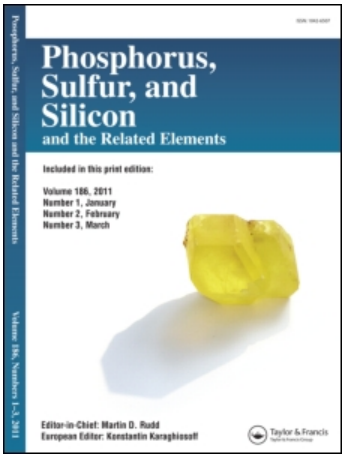

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REACTION OF RING AND SIDE CHAIN SUBSTITUTED 3-PHOSPHONOMETHYLCYCLOHEXENONES WITH AZIDOSILANE REAGENTS

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REACTION OF RING AND SIDE CHAIN SUBSTITUTED 3-PHOSPHONOMETHYLCYCLOHEXENONES WITH AZIDOSILANE REAGENTS

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Ring and side chain substituted 3-phosphonomethylcyclohexenones react with triazidochlorosilane (TACS) in acetonitrile or azidotrimethylsilane (TMS-N_3)/iodine/pyridine mixture in dichloromethane to afford ring expanded tetrazolo and γ-iodo-δ-ketoalk-2-enylphosphonate systems, respectively.

Keywords: 3-Phosphonoalkylcyclohexenone; formation of tetrazolo and γ-iodo-δ-ketoalk-2-enylphosphonate systems

INTRODUCTION

Products of the reaction of phosphorus-stabilised carbanions with α,β-unsaturated carbonyl compounds continue to attract considerable attention in synthesis. In this work, ring and side chain substituted 3-phosphonomethylcyclohexenones **1** used as precursors for further derivatization, were obtained *via* routes shown in Scheme 1.

While carbonyl addition of lithiated alkylphosphonate carbanions to cycloalkenones[1] or 3-chlorocyclohexenones[2] in THF occurs readily, the preparation of products **2** from benzylphosphonate precursor presented some problems. In the case of the reaction of (lithiobenzyl)phosphonate with cyclohexenone systems

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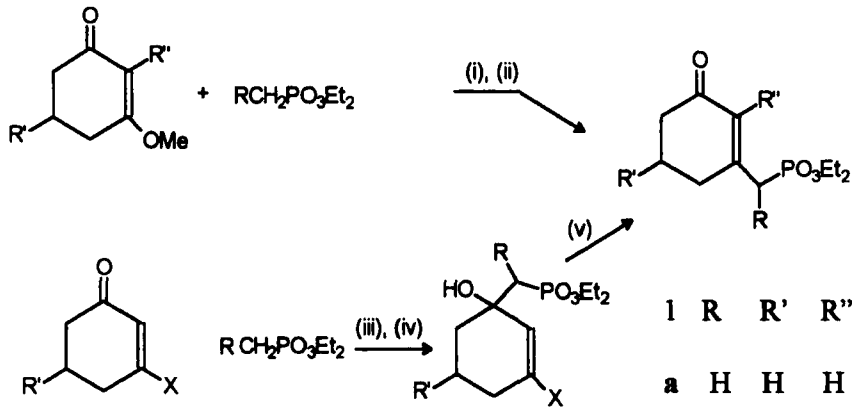


1	R	R'	R"
a	H	H	H
b	Me	H	H
c	H	Me	H
d	Me	Me	H
e	H	H	Me
f	Me	H	Me
g	Ph	H	H
h	Ph	Me	H

2	R'	X	R
a	H	H	Ph
b	Me	Cl	Ph

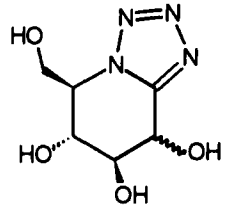
SCHEME 1 *Reagents*: (i) n-BuLi, THF; (ii) H_3O^+ at r.t.; (iii) n-BuLi, Et_2O; (iv) H_3O^+ at −78°C; (v) For **1g**: CrO_3, AcOH, $(CH_3)_2CO$; for **1h**: $CHCl_3$, H_2SO_4 then H_2O.

