First One-Pot Synthesis of Mikanecic Acid Derivatives from Allylic Phosphonates, via a Tandem-Sequence Horner–Wadworth–Emmons and Diels–Alder Reactions

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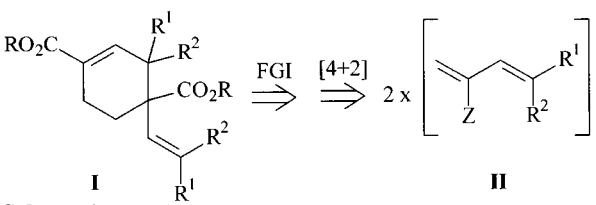
Abstract: This paper describes a new, simple, general and efficient one-pot synthesis of mikanecic acid derivatives from allylic phosphonates, ethyl chloroformate and aqueous formaldehyde. The overall process involves a cascade sequence linking together metallation–alkoxycarbonylation, Horner–Wadworth–Emmons and Diels–Alder reactions.

Key words: allylphosphonates, α-ethoxycarbonylallylphosphonates, mikanecic acid derivatives, alkenation, cycloaddition, one-pot synthesis

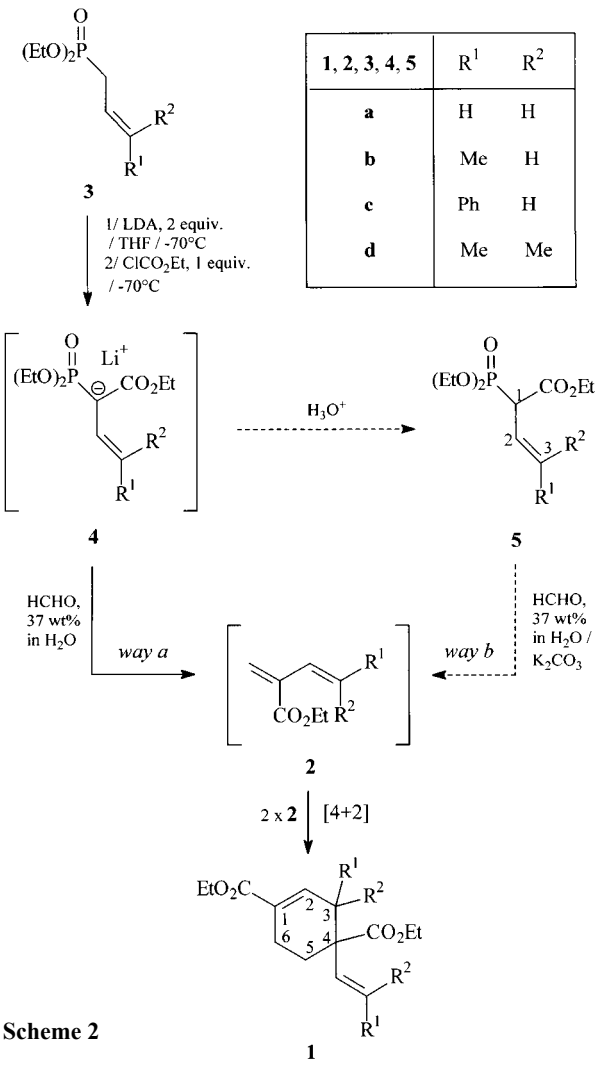
4-Vinylcyclohex-1-ene-1,4-dicarboxylic acid or "mikanecic acid" (**I,** $R^1 = R^2 = R = H$) is a terpenoid dicarboxylic acid isolable from natural alkaloids such as *Mikanoidine*[1] or *Sarracine*.[2] It has been the object of several synthesis attempts during the past three decades. All the methods already proposed for the synthesis of this natural product and its derivatives involved the in situ generation of an isoprenic precursor **II** [Z = CO_2R, CN, C(O)R], which spontaneously dimerizes by a selective head-to-head Diels–Alder reaction,[3] leading to **I**, after possible functional group interconversion (FGI), (Scheme 1). The precursory 1,3-dienes **II** have been generated either by thermolysis of suitable functional strained cycles as cyclopropanes,[3,4] cyclobutenes[5] and sulfolenes,[6–8] or more generally, by an elimination procedure applied to an α,β-unsaturated ester (or ketone) bearing a convenient leaving group (halogeno,[3,9–11] acetate,[2] mesylate[12–14] or carbamate[15]), in allylic or homoallylic[16] position. Finally, various functional substituted allenes have been also employed as sources of dienes **II**.[17–19] Most of the above-mentioned routes to mikanecic acid derivatives suffer either from difficulty of access to starting materials, or from drastic reaction conditions, low yields and often also, from lack of structural generality.



