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A Versatile Building Block for the Synthesis of Substituted Cyclopropanephosphonic Acid Esters

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Abstract: By the effect of iodine, solid K_2CO_3 and a lipophilic quaternary ammonium salt phosphonoacetic acid allylic esters 4 were converted to cyclopropanephosphonic acid derivatives anellated to a five membered lactone ring 6 serving as good starting material for biologically active products. The reaction of cyclopropanation has been assumed to proceed by SET induced radical type elemental steps. Direct evidences were given by ESR for the 6-endo regioselectivity in the closure of electrophilic radical 11. An interesting and new exchange reaction of phosphonic ester moiety by iodine is also observed.

INTRODUCTION

We reported¹ recently the synthesis of electrophilic cyclopropanes from the reaction of non activated olefins with malonic esters or similar CH acids in the presence of iodine, dry, solid K_2CO_3 and a lipophilic quaternary onium salt (Q^*X^-). The yields of the cyclopropane derivatives increased when the CH-acid moiety and the olefinic bond were in a proper position in the same molecule. In this case an intramolecular reaction proceeded and cyclopropane derivatives anellated to a lactone ring were formed (Scheme 1).

Scheme 1



These types of compounds are useful for the diastereoselective synthesis of polysubstituted cyclopropane derivatives [e.g. a simple synthesis of the cyclopropane part of deltamethrin² or the synthesis of aminocyclopropanecarboxylic acids $(ACC)^3$]. ACC and its derivatives have attracted special attention. These

compounds are widespread among various classes of natural products such as fatty acids, terpenes, steroids and aminoacids.^{4,5}

The carboxyl group can be replaced in these molecules by a phosphonic acid moiety. Due to the tetrahedral structure of the phosphonic acid moiety they are considered to act as 'transition state analogues' 6 and can serve as models for enzyme reactions 7 or as component in enzyme inhibitors.^{8,9}

In the light of the mechanism substantiated for the transformations of allylic esters of malonic acid 1 to 2 we hoped that phosphonoacetic acid allyl esters 4 would also react with iodine, in the presence of Q^+X^- (phase transfer catalyst) and K₂CO₃ as base in a similar way to give compounds 6 with phosphonic ester function on the carbon bearing the lactone carbonyl.

These compounds might serve as good starting materials not only for new, stereoselective synthesis of aminocyclopropanephosphonic acids but also for obtaining useful derivatives by transformation of the lactone unit in compounds 6 (c.g. by reduction into lactol and its subsequent reaction with a Wittig type reagent).

RESULTS AND DISCUSSION

Aiming at the synthesis of compounds 6 the corresponding phosphonoacetic esters 4 have been prepared first. Scheme 2



Compounds		Substituents					
3-13, 17	R ¹	R ²	R ³	R ⁴	Y		
а	Н	Н	Н	CH3	Н		
b	Н	Н	CH_3	CH_3	Н		
с	CH_3	CH_3	Н	CH_3	Н		
d	CH_3	CH_3	Н	C_2H_5	Н		
e	CH_3	CH_3	Н	CH_3	CCl_3		
f	CH_3	CH3	Н	C_2H_5	CCl ₃		
g	CH_3	Н	Н	CH_3	Н		
h	Н	CH_3	Н	CH ₃	Н		
i	CH_3	Н	Н	C_2H_5	Н		
j	Н	CH_3	Н	C ₂ H ₅	Н		

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Using standard methods¹⁰ the allylic alcohols were acylated by bromoacetyl bromide and the esters **3** obtained were heated with trialkyl phosphite¹¹ to give the desired products **4**. Both the acylation and the Arbuzov reaction steps occurred smoothly to provide products **3** and **4** respectively, in high purity and in good yield.

For the preparation of the target compounds 6 a benzene solution of iodine was added in small portions to the mixture of a given phosphonoacetic ester 4, dry solid K_2CO_3 , triethylbenzylammonium chloride (TEBAC) or tricaprylmethylammonium chloride (TCMC) catalyst in hot benzene. The reactions were monitored by GC-MS and ³¹P-NMR spectroscopy. In most cases column chromatography was used to obtain the pure products. Yields varied from moderate to good depending on the substituents (Table 1).

