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5(4*H*)-Oxazolones. Part VIII.[1] An Efficient Synthesis of Δ^1-Pyrroline-2-carboxylic Acid Derivatives Through Michael and Wittig Condensation

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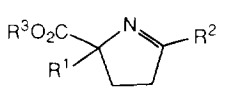
Abstract: Reaction of oxazolones **4** with triphenylvinylphosphonium bromide **3** afforded, through a Michael addition, the α-aminoesters **7** or acids **8** functionalized with a triphenylphosphonium group. Compounds **7** and **8** were transformed in good yields in the corresponding Δ^1-pyrroline-2-carboxylic acids **2** or esters **1** by intramolecular Wittig condensation in presence of sodium alkoxide in refluxing toluene. Intermolecular Wittig reaction of **7** with 4-nitrobenzalhdeyde afforded protected unsaturated α-aminoesters **9**.

It is well known[2,3] that Δ^1-pyrroline-2-carboxylic acid is an important metabolite in many biological processes concerning the biotransformation of glutamic acid into proline. The interest in the preparation of Δ^1-pyrroline-2-carboxylic acid nucleus, variously substituted on the ring, is connected with the possibility to convert it into pyrrole derivatives[4] by oxidation, but most of all into proline derivatives by reduction.[5-11]

Many different approaches[4-15] have been used for the synthesis of Δ^1-pyrroline-2-carboxylic acid derivatives. The viability of these methods depends on the availability of the substituted starting materials.

In this paper we report a new general method for the preparation of the title compounds substituted with an alkyl or aryl group at C-2 and C-5 both as esters **1** and as acids **2**, using the readily available and simple reagents triphenylvinylphosphonium bromide **3** and 5(4*H*)-oxazolones **4** which are readily accessible starting from *N*-acyl derivatives of α-aminoacids.



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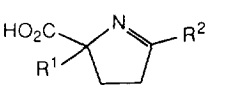
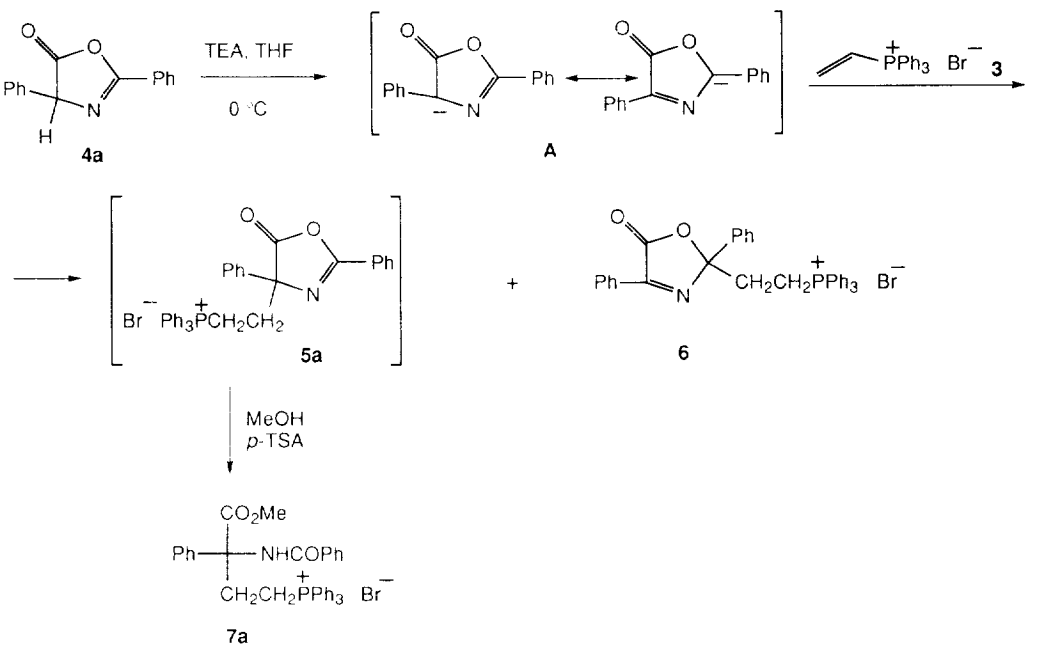