I **II**

Scheme 1

Pursuing our work on the reactivity of phosphonoallylic carbanions, [20–22] we found that treating allylic phosphonates **3** with an excess of lithium diisopropylamide (LDA) at –70 °C, then with ethyl chloroformate at the same temperature and finally with the commercial aqueous solution of formaldehyde near 0 °C, led directly to the corresponding mikanecic acid derivatives **1** in high yield (Scheme 2, *way a* and Tables 1 and 2). This procedure exemplifies the first synthesis of **1** via the tandem-sequence Horner–Wadworth–Emmons (HWE) and Diels–Alder reactions, realized in situ from the readily available phosphonates **3**.[20] The overall reaction was monitored by ^{31}P NMR spectroscopy: in the first step, phosphonate **3** was deprotonated with one equivalent of LDA, as previously described;[20]



1, 2, 3, 4, 5	R^1	R^2
a	H	H
b	Me	H
c	Ph	H
d	Me	Me

Scheme 2

then, the addition of ethyl chloroformate to the lithiated phosphonate, in the presence of the second equivalent of LDA, led quantitatively to the intermediate carbanion **4** [^{31}P NMR, δ (THF) ~ 35], whose formation was proved by quenching the resulting mixture with aqueous HCl, giving the corresponding allylic phosphonate α-ester **5** in very good yield (Tables 3 and 4).[23] Interestingly, when the quenching agent was the aqueous solution (37 wt %) of formaldehyde, the formation of diethyl phosphate [^{31}P NMR, δ (THF) ~ –1.7], as by-product of the HWE reaction, was complete after about 15 min at 0 to 5 °C.[24] Subsequent usual work up furnished the expected compound **1**, likely resulting from spontaneous Diels–Alder dimerization of the transient 2-carboalkoxybuta-1,3-diene **2**, the main product of the HWE reaction. We also showed that isolated phosphonates **5** could be readily transformed into mikanecic derivatives **1** when treated by aqueous formaldehyde in the presence of K_2CO_3 [25] (Scheme 2, *way b*), however the overall yield of the sequence **3** → **1** in *way b* was always lower than that obtained by the one-pot process (Table 1).

Table 1 Synthesis and Physical Data of Compounds **1**

Product	Yield (%)[a]		Bp °C/0.05 mm Hg[b] (Mp °C)
	Way a	*Way b*	
1a	78	57	87[c]
1b	81	62	106
1c	86	74	(119–120)[d]
1d	84	71	115[e]

[a] Yield of isolated product, calculated from starting allylic phosphonates **3**. Purification by column chromatography over silica gel (eluent: petroleum ether/Et_2O). Satisfactory microanalysis (**1c**) or HRMS: (**1a**, **1b**, **1d**) were obtained.
[b] Determined by bulb-to-bulb distillation.
[c] Lit. (ref. 11): 55 °C/0.001 mm Hg.
[d] Lit. (ref. 13): 111–113 °C.
[e] Lit. (ref. 5): 121–123/0.1 mm Hg.

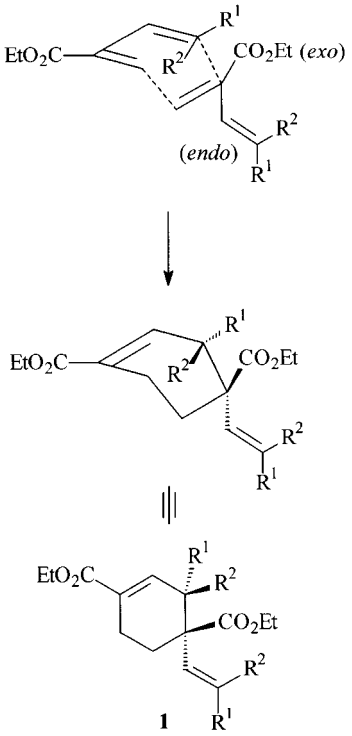
As previously reported,[13] the Diels–Alder dimerization of the expected intermediate diene **2** was highly regio- and stereoselective. Thus, in each example studied in the present work, careful examination of ^{1}H as well as ^{13}C NMR spectra (Table 2) showed a sole regioisomer having the typical "*para*-diester" structure **1**, resulting from the selective head-to-head Diels–Alder process. Moreover, for product **1b** a mixture of two isomers was obtained with a diastereomeric ratio higher than 95: 5, while for **1c** only