	³¹ P-NMR (ppm)			yield (%)	
	4	5	6	4	6(*)
a	22.1	-	17.4	73	traces
b	22.1	15.3	17.6	82	traces
с	22.4	-	20.8	9 0	61 (80)
d	19.8	-	17.9	93	50 (80)
e	21.0	16.0	18.3	78	18 (40)
f	18.4	-	15.3	81	23 (88)
g	22.3	-	19.8	88	32 (55)**
i	19.8	-	17.0	92	56 (77)**

Table 1 31 P-NMR shifts and yields of 4, 5 and 6

* Measured by GC

** Exo and endo-isomeric mixture

In the reaction of unsubstituted allylic ester 4a only traces of 6a can be detected and most of the starting ester 4a remains unreacted. Ester 4b was consumed fast but the yield of 6b was very low because the product decomposed rapidly under the reaction condition. Dimethylallylic esters 4c and 4d reacted fast and gave stable products 6c and 6d, respectively, in good yield.

Conversion of **4e**,**f** into **6e**,**f** was slow most probably because of the presence of the bulky trichlormethyl substituent and the yields were moderate. NMR spectra showed that only one isomer having the trichlorometyl group in exo-position is formed in each cases.

The E-isomer 4g gives isomer products 6g and 6h while the E-isomer 4i gives a mixture of products 6i and 6j with the exo-isomers 6g and 6i dominating.

Mechanism

During the transformation of 4 to 6 the corresponding iodo phosphonoacetic esters 5 were formed first as relative stable intermediates. The iodo compounds 5 can be detected and assigned by 31 P-NMR method in

those cases when the subsequent cyclopropanation steps are slow (4h,e). For the assignment of the 31 P-NMR spectra iodo intermediates 5, the iodo phosphonoacetic ester 8 has also been prepared in a separate experiment (Scheme 3).

Scheme 3



It has been shown in these transformations¹ that radical fission of iodo derivative **5** can not be exerted by light. Any attempts to substitute I_2 by Br_2 in the synthesis of **6** from **4** failed. A mixture of unidentifed products were formed. The surface of solid K₂CO₃ seems to be also important because strong bases like solid KOtBu, solid NaOCH₃ or their solutions in DMF initiate undesired side-reactions.

SET induced radical type processes can be assumed to exist in the transformation of 4 to 6. The initiation steps are shown in Schemes 4 and 5.



The electron source in the SET path can be the anion from **5** and/or the anion from **4**. Both can be formed continuously in small amounts on the surface of the solid K_2CO_3 and transferred into the solution by the phase transfer agent. A SET induced radical type fission under PTC conditions ¹² as well as the role of malonic ester anion as an electron source¹³ has already been recognized. Radical **11** was formed from the radical anion **9** by iodide elimination or from the anion of **4** by electron transfer. There is a double bond in a favorable position to the radical-center in **11**. Since the desired trajectories by the C-radical of 109° to the double bond in the plane of its p-orbitals are permitted both in the 5-exo-trig and in the 6-endo-trig ring closures^{14,15} both the radical **13** and the radical **12** can be formed.

Scheme 6



ESR spectra recorded for the reactions **4b**,**c**,**g** to **6b**,**c**,**g** in the presence of 2,6-dichloro-nitrosobenzene spin trap show that 6-endo-trig ring closures might proceed in each cases giving **12b**,**c** or **g** radicals, respectively. The ESR spectra for the reaction **4b** to **6b** after one hour reaction time (Fig.1) show superimposed spectra where a triplet and a doublet of a triplet appear. Their ratio depends on the reaction time. The triplet can be assigned to the nitrogen coupling (13.1 G) and originates from the reaction of **12b** with the spin trap while the doublet of triplet with a fairly large doublet splitting (19.2 G) characteristic for the phosphorus coupling is due to presence of radical **11b**. The lack of hydrogen splitting in radical **11b** may be explained by the dominance of a conformation in which the N-C-H dihedral angle is perpendicular to the C-N-p, plane of the unpaired electron.