(X = H, Cl), however, the amount of base, the type of solvent and the reaction temperature were found to determine the final outcome of the reaction. Carbonyl-addition products **2** were isolated in moderate yield as mixtures of diastereomers only when 2 mol equivalents of n-BuLi were employed in diethyl ether and the reaction and aqueous work-up were performed at −78°C.[3] The diastereomeric ratios of products **2** were easily estimated from the ^{31}P NMR peak integrals because of the differences in the chemical shift values ($\Delta\delta p = 0.7$ ppm). The tertiary allylic alcohols **2a** and **2b** were converted using literature methods to the corresponding previously undescribed δ-ketoalk-2-enylphosphonates **1a**[1] and **1h**.[2] Compound **1h** was isolated as a mixture of

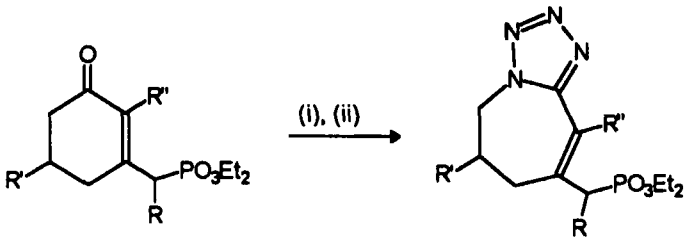
diastereomers of comparable phosphorus chemical shift values. Products **1** were used as starting materials for the preparation of further derivatives of cyclohexenone system as described below.

RESULTS AND DISCUSSION

With a view of preparing compounds with potential biological activity and to study structure-activity relationship, we were interested in introducing the tetrazole functionality into the cyclohexenonealkylphosphonates **1**. The tetrazole moiety in compounds such as nojiritetrazoles **3** has been found to play an im-



portant role in the biological activity of these glycosidase inhibitors.[4] In this work, seven δ-ketoalk-2-enylphosphonates **1a–f** and **1h** were converted to the hitherto unknown tetrazolo derivatives **4** using literature procedure,[5] previously applied to nonphosphorus containing cyclohexenone derivatives. Substrates **1** were treated with triazidochlorosilane (TACS), generated *in situ* from sodium azide and tetrachlorosilane in acetonitrile (Scheme 2). In all cases, only products **4** resulting from ring carbon-6 migration were isolated in moderate yields, and no isomers from the vinylic carbon-2 migration were detected. The regioselectivity of methylene group migration was easily demonstrated by the significant downfield shift of the signal of the methylene protons adjacent to the endocyclic nitrogen in compounds **4**. A similar regioselectivity was reported previously for cyclohexenone derivatives using trimethylsilyl azide (TMS-N_3)—trimethylsilyl trifluoromethanesulphonate mixture in dichloromethane.[6] The ring substituted derivatives **4c**, **d** and **g** showed the CH_2N proton nonequivalency in the NMR spectra with signals at *ca.* 4.20 and 4.60 ppm. The side chain substituted products were isolated as mixtures of diastereomers of comparable phosphorus chemical shift values. An attempted reaction of substrates **1a–d** with TMS-N_3 in trifluoroacetic acid, a reaction mixture known to convert cyclic ketones to amides and tetrazolo derivatives,[7] resulted in the recovery of the starting materials even after a week at room temperature. In the second part of this work, the preparation of γ-iodo-δ-ketoalk-2-enylphosphonates **5** from substrates **1** was



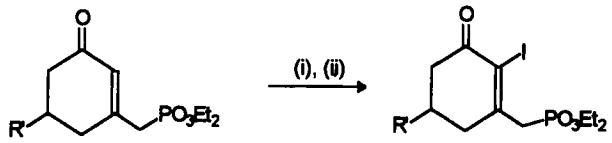
1

4	R	R'	R"
a	H	H	H
b	Me	H	H
c	H	Me	H
d	Me	Me	H
e	H	H	Me
f	Me	H	Me
g	Ph	Me	H

SCHEME 2 *Reagents*: (i) NaN_3, $SiCl_4$, CH_3CN; (ii) Na_2CO_3 (aq).

studied. Treatment of the methylphosphonate derivatives **1a** and **1c** with TMS-N_3 in dichloromethane followed by iodine/pyridine mixture in dichloromethane under conditions reported for cyclohex-2-enones,[8] afforded γ-iodo-δ-ketophosphonates **5a** and **5b**, respectively (Scheme 3). Ethylphosphonate derivatives **1b** and **1d**, however, failed to react under the same conditions probably due to steric factors preventing the initial conjugate addition of TMS-N_3. Iodination products **5** were easily distinguished from their precursors by the absence of the olefinic proton signal in the ^1H NMR spectrum.