Table 2 ^{1}H and ^{13}C NMR[a] and MS Data of Compounds **1**

Product	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C {^{1}H} NMR ($CDCl_3$/TMS) δ, *J* (Hz)	MS (70 eV) *m/z* (%)
1a	1.15–1.4 (m, 6 H, C*H*$_3$CH$_2$O), 1.7–2.85 (m, 6 H, H$_2$C-3, H$_2$C-5, H$_2$C-6), 4.15 (q, *J* = 7.1, 4 H, CH$_3$C*H*$_2$O), 5.15 (dd, *J* = 10.8, 1.6, 1 H, HC=C*H*$_E$), 5.55 (dd, *J* = 17.5, 1.6, 1 H, HC=C*H*$_Z$), 5.9 (dd, *J* = 17.5, 10.8, 1 H, *H*C=CH$_2$), 6.85–6.95 (m, 1 H, HC-2).[b]	14.0, 14.15 (*C*H$_3$CH$_2$O), 21.6 (C-6), 29.4 (C-5), 32.05 (C-3), 47.1 (C-4), 60.25 and 60.9 (CH$_3$*C*H$_2$O), 115.0 (HC=*C*H$_2$), 130.4 (C-1), 136.7 (H*C*=CH$_2$), 139.5 (C-2), 166.8 (O=*C*–C-1), 174.2 (O=*C*–C-4).	252 (M$^+$, 3), 207 (9), 206 (69), 179 (50), 151 (45), 133 (100), 105 (65), 79 (36), 53 (17).
1b[c]	0.95 (d, *J* = 6.8, 3 H, H$_3$CC-3), 1.2–1.4 (m, 6 H, C*H*$_3$CH$_2$O), 1.5–2.4 (m, 4 H, H$_2$C-5, H$_2$C-6), 1.65 (d, *J* = 5.9, 3 H, H$_3$CC=C), 2.5–3.4 (m, 1 H, HC-3), 4.0–4.25 (m, 4 H, CH$_3$C*H*$_2$O), 5.35 (d, *J* = 15.9, 1 H, *H*C=CHCH$_3$) 5.55 (dm, *J* = 15.9, 1 H, HC=C*H*CH$_3$), 6.8–6.95 (m, 1 H, HC-2).	14.05, 14.2 [14.0, 14.1] (*C*H$_3$CH$_2$O), 16.2 [15.9] (H$_3$*C*C-3), 18.2 [16.83] (HC=CH*C*H$_3$), 22.05 [21.55] (C-6), 24.8 [23.95] (C-5), 35.5 [36.8] (C-3), 50.0 [49.8] (C-4), 60.3, 60.7 [60.2] (CH$_3$*C*H$_2$O), 126.2 (HC=*C*HCH$_3$), 128.2 [128.8] (C-1), 131.5 [132.0] (H*C*=CHCH$_3$), 143.4 [141.7] (C-2), 167.2 [167.18] (O=*C*C-1), 174.9 [174.8] (O=*C*C-4).	280 (M$^+$, 21), 265 (1), 234 (96), 207 (78), 188 (36), 161 (100), 140 (41), 133 (73), 91 (51), 67 (42), 39 (19).[d]
1c[e]	1.2–1.4 (m, 6 H, C*H*$_3$CH$_2$O), 1.8–1.75 (m, 4 H, H$_2$C-5, H$_2$C-6), 4.1–4.3, (m, 4 H, CH$_3$C*H*$_2$O), 4.4 (d, *J* = 4.9, 1 H, HC-3), 5.75 (d, *J* = 16.4, 1 H, *H*C=CHPh), 6.2 (d, *J* = 16.4, 1 H, HC=C*H*Ph), 7.0–7.3 (m, 11 H, H$_{arom}$ and HC-2).	14.0, 14.1 (*C*H$_3$CH$_2$O), 22.05 (C-6), 24.75 (C-5), 47.6 (C-3), 51.05 (C-4), 60.3, 61.1 (CH$_3$*C*H$_2$O), 126.2, 127.1, 127.3, 127.8, 128.3, 129.35, 130.5, 131.6 (C$_{o-, m-, p-arom}$ and HC=*C*Ph), 130.0 (C-1), 136.7, 138.1 (C$_{i-arom}$), 139.1 (C-2), 166.8 (O=*C*C-1), 173.9 (O=*C*C-4).	404 (M$^+$, 2), 373 (2), 315 (4), 232 (5), 188 (4), 128 (7), 104 (100), 77 (7), 51 (4).
1d	1.0, 1.22 (2s, 6 H, (*H*$_3$C)$_2$C-3), 1.3–1.4 (m, 6 H, C*H*$_3$CH$_2$O), 1.45, 1.7 (2s, 6 H, (H$_3$C)$_2$C=C), 1.9–2.4 (m, 4 H, H$_2$C-5, H$_2$C-6), 4.1–4.3 (m, 4 H, CH$_3$C*H*$_2$O), 5.15 (s, 1 H, *H*C=C(CH$_3$)$_2$), 6.6 (s, 1 H, HC-2).	14.2, 14.25 (*C*H$_3$CH$_2$O), 18.5, 21.7 ((H$_3$*C*)$_2$C-3), 21.7 (C-6), 24.3, 26.8 ((H$_3$*C*)$_2$C=C), 27.2 (C-5), 38.8 (C-3), 51.3 (C-4), 60.4 (*C*H$_3$*C*H$_2$O), 124.15 (HC=*C*(CH$_3$)$_2$), 128.0 (C-1), 134.0 (H*C*=C(CH$_3$)$_2$), 147.2 (C-2), 167.3 (O=*C*C-1), 175.5 (O=*C*C-4).	308 (M$^+$, 27), 263 (11), 235 (9), 189 (16), 154 (100), 125 (49), 108 (32), 81 (32), 55 (18), 41 (27).