Fig. 2. shows a dublet of a triplet for the reaction of 4c to 6c. In this case the presence of only one radical can be substantiated, the structure of which corresponds to 12c. Interestingly, the intensity of spectra for the reaction of 4g to 6g was changing in time (Fig.3). The intensity of the doublet of triplet due to 11g was increasing compared to the other doublet of triplet for 12g. This change of the intensity ratio is caused by the concentration change of radical 11g which can be formed from two sources: from the anion of 4g and/or from the radical anion of 9g.

ESR spectral data showing the appearence of the radicals of similar type in the reactions **4b,c,g** to **6b,c,g** are in the Table 2.

Table 2 ESR spectral data

reaction 4 to 6	hfc in G for	hfc in G for	
	11 + spin trap	12 + spin trap	
b	doublet (19.4) of triplet (13.2)	triplet (13.2)	
с	no signal	doublet (5.5) of triplet (12.2)	
g	doublet (25.4) of triplet (12.2)	doublet (7.7) of triplet (13.4)	

The radical chain propagation steps involving radical 12 and the iodo derivative 5 with the formation of 14 (Scheme 7) as well as the transformation of 11 to 12 are shown in Scheme 6. Scheme 7



Formation of the stable end product 6 from 14 in an intramolecular reaction should start with the removal of an acidic proton from the carbon at the phosphorus moiety by the surface of K_2CO_3 resulting in the formation of the anion of 14 (Scheme 8).



Although an intramolecular nucleophilic displacement of the iodide by the intermediate carbanion in 14 would give the desired end product 6 an alternative mechanism involving a SET initiation step may also be assumed to be operating, especially in those cases where the iodine is attached to a tertiary carbon atom (like in the reaction of 4b to 6b). This has been suggested by Walborsky and Topolski for similar processes.¹⁶

The elemental steps leading from 4 to 6 are summarized in Scheme 9.

Scheme 9



In the transformation of 4e, not 6e but iodoacetic ester 17e is the main product (Scheme 10). A small amount of iodoacetic ester 17c was also formed from 4c and 4d, respectively.

Scheme 10



In these cases an unusual P-C bond fission occurs which, to our best knowledge, has not been reported in the literature, yet.

Experiments for transformation of lactone 6 into other derivatives are in progress and the results will be published in due course.

EXPERIMENTAL

IR spectra were recorded on a Perkin Elmer FT-IR instrument. ¹H-NMR and ¹³C NMR spectra were taken by a Bruker AW-80 and a Bruker WM-250 spectrometer, ³¹P NMR spectra by a JEOL FX-100 spectrometer, all in CDCl₃ solution. Chemical shifts are given on the δ scale. ESR spectra were recorded on a JEOL JES-FE/3X instrument with 100 kHz modulation. All spectra were taken at 60 °C, in oxygen-free benzene solutions, in the magnetic field range of 3180 to 3280 G with the modulation width of 2 G. The G factor was determined by the two center lines of Mn hyperfine pattern of the Mg(Mn)O internal standard. GC-MS measurements were recorded on Hewlet-Packard 5890 II. GC and Hewlet-Packard 5971 MS detector, 1800 eV, 200 °C. TLC was performed on Merck Kieselgel 60 F₂₅₄ plates with benzene-methanol eluent (9:1). Column chromatography was carried out on Merck Kieselgel 60 to 200 mesh, with the same eluent.

Preparation of bromoacetic acid esters 3 (General procedure)

The appropriate alcohol (50 mmol), triethyl amine (45 mmol), and 4-dimethylamino pyridine (5 mmol) were dissolved in benzene (60 cm³). Bromoacetyl bromide (50 mmol) in benzene (30 cm³) was added dropwise into the cooled solution. The reaction mixture was refluxed for 0.5 hr. The precipitated salt was removed by filtration. The solvent was evaporated under reduced pressure and the residue was fractionated.

Allyl bromoacetate, **3a** 70% (purified by fractionation) b.p.:78°C/16 Torr, (lit. b.p.¹⁷:73°C/10 Torr), IR(neat): 1725 cm⁻¹.

2-Methyl-prop-2-ene-1-yl bromoacetate **3b** 78% (by fractionation) b.p.:82-84°C/10 Torr, IR(neat): 1725 cm⁻¹, ¹H-NMR (80 MHz) 1.70(s, 3H), 3.80(s, 2H), 4.55(s, 2H), 4.95(m, 2H). Anal. calcd. for $C_6H_9BrO_2$: C 37.33, H 4.70, found C 37.28, H 4.67.

