Pergamon

Tetrahedron Vol. 51, No. 33, pp. 9167-9178, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00522-6

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

László Tőke[a]*, Zsuzsa M. Jászay[b], Imre Petneházy[a], György Clementis[c], Györgyi D. Vereczkey[c], István Kövesdi[c], Antal Rockenbauer[d] and Katalin Kováts[a]

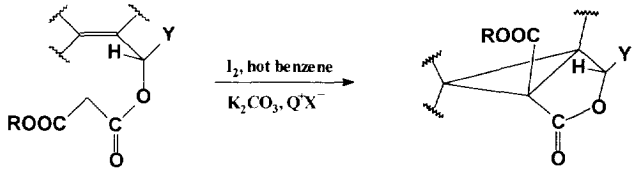
[a] Department of Organic Chemical Technology, Technical University of Budapest, H-1521 Budapest, P.O.B. 91, Hungary
[b] Organic Chemical Technological Research Group of the Hungarian Academy of Sciences, H-1521 Budapest, P.O.B. 91, Hungary
[c] EGIS Pharmaceuticals Ltd., H-1475, Budapest P.O.B. 100, Hungary
[d] Central Research Institute for Chemistry, Hungarian Academy of Sciences, H-1525 Budapest, P.O.B. 17, Hungary

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 reported[1] 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



1 2

These types of compounds are useful for the diastereoselective synthesis of polysubstituted cyclopropane derivatives [e.g. a simple synthesis of the cyclopropane part of deltamethrin[2] 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]

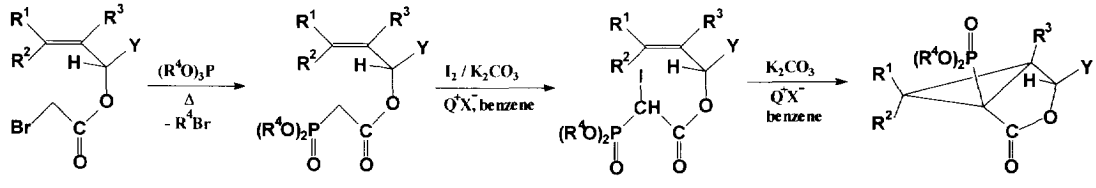
In the light of the mechanism substantiated for the transformations of allylic esters of malonic acid **1** to **2** we hoped that phosphonoacetic acid allyl esters **4** would also react with iodine, in the presence of Q^+X^- (phase transfer catalyst) and K_2CO_3 as base in a similar way to give compounds **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** (e.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



3 4 5 6

Compounds	Substituents				
3-13, 17	**R^1**	**R^2**	**R^3**	**R^4**	**Y**
a	H	H	H	CH_3	H
b	H	H	CH_3	CH_3	H
c	CH_3	CH_3	H	CH_3	H
d	CH_3	CH_3	H	C_2H_5	H
e	CH_3	CH_3	H	CH_3	CCl_3
f	CH_3	CH_3	H	C_2H_5	CCl_3
g	CH_3	H	H	CH_3	H
h	H	CH_3	H	CH_3	H
i	CH_3	H	H	C_2H_5	H
j	H	CH_3	H	C_2H_5	H

Using standard methods[10] the allylic alcohols were acylated by bromoacetyl bromide and the esters **3** obtained were heated with trialkyl phosphite[11] 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 ^{31}P-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).

Table 1 ^{31}P-NMR shifts and yields of **4, 5** and **6**

	^{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
c	22.4	-	20.8	90	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)**

* 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.

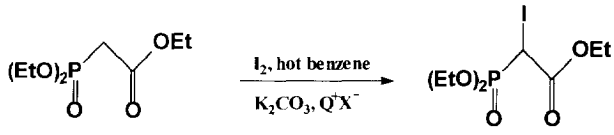
The E-isomer **4g** gives isomer products **6g** and **6h** while the E-isomer **4i** gives a mixture of products **6i** and **6j** with the exo-isomers **6g** and **6i** dominating.