[a] For numbering of the carbon atoms of cyclohexene ring, see Scheme 2.
[b] 60 MHz ^{1}H NMR spectrum of **1a** was given in ref. 3 and 9.
[c] As a mixture of two diastereomers, in a ratio higher than 95:5 (determined by GC measurements). Main data refer to the *major* diastereomer; values in square brackets, in the ^{13}C{^{1}H} NMR spectrum, refer to the *minor* one.
[d] Not any significant difference was observed between the two diastereomers.
[e] As a sole diastereomer.

one diastereomer was detected.[26] In each case, NMR spectra of the major diastereomer are in good agreement with those of the corresponding dimethyl esters,[13] in which the ester group is *exo* and the alkenyl chain is *endo* with respect to the roof-like cyclohexene moiety (Scheme 3; only one enantiomer was represented), as that was already proved by Hoffmann et al.[13] In particular, the chemical shifts of the carbons of the cyclohexene part (C-1 to C-6)



Scheme 3

of the two diastereomers of **1b** (*major* and *minor*) or of the sole diastereomer of **1c**, are in very good agreement with those reported for the dimethyl esters and they can be therefore securely used as criteria for stereochemical assignment.[27]

In conclusion, we describe here a new, efficient and highly diastereoselective one-pot synthesis of mikanecic acid derivatives from readily available allylic phosphonates and standard materials, which illustrates again the advantage of the in situ generation of HWE reagents. The extension of this methodology is currently being investigated in our laboratory.

All reactions were carried out using standard techniques. Solvents were purified by conventional methods prior to use. Reagents were purchased from common commercial suppliers. TLC was performed on Merck 60 F-254 silica gel plates and column chromatography over silica gel (230–400 mesh). Elemental microanalyses were carried out on a Carlo Erba EA 1110 analyser. Mass spectra under electronic impact at 70 eV (m/z and relative abundance in %, are given) were obtained with a GC/MS Hewlett Packard 5970 mass selective detector. HRMS measurements under chemical ionisation at 200 eV were performed on a Jeol AX 500 spectrometer. NMR spectra were recorded on a Bruker AC 200 spectrometer operating at 200 MHz for proton, 50.3 MHz for carbon and 81.01 MHz for phosphorus; chemical shifts (δ) are expressed in ppm relative to TMS for ^1H and ^{13}C nuclei and to H_3PO_4 for ^{31}P nucleus; coupling constants (*J*) are given in Hz; coupling multiplicities are reported using conventional abbreviations. Starting allylic phosphonates **3** were prepared according to ref. 20.

