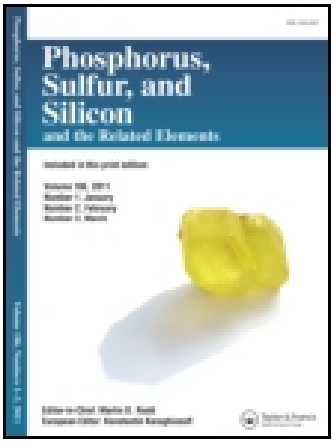

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

NEBER REARRANGEMENT OF O-MESYLOXIME DERIVATIVES OF THE RING AND SIDE CHAIN SUBSTITUTED 3-PHOSPHONOMETHYLCYCLOHEXENONES

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Published online: 04 Oct 2006.

To cite this article: Malose J. Mphahlele & Tomasz A. Modro (1997) NEBER REARRANGEMENT OF O-MESYLOXIME DERIVATIVES OF THE RING AND SIDE CHAIN SUBSTITUTED 3-PHOSPHONOMETHYLCYCLOHEXENONES, Phosphorus, Sulfur, and Silicon and the Related Elements, 127:1, 131-142, DOI: 10.1080/10426509708040503

To link to this article: http://dx.doi.org/10.1080/10426509708040503

Phosphorus, Sulphur, and Silicon, 1997, Vol. 127, pp. 131–142
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NEBER REARRANGEMENT OF O-MESYLOXIME DERIV ATIVES OF THE RING AND SIDE CHAIN SUBSTITUTED 3-PHOSPHONOMETHYLCYCLOHEXENONES

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(Received 4 March 1997; In final form 1 April 1997)

The O-mesyloxime derivatives of the ring and side chain substituted 3-phosphonomethylcyclohexenones undergo basic aluminum oxide—promoted Neber rearrangement to afford the corresponding vinyl aminocyclohexenonealkylphosphonates, regioselectively. No products resulting from the expected Beckmann rearrangement were detected.

Keywords: 3-Phosphonoalkylcyclohexenone oxime derivatives; Neber rearrangement; vinylic aminocyclohexenonealkylphosphonates

INTRODUCTION

Nitrogen and phosphorus are widely distributed in molecules of biochemical importance and are known to be associated with biological activity.[1] Antibacterial, antiviral, pesticidal, insecticidal and herbicidal activities associated with some aminophosphonic acids have been found to be caused by the combination of the amino group and the phosphonic acid moiety in those systems.[2] Applications of these compounds in pharmaceutical and agrochemical industries has led to an increased interest in the synthesis of nitrogen containing phosphonic acid derivatives with increased potency.[3] Continued interest in modified nitrogen containing phosphonic acid derivatives lies in the potential changes in bi-

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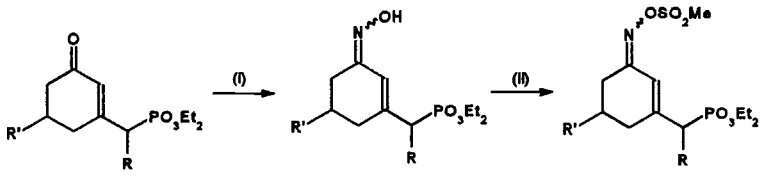
ological activities caused by such structural modifications. We have recently synthesized a series of tetrazolo derivatives of the ring and side chain substituted 3-phosphonomethylcyclohexenones[4] with the aim of screening these compounds for potential biological activity and to study the structure-activity relationship. As part of our continued interest on the synthetic applications of the 3-phosphonoalkylcycloalkenones,[4,5] in this work we have investigated the introduction of the amino group into the cyclohexenone framework starting from the oxime derivatives. The aim of this work was to establish a general route to hitherto unknown vinylic aminophosphonic acid derivatives of cyclohexenone system and to shed some light on the mechanism of their formation. The 3-phosphonomethylcyclohexenone derivatives used as starting materials were synthesized as described in our previous communications from lithioalkylphosphonates and β-chloro- or β-methoxycyclohexenones.[4–6] Alternatively these substrates could be prepared by the Wittig-Horner reaction of the bis β-ketophosphonates[7] or by the oxidation of alcohols obtained in the carbonyl addition of lithioalkylphosphonates to cycloalkenones.[8]