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 (**4b,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

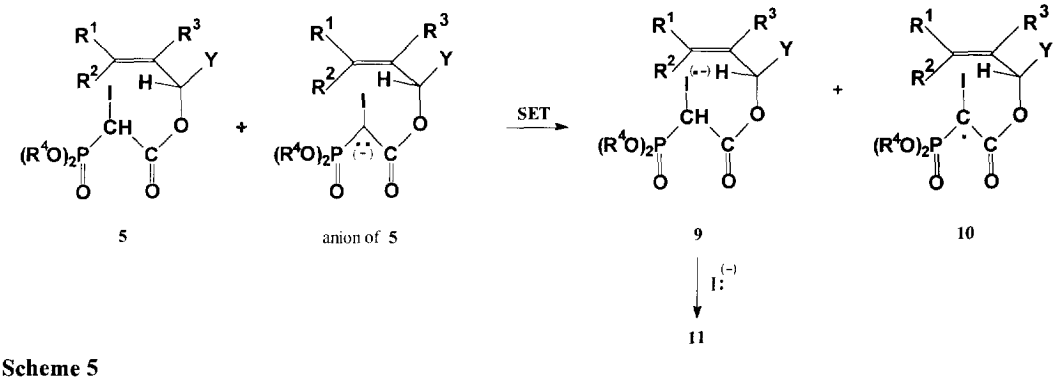


7 **8**

It has been shown in these transformations[1] 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 K_2CO_3 seems to be also important because strong bases like solid KOtBu, solid $NaOCH_3$ or their solutions in DMF initiate undesired side-reactions.

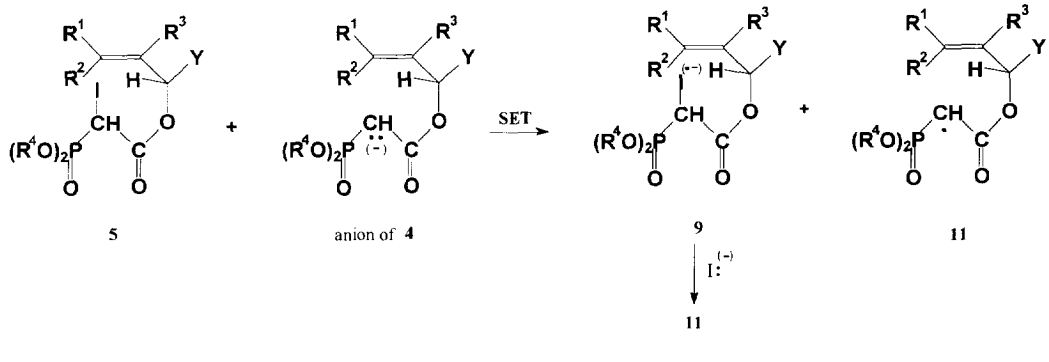
SET induced radical type processes can be assumed to exist in the transformation of **4** to **6**. The initiation steps are shown in Schemes 4 and 5.

Scheme 4



5 anion of **5** **9** **10** **11**

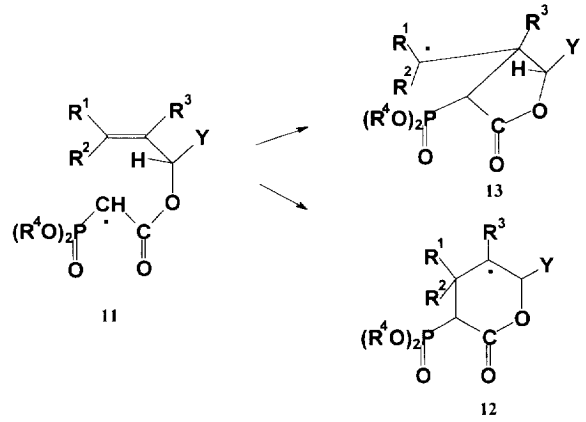
Scheme 5



5 anion of **4** **9** **11** **11**

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 source[13] 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 **6 b,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_z plane of the unpaired electron.

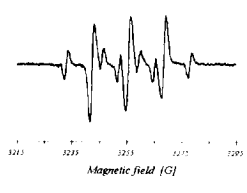


Fig. 1.

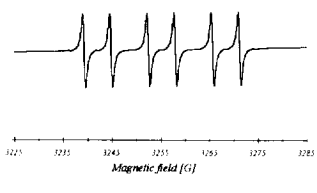


Fig. 2.

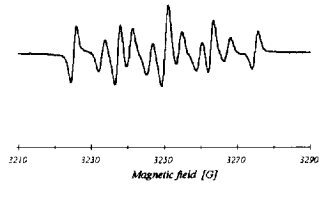


Fig.3.

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**.

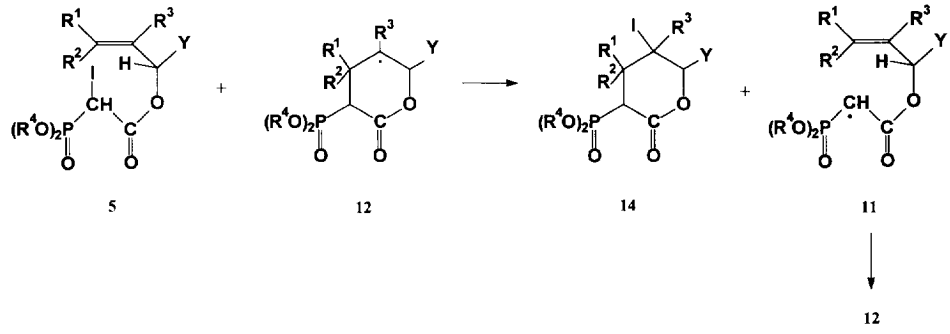
ESR spectral data showing the appearence of the radicals of similar type in the reactions **4b,c,g** to **6b,c,g** are in the Table 2.