Diethyl 1-Ethoxycarbonylalk-2-enylphosphonates 5; General Procedure

To a solution of LDA (22 mmol) in THF (15 mL) at –70 °C was added a solution of phosphonate **3** (10 mmol) in THF (5 mL) over 20 min. Then, a solution of ethyl chloroformate (2.17 g, 20 mmol) in THF (5 mL) was added dropwise, and the mixture was stirred for 2h at –70 °C and for 15 mn at– 20 °C. The resulting mixture was then quenched at 0 °C by aqueous 4M HCl, until pH ~1. Et_2O (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to give the crude product, which was purified by flash chromatography over silica gel (eluent: CH_2Cl_2) leading to the pure phosphonate **5** (Tables 3 and 4).

Table 3 Synthesis, Physical and ^{31}P NMR Data of Compounds **5**

Product	^{31}P NMR ($CDCl_3$)	Yield (%)[a]	Bp °C/mm Hg[b]
5a	17.8	88	90/0.01
5b	17.9	86	110/0.5
5c	16.8	81	150/0.3
5d	18.0	88	105/0.25

[a] Yield of purified products (oils). Purification by flash chromatography (silica gel; eluent: CH_2Cl_2). Satisfactory microanalyses obtained: C ± 0.31, H ± 0.49.
[b] Determined by bulb-to-bulb distillation.

Diethyl Mikanecic Acid Esters and Substituted Analogues 1; General Procedure

Way a: To a solution of the in situ generated lithiated derivative of phosphonate **5** (prepared as above, at –20 °C), was added, rapidly and with vigorous stirring, an aqueous solution (37 wt %) of formaldehyde (15 mmol). A fast increase in temperature of the mixture and formation of a white precipitate were observed. Stirring was continued at 5 °C for about 15 min. Then, H_2O (5 mL) and Et_2O (15 mL) were added at r.t. The organic layer was washed with H_2O (5 mL) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure (15 mm Hg) at 50 °C and the remaining volatiles were removed by bulb-to-bulb distillation at 70 °C under reduced pressure (2.5 mm Hg). The resulting crude product, which was analyzed by GC for possible diastereoselectivity determinations, was then purified by column chromatography over silica gel (eluent: petroleum ether / Et_2O: 1/1), giving the pure product **1** (Tables 1 and 2).

Way b : To pure phosphonate **5** (10 mmol), was added at r.t. dried K_2CO_3 (30 mmol) and then a solution (37% wt) of formaldehyde (20 mmol) in H_2O, under magnetic stirring. An exothermic reaction developed over a period of about 10 min, at the end of which ^{31}P NMR spectrum showed a single peak at δ ~1.5 ppm. The mixture was then hydrolyzed with a saturated solution of NH_4Cl (7 mL) and extracted with Et_2O (3 × 15 mL). Subsequent work-up and purification were carried out as described above in *way a*.

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Table 4 ^{1}H and ^{13}C NMR[a] and MS Data of Compounds **5**