2

Azalactones **4** are very reactive intermediates for the preparation of many classes of heterocycles.[16] Their use takes advantage both of the possibility to deprotonate C-4 generating a carbanionic centre and of the presence of two electrophilic centres: the carbonyl group and C-2. Triphenylvinylphosphonium bromide **3** can be considered the ideal reagent to be condensed with compounds **4** to give pyrroline acid derivatives **1** and **2** because of its dual electrophilic (carbon β to the triphenylphosphonium group) and nucleophilic (as a consequence of the ylide generation) nature.[17-19]

RESULTS AND DISCUSSION

The reaction of oxazolone **4a** with **3** in anhydrous tetrahydrofuran at 0 °C in the presence of a catalytic amount of triethylamine (TEA) resulted in the formation of 5(4*H*)-oxazolone **5a** and 5(2*H*)-oxazolone **6** deriving respectively from Michael addition of the two nucleophilic sites of the mesomeric carbanions **A** to the vinyl group of compound **3**. This outcome is general for oxazolones in Michael addition to α,β-unsaturated compounds substituted with electronwithdrawing groups.[20] The high reactivity of the lactone group of 5(4*H*)-oxazolones toward nucleophiles prevented us from isolating **5a** which underwent ring cleavage also with weak nucleophiles. Nevertheless, the formation of this labile intermediate was detected by monitoring the reaction by IR (absorption at 1820 cm^{-1} [21]). Elaboration of the reaction afforded a mixture of products deriving from the attack of nucleophiles (i.e. moisture, alcohol used in the chromatography) on the lactone group. To avoid this problem, the reaction was quenched with methanol and *p*-toluensulfonic acid (*p*-TSA) as catalyst. Under these conditions the intermediate **5a** was transformed in the corresponding ester **7a**. (Scheme 1)

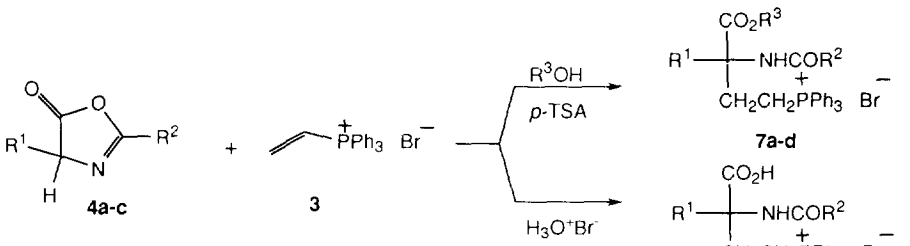


Scheme 1

The more stable 5(2*H*)-oxazolone **6** was isolated and characterised by IR spectrum (ν_{max} 1770 cm^{-1}, CO group).[21] The presence of the CH_2CH_2P group is supported by ^1H NMR spectrum (two multiplets at 3.3-3.7 and 2.5-2.7 ppm) and ^{31}P NMR spectrum (25.3 ppm). The structure of compound **7a** is confirmed by IR (ν_{max} 1720 cm^{-1}, CO_2Me) and ^1H NMR where, besides the signal associated with the ester function (3.6 ppm), two multiplets at 4.5-4.7 ppm (*CH*CP) and 2.8-3.1 ppm ($CHCH_2P$) are present. The phosphonium salt structure is associated with a signal at 26.2 ppm in the ^{31}P NMR spectrum and at 20.0 ppm, $J_{C\text{-}P}$ = 53 Hz, in the ^{13}C NMR.