The presence of the tetrazole group and the phosphonic ester function in compounds **5** make these systems potential candidates for the screening of biological activity. Compounds **1**, **4** and **5** contain the allylic phosphonate moiety and the α-acidic protons that could allow further structural transformations.



1 **5** R'

a H

b Me

SCHEME 3 *Reagents*: (i) TMS-N_3, CH_2Cl_2; (ii) I_2/Pyridine, CH_2Cl_2.

EXPERIMENTAL

Solvents and commercially available reagents were purified by conventional methods before use. Reactions involving lithiated reagents were carried out in an atmosphere of dry nitrogen. For column chromatography Merck kieselgel 60 (0.063–0.200 mm) was used as a stationary phase. Low resolution mass spectra were recorded on a Varian MAT-212 double focusing direct-inlet spectrometer at an ionization potential of 70 eV. IR spectra were recorded on a Bomem Inc. Michelson 100 spectrometer as solutions in CCl_4. NMR spectra were recorded on a Bruker AC 300 spectrometer for solutions in $CDCl_3$, and the chemical shift values are given relative to the solvent peaks (^1H: 7.24 ppm; ^{13}C: 77.0 ppm). ^{31}P NMR chemical shift values are given relative to 85% H_3PO_4 as an external standard. Diastereomeric nuclei are represented by superscripts a and b. Elemental analyses (C/H/N) were carried out at the Chemistry Department, University of Cape Town.

Preparation of Compounds 2 General Procedure. A solution of n-BuLi (1.6 M solution in hexane; 2 mol equiv.) was added dropwise to a stirred solution of diethyl benzylphosphonate (1 mol equiv.) in dry ether (0.5 ml per mmol of phosphonate) at −78°C. The mixture was stirred at this temperature for 1 h and then a solution of cyclohexenone derivative (1 mol equiv.) in ether (0.1 ml per mmol of alkenone) was added dropwise. After stirring for additional 2 h at −78°C a sat. solution of NH_4Cl was added and the mixture was allowed to warm to room temperature. The aqueous phase was extracted with chloroform and the combined organic layers were washed with water, dried (Na_2SO_4) and evaporated. The following products were isolated as mixtures of two diastereomers:

Diethyl (1-hydroxycyclohex-2-enyl)benzylphosphonate **2a**. Oil; purified by column chromatography (EtOAc-$CHCl_3$, 3:2 v/v) (65%); δ_H 0.93 and 0.97 (3H, two t, J^a_{HH} 7.2 and J^b_{HH} 7.3 Hz), 1.30 and 1.32 (3H, two t, J^a_{HH} 7.1 and J^b_{HH} 7.1 Hz), 1.50–2.20 (4H, m), 3.19–3.50 (2H, two d, J^a_{HP} 22.8 and J^b_{HP} 23.6 Hz), 3.51 and 3.82 (2H, two m, $OCH_2{}^a$), 4.10 (2H, m, $OCH_2{}^b$), 4.33 and 4.49 (1H, two br s, OH^a and OH^b), 5.62–6.03 (2H, m) and 7.22–7.46 (5H, m); δ_c 15.9 and 16.2 (two d, J^a_{CP} 6.0 and J^b_{CP} 6.3 Hz), 18.7 (s), 24.7 (s), 34.0 and 36.4 (two d, J^a_{CP} 11.5 and J^b_{CP} 6.5 Hz), 53.7 and 55.0 (two d, J^a_{CP} and J^b_{CP} 130.2 Hz), 61.6 and 63.1 (two d, J^a_{CP} 7.0 and J^b_{CP} 10.9 Hz), 71.2 and 71.3 (two s), 127.2 (s), 128.1 (d, J_{CP} 7.4 Hz), 128.3 (s), 130.2 (d, J_{CP} 10.0 Hz), 130.6 (d, J_{CP} 7.3 Hz), 132.8 (d, J_{CP} 4.6 Hz) and 134.1 (d, J_{CP} 5.5 Hz); $\delta^a{}_P$ 27.9 (37%) and $\delta^b{}_P$ 28.6 (63%); ν_{max}/cm^{-1} 1236 (P═O) and 3430 (OH); m/z 306 (M-18, 2.5), 228 (58.9), 200 (14.9), 172 (42.4), 96 (16.4) and 91 (100). Anal. calcd for $C_{17}H_{25}O_4P$: C, 63.15 and H, 7.48. Found: C, 62.50 and H, 7.35.