3-Methyl-but-2-ene-1-yl bromoacetate **3c** 86% (by fractionation) b.p.:58-62°C/0.8 Torr, IR(neat): 1718 cm⁻¹, ¹H-NMR (80 MHz) 1.77(s, 3H), 1.80(s 3H) 3.80(s, 2H), 4.65(d, 2H, J=12 Hz), 5.30(t, 1H). Anal. calcd. for $C_7H_{11}BrO_2$: C 40.60, H 5.35, found C 40.66, H 5.40.

(4-Methyl-1,1,1-trichloro-pent-3-ene)-2-yl bromoacetate **3e** 83% (by fractionation) b.p.:82-84°C/0.5 Torr, IR(neat): 1715 cm⁻¹, ¹H-NMR (80 MHz) 1.75(s, 3H), 1.80(s 3H) 3.82(s, 2H), 5.30(d, 1H, J=9.5 Hz), 6.00(d, 1H). Anal. calcd. for $C_8H_{10}BrCl_3O_2$: C 29.62, H 3.11, found C 29.72, H 3.21.

(*E*)-*But-2-ene-1-yl bromoacetate* **3g** 88% (by fractionation) b.p.:90-92°C/10 Torr, IR(neat): 1720 cm⁻¹, ¹H-NMR (80 MHz) 1.70(d, 3H, J=8 Hz), 3.80(s, 2H), 4.80(d, 2H, J=7 Hz), 5.60(m, 1H), 5.80(m, 1H). Anal. calcd. for $C_6H_9BrO_2$: C 37.33, H 4.70, found C 37.39, H 4.77.

Preparation of phosphonoacetic acid esters 4 (General procedure)

The mixture of 3 (20 mmol) and the appropriate phosphite (30 mmol) was kept at 120 $^{\circ}$ C in an oil bath for 1.5 hour, while nitrogen gas was bubbled through. The resulting reaction mixture was fractionated under reduced presure or purified by column chromatography with an eluent benzene-methanol (9:1).

Dimethylphosphorylacetic acid allyl ester **4a** 73% (by fractionation) b.p.:102-104°C/0.4 Torr, IR(neat): 1720, 1250, 1010 cm⁻¹, ¹H-NMR (80 MHz) 3.00(d, 2H, $J_{PH}=24$ Hz), 3.75(d, 6H, $J_{PH}=12$ Hz), 4.60(d, 2H, J=7 Hz), 5.20(m, 2H), 5.80(m, 1H), ³¹P-NMR (100 MHz) 22.1. Anal. calcd. for $C_7H_{13}O_5P$: C 40.39, H 6.30, found C 40.45, H 6.37. Ms m/z(%) : 209 (M⁺, 5.6), 151 (100), 124 (38.2), 109 (41.4).

Dimethylphosphorylacetic acid 2-methylprop-2-enyl ester **4b** 82% (by fractionation) b.p.:106-108°C/0.4 Torr, IR(neat): 1710, 1250, 1005 cm⁻¹, ¹H-NMR (80 MHz) 1.78(s, 3H), 3.00(d, 2H, J_{PH} =24 Hz), 3.80(d, 6H, J_{PH} =12 Hz), 4.55(s, 2H), 4.90(m, 2H), ³¹P-NMR (100 MHz) 22.1. Anal. calcd. for C₈H₁₅O₅P: C 43.25, H 6.80, found C 43.32, H 6.88. Ms m/z(%) : 222 (M⁺, 3.8), 151 (100), 137 (4.6), 124 (14.4), 109 (31.2).

Dimethylphosphorylacetic acid 3-methylbut-2-enyl ester **4c** 90% (by fractionation) b.p.:84-86°C/0.2 Torr, IR(neat): 1715, 1250, 1010 cm⁻¹, ¹H-NMR (80 MHz) 1.70(s, 3H), 1.80(s, 3H), 2.95(d, 2H, J_{PH}=24 Hz), 3.75(d, 6H, J_{PH}=12 Hz), 4.60(d, 2H, J=8 Hz), 5.35(t, 1H), ³¹P-NMR (100 MHz) 22.4. Anal. calcd. for C₉H₁₇O₅P: C 45.76, H 7.25, found C 45.70, H 7.19. Ms m/z(%) 236: (M⁺, 4.6), 151 (100), 137 (6.8), 124 (24.4), 109 (34.2).