The regiochemistry of the above reaction was improved using a mixture of tetrahydrofuran and dimethylformamide as solvent at 0 °C and TEA as catalyst. In this case only azalactones **5** were obtained starting from oxazolones **4** and triphenylvinylphosphonium bromide **3**. Intermediates **5** are transformed in good yields (67-87%), without isolation, into the corresponding α-*N*-acylamino methyl esters **7a,b**, ethyl esters **7c,d** or acids **8a,b** by reaction with methanol, ethanol and *p*-TSA as catalyst or aqueous hydrogen bromide, respectively. (Scheme 2)

The ^{1}H NMR spectra of esters **7a-d** confirmed the assigned structure. Similar ^{1}H NMR spectra were obtained for the acid derivatives **8**. A difference was observed for the signal associated with C*H*CP which is shifted in the 2.9-3.4 ppm region.



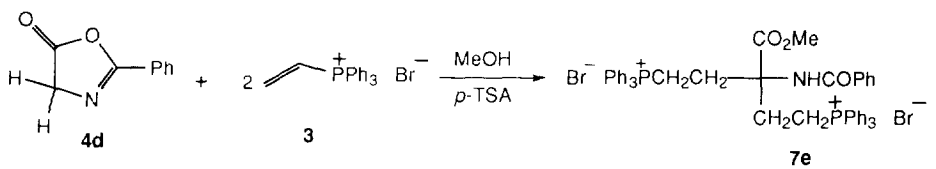
4a: $R^1 = R^2 = Ph$
4b: $R^1 = Ph$, $R^2 = Ph\text{-}4\text{-}Me$
4c: $R^1 = Me$, $R^2 = Ph$

7a: $R^1 = R^2 = Ph$, $R^3 = Me$
7b: $R^1 = Ph$, $R^2 = Ph\text{-}4\text{-}Me$, $R^3 = Me$
7c: $R^1 = Ph$, $R^2 = Ph\text{-}4\text{-}Me$, $R^3 = Et$
7d: $R^1 = Me$, $R^2 = Ph$, $R^3 = Et$

8a: $R^1 = R^2 = Ph$
8b: $R^1 = Ph$, $R^2 = Ph\text{-}4\text{-}Me$

Scheme 2

The reaction of oxazolone **4d** with **3** afforded the aminoester **7e** in which two molar equivalents of salt **3** reacted with the carbanion. All attempts to obtain the monoalkylation product failed, though different experimental conditions were tried. (Scheme 3)

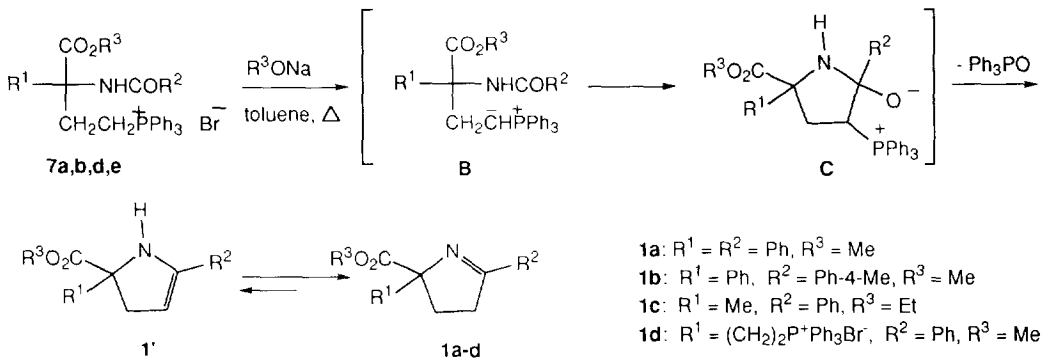


Scheme 3

Compounds **7a,b,d,e** underwent intramolecular Wittig condensation by treatment with a suitable alkoxide (MeONa or EtONa) in refluxing toluene giving good yields (48-92 %) of Δ^1-pyrroline-2-carboxylates **1a-e**.[22] Scheme 4 depicts a rationalisation of our results. The phosphonium salt **7** is deprotonated giving the ylide

intermediate **B** which, through an intramolecular Wittig condensation, reacts with the carboxamido group producing the betaine **C**. After triphenylphosphine oxide elimination the Δ^2-pyrroline-2-carboxylate **1'** is formed which tautomerises to the more stable Δ^1-derivative **1**.[23]