Table 2 ESR spectral data

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

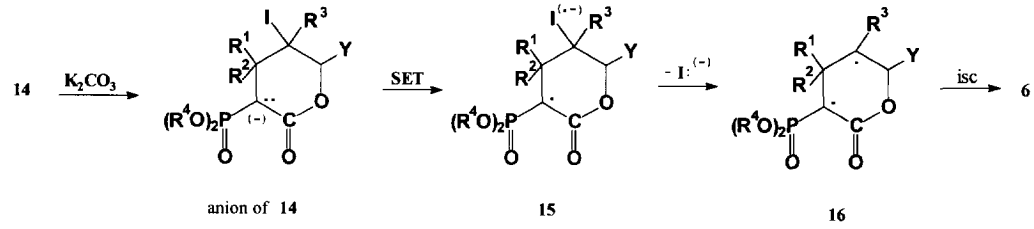
The radical chain propagation steps involving radical **12** and the iodo derivative **5** with the formation of **14** (Scheme 7) as well as the transformation of **11** to **12** are shown in Scheme 6.

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).

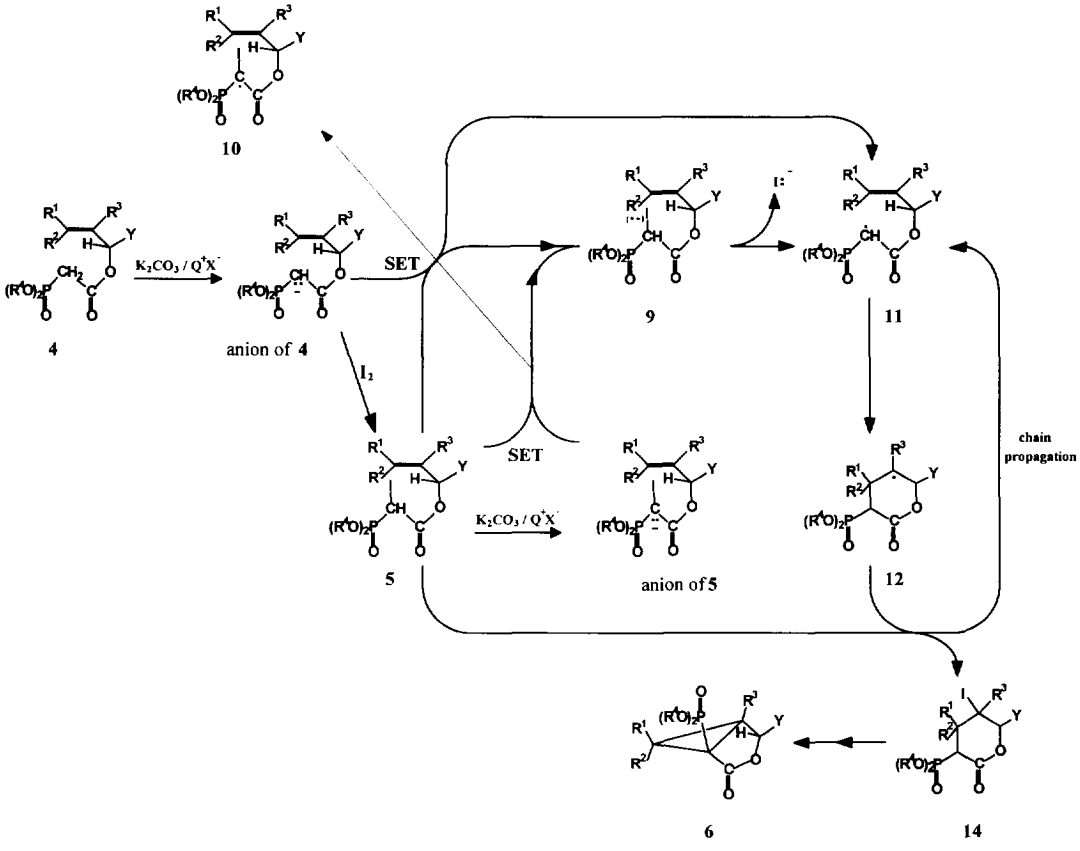
Scheme 8



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]

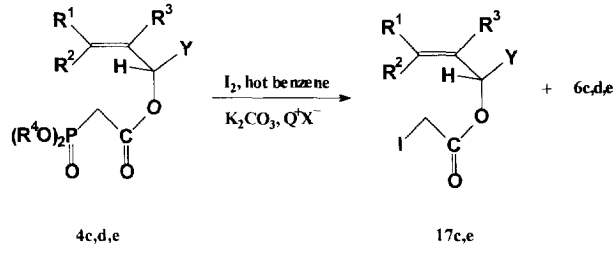
The elemental steps leading from **4** to **6** are summarized in Scheme 9.