Diethyl (3-chloro-1-hydroxy-5-methylcyclohex-2-enyl)benzylphosphonate **2b**. Oil; purified by column chromatography (EtOAc-$CHCl_3$, 3:2 v/v) δ_H 0.91 and 0.92 (3H, two d, J^a_{HH} 4.2 and J^b_{HH} 4.2 Hz), 0.96 and 1.01 (3H, two t, J^a_{HH} and J^b_{HH} 7.0 Hz), 1.31 and 1.32 (3H, two t, J^a_{HH} and J^b_{HH} 7.1 Hz), 1.60 (1H, m), 1.77–2.00 (2H, m), 2.15–2.35 (2H, m), 3.20 and 3.28 (1H, two d, J^a_{HP} 23.0 and J^b_{HP} 21.6 Hz), 3.64 and 3.83 (2H, two m, $OCH_2{}^a$), 4.10 (2H, m, $OCH_2{}^b$), 4.56 (1H, br s, OH^a), 5.00 (1H, br s, OH^b), 5.46 ($1H^a$, s), 6.06 ($1H^b$, s) and 7.21–7.45 (5H, m); δ_C 16.0 and 16.3 (two d, J^a_{CP} 7.2 and J^b_{CP} 6.2 Hz), 21.0 and 21.2 (two s), 26.0 (s), 27.9 (s), 40.7 and 41.3 (two d, J_{CP} 4.4 and 6.9 Hz), 53.7 (d, J^a_{CP} 131.9 Hz), 55.5 (d, J^b_{CP} 131.9 Hz), 61.6 and 62.0 (two d, J^a_{CP} 7.6 and 7.7 Hz), 63.2 and 63.6 (two d, J^b_{CP} 7.7 and 6.5 Hz) 73.5 and 74.3 (two s), 126.6 (d, J_{CP} 8.4 Hz), 127.6 (s), 128.3 (s), 128.4 (s), 128.8 (d, J_{CP} 11.6 Hz), 130.7 (d, J_{CP} 6.6 Hz); $\delta^a{}_P$ 27.0 (55%) and $\delta^b{}_P$ 27.3 (45%); ν_{max}/cm^{-1} 1233 (P═O) and 3433 (OH); m/z 228 (100), 172 (44.9), 118 (28.4), 102 (35.2), 91 (89.5). Anal. calcd for $C_{18}H_{26}ClO_4P$: C, 57.99 and H, 7.03. Found: C, 57.50 and H, 7.21.

Preparation of Substrates 1

Preparation of **1a–d** was described before.[2] Substrates **1e** and **1f** were prepared from 3-methoxy-2-methylcyclohex-2-en-1-one and the corresponding alkylphosphonate as described for **1a–d**. The analytical data for **1e** was found to be in agreement with the literature data[9] for the same compound prepared by a different route; δ_p 25.4 ppm.

Diethyl 1-(3-oxo-2-methylcyclohex-1-enyl)ethylphosphonate **1f**. Oil; purified by column chromatography (EtOAc) (55%); δ_H 1.23–1.41 (9H, m), 1.81 (3H, d, J_{HP} 2.2 Hz), 1.86–1.96 (2H, m), 2.28–2.67 (4H, two m), 3.30 (1H, dq, J_{HH} 7.1

and 14.2, J_{HP} 25.7 Hz), and 3.98–4.16 (4H, m); δ_C 10.7 (s), 12.2 (d, J_{CP} 6.5 Hz), 16.2 (d, J_{CP} 6.0 Hz), 22.2 (s), 26.6 (s), 36.4 (d, J_{CP} 137.2 Hz), 37.6 (s), 61.7 and 62.1 (two d, J_{CP} 7.5 and 6.7 Hz), 132.9 (d, J_{CP} 12.0 Hz), 153.8 (d, J_{CP} 8.1 Hz) and 198.6 (s); δ_P 29.1; ν_{max}/cm^{-1} 1256 (P═O) and 1670 (C═O); m/z 274 (M^+, 25.0), 137 (29.5), 135 (100) and 121 (42.0). Anal. calcd for $C_{13}H_{23}O_4P$: C, 56.92 and H, 8.45. Found: C, 56.40 and H, 8.30.