RESULTS AND DISCUSSION

In this work substrates **1** were converted to the previously undescribed oxime derivatives **2** following the literature method[9] (Scheme 1). The oximes **2** were isolated as mixtures of the *anti* and *syn* isomers as determined by ^{1}H NMR spectroscopy. The assignments of the *syn* and *anti* configurations are based on the influence of the hydroxyl group on the chemical shift of the olefinic proton [*ca.* δ_H 6.01 ppm (*anti*) and δ_H 6.70 ppm (*syn*)], and also by comparison with the literature assignment for the non-phosphorus cyclohexenone oxime derivatives.[10a,b] A significant downfield shift of the vinylic proton signal in the *syn* isomer is taken as a consequence of the deshielding effect of the neighbouring hydroxyl group. The proportions of the isomers were estimated from the ^{31}P NMR peak integrals because of the differences in the chemical shift values (Δ δ_P 0.35 ppm), and in all cases the *anti* isomer was found to predominate. The oxime derivatives **2** were converted to the corresponding mixture of *syn* and *anti* (predominant) O-mesyloxime derivatives **3** following the literature procedure[9] (Scheme 1).

The participation of the α,β-unsaturated cyclohexenone systems in the Beckmann rearrangement is well documented.[9–11] However, the reaction conditions often used to induce the Beckmann rearrangement involve[12] or generate[10b] strongly acidic media. The sensitivity of some oximes to strongly acidic media and the difficulties involved in the isolation of the product(s) under such con-



1 2 3

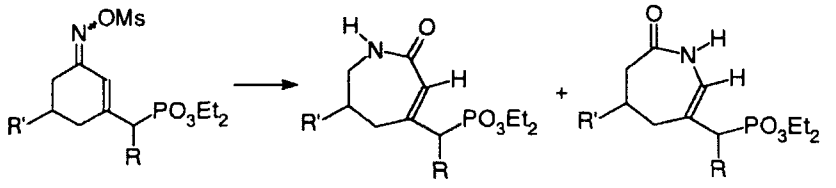
2 / 3	R	R'	*Syn**	*Anti**
a	H	H	minor	major
b	Me	H	minor	major
c	H	Me	minor	major

Reagents: (i) NH_2OH. HCl, $NaOAc.3H_2O$, EtOH; (ii) CH_3SO_2Cl, NEt_3, THF

*The prefix *syn* or *anti* imply that OH (or OSO_2CH_3) and C-C double bond are on the same or the opposite side of the C-N double bond, respectively.

ditions often complicate the application of this reaction. However, it has been established that the convertion of the oximes to the corresponding O-mesylate[9] or O-tosylate[13] derivatives promote the Beckmann rearrangement under relatively mild basic conditions. For example, the O-mesyloxime derivative of 3-ethoxycyclohex-2-en-1-one generated *in situ* from the *syn* oxime was reported to afford the ring enlarged amide product *via* the methylene (6-CH_2) shift when the reaction mixture was treated with water at room temperature.[9] Our attempts to induce the Beckmann rearrangement of the *in situ* generated O-mesyloximes of **1** in analogy with the oxime of 3-ethoxycyclohexenone led to the isolation of products **3** as mixtures of *syn* and *anti* (predominant) isomers (Scheme 1).

Among the many procedures developed to induce the Beckmann rearrangement of cyclic oximes is the basic Al_2O_3—promoted rearrangement of the oxime sulfonates.[13] At the outset of this investigation and in analogy with the latter reaction we had expected to obtain either the ring—expanded α,β-unsaturated lactam **4a** or its enamine isomer **4b** *via* Al_2O_3—promoted Beckmann rearrangement of **3** (Scheme 2). However, application of this method to the O-mesyloxime **3a** led to the isolation of a product consisting of the cyclohexenonealkylphosphonate moiety, but lacking in the ^1H NMR spectrum the olefinic proton signal