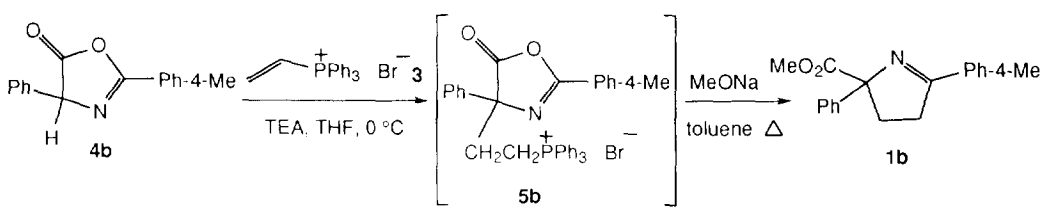
It is worth noting that this reaction represent an unusual example of Wittig condensation of phosphonium ylide with an amidic group. Other examples have been described only occasionally.[17,24,25]



Scheme 4

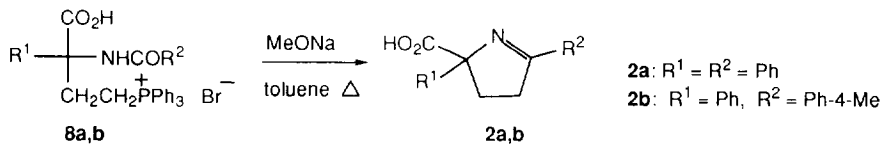
^{1}H NMR and ^{13}C NMR spectroscopy was used to confirm the structure of compounds **1**. The spectra of the esters **1a,b** (R^1 = Ar) show two multiplets associated with one of H-3 and CH_2-4 (2.9-3.2 ppm), and with the other H-3 (2.2-2.3 ppm), respectively. In the spectrum of **1c** (R^1 = Me) three multiplets are present at 3.0-3.2 ppm (H-4), 2.4-2.6 ppm (H-3) and 1.8 ppm (H-3). A NOESY experiment shows that the last one is associated with H-3 *cis* to the methyl group. The spectroscopic data are also consistent with the proposed structure of compound **1d.** Three multiplets are present at 2.9-3.2 ppm (H-4), 2.2-2.7 ppm (H-3, CH_2 and C*H*CH_2P) and 1.9-2.2 ppm (H-3, C*H*CH_2P) in the ^{1}H NMR spectrum. A signal at 25.2 ppm ($J_{C\text{-}P}$ = 72 Hz, CP) is characteristic in the ^{13}C NMR.

An interesting synthetic improvement in the preparation of Δ^1-pyrroline-2-carboxylates was found in the possibility to perform a "one pot" reaction starting from oxazolone **4** and salt **3** without isolation of intermediates. In fact, reaction of **4b** and **3** in THF/DMF at 0 °C and TEA as catalyst, solvent elimination, and treating of the crude **5b** with MeONa in refluxing toluene gave a good yield (50 %) of the expected pyrroline derivative **1b**. (Scheme 5)



Scheme 5

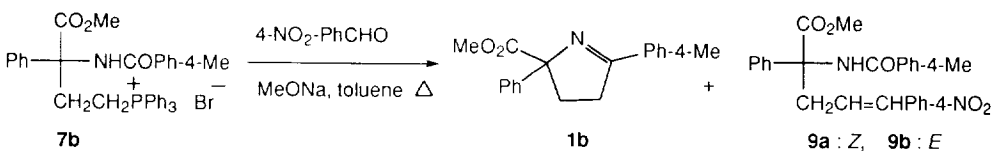
The intramolecular Wittig reaction was carried out also starting from the acids **8** using the same conditions described for the preparation of esters **1**. Starting from **8a,b** the Δ^1-pyrroline-2-carboxylic acids **2a,b** are isolated in satisfactory yields (45-68 %). Spectroscopic data are in agreement with the proposed structure. (Scheme 6)