Diethylphosphorylacetic acid 3-methylbut-2-enyl ester 4d 82% (by fractionation) b.p.:110-112°C/0.3 Torr, IR(neat): 1715, 1255, 1020 cm⁻¹, ¹H-NMR (80 MHz) 1.30(t, 6H, J_{HH}=6 Hz), 1.65(s, 3H), 1.70(s, 3H), 2.90(d, 2H, J_{PH}=24 Hz), 3.8-4.2(m, 4H), 4.60(d, 2H, J=8 Hz), 5.35(t, 1H), ³¹P-NMR (100 MHz) 19.8. Anal. calcd. for C₁₁H₂₁O₅P: C 50.00, H 8.01, found C 50.10, H 8.08.

Dimethylphosphorylacetic acid 1,1,1-trichloro-4-methylpent-3-ene-2-yl ester 4e 52% (by chromatography) IR(neat): 1715, 1250, 1010 cm⁻¹. ¹H-NMR (80 MHz) 1.80(s, 3H), 1.82(s, 3H), 3.00(d, 2H, $J_{PH}=24$ Hz), 3.80(d, 6H, $J_{PH}=12$ Hz), 5.30(d, 1H), 6.05(d, 1H, J=8 Hz), ³¹P-NMR (100 MHz) 21.0. Anal. calcd. for C₁₀H₁₆Cl₃O₅P: C 33.97, H 4.56, found C 33.90, H 4.50. Ms m/z(%) 353: (M⁺, 3,4), 151 (100), 124 (16.2), 109 (29.2).

Diethylphosphorylacetic acid 1,1,1-trichloro-4-methylpent-3-ene-2-yl ester **4f** 58% (by chromatography) IR(neat): 1720, 1280, 1010 cm⁻¹, ¹H-NMR (80 MHz) 1.35(t, 6H, J_{HH} ==7 Hz), 1.88(s, 3H), 1.92(s, 3H), 3.10(d, 2H, J_{PH} =22 Hz), 3.8-4.6(m, 4H), 5.40(d, 1H, J=9 Hz), 6.15(d, 1H), ³¹P-NMR (100 MHz) 18.4. Anal. calcd. for $C_{12}H_{20}Cl_3O_4P$: C 37.77, H 5.28, found C 37.60, H 5.12.

Dimethylphosphorylacetic acid E-but-2-enyl ester **4g** 70% (by fractionation) b.p.:97-102°C/0.4 Torr, IR(neat): 1715, 1250, 1005 cm⁻¹, ¹H-NMR (80 MHz) 1.70(d, 3H, J=7 Hz), 2.90(d, 2H, J_{PH} =24 Hz), 3.75(d, 6H, J_{PH} =11 Hz), 4.55(d, 2H, J=8 Hz), 4.65(m, 2H), ³¹P-NMR (100 MHz) 22.3. Anal. calcd. for C₈H₁₅O₅P: C 43.25, H 6.80, found C 43.32, H 6.89. Ms m/z(%) 222: (M⁺, 6,4), 151 (100), 124 (29.2), 109 (34.2).

Preparation of cyclopropane lactones 6 and isolation of iodoacetic esters 17 (General procedure)

To the mixture of phosphonoacetic ester **4a-h** (20 mmol), K_2CO_3 (9.7 g, 70 mmol), TEBAC (0.22g, 1 mmol) and benzene (30 cm³), iodine (6.0 g, 24 mmol) in benzene (75 cm³) was added dropwise for 1.5 hours at reflux temperature with efficient stirring. After a further 30 min heating the mixture was cooled, the solid was filtered off, the filtrate was washed with 10% $Na_2S_2O_3$ solution and with water, dried over Na_2SO_4 , the solvent was evaporated, the residue purified or the appropriate cyclopropane lactone **6** and the iodoacetic ester **17** were separated by column chromatography.

3-Oxa-bicyclo[3,1,0]hexane-2-one-1-phosphonic acid dimethyl ester 6a, traces ³¹P-NMR (100 MHz) 17.4, Ms m/z(%) 206: (M⁺, 8.5), 176 (21.2), 150 (63.1), 127 (62.8), 109 (100).