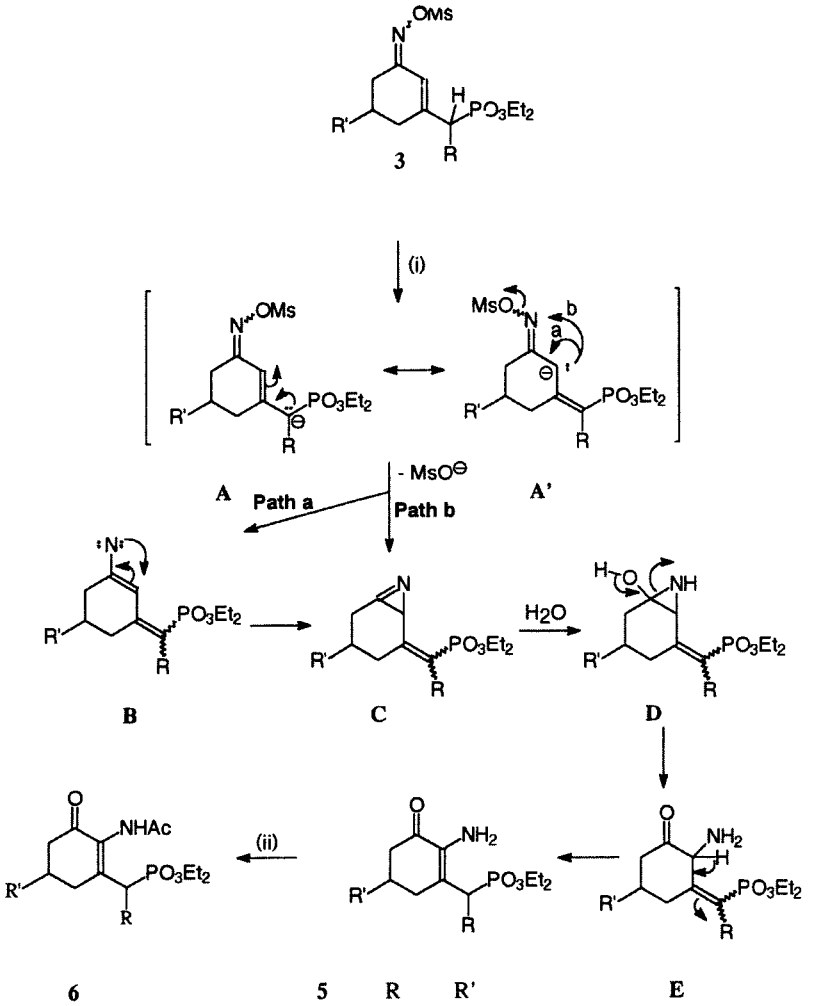


3 4a 4b

OMs = OSO_2CH_3

and not containing the OSO_2Me signal thus distinguishing itself from the corresponding precursors **1a**, **2a** and **3a**. The compound was found by mass spectroscopic and elemental analyses to contain nitrogen, and its ^{13}C NMR spectral data (proton coupled and decoupled) revealed the presence of a non-proton bearing vinylic C-2 and a carbonyl carbon resonance at *ca.* δc 194.5 ppm thus ruling out the possibility of the corresponding alkenone **1a** and the oxime **2a** precursors. The possibility of the formation of the ring-expanded amide(s) **4** was ruled out by the absence of the lactam carbonyl carbon resonance in the ^{13}C NMR spectrum. The structure of the product was unambigously determined (using a combination of ^1H NMR, ^{13}C NMR, IR and mass spectroscopic techniques and by elemental analysis) as that of the vinylic aminocyclohexenonemethylphosphonate **5a** formed *via* the Neber rearrangement[14–16] of **3a** (Scheme 3).

The above observation was then extended to the O-mesyloxime derivatives **3b** and **c** to establish the generality of this reaction. In all cases the corresponding vinyl aminocyclohexenone products **5** were formed regioselectively. The presence of a vinylic amino group was also confirmed by acetylation of product **5b** to the corresponding vinylic acetamide derivative **6** using acetic anhydride in pyridine. The formation of the vinyl aminocyclohexenone systems **5** *via* the Neber rearrangement can be explained by the mechanism shown in Scheme 3. The reaction presumably begins with the abstraction of the acidic α-hydrogen (α relative to phosphorus) by aluminum oxide to afford a resonance stabilized carbanion **A**. The ease of abstraction of this proton is probably a consequence of the increased activation by the adjacent phosphonate moiety and by the conjugated framework. We propose two plausible routes leading to the formation of the azirine intermediate[14] **C** from the carbanion intermediate **A**. One possible route may involve elimination of the mesylate anion from the resonance hybrid **A'** to generate a nitrene intermediate **B**. On the other hand, elimination of the mesylate anion may occur by a concerted mechanism involving its displacement