8a,b **2a,b**

Scheme 6

Finally, compounds **7** proved to be valuable starting materials for the preparation of a protected form of α-aminoacids through reaction with aldehydes. For example **7b** on reaction with 4-nitrobenzaldehyde afforded a major amount (65 %) of a mixture of compounds **9a,b** (*Z*/*E* ratio = 1 : 2) besides a minor amount of the product of the intramolecular reaction, i.e. **1b**. (Scheme 7)[26]



7b **1b** **9a** : *Z*, **9b** : *E*

Scheme 7

EXPERIMENTAL

Melting points were determined using a Büchi 510 (capillary) apparatus. IR spectra were recorded on a JASCO IR Report 100 spectrophotometer. NMR spectra were obtained with Bruker AC 200 and Varian Gemini 200 instruments. TLC: ready-to-use silica gel plates. Column chromatography: silica gel [Kieselgel 60-70 230 ASTM (Merck)] with the eluant indicated.

Materials Phosphonium salt **3** is an available compound. Oxazolones **4a,b**,[21] **4c-e**[29] are known compounds.

2-[(2,4-Diphenyl-5(2H)-oxazolon-2-yl)-ethyl]-triphenylphosphonium Bromide ***6*** *and (3-Benzoylamino-3-carboxymethyl-3-phenyl-propyl)-triphenylphosphonium Bromide* ***7a***. Azalactone **4a** (800 mg, 3.37 mmol) and salt **3** (1.2 g, 3.37 mmol) were suspended and stirred in anhydrous THF (10 mL) at 0 °C under nitrogen atmosphere. A catalytic amount of TEA (34 mg, 0.34 mmol) was added after which the suspension turned orange. After 4 h the temperature was increased to 25 °C and the reaction mixture was quenched with MeOH (1 mL) and *p*-TSA (64 mg, 0.34 mmol). The solution was stirred for a night and then evaporated to dryness at T <

50 °C. The residue was chromatographed on silica gel column (CH_2Cl_2/MeOH, 1:0 to 0:1). Compounds **7a** (930 mg, 47 %) and **6** (200 mg, 15 %) were obtained as pure solids after recrystallization from CH_2Cl_2/*n*-pentane.
6: Mp.: 240 °C. IR (nujol): 1770 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): 2.5-2.7, 3.3-3.7 (m, 4H, CH_2CH_2P), 7.4-8.4 (m, 13 H, Aryl-H) ppm.

General Procedure for the Preparation of α-Aminoesters 7 and Acids 8. Azalactone **4** (5 mmol) and salt **3** (1.8 g, 5 mmol) were suspended and stirred in a mixture of anhydrous THF (12 mL)/DMF (3 mL) at 0 °C under nitrogen atmosphere. A catalytic amount of TEA (50 mg, 0.5 mmol) was added after which the suspension turned orange. After 4 h the temperature was increased to 25 °C and the reaction mixture was quenched with MeOH (1 mL) (for the synthesis of methyl esters **7a,b**) or EtOH (1 mL) (for the synthesis of ethyl esters **7c,d**) and *p*-TSA (95 mg, 0.5 mmol) as catalyst. The acids **8a,b** were prepared quenching the reaction mixture with HBr (1 mL, 10 %). Compound **7e** was obtained in the same way starting from oxazolone **4d** (1.0 g, 80%, 5 mmol) and **3** (3.7 g, 10 mmol). The solution was stirred for a night and then evaporated until dryness at T< 50 °C. The residue was chromatographed on silica gel column (CH_2Cl_2/ MeOH, 1:0 to 0:1 for **7a,b,e** and **8a,b**; CH_2Cl_2/ EtOH, 1:0 to 0:1 for **7c,d**). Compounds **7** and **8** were isolated and recrystallized from CH_2Cl_2/*n*-pentane. Yields and analytical data are given in Table 1, spectroscopic data are reported in Table 2.