Ketophosphonate **1g** was prepared from **2a** following a literature procedure.[1] *Diethyl (3-oxocyclohexen-2-enyl)benzylphosphonate* **1g**. Oil; purified by column chromatography (EtOAc) (70%); δ_H 1.08 (3H, t, J_{HH} 7.0 Hz), 1.25 (3H, t, J_{HH} 7.0 Hz), 1.93 (2H, quint., J_{HH} 6.1 and 9.0 Hz), 2.26–2.56 (4H, m), 3.75–4.12 (5H, m), 6.27 (s) and 7.25–7.43 (5H, m); δ_C 16.1 and 16.3 (two d, J_{CP} 6.0 Hz), 22.6 (s), 29.2 (d, J_{CP} 5.8 Hz), 37.1 (s), 53.2 (d, J_{CP} 138.2 Hz), 62.6 and 63.0 (two d, J_{CP} 6.9 and 7.4 Hz), 127.9 (s), 128.7 (s), 129.0 (d, J_{CP} 9.2 Hz), 129.6 (d, J_{CP} 8.1 Hz), 133.6 (s), 159.7 (d, J_{CP} 5.7 Hz) and 199.4 (s); δ_P 23.0; ν_{max}/cm^{-1} 1252 (P═O) and 1679 (C═O); m/z 322 (M^+, 29.9), 185 (33.5), 184 (100) and 167 (28.4). Anal. calcd for $C_{17}H_{23}O_4P$: C, 63.35 and H, 7.19. Found: C, 62.90 and H, 7.25.

Ketophosphonate **1h** was prepared from **2b** using the method described in our previous communication.[2] *Diethyl (3-oxo-5-methylcyclohex-2-enyl)benzylphosphonate* **1h**. Oil; purified by column chromatography (EtOAc-$CHCl_3$, 3:2 v/v) (75%); δ_H 0.98 (d, J_{HH} 6.3 Hz), 1.08 (3H, m), 1.24 (3H, t, J_{HH} 7.0 Hz), 1.90–2.62 (5H, m), 3.76–4.08 (5H, m), 6.26 (1H, s), 7.24–7.42 (5H, m); δ_C 16.1 and 16.3 (two d, J_{CP} 6.3 and 5.7 Hz), 20.6 and 20.9 (two s), 29.8 and 30.2 (two s), 37.3 and 37.4 (two s), 45.2 and 45.3 (two s), 53.0 and 54.0 (two d, J^a_{CP} 138.2 and J^b_{CP} 128.6 Hz), 62.5 and 62.9 (two d, J^a_{CP} and J^b_{CP} 6.1 Hz), 127.8 (d, J_{CP} 3.0 Hz), 128.5 (d, J_{CP} 3.2 Hz), 128.7 (s), 129.6 (d, J_{CP} 4.8 Hz), 133.4 and 133.6 (two d, J^a_{CP} and J^b_{CP} 6.6 Hz), 158.7 (d, J_{CP} 16.2 Hz) and 198.6 (s); δ^a_P 22.9 and δ^b_P 23.0; ν_{max}/cm^{-1} 1236 (P═O) and 1675 (C═O); m/z 336 (M^+, 11.2), 199 (22.5), 198 (100), 183 (24.5) and 28 (27.8). Anal. calcd for $C_{18}H_{25}O_4P$: C, 64.27 and H, 7.49. Found: C, 63.90 and H, 7.25.

Preparation of ring and side chain tetrazole derivatives of alkylphosphonic esters **4**–*General procedure.*[5] A mixture of phosphonate **1** (1 mol equiv.), tetrachlorosilane (1.1 mol equiv) and sodium azide (3.2 mol equiv.) in acetonitrile (5 ml per mmol of **1**) was stirred at room temperature with the exclusion of moisture. After 24 h at room temperature the mixture was poured into ice-cold sodium carbonate solution and then extracted with chloroform. The organic phase was washed with water, dried (Na_2SO_4) and the solvent was evaporated. The following products were prepared:

4a: Oil; purified by column chromatography ($CHCl_3$-Acetone, 4:1 v/v) (51%); δ_H 1.30 (6H, t, J_{HH} 7.1 Hz), 2.19 (2H, quint., J_{HH} 5.5 and 8.2 Hz), 2.78 (2H, d, J_{HP} 22.9 Hz), 2.81 (2H, m), 4.11 (4H, dq, J_{HH} 7.2 and J_{HP} 11.1 Hz), 4.57

(2H, t, J_{HH} 5.2 Hz) and 6.67 (1H, d, J_{HP} 5.5 Hz); δ_C 16.4 (d, J_{CP} 5.4 Hz), 23.3 (s), 35.4 (s), 38.3 (d, J_{CP} 136.6 Hz), 49.1 (s), 62.4 (d, J_{CP} 7.1 Hz), 112.6 (d, J_{CP} 12.5 Hz), 135.7 (s) 144.3 (s) and 150.5 (s); δ_P 24.7; ν_{max}/cm^{-1} 1244 (P═O) and 1554 (C═N); m/z 286 (M^+, 100), 258 (31.8), 230 (15.6), 149 (70.3), 137 (96.7), 121 (89.3) and 120 (60.6); Anal. Calcd for $C_{11}H_{19}N_4O_3P$: C, 46.15, H, 6.69 and N, 19.57. Found: C, 45.71, H, 6.87 and N, 19.93.