5-Methyl-3-oxa-bicyclo[3, l,0]hexane-2-one-1-phosphonic acid dimethyl ester **6b**, traces ³¹P-NMR (100 MHz) 17.6, Ms m/z(%) 248: (M⁺, 14.1), 233 (10.2), 204 (13.1), 138 (61.2), 111 (100).

6.6-Dimethyl-3-oxa-bicyclo[3,1,0]hexane-2-one-1-phosphonic acid dimethyl ester **6c**, 61% (by chromatography) IR(neat): 1750, 1260, 995 cm⁻¹, ¹H-NMR (80 MHz) 1.25(s, 3H), 1.52(s, 3H), 2.62(td, 1H, $J_{HH}=6$ Hz, $J_{PH}=13$ Hz), 3.80 and 3.86(d, 6H, $J_{PH}=8$ Hz), 4.2-4.5(m, 2H), ³¹P-NMR (100 MHz) 20.8. Anal. calcd. for $C_9H_{15}O_5P$: C 46.16, H 6.46, found C 46.10, H 6.35, Ms m/z(%) 234: (M⁺, 5.5), 216 (20.4), 193 (100), 165 (26.8), 110 (44.2).

3-Methyl-but-2-ene-1-yl iodoacetate **17c** 7% from **4c**, traces from of **4d** (by chromatography) IR(neat): 1705 cm⁻¹, ¹H-NMR (80 MHz) 1.75(s, 3H), 1.80(s, 3H), 3.70(s, 2H), 4.65 (d, 2H, J=12 Hz), 5.25 (d, 1H). Anal. calcd. for $C_7H_{11}IO_2$: C 33.09, H 4.36, found C 32.97, H 4.23.

6,6-Dimethyl-3-oxa-bicyclo[3,1,0]hexane-2-one-1-phosphonic acid diethyl ester **6d**, 50% (by chromatography) IR(neat): 1750, 1260, 995 cm⁻¹, ¹H-NMR (80 MHz) 1.21(s, 3H), 1.38(t, 3H, $J_{HH}=6.8$ Hz), 1.40(t, 3H, $J_{HH}=7.1$ Hz), 1.48(s, 3H), 2.60(td, 1H, $J_{HH}=6.2$ Hz, $J_{PH}=13.1$ Hz), 4.20(dq, 4H, $J_{PH}=13.1$ Hz), 4.1-4.5(m, 2H), ³¹P-NMR (100 MHz) 17.9. Anal. calcd. for C₁₁H₁₉O₅P: C 50.38, H 7.30, found C 50.25, H 7.18, Ms m/z(%) 262: (M⁺, 5.0), 234 (3.0), 165 (100), 138 (25.8), 111 (30.2).

6,6-Dimethyl-4-trichloromethyl-3-oxa-bicyclo[3,1,0]hexane-2-one-1-phosphonic acid dimethyl ester **6e**, 18% (by crystallisation from ether), m.p.:152-153°C, IR(KBr): 1780, 1245, 1030 cm⁻¹, ¹H-NMR (250 MHz) 1.28(s, 3H), 1.61(s, 3H), 2.90(d, 1H, J_{PH}=11 Hz), 3.80 and 3.89(d, 6H, J_{PH}=11 Hz), 4.62(d, 1H, J_{PH}=3 Hz), ¹³C-NMR (250 MHz): 17.0, 21.8, 30.3, 35.9, 38.7, 53.3, 53.5, 83.8, 98.0, 170.2, ³¹P-NMR (100 MHz) 18.3. Anal. calcd. for C₁₀H₁₄Cl₃O₅P: C 34.17, H 4.01, found C 34.26, H 4.16, Ms m/z(%) 351: (M⁺, 5.5), 309 (57.0), 233 (100), 192 (23.8), 110 (76.2).

