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5-Oxazolones. Part V[1]. Reaction of 4-Alkylidene-5(4H)-Oxazolones with Ethyl 3-Oxo-4-triphenylphosphoranylidene-butyrate

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Abstract: The reaction of 4-alkylidene-5(4H)-oxazolones **2a-e** with ethyl 3-oxo-4-triphenyphosphoranylidene-butyrate **1** affords dihydrobenzoxazoles **3a-c** and the diastereoisomeric 1,3-cyclohexanedione ylides **4a-e** and **5a-e**. **3a** is oxidized to the corresponding benzoxazoles **7a,b** with iodine.

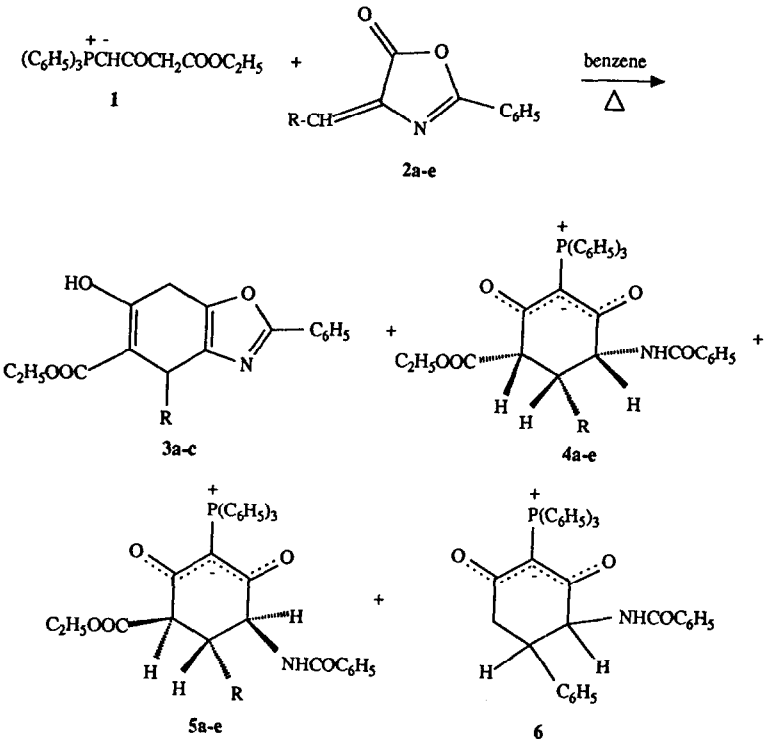
Recent work from our research group dealt with the reaction of 5(4H)-oxazolone compounds with phosphonium ylides.[1] As a further development of this reaction we now report on the results of the intramolecular cyclization of the phosphonium ylide functional group onto the oxazolone carbonyl group in the reaction products of ethyl 3-oxo-4-triphenylphosphoranylidene-butyrate **1** with the 4-alkylidene-5(4H)-oxazolones **2**. This reaction affords an entry to dihydrobenzoxazole compounds and 1,3-cyclohexanedione ylides.

The reaction of **1** with oxazolones **2a-e** was slow at room temperature in benzene solution, but proceeded at a satisfactory rate at reflux temperature. The reaction of substrates **2a-c** resulted in a mixture of the corresponding dihydrobenzoxazoles derivatives **3a-c** and of the diastereoisomeric 1,3-cyclohexanedione ylides **4a-c** and **5a-c**,

respectively. Triphenylphosphane oxide was also present in the reaction mixture. In the case of the reaction between **2a** and **1** a small amount of a fourth product was isolated. This compound could not be satisfactorily purified but was identified as the ylide **6** according to its spectroscopic and mass data. Probably, this by-product was formed from **4a** and/or **5a** by thermal elimination of carbon dioxide and ethylene.