4b: Oil; purified by column chromatography ($CHCl_3$–Acetone, 4:1 v/v) (55%); δ_H 1.29 (6H, t, J_{HH} 7.1 Hz), 1.43 (3H, dd, J_{HH} 7.3 and J_{HP} 17.9 Hz), 2.14–2.22 (2H, m), 2.69–2.91 (2H, m), 4.09 (4H, dq, J_{HH} 7.1 and J_{HP} 11.1 Hz), 4.57 (2H, t, J_{HH} 5.2 Hz) and 6.70 (1H, d, J_{HP} 5.0 Hz); δc 14.0 (s), 16.5 (s), 23.3 (s), 34.1 (s), 42.1 (d, J_{CP} 136.4 Hz), 49.3 (s), 62.5 (d, J_{CP} 8.2 Hz), 111.3 (d, J_{CP} 11.5 Hz), 135.7 (s) and 150.8 (s); δ_P 27.6; ν_{max}/cm^{-1} 1249 (P═O) and 1549 (s, C═N); m/z 300 (M^+, 22.8), 272 (6.4), 164 (28.2), 163 (100), 151 (20.1) and 27 (18.5). Anal. calcd for $C_{12}H_{21}N_4O_3P$: C, 48.00, H, 7.05 and N, 18.66. Found: C, 48.19, H, 7.20 and N, 18.57.

4c: Oil; purified by column chromatography ($CHCl_3$–Acetone; 4:1 v/v) (54%); δ_H 1.11 (3H, d, J_{HH} 6.9 Hz), 1.30 (6H, t, J_{HH} 7.0 Hz), 2.36 (1H, m), 2.68 (2H, m), 2.75 (2H, d, J_{HP} 23.0 Hz), 4.10 (4H, dq, J_{HH} 7.1 and 14.1 Hz), 4.21 (1H, dd, J_{HH} 9.0 and 14.1 Hz), 4.61 (1H, d, J_{HH} 14.1 Hz) and 6.65 (1H, d, J_{HP} 4.4 Hz); δ_C 16.4 (d, J_{CP} 5.4 Hz), 18.5 (s), 28.8 (s), 38.4 (d, J_{CP} 136.6 Hz), 43.1 (s), 54.4 (s), 62.4 (d, J_{CP} 6.5 Hz), 112.4 (d, J_{CP} 11.8 Hz), 149.7 (d, J_{CP} 28.6 Hz) and 150.1 (s); δ_P 24.7; ν_{max}/cm^{-1} 1250 (P═O) and 1551 (C═N); m/z 300 (M^+, 22.7), 285 (46.8), 257 (41.1), 163 (49.1) and 29 (100). Anal. calcd for $C_{12}H_{21}N_4O_3P$: C, 48.00, H, 7.05 and N, 18.66. Found: C, 48.13, H, 7.16 and N, 18.46.

4d: Oil; purified by column chromatography ($CHCl_3$–Acetone, 4:1 v/v) (65%); δ_H 1.12 (3H, d, J_{HH} 6.9 Hz), 1.29 (6H, t, J_{HH} 7.1 Hz), 1.42 (3H, dd, J_{HH} 7.2 and J_{HP} 17.9 Hz), 2.31–2.89 (4H, m), 4.03–4.14 (4H, m), 4.22 (1H, dt, J_{HH} 8.7 and 14.1 Hz), 4.62 (1H, two dd, J_{HH} 1.8, 3.9 and 14.0 Hz) and 6.69 (1H, d, J_{HP} 5.1 Hz); δ_C 13.8 and 14.1 (two d, J^a_{CP} 5.4 and J^b_{CP} 6.5 Hz), 16.5 (s), 18.5 (d, J_{CP} 3.1 Hz), 28.8 (d, J_{CP} 4.9 Hz), 41.5 and 41.9 (two s), 42.0 (s), 42.2 and 42.3 (two d, J^a_{CP} 135.4 and J^b_{CP} 136.1 Hz), 54.6 (s), 62.5 (d, J_{CP} 7.6 Hz), 111.1 (d, J_{CP} 11.6 Hz), 135.9 (s) and 155.0 (s); δ^a_P 27.5 and δ^b_P 27.6; ν_{max}/cm^{-1} 1249 (P═O) and 1549 (C═N); m/z 314 (M^+, 28.1), 299 (16.2), 271 (13.8), 178 (22.9), 177 (100), 176 (2.4) and 149 (28.4). Anal. calcd for $C_{13}H_{23}N_4O_3P$: C, 49.68, H, 7.55 and N, 17.82. Found: C, 49.72, H, 7.52 and N, 17.54.