Product	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	$^{13}C\{^{1}H\}$ NMR ($CDCl_3$/TMS) δ, *J* (Hz)	MS (70 eV) *m/z* (%)
5a	1.3 (m, 9 H, C*H*$_3$CH$_2$O), 3.7 (dd, *J* = 18.0, 7.9, 1 H, HC-1), 4.0–4.3 (m, 6 H, CH$_3$C*H*$_2$O), 5.2–5.4 (m, 2 H, H$_2$C-3), 5.9–6.1 (m, 1 H, HC-2).	14.8 (s, *C*H$_3$CH$_2$OC), 15.1 (d, *J* = 6.2, *C*H$_3$CH$_2$OP), 51.2 (d, *J* = 130.5, C-1), 61.5 (s, CH$_3$*C*H$_2$OC), 62.8, 63.0 (2d, *J* = 7, 6.6, CH$_3$*C*H$_2$OP), 120.0 (d, *J* = 12.5, C-3), 128.0 (d, *J* = 11.3, C-2), 168.0 (d, *J* = 6.1, C=O).	250 (M$^+$, 11), 235 (94), 205 (96), 204 (45), 177 (73), 149 (100), 121 (83), 81 (42), 68 (44), 39 (33).
5b	1.2–1.4 (m, 9 H, C*H*$_3$CH$_2$O), 1.75 (dd, *J* = 5.1, 4.8, 3 H, H$_3$C–C-3), 3.7 (dd, *J* = 23.8, 7.9, 1 H, HC-1), 4.05–4.35 (m, 6 H, CH$_3$C*H*$_2$O), 5.6–5.8 (m, 2 H, HC-2, HC-3).	15.9–16.5 (m, *C*H$_3$CH$_2$OC, *C*H$_3$CH$_2$OP), 18.0 (d, *J* = 2.5, H$_3$*C*–C-3), 50.0 (d, *J* = 132.1, C-1), 63.0–64.0 (m, CH$_3$*C*H$_2$OC and CH$_3$*C*H$_2$OP), 120.3 (d, *J* = 11.4, C-2), 132.0 (d, *J* = 13.2, C-3), 170.0 (d, *J* = 4.6, C=O).	264 (M$^+$, 4), 244 (3), 216 (18), 191 (100), 177 (3), 163 (18), 135 (30), 99 (13), 81 (11), 53 (10), 39 (4).
5c	1.25–1.4 (m, 9 H, C*H*$_3$CH$_2$O), 3.9 (dd, *J* = 24.0, 9.5, 1 H, HC-1), 4.1–4.3 (m, 6 H, CH$_3$C*H*$_2$O), 6.35 (ddd, *J* = 15.9, 9.5, 6.2, 1 H, HC-2), 6.6 (dd, *J* = 15.9, 4.9, 1 H, HC-3), 7.2–7.5 (m, 5 H, H$_{arom}$).	13.0 (s, *C*H$_3$CH$_2$OC), 16.1 (d, *J* = 6.2, *C*H$_3$CH$_2$OP), 50.1 (d, *J* = 130.5, C-1), 61.0 (s, CH$_3$*C*H$_2$OC), 62.8, 63.2 (2 d, *J* = 7.1, 6.8, CH$_3$*C*H$_2$OP), 118.2 (d, *J* = 9.0, C-2), 126.0, 127.7, 128.2 (3s, C$_{o\text{-}, m\text{-}, p\text{-}arom}$), 134.2 (d, *J* = 13.0, C-3), 136.0 (s, C$_{i\text{-}arom}$), 167.0 (d, *J* = 5.8, C=O).	326 (M$^+$, 26), 280 (15), 253 (19), 197 (27), 144 (96), 115 (100), 81 (14), 65 (7), 40 (4).
5d	1.2–1.4 (m, 9 H, C*H*$_3$CH$_2$O), 1.7, 1.8 (2dm, *J* = 4.2, 3.7, 6 H, (*H*$_3$C)$_2$C-3), 3.95 (dd, *J* = 23.9, 10.2, 1 H, HC-1), 4.15–4.3 (m, 6 H, CH$_3$C*H*$_2$O), 5.3–5.45 (m, 1 H, HC-2).	14.1 (s, *C*H$_3$CH$_2$OC), 16.2 (d, *J* = 6.1, *C*H$_3$CH$_2$OP), 18.2 and 25.9 (2d, *J* = 2.5, 3.1, (H$_3$*C*)$_2$C-3), 46.1 (d, *J* = 132.7, C-1), 61.5 (s, CH$_3$*C*H$_2$OC), 62.8, 63.2 (2 d, *J* = 7.2, 6.8, CH$_3$*C*H$_2$OP), 113.2 (d, *J* = 9.2, C-2), 138.0 (d, *J* = 13.1, C-3), 168.2 (d, *J* = 5.2, C=O).	278 (M$^+$, 28), 232 (16), 205 (100), 177 (19), 149 (43), 138 (22), 111 (28), 67 (32), 39 (9).

[a] For numbering of the allylic carbon atoms, see Scheme 2.

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(26) Diastereomeric ratios varing from 5:1 to 10:1 have been reported for the corresponding dimethyl esters (ref. 13).
(27) Chemical shift differences for carbons C-1 to C-6, between compounds **1** (**1b**-*major*, **1b**-*minor* and **1c** in Table 2) and the corresponding dimethyl esters (ref. 13) do not exceed ± 0.5 ppm.