Reagents: (i) Al_2O_3, C_6H_6, then MeOH; (ii) Ac_2O, Pyridine

by the lone pair of electrons leading directly to the azirine **C**. The first possibility involving the formation of the nitrene **B** is consistent with the mechanism proposed previously by House and Berkowitz for the Neber rearrangement of the open chain oxime tosylates.[14] On the other hand, the direct formation of **C** from **A** will be consistent with the mechanisms proposed for Neber rearrangement of oxime tosylates[15] and dimethylhydrazone methyliodides[16] of the 3-arylcyclohexenones and 2-phenylcyclohexanones, respectively. Further reaction of the azirine **C** with methanol or moisture would then afford the aziridine intermediate **D** which upon ring opening and subsequent prototropic isomerization yields the conjugated vinyl aminocyclohexenone product **5**. We believe the mechanism shown in Scheme 3 accounts for the formation of Neber products **5** in an attempted experiment of Beckmann rearrangement of **3**. To our knowledge, the Neber rearrangement conditions described in literature typically involve the use of strong alkoxide bases and the reaction occurs under reflux.[14–16] In our opinion, application of these conditions of thermodynamic control to systems **3** would probably lead to a mixture of aminocyclohexenone derivatives resulting from the initial abstractions of protons α to C=O, to C=C and to phosphorus. Mikolajczyk and Mikina[7] carried out a detailed study of hydrogen-deuterium exchange on systems **1** and found that under conditions of thermodynamic control (MeONa in MeOD), all methylene protons adjacent to phosphorus, C=O and C=C are exchanged. To our knowledge, the above observation of the effect of Al_2O_3 represents the first example of the synthesis of vinylic α-aminoketones from α,β-unsaturated carbonyl compounds under mild conditions, and is probably the first example of Al_2O_3—promoted Neber rearrangement.

The synthetic application and the scope of the Neber rearrangement described in this paper are currently under investigation in our laboratories. The oxime derivatives **2** and **3** and the vinylic aminophosphonates **5** prepared in this work are suitable systems for further transformation and for biological activity studies. Vinylic α-aminocycloalkenones, for example, can serve as the building blocks for heterocycles such as the imidazoles, oxazoles and pyrazines with potential pharmaceutical applications.

EXPERIMENTAL

Solvents and commercially available reagents were purified by conventional methods before use. Melting point for compound **2a** was recorded on a Gallenkamp apparatus and is uncorrected. 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 the ionization potential of 70 eV . Unless otherwise stated the IR spectra were recorded as solutions in CCl_4 on a Bomem Inc. Michelson 100 spectrometer. 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. Elemental analyses (C/H/N) were carried out at the Department of Chemistry, University of Cape Town. Compounds **1a–1d** were obtained as described before.[5,6] Basic aluminum oxide (Brockmann, activity grade 1) was purchased from Merck.

Preparation of Oxime Derivatives 2- General Procedure[9]

A stirred mixture of **1** (4.9 mmol), hydroxylamine hydrochloride (9.8 mmol) and sodium acetate trihydrate (9.8 mmol) in ethanol (10 ml per mmol of **1**) was refluxed for 1.5 h and allowed to cool. The mixture was filtered and evaporated and the residue was taken up in ether and then filtered. The ethereal solution was washed with water, dried (Na_2SO_4) and evaporated. The product was purified by column chromatography (EtOAc) to afford a mixture of *syn* and *anti* oximes **2**.

Diethyl (3-oximinocyclohex-1-enyl)methylphosphonate 2a

solid, (85%), m.p. 83–85°C; δ_H 1.29 (6H, t, J_{HH} 7.1 Hz, *anti*), 1.30 (6H, t, J_{HH} 7.1 Hz, *syn*), 1.76 (2H, quintet, J_{HH} 6.3 and 9.6 Hz, *anti*), 1.81 (2H, quintet, J_{HH} 6.4 and 9.6 Hz, *syn*), 2.29 (2H, t, J_{HH} 6.3 Hz, *anti*), 2.35 (2H, t, J_{HH} 6.2 Hz, *syn*), 2.54 (2H, t, J_{HH} 6.6 Hz), 2.66 (2H, d, J_{HP} 23.0 Hz, *anti*), 2.69 (2H, d, J_{HP} 23.2 Hz, *syn*), 4.08 (4H, dq, J_{HH} 7.1 and J_{HP} 11.1 Hz), 6.02 (1H, d, $^4J_{HP}$ 5.2 Hz, *anti*) and 6.74 (1H, d, $^4J_{HP}$ 5.0 Hz, *syn*); δ_C 16.3 (d, J_{CP} 6.0 Hz), 21.0 (s, *anti*), 21.4 (s, *anti*), 22.4 (s, *syn*), 27.5 (s, *syn*), 29.7 (s, *anti*), 30.8 (s, *syn*), 35.7 (d, J_{CP} 137.0 Hz, *anti*), 36.1 (d, J_{CP} 136.4 Hz, *syn*), 62.1 (d, J_{CP} 6.6 Hz, *anti*), 62.2 (d, J_{CP} 7.6 Hz, *syn*), 116.8 (d, J_{CP} 12.7 Hz, *syn*), 123.8 (d, J_{CP} 13.0 Hz, *anti*), 138.8 (d, J_{CP} 12.5 Hz, *anti*), 142.8 (d, J_{CP} 12.3 Hz, *syn*), 153.0 (d, J_{CP} 4.6 Hz, *syn*) and 156.2 (d, J_{CP} 4.8 Hz, *anti*); δ_P 25.9 (*syn*, 27.0%) and 26.2 (*anti*, 73.0%); ν_{max}/cm^{-1} ($CHCl_3$) 1299.8 (P=O), 1574.9 (C=N), 3267.1 and 3585.7 (OH); m/z 244 ($M^+ - 17$, 5.2), 216 (20.3), 134 (100) and 120 (23.3). Anal. calcd. for $C_{11}H_{20}NO_4P$ (261.26): C, 50.57, H, 7.72 and N, 5.36%. Found: C, 50.96, H, 7.83 and N, 5.43%.