4-Methyl-1, 1, 1-trichloro-pent-3-ene-2yl-iodoacetate 17e 25% from 4e (by chromatography) IR(neat): 1705 cm⁻¹, ¹H-NMR (80 MHz) 1.75(s, 3H), 1.80(s, 3H), 3.70(s, 2H), 5.25 (d, 1H, J=9.5 Hz), 6.00(d, 1H), Anal. calcd. for $C_8H_{10}Cl_3IO_5$: C 25.87, H 2.71, found C 25.98, H 2.86,

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6,6-Dimethyl-4-trichloromethyl-3-oxa-bicyclo[3,1,0]hexane-2-one-1-phosphonic acid diethyl ester **6f**, 23% (by crystallisation from ether after chromatography), m.p.:106-107°C, IR(KBr): 1708, 1250, 1000 cm⁻¹, ¹H-NMR (80 MHz) 1.28(s, 3H), 1.40(t, 3H, J_{HH}=6.9 Hz), 1.42(t, 3H, J_{HH}=7.2 Hz), 1.61(s, 3H), 2.95(d, 1H, J_{PH}=11.2 Hz), 4.20(dq, 4H, J_{PH}=13.1 Hz), 4.60(d, 1H, J_{PH}=3 Hz), Anal. calcd. for C₁₂H₁₈Cl₃O₅P: C 37.97, H 4.78, found C 37.81, H 4.66, Ms m/z(%) 378: (M⁺, 6.0), 337 (34.0), 309 (20), 280 (57.8), 261 (100). ³¹P-NMR (100 MHz) 15.3.

6-Methyl-3-oxa-bicyclo[*3*, *1*, *0*]*hexane-2-one-1-phosphonic acid dimethyl ester* **6g** exo, **6h** endo 32% isomeric mixture (by chromatography) Anal. calcd. for $C_8H_{13}O_5P$: C 43.64, H 5.95, found C 43.76, H 6.11, Ms m/z(%) 220: (M⁺, 2.5), 202 (31.0), 110 (100), 94 (45.8), IR (neat) : 1715, 1250, 1000 cm⁻¹, **6g** ¹H-NMR (250 MHz) 1.48(d, 3H, J_{HH}=6.3 Hz), 1.60-1.80(m, 1H), 2.55-2.70(m, 1H), 3.84(d, 3H, J_{PH}=11.1 Hz) 3.87(d, 3H, J_{PH}=11.0 Hz) 4.30(dd, 1H, J_{AB}=9.8 Hz J_{AH}=4.5 Hz) and 4.35(dd, 1H, J_{BH}=3.0 Hz), ¹³C-NMR (250 MHz) 12.1, 25.8, 26.7, 31.1, 52.6, 53.2, 67.7, 170.6, ³¹P-NMR (100 MHz) 19.8, **6h** ¹H-NMR (250 MHz) 1.25(d, 3H, J_{HH}=6.1 Hz), 2.10-2.30(m, 1H), 2.65-2.85(m, 1H), 3.84(d, 3H, J_{PH}=11.1 Hz) 3.87(d, 3H, J_{PH}=11.0 Hz) 4.20(dd, 1H, J_{AB}=10.5 Hz J_{AH}=5.2 Hz) and 4.50(dd, 1H, J_{BH}=3.4 Hz), ¹³C-NMR (250 MHz) 7.2, 12.2, 22.3, 29.0, 52.6, 53.2, 64.1, 169.8, ³¹P-NMR (100 MHz) 19.8.

6-Methyl-3-oxa-bicyclo[*3*, *1*, *0*]*hexane-2-one-1-phosphonic acid diethyl ester* **6i** exo, **6j** endo 56% isomeric mixture (by chromatography) Anal. calcd. for $C_{10}H_{17}O_5P$: C 48.40, H 6.90, found C 48.76, H 7.01, IR (neat) : 1715, 1250, 1000 cm⁻¹, **6i** ¹H-NMR (250 MHz) 1.36(t, 3H, J_{HH}=6.8 Hz), 1.39(t, 3H, J_{HH}=7.3 Hz), 1.49(d, 3H, J_{HH}=6.3 Hz), 1.55-1.70(m, 1H), 2.50-2.65(m, 1H), 4.20(dq, 4H, J_{PH}=13.0 Hz), 4.30 and 4.30 (m, 2H), ¹³C-NMR (250 MHz) 12.0, 15.8, 15.9, 26.1, 26.5, 31.0, 67.5, 62.2, 62.6, 172.0, ³¹P-NMR (100 MHz) 19.8, **6j** ¹H-NMR (250 MHz) 1.36(t, 3H, J_{HH}=6.8 Hz), 1.39(t, 3H, J_{HH}=7.3 Hz), 1.23(d, 3H, J_{HH}=6.4 Hz), 2.05-2.25(m, 1H), 2.60-2.80(m, 1H), 4.20(dq, 4H, J_{PH}=13.0 Hz), 4.20 and 4.45 (m, 2H), ¹³C-NMR (250 MHz) 7.1, 12.0, 15.8, 15.9, 22.1, 29.0, 62.2, 62.6, 63.9, 171.9, ³¹P-NMR (100 MHz) 17.0.