Substrates **2d,e** did not produce the corresponding dihydrobenzoxazoles in appreciable yield: only **4d,e** and **5d,e** respectively, were isolated and identified. (Scheme 1)

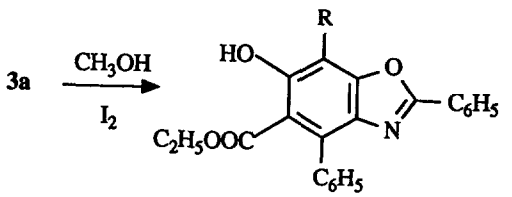
Scheme 1



2/3/4/5	R
a	C_6H_5
b	C_6H_4-OCH_3-4
c	CH_3
d	C_6H_4-Cl-4
e	CH=CH-C_6H_5

The structures of all products were established by analytical and spectroscopic techniques (IR, ^{1}H-, ^{13}C- and ^{31}P-NMR, MS). The data are listed in Table 3. In particular the ^{1}H-NMR spectrum of compounds **3** shows a well defined ABX pattern associated with the H atoms in positions 4 and 7. The chemical shifts are in the expected range (H-4: δ 4.9-4.7; CH_2 : δ 3.8-3.7 and 3.9-3.8) as well as the homoallylic coupling constants (4.6 and 5.1-5.2 Hz), whereas a very large one is observed for the geminal hydrogens (21.8-21.4 Hz). These assignements have been confirmed by simulation of the spectrum ^{1}H-NMR of **3a**. As a further structure confirmation compound **3a** was oxidized by iodine in methanol,[2] to the corresponding aromatic benzoxazole derivative **7a**. A minor amount of the iodinated analogue **7b** was also formed, which was not surprising since the iodination of phenols with iodine is known.[3] (Scheme 2)

Scheme 2



7	R
a	H
b	I

For compounds **4** and **5** three CO bands are observed in the 1700-1730, 1620-1650 and 1550-1560 cm^{-1} ranges. The first two bands are to be assigned to the ester and amide groups. As expected,[4] the extensive conjugation existing in the α,α'-dicarbonyl ylide system of **4** and **5**, lowers the carbonyl frequency to the observed range of about 1550 cm^{-1}.

Compounds **4** and **5** represent only two of the four diastereoisomers which could exist for this structure. The ^{1}H-NMR spectra of **4a** and **5a** are here described in detail since they allow their configuration to be established. A similar argument holds for compounds **4b-e** and **5b-e** as well. For the sake of clarity the data associated with H-3, H-4, H-5 and N-H are collected in Table 1. For **4a** the N-H signal is not detectable being overlapped by the aromatic protons, whereas an AMX-system is associated with the other three relevant hydrogens. In the case of **5a** the N-H signal is shifted to higher field and easily detectable, but only by a 400 MHz spectrum was the overcrowded signal group

associated with H-4, H-5 and the ester CH_2 clarified.

Table 1.

Comp.	Chemical shift				J(Hz)				
	N-H	H-3	H-4	H-5	$NH-H_3$	$P-H_3$	$P-H_5$	H_3-H_4	H_4-H_5
4a	a)	5.4	4.55	3.7	4.9	1.7	2.6	6.2	1.45
5b	6.4	5.2	3.95	4.1	8.4	1.2	0.9	11.8	12.0

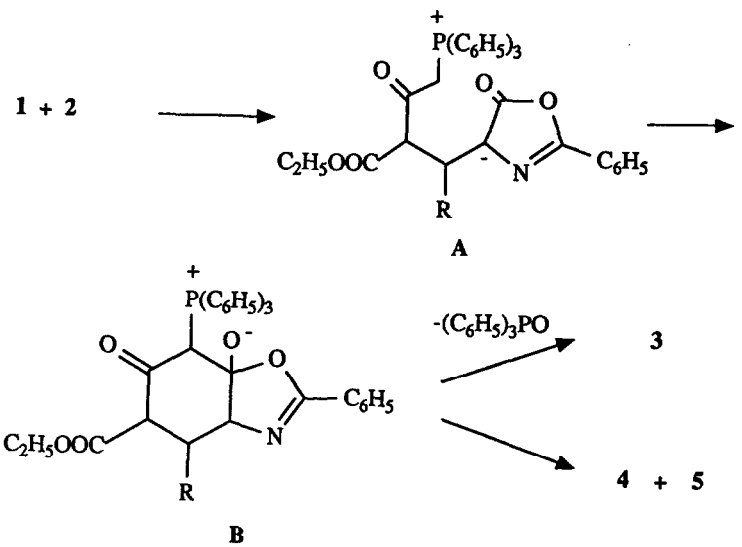
a) Overlapped by aromatic signals (6.6-7.8 ppm)