General Procedure for the Preparation of Δ^1-Pyrroline-2-carboxylates 1. Ester **7** (1 mmol) was suspended in anhydrous toluene (15 mL) under nitrogen atmosphere. The mixture was heated at 110 °C and MeONa (54 mg, 1 mmol) was added in 15 min. after which the suspension turned orange. After 1h the solvent was evaporated and the crude reaction mixture was chromatographed on silica gel column (AcOEt/cyclohexane, 3:7). Compounds **1a,c** were isolated as pure oils, esters **1b,d** were further purified by recrystallization from CH_2Cl_2/*n*-pentane. Yields and analytical data are given in Table 1, spectroscopic data are reported in Table 3.

General Procedure for the Preparation of Δ^1-Pyrroline-2-carboxylic Acids 2. Acid **8** (1 mmol) was suspended in anhydrous toluene (15 mL) under nitrogen. The mixture was heated at 110 °C and MeONa (108 mg, 2 mmol) was added in 15 min. after which the suspension turned orange. After 1h the solvent was evaporated and the crude reaction mixture was taken up with CH_2Cl_2 (30 mL) and washed with a solution of Na_2CO_3 (2 x 20 mL, 20 %). The combined aqueous layers were acidified with HCl (10 %, Congo Red) and extracted with CH_2Cl_2 (3 x 30 mL). After drying over Na_2SO_4 and evaporation compound **2** was further purified by recrystallization from CH_2Cl_2/*n*-pentane. Yields and analytical data are given in Table 1, spectroscopic data are reported in Table 3.

Synthesis of Methyl 5-(4-methylphenyl)-2-phenyl-3,4-dihydro-2H-pyrroline-2-carboxylate 1b through "One Pot" Reaction. Azalactone **4b** (415 mg, 1.65 mmol) and salt **3** (608 mg, 1.65 mmol) were stirred in anhydrous THF (5 mL)/DMF (1 mL) at 0 °C under nitrogen atmosphere. A catalytic amount of TEA (17 mg, 0.17 mmol) was added after which an orange suspension was formed. After 4 h the temperature was increased to 25 °C and the solvents were evaporated at T< 50 °C. The crude mixture was taken up with anhydrous toluene (20 mL) and heated at 110 °C under nitrogen. MeONa (89 mg, 1.65 mmol) was added in 15 min. after which the suspension turned orange. After 1h the solvent was evaporated and the crude reaction mixture was

chromatographed on silica gel column (AcOEt/cyclohexane, 3:7). Compound **1b** was isolated in 52 % yield after recrystallization from CH_2Cl_2/*n*-pentane.

Reaction of Ester 7b with 4-Nitrobenzaldehyde. The ester **7b** (200 mg, 0.3 mmol) and 4-nitrobenzaldehyde (50 mg, 0.3 mmol) were suspended in anhydrous toluene (10 mL) and heated to reflux under nitrogen. MeONa (16.2 mg, 0.3 mmol) was added in 15 min.. After 1h the solvent was evaporated and the crude reaction mixture was chromatographed on silica gel column (AcOEt/cyclohexane, 3:7) giving two main fractions: **1b** (11 %) and a mixture of olefins **9a,b** (*Z*/*E* , 1:2; 65 %) which were recrystallized from CH_2Cl_2/*n*-pentane.

(Z)-Methyl 2-(4-methyl-benzoylammno)-5-(4-nitro-phenyl)-2-phenyl-pent-4-enoate ***9a*** . IR (nujol): 3400 (NH), 1730 (CO_2Me), 1660 (CONH) cm^{-1}. ^1H NMR ($CDCl_3$): 2.4 (s, 3 H, Me), 3.6 (s, 3 H, OMe), 3.6-3.7 (m, 1H, H-3), 4.0-4.2 (m, 1H, H-3), 5.7-5.9 (m, 1 H, H-4), 6.5 (d, $J_{4,5}$ = 12.2 Hz, 1 H, H-5), 7.2-8.2 (m, 13 H, Aryl-H) ppm.