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



4c,d,e 17c,e

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. ^{1}H-NMR and ^{13}C NMR spectra were taken by a Bruker AW-80 and a Bruker WM-250 spectrometer, ^{31}P NMR spectra by a JEOL FX-100 spectrometer, all in $CDCl_3$ 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 F_{254} 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 cm^3). Bromoacetyl bromide (50 mmol) in benzene (30 cm^3) 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}, ^{1}H-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}, ^{1}H-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}, ^{1}H-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}, ^{1}H-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 °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 columnn 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}, ^{1}H-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), ^{31}P-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}, ^{1}H-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), ^{31}P-NMR (100 MHz) 22.1. Anal. calcd. for $C_8H_{15}O_5P$: 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}, ^{1}H-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), ^{31}P-NMR (100 MHz) 22.4. Anal. calcd. for $C_9H_{17}O_5P$: 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}, ^{1}H-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), ^{31}P-NMR (100 MHz) 19.8. Anal. calcd. for $C_{11}H_{21}O_5P$: 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}, ^{1}H-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), ^{31}P-NMR (100 MHz) 21.0. Anal. calcd. for $C_{10}H_{16}Cl_3O_5P$: 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}, ^{1}H-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), ^{31}P-NMR (100 MHz) 18.4. Anal. calcd. for $C_{12}H_{20}Cl_3O_5P$: 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}, ^{1}H-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), ^{31}P-NMR (100 MHz) 22.3. Anal. calcd. for $C_8H_{15}O_5P$: 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 cm^3), iodine (6.0 g, 24 mmol) in benzene (75 cm^3) 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 ^{31}P-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[3,1,0]hexane-2-one-1-phosphonic acid dimethyl ester **6b**, traces ^{31}P-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}, ^{1}H-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), ^{31}P-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}, ^{1}H-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}, ^{1}H-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), ^{31}P-NMR (100 MHz) 17.9. Anal. calcd. for $C_{11}H_{19}O_5P$: 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}, ^{1}H-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), ^{13}C-NMR (250 MHz): 17.0, 21.8, 30.3, 35.9, 38.7, 53.3, 53.5, 83.8, 98.0, 170.2, ^{31}P-NMR (100 MHz) 18.3. Anal. calcd. for $C_{10}H_{14}Cl_3O_5P$: 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}, ^{1}H-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,

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}, ^{1}H-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 $C_{12}H_{18}Cl_3O_5P$: 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). ^{31}P-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** ^{1}H-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), ^{13}C-NMR (250 MHz) 12.1, 25.8, 26.7, 31.1, 52.6, 53.2, 67.7, 170.6, ^{31}P-NMR (100 MHz) 19.8, **6h** ^{1}H-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), ^{13}C-NMR (250 MHz) 7.2, 12.2, 22.3, 29.0, 52.6, 53.2, 64.1, 169.8, ^{31}P-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** ^{1}H-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), ^{13}C-NMR (250 MHz) 12.0, 15.8, 15.9, 26.1, 26.5, 31.0, 67.5, 62.2, 62.6, 172.0, ^{31}P-NMR (100 MHz) 19.8, **6j** ^{1}H-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), ^{13}C-NMR (250 MHz) 7.1, 12.0, 15.8, 15.9, 22.1, 29.0, 62.2, 62.6, 63.9, 171.9, ^{31}P-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 cm^3), iodine (6.0 g, 24 mmol) in benzene (75 cm^3) 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. Iodination was monitored by GC. ^{31}P-NMR (100 MHz)

ACKNOWLEDGEMENTS

This work was partially supported by the Hungarian Academy of Sciences and by the National Science Foundation (OTKA 869/1991).

REFERENCES

1. Tőke, L.; Hell, Z.; Szabó, G. T.; Tóth, G.; Rockenbauer, A. *Tetrahedron* **1993**, *49*, 5133-5146.
2. (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.
5. (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.
8. (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,
11. 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
13. 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.
15. 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.

(*Received in UK* 1 *May* 1995; *revised* 23 *June* 1995; *accepted* 30 *June* 1995)