4e: Oil; purified by column chromatography ($CHCl_3$–Acetone, 4:1 v/v) (60%); δ_H 1.32 (6H, t, J_{HH} 7.0 Hz), 2.22 (2H, quint., J_{HH} 6.1 and 9.1 Hz), 2.31 (3H, d, J_{HP} 4.4 Hz), 2.62 (2H, br d, J_{HH} 5.8 Hz), 2.86 (2H, d, J_{HP} 23.6 Hz), 4.09 (4H, dq, J_{HH} 7.2 and J_{HP} 11.1 Hz) and 4.49 (2H, t, J_{HH} 6.1 Hz); δ_C 16.4 (d, J_{CP}

6.0 Hz), 18.1 (d, J_{CP} 2.4 Hz), 25.8 (s), 34.7 (d, J_{CP} 137.2 Hz), 35.0 (s), 48.4 (s), 62.2 (d, J_{CP} 7.2 Hz), 119.9 (d, J_{CP} 12.7 Hz), 137.5 (d, J_{CP} 12.4 Hz) and 150.1 (d, J_{CP} 3.9 Hz); δ_P 25.9; ν_{max}/cm^{-1} 1250 (P=O) and 1551 (C=N); m/z 300 (M^+, 55.0), 163 (100) and 135 (68.0). Anal. Calcd for $C_{12}H_{21}N_4O_3P$: C, 48.00, H, 7.05 and N, 18.66. Found: C, 47.50, H, 7.15 and N, 18.20.

4f: Oil; purified by column chromatography ($CHCl_3$-Acetone, 4:1 v/v) (50%); δ_H 1.22–1.48 (9H, m), 2.28 (3H, d, J_{HP} 4.0 Hz), 2.29–2.53 (4H, m), 3.39 (1H, dq, J_{HH} 7.1, 14.3 and J_{HP} 23.8 Hz), 4.02–4.20 (4H, m) and 4.43 and 4.50 (2H, m, J_{HH} 7.0 and 14.0 Hz); δ_C 12.8 (d, J_{CP} 6.2 Hz), 16.5 (d, J_{CP} 5.3 Hz), 17.1 (s), 27.0 (s), 28.6 (s), 36.1 (d, J_{CP} 139.1), 47.4 (s), 62.1 and 62.3 (two d, J_{CP} 7.5 Hz), 120.7 (d, J_{CP} 14.3 Hz), 135.7 (s), 143.3 (d, J_{CP} 8.2 Hz) and 150.2 (s); δ_P 29.1; ν_{max}/cm^{-1} 1245 (P=O) and 1553 (C=N); m/z 314 (M^+, 21.6), 177 (100), 149 (54.9) and 148 (19.6). Anal. calcd for $C_{13}H_{23}N_4O_3P$: C, 49.68, H, 7.38 and N, 17.82. Found: C, 49.58, H, 7.55 and N, 17.39.