Diethyl 1-(3-oximinocyclohex-1-enyl)ethylphosphonate 2b

oil; (72%); δ_H 1.28 (6H, t, J_{HH} 7.1 Hz), 1.37 (3H, dd, J_{HH} 7.5 and J_{HP} 18.2 Hz), 1.77 (2H, m), 2.29 (2H, m), 2.45 – 2.80 (3H, m), 2.25 – 2.38 (2H, m), 4.07 (4H, dq, J_{HH} 7.1 and J_{HP} 11.1 Hz), 6.05 (1H, d, $^4J_{HP}$ 5.1 Hz, *anti*) and 6.78 (1H, d, $^4J_{HP}$ 5.1 Hz, *syn*); δ_C 13.2 (d, J_{CP} 6.0 Hz, *anti*), 13.4 (d, J_{CP} 6.3 Hz, *syn*), 16.4 (d, J_{CP} 5.9 Hz, *anti*), 21.2 (s, *anti*), 21.9 (s, *anti*), 22.5 (s, *syn*), 28.0 (s, *syn*), 28.2 (s, *anti*), 29.2 (s, *syn*), 40.0 (d, J_{CP} 136.7 Hz, *anti*), 40.5 (d, J_{CP} 136.3 Hz, *syn*), 62.2 (d, J_{CP} 6.5 Hz, *anti*), 62.3 (d, J_{CP} 7.0 Hz, *syn*), 115.80 (d, J_{CP} 12.5 Hz, *syn*), 122.4 (d, J_{CP} 12.7 Hz, *anti*), 135.7 (d, J_{CP} 12.5 Hz, *anti*), 144.9 (d, J_{CP} 9.7 Hz, *syn*), 150.1 (d, J_{CP} 4.6 Hz, *syn*) and 156.7 (d, J_{CP} 4.9 Hz, *anti*); δ_P 28.8 (*syn*, 23.3%) and 29.1 (*anti*, 77.7%); ν_{max}/cm^{-1} 1237.4 (P=O), 1552.3 (C=N), 3275.2 and 3599.3 (OH); m/z 275 (M^+, 6.4), 258 (55.1), 202 (25.7) and 120 (100). Anal. calcd. for $C_{12}H_{22}NO_4P$ (275.28): C, 52.36, H, 8.05 and N, 5.09%. Found: C, 51.58, H, 8.11 and N, 5.19%.