Preparation of iodophosphonoacetic acid ethyl esters 8 (General procedure)

To a mixture of ethyl phosphonoacetate 7 (4.5g, 20 mmol), K_2CO_3 (9.7g, 70 mmol), TEBAC (0.22g, 1 mmol) and benzene (30 cm³), iodine (6.0 g, 24 mmol) in benzene (75 cm³) was added dropwise for 1.5 hours at reflux temperature with efficient stirring. After a further 30 min heating the mixture was cooled, the solid was filtered off, the filtrate was washed with 10% Na₂S₂O₃ solution and with water, dried over Na₂SO₄, the solvent was evaporated. Iodination was monitored by GC. ³¹P-NMR (100 MHz)

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REFERENCES

- 1. Tőke, L.; Hell, Z.; Szabó, G. T.; Tóth, G.; Rockenbauer, A. Tetrahedron 1993, 49, 5133-5146.
- (a) Kondo, K.; Takashima, T.; Tunemoto, D. Chemistry Letters 1979, 1185-1188. (b) Arlt, D.; Jantelat, M.; Lantzsch, R. Angew. Chemie 1981, 93, 719-840.
- 3. Koskinen, A. M. P.; Munoz, L. J. Org. Chem. 1993, 58, 879-886.
- 4. Groth, U.; Lehmann, L.; Richter, L.; Schöllkopf, U. Liebigs Ann. Chem 1993, 427-431 and references cited therein.
- (a) Issleib, K. Nachr. Chem. Tech. 1987, 35, 1037-1042. (b) Petrillo, E. W.; Spitzmiller, E. R. Tetrahedron Lett. 1979, 4929-4930. c. Gruszecka, E.; Soroka, M.; Mastalerz, P. Pol. J. Chem. 1979, 53, 937-939.
- 6. Wolfenden, R., Annu. Rev. Biophys. Bioeng. 1976, 5, 271-306.
- 7. Bartlett, P.A.; Kezer, W. B. J. Am. Chem. Soc. 1984, 106, 4282-4283.
- (a) Jakobsen, N. A.; Bartlett, P. A. J. Am. Chem. Soc. 1981, 103, 654-657 (b) Kupczyk-Subotkowska, L.; Mastalerz, P. Int. J. Pept. Protein Res. 1983, 21, 485-490.
- 9. Dulariey, E. L. J. Antibiot. 1970, 23, 567-568.
- 10. Höfle, G.; Steglich, W.; Vorbrüggen, H. Angew. Chem. 1978, 90, 602,
- Sasse, K. Phosphonsauren und Derivate in Methoden der Organischen Chemie (Houben-Weyl); Vol. 12/1; Müller, E.; Georg ThiemeVerlag: Stuttgart-New York, 1963; p. 436.
- 12. Gruzet, M. P.; Surzm, J-M.; Vanella, P.; Ghiglione, C.; Maldane, J. Tetrahedron Letters 1985, 26, 1023
- Kornblum, N.; Davies, T. M.; Earl, G. W.; Holy, N. L.; Kerber, R. C.; Musser, M. T.; Snow, D. H. J. Am. Chem. Soc. 1967, 89, 725
- 14. Baldwin, J. E. J. Chem. Soc. Chem. Commun. 1976, 734.
- Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Tomas, R. C. J. Chem. Soc. Chem. Commun. 1976, 736.
- 16. Walborsky, H.M.; Topolski, M. Tetrahedron Letters 1993, 34, 7681-7684.
- 17. Clarke, H. T. J. Chem. Soc. 1910, 97, 416.

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