4g: Oil; purified by column chromatography ($CHCl_3$-EtOAc, 2:3 v/v) (65%); δ_H 1.00 and 1.02 (3H, two d, J^a_{HH} 5.6 and J^b_{HH} 5.9 Hz), 1.11 (3H, t, J_{HH} 7.1 Hz), 1.26 (3H, t, J_{HH} 7.1 Hz), 2.21–2.90 (3H, m), 3.78–4.28 (5H, m), 4.24 (1H, dd, J_{HH} 8.3 and 14.1 Hz), 4.54 (1H, m), 7.06 (1H, d, J_{HP} 3.4 Hz) and 7.23–7.50 (5H, m); δ_C 16.2 and 16.4 (two d, J^a_{CP} 5.1 and J^b_{CP} 6.6 Hz), 18.0 and 18.7 (two s), 28.1 and 29.1 (two s), 41.2 and 41.4 (two s), 54.4 and 54.6 (two s), 54.8 and 54.9 (two d, J^a_{CP} and J^b_{CP} 138.2 Hz), 62.6 and 63.1 (two d, J^a_{CP} and J^b_{CP} 6.5 Hz) 112.7 and 112.9 (two s), 128.0 (s), 128.9 (s), 129.7 (s) and 150.1 (d, J_{CP} 3.0 Hz); δ^a_P 23.3 and δ^b_P 23.4; ν_{max}/cm^{-1} 1255 (P=O) and 1554 (C=N); m/z 376 (M^+, 100), 239 (47.9), 177 (43.2) and 91 (24.9). Anal. calcd for $C_{18}H_{25}N_4O_3P$: C, 57.44, H, 6.69 and N, 14.89. Found: C, 56.99, H, 6.60 and N, 14.75.

Reaction of substrates 1 with azidotrimethylsilane/iodine/pyridine mixture. General procedure.[8] TMS − N_3 (2 mol equiv.) was added dropwise under nitrogen to a stirred solution of **1** (1 mol equiv.) in dry dichloromethane (2.5 ml per mmol of **1**) at 0°C. The mixture was stirred at this temperature for 2 h and then treated with a solution of iodine (2 mol equiv) in dichloromethane (2.5 ml per mmol of **1**) and pyridine (2.5 ml per mmol of **1**). The mixture was stirred at room temperature for 24 h and then diluted with ether. The organic layer was washed with 10% HCl, sat. $NaHCO_3$, 10% $Na_2S_2O_3$ and brine. The organic phase was dried ($MgSO_4$), filtered and evaporated. The following products were prepared:

Diethyl (2-iodo-3-oxocyclohex-1-enyl)methylphosphonate **5a**. Oil; purified by column chromatography ($CHCl_3$-Acetone, 3:1 v/v) (50%); δ_H 1.32 (6H, t, J_{HH} 7.1 Hz), 1.97 (2H, quint., J_{HH} 6.1 and 9.6 Hz), 2.61 (2H, t, J_{HH} 6.8 Hz), 2.71 (2H, q, J_{HH} 5.3 and 10.3 Hz), 3.22 (2H, d, J_{HP} 24.4 Hz) and 4.13 (4H, dq, J_{HH} 7.1 and J_{HP} 11.1 Hz); δ_C 16.4 (d, J_{CP} 5.5 Hz), 22.1 (s), 33.1 (s), 36.4 (s), 43.7 (d,

J_{CP} 133.9 Hz), 62.6 (d, J_{CP} 6.6 Hz), 110.3 (d, J_{CP} 6.7 Hz), 160.6 (d, J_{CP} 10.7 Hz) and 192.1 (s); δ_P 22.9; ν_{max}/cm^{-1} 1252 (P═O) and 1680 (C═O); m/z 374 (0.4), 373 (3.6), 372 (M^+, 12.2), 245 (100), 217 (30.1), 189 (100), 107 (78.5), 80 (7.8) and 79 (80.3). Anal. calcd for $C_{11}H_{18}IO_4P$: C, 37.52 and H, 4.72. found: C, 37.46 and H, 4.91.

Diethyl (2-iodo-3-oxo-5-methylcyclohex-1-enyl)methylphosphonate **5b**. Oil; purified by column chromatography ($CHCl_3$-EtOAc, 4:1 v/v) (44%); δ_H 1.05 (3H, d, J_{HH} 6.1 Hz), 1.31 (6H, t, J_{HH} 7.1 Hz), 2.18–2.41 (3H, m), 2.67–2.84 (2H, m), 3.21 (2H, d, J_{HP} 24.5 Hz) and 14.06–14.18 (4H, m); δ_C 16.4 (d, J_{CP} 5.3 Hz), 20.2 (s), 29.5 (s), 41.1 (s), 43.6 (d, J_{CP} 133.3 Hz), 44.3 (s), 44.5 (s), 62.6 (d, J_{CP} 7.0 Hz), 135.7 (s) and 191.0 (s); δ_P 22.8; ν_{max}/cm^{-1} 1256 (P═O) and 1681 (C═O); m/z 386 (M^+, 6.9), 259 (77.3), 203 (100) and 121 (88.4). Anal. calcd for $C_{12}H_{20}IO_4P$: C, 39.21 and H, 5.06. Found: C, 38.96 and H, 5.30.

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