Molecular models inspection indicates both for **4a** and **5a** a half-chair conformation with pseudo-equatorial phenyl substituent on C-4. Considering that J values greater than 10 Hz are evidence of a pseudo-diaxial pair of neighbouring hydrogen atoms, whereas coupling constants between 1 and 7 Hz are indicative of an axial-equatorial relation, it is deduced that in compound **5a** all the three hydrogen substituents (i.e. H-3, H-4 and H-5) should bear a pseudo-diaxial relationship (trans configuration). For **4a** the pseudo-axial H-4 should have on both sides pseudo-equatorial hydrogens (cis configuration). Accordingly the 3r-benzoylamino-4c-phenyl-5c-ethoxycarbonyl configuration has to be assigned to **4a** and the 3r-4t-5c configuration to **5a**.

The mechanistic picture depicted in Scheme 3 allows our results to be rationalized. As in other cases[5] ylide **1** shows its ambident nucleophilicity at α and γ atoms. In contrast to the earlier examples, where an addition of a base was found necessary, the reaction of compound **1** with oxazolones **2** gave far better results when performed in absence of base. A Michael addition has to be assumed as the first reaction step and the first formed intermediate (A) reacts in the tautomeric ylide form thus producing the bicyclic intermediate (B) by reaction of the ylide carbon on the lactone group. From (B) both **3** and **4,5** are derived. In the former case triphenylphosphane oxide is eliminated followed by aromatization of the oxazoline ring. In the second case cleavage of the oxazoline ring takes place. The intramolecular ring closure by which (A) is transformed into (B) is another synthetically useful example of the reactivity of 5(4H)-oxazolones with phosphonium ylides. As already observed in intermolecular reactions,[1] competition

exists between ring cleavage of the oxazolone ring (ylide products) and triphenylfosphane oxide elimination (oxazole products).

Scheme 3



EXPERIMENTAL

Melting points: Büchi 510 (capillary) apparatus. IR spectra: PYE UNICAM SP3-200S Philips spectrophotometer. NMR experiments performed on Bruker AC 200 and AC 400 instruments with operating frequencies of 50.3 and 81.015 MHz, respectively, for ^{13}C and ^{31}P nuclei with TMS as internal standard in the solvent indicated and H_3PO_4 in D_2O as external standard for ^{31}P-NMR. Identification of adjacent vicinally coupled protons was established by a COSY experiment. Spectra were acquired with 4 scans per block and 3 s between acquisition. The simulation of the ABX portion of the ^1H- spectrum of **3a** was performed using the PANIC program. ^1H-NMR spectrum of **4a** has also been made using paramagnetic shift reagents to increase dispersion. For a better understanding of vicinal couplings ^1H-^{31}P spectra were acquired. They were performed using BSV-3 unit, equipped with a second synthesizer and decoupler and a power selective amplifier.

Homonuclear 2D J-resolved spectra were acquired with 4 scans per block and 2 s between acquisition. The 2D matrix consisted of 512 x 2K blocks. ^{13}C resonances were assigned by heteronuclear ^{13}C-^{1}H shift correlation experiments which were recorded with 256 scans per block and 3 s of relaxation delay. The 2D matrix consisted of 512 x 1K blocks. - Column chromatography: silica gel, with the eluents indicated. - MS: Varian MAT 311-A instrument.