(E)-Methyl 2-(4-methyl-benzoylamino)-5-(4-nitro-phenyl)-2-phenyl-pent-4-enoate ***9b***. IR (nujol): 3400 (NH), 1730 (CO_2Me), 1660 (CONH) cm^{-1}. ^1H NMR ($CDCl_3$): 2.4 (s, 3 H, Me), 3.53, 4.03 (tdd, $J_{3,4} = J_{3',4} = 7.3$ Hz, J_{gem} = 14 Hz, 2 H, H-3), 3.8 (s, 3 H, OMe), 6.28 ($J_{3,4} = J_{3',4}$ = 7.3 Hz, $J_{4,5}$ = 15.8 Hz, 1 H, H-4), 6.58 (d, $J_{4,5}$ = 15.8 Hz, 1 H, H-5), 7.2-8.2 (m, 13 H, Aryl-H) ppm.

Table 1. Yields and Analytical Data for Compounds **1,2,7** and **8**.

Product	Formula	Yield (%)	m.p. °C	Calcd. % (Found) C	H	N
1a	$C_{18}H_{17}NO_2$	72	oil	77.39 (77.50)	6.13 (6.05)	5.01 (5.10)
1b	$C_{19}H_{19}NO_2$	92	132	77.79 (77.75)	6.53 (6.49)	4.77 (4.80)
1c	$C_{14}H_{17}NO_2$	65	oil	72.69 (72.61)	7.41 (7.36)	6.06 (4.13)
1d	$C_{32}H_{31}BrNO_2P$	48	190	67.13 (67.10)	5.46 (5.40)	2.45 (2.40)
2a	$C_{17}H_{15}NO_2$	68	182	76.96 (76.78)	5.70 (5.78)	5.28 (5.22)
2b	$C_{18}H_{17}NO_2$	45	135	77.39 (77.35)	6.14 (6.10)	5.01 (5.08)
7a	$C_{36}H_{33}BrNO_3P$	67	165	65.09 (65.15)	5.01 (5.10)	2.11 (2.18)
7b	$C_{37}H_{35}BrNO_3P$	82	179	68.09 (68.15)	5.41 (5.41)	2.15 (2.20)
7c	$C_{38}H_{37}BrNO_3P$	87	205	68.47 (68.47)	5.59 (5.47)	2.10 (2.09)
7d	$C_{32}H_{33}BrNO_3P$	80[a]	195	65.08 (65.09)	5.63 (5.77)	2.37 (2.46)
7e	$C_{50}H_{47}Br_2NO_3P_2$	80[a]	140 (dec.)	64.45 (64.40)	5.08 (5.15)	1.50 (1.44)
8a	$C_{35}H_{31}BrNO_3P$	65	203	67.31 (67.00)	5.00 (5.10)	2.24 (2.10)
8b	$C_{36}H_{33}BrNO_3P$	81	206	67.71 (67.53)	5.21 (5.10)	2.19 (2.00)

[a] Yield starting on impure oxazolone **4**.

Table 2. Spectroscopic Data for Compounds **7, 8**.*

	ν_{max}/cm^{-1} [a]		$\delta_H(CDCl_3)$, (*J* /Hz)			
Product	NH and/or OH	C=O	NH	Arom.	CH_2CH_2P	Other
7a	3370	1720, 1640	9.5	8.4-7.3	4.7-4.5, 3.1-2.8	3.62 (CO_2Me)
7b	3350	1730, 1630	9.5	8.3-7.3	4.7-4.4, 3.1-2.8	3.63 (CO_2Me), 2.4 (Me)
7c	3350	1720, 1630	9.3	8.3-7.2	4.7-4.4, 3.1-2.8	4.2-4.0, 1.0 (CO_2Et), 2.4 (Me)
7d	3200	1720, 1640	8.8	8.3-7.4	4.4-4.1, 3.6-3.3, 2.8-2.5, 2.4-2.1	4.1, 1.1 (CO_2Et),1.8 (Me)
7e	3400	1720, 1640	9.2	8.2-7.3	4.7-4.4, 3.8-3.6, 3.2-2.7	3.5 (CO_2Me)
8a	3600-3100	1650, 1630	9.3	8.0-7.0	3.5-2.9	2.2 (OH)
8b	3600-3100	1650, 1630	9.3	7.9-7.0	3.4-2.4	2.2 (OH), 2.4 (Me)