Diethyl (5-methyl-3-oximinocyclohex-1-enyl)methylphosphonate 2c

oil; (73%); δ_H 1.00 (3H, d, J_{HH} 6.0 Hz, *syn*), 1.03 (3H, d, J_{HH} 6.0 Hz, *anti*), 1.24 (6H, t, J_{HH} 7.1 Hz, *syn*), 1.30 (3H, dt, J_{HH} 2.6 and 7.1 Hz, *anti*), 1.78 – 2.10 (6H, m), 2.29 – 2.43 (2H, m, *syn* and *anti*), 2.65 (2H, d, J_{HP} 23.0 Hz, *anti*), 2.69 (2H, d, J_{HP} 23.3 Hz, *syn*), 2.98 (2H, br d, J_{HH} 13.5 Hz, *syn* and *anti*), 4.09 (4H, dq, J_{HH} 2.0, 7.0 and J_{HP} 11.0 Hz), 6.01 (1H, d, $^4J_{HP}$ 5.5 Hz, *anti*), and 6.73 (1H, d, $^4J_{HP}$ 5.0 Hz, *syn*); δ_C 16.3 (d, J_{CP} 6.0 Hz), 20.8 (s, *syn*), 21.1 (s, *anti*), 27.9 (s, *anti*), 29.2 (s, *syn*), 29.5 (s, *anti*), 35.0 (s, *syn*), 35.6 (d, J_{CP} 137.3 Hz, *anti*), 35.9 (d, J_{CP} 136.5 Hz, *syn*), 38.0 (s, *anti*), 39.1 (s, *syn*), 62.2 (d, J_{CP} 6.3 Hz), 116.5 (d, J_{CP} 12.5 Hz, *syn*), 123.5 (d, J_{CP} 12.8 Hz, *anti*), 138.3 (d, J_{CP} 12.3 Hz, *syn*), 142.2 (d, J_{CP} 11.6 Hz, *syn*), 153.3 (d, J_{CP} 4.6 Hz, *syn*) and 156.6 (d, J_{CP} 4.8 Hz, *anti*), δ_P 25.7 (*syn*, 24.0%) and 26.1 (*anti*, 76.0%); ν_{max}/cm^{-1} 1237.7 (P=O), 1552.4 (C=N), 3274.4 and 3601.1 (OH); m/z 275 (M^+, 23.7), 258 (60.3), 230 (38.0), 202 (100), 120 (95.0) and 29 (44.3). Anal. calcd. for $C_{12}H_{22}NO_4P$ (275.28): C, 52.36, H, 8.05 and N, 5.09%. Found: C, 52.06, H, 8.21 and N, 5.36%.

Preparation of O-mesyloximes 3-General Procedure[9]

A stirred mixture of oxime **2** (1.73 mmol) and triethylamine (2.08 mmol) in THF (8 ml per mmol of **2**) at 0–5° C was treated dropwise with methanesulfonylchloride (2.08 mmol). After 1h at 5° C the mixture was quenched with water (10 ml per mmol of **2**) and then stirred for additional 2h at room tem-

perature. The mixture was extracted with chloroform and the combined organic layers were washed with water and then dried (Na_2SO_4). The solvent was evaporated and the residue was purified by column chromatography to afford a mixture of *syn* and *anti* O-mesyloxime derivatives **3**.

3a: oil; purified by column chromatography (EtOAc—$CHCl_3$, 3:1 v/v) (85%); δ_H 1.24 (6H, t, J_{HH} 11.0 Hz, *syn*), 1.31 (6H, t, J_{HH} 7.1 Hz, *anti*), 1.80 (2H, quintet, J_{HH} 6.3 and 9.6 Hz, *anti*), 1.89 (2H, quintet, J_{HH} 6.4 Hz and 9.7 Hz, *syn*), 2.35 (2H, m, J_{HH} 5.1 and 10.8 Hz, *anti*), 2.42 (2H, m, J_{HH} 5.0 and 10.8 Hz, *syn*), 2.63 (2H, t, J_{HH} 6.7 Hz), 2.71 (2H, d, J_{HP} 23.4 Hz), 3.12 (3H, s), 4.10 (4H, dq, J_{HH} 7.2 and J_{HP} 11.0 Hz), 6.12 (1H, d, $^4J_{HP}$ 5.0 Hz, *anti*) and 6.63 (1H, d, $^4J_{HP}$ 5.1 Hz, *syn*), δ_C 16.3 (d, J_{CP} 6.0 Hz, *anti*), 20.5 (s, *anti*), 21.8 (s, *syn*), 23.1 (s, *anti*), 27.1 (s, *syn*), 29.7 (s, *anti*), 30.8 (s, *syn*), 36.2 (d, J_{CP} 136.9 Hz, *anti*), 36.3 (s, *anti*), 36.4 (d, J_{CP} 136.3 Hz, *syn*), 62.2 (d, J_{CP} 6.6 Hz), 115.9 (d, J_{CP} 11.8 Hz, *syn*), 120.8 (d, J_{CP} 12.7 Hz, *anti*), 146.9 (d, J_{CP} 11.4 Hz, *anti*), 151.2 (s, *syn*), 163.8 (d, J_{HH} 4.5 Hz, *anti*), and 167.6 (s, *syn*); δ_P 24.3 (*syn*, 8.7%) and 24.9 (*anti*, 91.3%); ν_{max}/cm^{-1} 1184.7 and 1376.3 (SO_2), 1254.9 (P=O), and 1637.2 (C=N); m/z 261 (14.2), 245 (12.6), 109 (53.4) and 107 (100).