Ethyl 3-oxo-4-triphenylphosphoranylidene-butyrate (**1**)[5] and 5(4H)-oxazolones **2a,b, d**[6], **2c**[7] and **2e**[8] are known compounds.

REACTION OF 5(4H)-OXAZOLONES 2a-e with 1:

General Procedure:

A mixture of **1** (5.0 mmol) and **2** (5.0 mmol) was refluxed in benzene (40 ml). After solvent evaporation the crude mixture was chromatographed with n-pentane/ethyl acetate (1:0 to 0:1 v/v). Besides unreacted starting material (**2a**: 10%, **2c**: 30%, **2e**: 3%), compounds **3a-c**, **4a-e**, **5a-e** and **6** were isolated. Reaction and analytical data are given in Table 2, spectral data in Table 3.

Ethyl 6-hydroxy-2,4-diphenyl-benzoxazole-5-carboxylate (7a) and Ethyl 6-hydroxy-7-iodo-2,4-diphenyl-benzoxazole-5-carboxylate (7b):

3a (500 mg, 1.4 mmol) in methanol (30 ml) was refluxed with an excess of iodine (2.3 g, 9.1 mmol) for 35 h. The solvent was evaporated and the residue was taken up with CH_2Cl_2. 30 ml). The organic layer was washed with acqueous sodium bisulphite (3x10 ml) until complete reduction of the excess of I_2, dried with Na_2SO_4 and evaporated. The residue was cromatographed with n-pentane/CH_2Cl_2 (1:0 to 0:1 v/v) yielding two fractions: the first fraction, containing **7a**, was crystallized from iPr_2O (350 mg, 69%); m.p. 167°C.

$C_{22}H_{17}NO_4$ (359)

Calcd.	C	73.53	H	4.70	N 3.89
Found	C	73.00	H	4.68	N 3.85

The second fraction yielded pure **7b** (180 mg, 26%); m.p. 191-194°C (iPr_2O).

$C_{22}H_{16}INO_4$ (485)

Calcd.	C	54.43	H	3.29	N 2.88
Found	C	54.00	H	3.01	N 2.56

Table 2.

Starting Compounds	Reaction Time (h)	Products	Yield[a] (%)	Recryst. solvent (M.p. °C)	Empirical Formula	M.w.	Calcd. (Found) C	H	N
1+2a	48	3a	14	CH_2Cl_2/iPr_2O (217)	$C_{22}H_{19}NO_4$	361	73.13(73.20)	5.26(5.43)	3.87(4.05)
		4a	52	Me_2CO/iPr_2O (210)	$C_{40}H_{34}NO_5P$	639	75.11(74.86)	5.32(5.63)	2.19(2.32)
		5a	4	CH_2Cl_2/iPr_2O (240)	$C_{40}H_{34}NO_5P$	639	75.11(75.02)	5.32(5.31)	2.19(2.07)
		6	23	b)	$C_{37}H_{30}NO_3P$	567[c]			
1+2b	72	3b	5	Me_2CO (173)	$C_{23}H_{21}NO_5$	391	70.58(70.42)	5.37(5.54)	3.58(3.55)
		4b	30	Et_2O (125)	$C_{41}H_{36}NO_6P$	669	73.54(73.32)	5.38(5.88)	2.09(2.33)
		5b	10	Et_2O (237)	$C_{41}H_{36}NO_6P$	669	73.54(73.12)	5.38(5.23)	2.09(2.00)
1+2c	1	3c	3	Me_2CO/iPr_2O (141)	$C_{17}H_{17}NO_4$	299	68.23(67.91)	5.68(5.55)	4.68(4.47)
		4c	25	Me_2CO/iPr_2O (154)	$C_{35}H_{32}NO_5P$	577	72.79(72.41)	5.54(5.63)	2.42(2.42)
		5c	25	Et_2O (154)	$C_{35}H_{32}NO_5P$	577	72.79(72.97)	5.54(5.74)	2.42(2.42)
1+2d	48	4d	69	Me_2CO (162)	$C_{39}H_{33}ClNO_5P$	661	70.75(70.40)	4.99(5.29)	2.10(2.00)
		5d	2	Me_2CO (220)	$C_{39}H_{33}ClNO_5P$	661	70.75(70.56)	4.99(4.95)	2.10(2.39)
1+2e	48	4e	7	b)	$C_{42}H_{36}NO_5P$	665			
		5e	20	Me_2CO (213)	$C_{42}H_{36}NO_5P$	665	75.78(75.46)	5.41(5.51)	2.10(2.43)