[a] Nujol. * *Appendix*: δ_C ($CDCl_3$) **7a**: 20.0 (d, J_{CP} = 53 Hz, CH_2P), 28.6 (CH_2), 53.6 (OMe), 66.1 (d, J_{CP} = 16.4 Hz, CNH), 105.2-137.0 (C arom) 168.0 (CONH), 172.4 (CO_2Me). **7c**: 13.4 CH_3CH_2), 18.8 (d, J_{CP} = 52 Hz, CH_2P), 21.2 (Me), 27.7 (CH_2), 61.7 (OCH_2), 65.4 (d, J_{CP} = 16 Hz, CNH), 117.4-141.9 (C arom) 167.2 (CONH), 171.2 (CO_2Et). **7d**: 14.4 CH_3CH_2), 19.2 (d, J_{CP} = 53 Hz, CH_2P), 23.6 (Me), 28.2 (CH_2), 61.7 (OCH_2), 59.6 (d, J_{CP} = 15 Hz, CNH), 117.8-135.4 (C arom) 167.3 (CONH), 174.1 (CO_2Et). **8b**: 19.7 (d, J_{CP} = 54.5 Hz, CH_2P), 21.5 (CH_3), 28.1 (CH_2), 66.8 (d, J_{CP} = 17.3 Hz, CNH), 104.1-142.4 (C arom) 165.9 (CONH), 173.8 (CO_2H). δ_P ($CDCl_3$) **7b**: 26.17. **7c**: 26.2. **7d**: 25.9. **8b**: 25.2.

Table 3. Spectroscopic Data for Compounds **1, 2**.*

	ν_{max}/cm^{-1} [a]			$\delta_H(CDCl_3)$, (*J* /Hz)
Product	C=O	Arom.	CH_2CH_2	Other
1a	1720	8.1-7.2	3.3-2.9, 2.3-2.2	3.72 (CO_2Me)
1b	1720	7.9-7.2	3.2-2.9, 2.3-2.2	3.7 (CO_2Me), 2.4 (Me)
1c	1720, 1605	7.8-7.4	3.2-3.0, 2.6-2.4, 2.0-1.8	4.2, 1.2 (CO_2Et), 1.6 (Me)
1d	1720, 1610	7.9-7.3	3.2-2.9, 2.7-2.2, 2.2-1.9	3.7 (CO_2Me)
2a	1660	8.2-7.2	3.3-2.7, 2.7-2.3	9.1 (OH)
2b	1660	8.0-7.2	3.7-3.4, 3.2-2.9, 2.5-2.4,	8.8 (OH), 2.4 (Me)

[a] Nujol. * *Appendix*: δ_C ($CDCl_3$) **1c**: 14.6 CH_3CH_2), 25.5 (Me), 34.4 (CH_2), 36.0 (CH_2), 61.5 (OCH_2), 80.1 (C), 128.4-134.6 (C arom) 174.3 (C=N), 175.1 (CO_2Et). **1d**: 25.2 (d, J_{CP} = 72.3 Hz, CH_2P), 31.5 (CH_2), 33.0 (CH_2-3), 35.9 (CH_2-4), 52.8 (OMe), 83.3 (d, J_{CP} = 14.1 Hz, C), 128.5-134.3 (C arom) 174.6 (C=N), 175.6 (CO_2Me).

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