3b: oil; purified by column chromatography (EtOAc—$CHCl_3$, 1:2 v/v) (80%); δ_H 1.29 (6H, t, J_{HH} 7.0 Hz, *anti*), 1.36 (3H, dd, J_{HH} 7.3 and J_{HP} 18.1 Hz, *anti*), 1.37 (3H, dd, J_{HH} 7.2 and J_{HP} 18.1 Hz, *syn*), 1.78 (2H, quintet, J_{HH} 6.3 and 9.8 Hz, *anti*), 1.81 (2H, quintet, J_{HH} 6.3 and 9.6 Hz, *syn*), 2.23 – 2.45 (4H, m, *syn* and *anti*), 2.63 (2H, dt, J_{HH} 3.0 and 6.7 Hz), 2.67 (1H, dq, J_{HH} 7.5 and J_{HP} 24.9 Hz), 3.11 (3H, s, *syn*), 3.12 (3H, s, *anti*), 4.02 – 4.22 (4H, m), 6.14 (1H, d, $^4J_{HP}$ 5.6 Hz, *anti*) and 6.63 (1H, d, $^4J_{HP}$ 4.5 Hz, *syn*); δ_C 13.3 (d, J_{CP} 5.6 Hz), 14.9 (d, J_{CP} 6.0 Hz), 20.7 (s), 23.6 (s), 28.5 (s), 36.4 (s), 40.5 (s), 62.3 (d, J_{CP} 6.9 Hz), 119.6 (d, J_{CP} 11.5 Hz), 150.2 (d, J_{CP} 4.1 Hz) and 164.1 (s); δ_P 27.4 (*syn*, 13.2) and 28.0 (*anti*, 86.8%); ν_{max}/cm^{-1} 1184.8 and 1376.8 (SO_2), 1251.0 (P=O) and 1630.4 (C=N); m/z 259 (13.1), 123 (31.9), 122 (33.8), 121 (100) and 120 (48.0).

3c: oil; purified by column chromatography (EtOAc—$CHCl_3$, 1:2 v/v) (75%); δ_H 1.04 (3H, d, J_{HH} 6.1 Hz), 1.23 (3H, t, J_{HH} 7.1 Hz, *syn*), 1.31 (3H, t, J_{HH} 7.1 Hz, *anti*), 1.93 – 2.10 (3H, m), 2.40 (1H, dd, J_{HH} 3.4 and 17.4 Hz), 2.70 (2H, d, J_{HP} 23.3 Hz, *anti*), 3.00 (1H, d, J_{HH} 13.0 Hz), 3.10 (3H, s, *syn*), 3.12 (3H, s, *anti*), 4.09 (4H, dq, J_{HH} 7.1 and J_{HP} 11.2 Hz), 6.10 (1H, d, $^4J_{HP}$ 4.9 Hz, *anti*) and 6.20 (1H, d, $^4J_{HP}$ 5.0 Hz, *syn*); δ_C 16.3 (d, J_{CP} 6.0 Hz), 20.5 (s, *syn*), 20.7 (s, *anti*), 27.8 (s, *anti*), 29.1 (s, *syn*), 31.0 (s, *anti*), 34.9 (s, *syn*), 36.1 (d, J_{CP} 6.8 Hz, *anti*), 36.2 (d, J_{CP} 136.9 Hz, *syn*), 36.3 (s, *anti*), 36.4 (d, J_{CP} 136.3 Hz, *syn*), 62.2 (d, J_{CP} 6.6 Hz), 115.9 (d, J_{CP} 11.8 Hz, *syn*), 120.8 (d, J_{CP} 12.7 Hz, *anti*), 146.9 (d, J_{CP} 11.4 Hz, *anti*), 151.2 (s, *syn*), 163.8 (d, J_{CP} 4.5 Hz, *anti*),

and 167.6 (s, *syn*); δ_P 24.3 (*syn*, 9.0%) and 24.9 (*anti*, 91.0%); ν_{max}/cm^{-1} 1182.1 and 1375.5 (SO_2), 1255.4 (P=O) and 1640.7 (C=N); m/z 259 (9.0), 188 (28.3), 123 (26.9), 121 (100), 106 (34.2) and 79 (15.7).