[a] Yields are not optimized [b] Cannot be crystallized satisfactorily [c] Determined by MS.

Table 3. Spectral data

Compd.	IR (Nujol; cm^{-1}) NH	IR (Nujol; cm^{-1}) CO	^{1}H-HNR (δ) ($CDCl_3$)
3a		1680	1.1 (t, J = 7 Hz, 3H, CH_3), 3.8, 3.9, 4.9 (ABX system, $J_{(AB)}$= 21.8 Hz, $J_{(AX)}$, $J_{(BX)}$= 4.6, 5.2 Hz, 3H, CH_2 and CH) 4.1-4.2 (m, 2H, OCH_2), 7.1-7.4, 7.9-8.0 (m, 10H, Aryl H), 13.0 (s, 1H, OH)
3b		1680	1.1 (t, J = 7 Hz, 3H, CH_3), 3.7 (s, 3H, OCH_3) 3.7, 3.9, 4.9 (ABX system, $J_{(AB)}$= 21.4 Hz, $J_{(AX)}$, $J_{(BX)}$= 4.7, 5.1 Hz, 3H, CH_2 and CH), 4.1 (q, J = 7 Hz, 2H, OCH_2), 6.8-7.5 7.9-8.0 (m, 9H, Aryl H), 12.9 (s, 1H, OH)
3c		1680	1.3 (d, J = 7 Hz, 3H, CH_3), 1.4 (t, J = 7 Hz, 3H, $CH_2\underline{CH_3}$), 3.7-4.7 (m, 3H, CH_2 and CH), 4.3-4.4 (m, 2H, OCH_2), 7.4-8.1 (m, 5H, Aryl H), 12.9 (s, 1H, OH)
4a	3360	1720, 1650, 1540	1.4 (t, J = 7 Hz, 3H, CH_3), 3.8 (AMX system, $J_{(H5-H4)}$= 1.45 Hz, $J_{(P-H)}$= 2.6 Hz, 1H, H-5), 4.3-4.5 (m, 2H, OCH_2), 4.5 (AMX system, $J_{(H4-H3)}$= 6.2 Hz, $J_{(H5-H4)}$= 1.45 Hz, 1H, H-4), 5.4 (AMX system, $J_{(H4-H3)}$= 6.2 Hz, $J_{(P-H)}$= 1.7 Hz, $J_{(N-H)}$= 4.9 Hz, 1H, H-3), 7.0-7.7 (m, 26H, Aryl H and NH)
4b	3360	1710, 1640, 1550	1.6 (t, J = 7 Hz, 3H, CH_3), 3.7-3.8 (m, 4H, OCH_3 and H-5), 4.4-4.5 (m, J = 7 Hz, 2H, CH_2), 4.5 (AMX system, $J_{(H4-H3)}$= 5.5 Hz, 1H, H-4), 5.4 (AMX system, $J_{(H4-H3)}$= 5.5 Hz, $J_{(N-H)}$= 4.9 Hz, 1H, H-3), 6.6-7.7 (m, 24 H, Aryl H), 7.0 (d, J = 4.9 Hz, 1H, NH)
4c	3380	1720, 1650, 1560	1.1 (d, J = 7 Hz, 3H, CH_3), 1.4 (t, J = 7 Hz, 3H, $OCH_2\underline{CH_3}$), 3.3-3.4 (m, 2H, H-5 and H-4), 4.3-4.4 (m, 2H, CH_2), 5.0-5.1 (m, 1H, H-3), 7.2-7.8 (m, 21H, Aryl H and NH)
4d	3340	1700, 1640, 1540	1.4 (t, J = 7 Hz, 3H, CH_3), 3.7 (AMX system, $J_{(P-H)}$= 2.4 Hz, $J_{(H5-H4)}$= 1.4 Hz, 1H, H-5), 4.3-4.5 (m, 2H, CH_2), 4.7 (AMX system, $J_{(H5-H4)}$= 1.4 Hz, $J_{(H4-H3)}$= 5.9 Hz, 1H, H-4), 5.3 (AMX system, $J_{(P-H)}$= 1.5 Hz, $J_{(H4-H3)}$= 5.9 Hz 1H, H-3), 6.9-7.7 (m, 25H, Aryl H and NH)
4e	3360	1720, 1640, 1560	1.4 (t, J = 7 Hz, 3H, CH_3), 3.7 (AMX system, $J_{(P-H)}$, $J_{(H5-H4)}$= 2.2 Hz, 1H, H-5), 4.2 (AMX system, $J_{(H4-CH)}$= 7.4 Hz, $J_{(H5-H4)}$= 2.2 Hz, $J_{(H4-H3)}$= 5.2 Hz, 1H, H-4), 4.3-4.5 (m, 2H, CH_2), 5.2 (AMX system, $J_{(H4-H3)}$= 5.2 Hz, $J_{(N-H)}$= 4.5 Hz, $J_{(P-H)}$=1.4 Hz, 1H, H-3), 6.2 (dd, $J_{(CH=CH)}$= 15.8 Hz, $J_{(H4-CH)}$= 7.4 Hz, 1H, $\underline{CH}$=CHC_6H_5), 6.5 (d, $J_{(CH=CH)}$= 15.8 Hz, 1H, =CHC_6H_5), 7.2-7.8 (m, 26H, Aryl H and NH)
5a	3330	1720, 1650, 1560	0.9 (t, J = 7 Hz, 3H, CH_3), 3.8-4.0 (m, 4H, H-5, H-4 and OCH_2), 5.1-5.2 (m, $J_{(H4-H3)}$= 11.6 Hz, $J_{(N-H)}$= 8.4 Hz, 1H, H-3), 6.3 (d, J = 8.4 Hz, 1H, NH), 7.1-7.8 (m, 25H, Aryl H)

