 10.1002/jms