5b	3390	1710, 1620, 1560	0.9 (t, J = 7 Hz, 3H, CH_3), 3.7 (s, 3H, OCH_3), 3.8-4.0 (m, 4H, H-5, H-4 and OCH_2), 5.1-5.2 (m, $J_{(N-H)}$= 8.5 Hz, $J_{(H4-H3)}$= 11.5 Hz, 1H, H-3), 6.3 (d, J = 8.5 Hz, 1H, NH), 6.7-7.7 (m, 24H, Aryl H)
5c	3315	1730, 1650, 1560	1.1 (d, J = 8.3 Hz, 3H, CH_3), 1.2 (t, J = 7 Hz, 3H, $CH_2\underline{CH_3}$), 2.6-2.7 (m, 1H, H-4), 3.4-3.5 (m, 1H, H-5), 4.1-4.3 (m, 2H, CH_2), 4.7-4.8 (m, 1H, H-3), 6.9 (d, J = 8.3 Hz, 1H, NH), 7.2-7.8 (m, 20H, Aryl H)
5d	3400	1720, 1640, 1560	0.9 (t, J = 7 Hz, 3H, CH_3), 3.9-4.0 (m, 4H, H-5, H-4 and OCH_2), 5.1-5.3 (m, $J_{(N-H)}$= 8.3 Hz, 1H, H-3), 6.5 (d, J = 8.3 Hz, 1H, NH), 7.1-7.7 (m, 24H, Aryl H)
5e	3310	1720, 1650, 1560	1.1 (t, J = 7 Hz, 3H, CH_3), 3.4 (AMX system, $J_{(H5-H4)}$= 11.7 Hz, $J_{(H4-CH)}$= 8.4 Hz, $J_{(H4-H3)}$= 11.7 Hz, 1H, H-4), 3.8 (d, $J_{(H5-H4)}$= 11.7 Hz, 1H, H-5), 3.9-4.1 (m, 2H, CH_2), 5.1 (dd, $J_{(H4-H3)}$= 11.7 Hz, $J_{(N-H)}$= 8.1 Hz, 1H, H-3), 6.3 (dd, $J_{(CH=CH)}$= 15.6 Hz, $J_{(H4-CH)}$= 8.4 Hz, 1H, $\underline{CH}$=CHC_6H_5), 6.5 (d, $J_{(CH=CH)}$= 15.6 Hz, 1H, =$\underline{CH}C_6H_5$), 7.0-7.9 (m, 25H, Aryl H)
6	3330	1660	2.6-3.4 (m, 2H, H-5), 3.9-4.4 (m, 1H, H-4), 5.0-5.2 (m, 1H, H-3), 6.9-8.0 (m, 26H, Aryl H and NH)
7a		1660	0.7 (t, J = 7 Hz, 3H, CH_3), 3.9 (q, J = 7 Hz, 2H, CH_2), 7.2 (s, 1H, H-7), 7.4-8.2 (m, 10H, Aryl H), 11.3 (s, 1H, OH)
7b		1650	0.8 (t, J = 7 Hz, 3H, CH_3), 4.0 (q, J = 7 Hz, 2H, CH_2), 7.3-8.2 (m, 10H, Aryl H), 11.9 (s, 1H, OH)

Appendix: ^{13}C-NMR (δ)($CDCl_3$) : **3a** 13.9 (CH_3), 28.5 (CH_2), 40.4 (CH), 60.9 (OCH_2), 101.8 (C-5), 126.4-130.2 (Aryl CH), 127.6, 136.8 (Aryl C), 139.7 (C-3a), 143.1 (C-7a), 161.6 (C-2), 168.2 (C-6), 172.2 (CO). **4a**: 14.4 (CH_3), 43.8 (C-4), 55.9, 58.3 (C-3, C-5), 61.9 (CH_2), 84.0 (d, $J_{(P-C)}$= 101.4 Hz, C-1), 124.0 (d, $J_{(P-C)}$= 92.3 Hz, Aryl C-P), 130.0, 134.7 (Aryl C), 127.2-133.6 (Aryl CH), 167.5 (CONH), 171.2 ($\underline{C}OOC_2H_5$), 178.0, 188.9 (C-2 and C-6). **5a** : 13.9 (CH_3), 48.8 (C-4), 58.3, 61.4 (two d, $J_{(P-C)}$= 10.3, 8.9 Hz, C-3 and C-5), 60.8 (CH_2), 81.9 (d, $J_{(P-C)}$= 113.0 Hz, Aryl C-P), 124.5 (d, $J_{(P-C)}$= 92.0 Hz, Aryl C-P), 127.0-133.7 (Aryl CH), 134.7, 138.7 (Aryl C), 168.1 (CONH), 169.9 ($\underline{C}OOC_2H_5$), 188.8, 190.2 (two d, $J_{(P-C)}$= 4.7, 5.2 Hz, C-2 and C-6).

^{31}P-NMR (δ) ($CDCl_3$): **4a**: 13.3. **5a**: 13.9.

Spectral data: **3a**: (FD), m/z = 361(M^+). **4a**: (FD), m/z = 639(M^+), 568. **5a**: (FD), m/z = 639(M^+), 567, 278, 121. **6**: (FD), m/z = 567(M^+). **7a**: (EI), m/z = 359(M^+) (30), 313 (100), 126 (71) 105 (34). **7b**: (EI), m/z = 485 (M^+) (32), 439 (83), 252 (34), 153 (96), 105 (100).

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