Reaction of O-mesyloximes 3 with Aluminum Oxide; Preparation of 5—General Procedure

A solution of O-mesyloxime **3** (1 mmol) in benzene (1 ml) was adsorbed on a column of aluminum oxide (5 g). After 30 minutes the column was eluted with a benzene—methanol mixture (1:2 v/v) and the organic solution was evaporated. The residue was purified by column chromatography to afford the vinyl aminocyclohexenonealkylphosphonate **5**.

Diethyl (2-amino-3-oxocyclohexen-1-enyl)methylphosphonate 5a

oil; purified by column chromatography (EtOAc) (58%); δ_H 1.31 (6H, t, J_{HH} 7.1 Hz), 1.93 (2H, quintet, J_{HH} 6.4 and 9.7 Hz), 2.35–2.45 (4H, two m), 2.70 (2H, d, J_{HP} 23.6 Hz) and 4.10 (4H, dq, J_{HH} 7.0 and J_{HP} 11.1 Hz); δ_C 16.4 (d, J_{CP} 5.2 Hz), 22.3 (s), 30.7 (d, J_{CP} 2.8 Hz), 31.6 (d, J_{CP} 131.9 Hz), 36.8 (s), 62.3 (d, J_{CP} 6.6 Hz), 122.5 (d, J_{CP} 14.9 Hz), 138.4 (d, J_{CP} 9.5 Hz), and 194.6 (s); δ_P 27.3; ν_{max}/cm^{-1} 1232.2 (P=O), 1675.2 (C=O), and 3327.0 and 3420.8 (NH_2); m/z 261 (M^+, 34.9), 232 (26.1), 124 (100), 122 (60.6) and 96 (37.5). Anal. calcd. for $C_{11}H_{20}NO_4P$ (261.26): C, 50.57, H, 7.72 and N, 5.36%. Found: C, 50.12, H, 7.85 and N, 5.08%.

Diethyl 1-(2-amino-3-oxocyclohexen-1-enyl)ethylphosphonate 5b

oil; purified by column chromatography (EtOAc—Acetone, 3:1 v/v) (63%); δ_H 1.21–1.41 (9H, m), 1.76–2.02 (2H, m), 2.28–2.67 (4H, m), 3.16 (1H, dq, J_{HH} 7.3, 14.5 and J_{HP} 25.0 Hz) and 4.05–4.16 (4H, m); δ_C 11.4 (d, J_{CP} 6.3 Hz), 16.4 (d, J_{CP} 6.0 Hz), 22.3 (s), 26.4 (s), 34.9 (d, J_{CP} 138.2 Hz), 36.8 (s), 62.0 and 62.4 (two d, J_{CP} 5.0 and J_{CP} 7.5 Hz), 119.5 (d, J_{CP} 11.5 Hz) 138.0 (d, J_{CP} 10.4 Hz) and 194.9 (s); δ_P 30.1; ν_{max}/cm^{-1} 1232.2 (P=O), 1675.2 (C=O), and 3325.1 and 3420.8 (NH_2); m/z 275 (M^+, 100), 201 (21.6), 139 (64.1), 138 (95.3), 136 (62.5), 121 (53.7) and 110 (61.4). Anal. calcd. for $C_{12}H_{22}NO_4P$ (275.28): C, 52.36, H, 8.05 and N, 5.09%. Found: C, 51.90, H, 8.15 and N, 4.77%.

Diethyl (2-amino-5-methyl-3-oxocyclohex-1-enyl)methylphosphonate 5c

oil, purified by column chromatography (EtOAc) (53%); δ_H 1.02 (3H, d, J_{HH} 5.8 Hz), 1.30 (6H, dt, J_{HP} 1.9 and J_{HH} 7.1 Hz), 2.04–2.19 (3H, m), 2.35–2.84 (4H, m), 4.01 (2H, br s) and 4.03–4.15 (4H, m); δ_C 16.5 (d, J_{CP} 5.8 Hz), 21.0 (s), 29.9 (s), 31.6 (d, J_{CP} 138.3 Hz), 39.2 (d, J_{CP} 2.9 Hz), 44.9 (s), 62.3 (d, J_{CP} 12.8 Hz), 121.2 (d, J_{CP} 14.8 Hz), 138.2 (s), and 194.8 (s); δ_P 27.3; ν_{max}/cm^{-1} 1232.2 (P=O), 1677.0 (C=O), and 3324.0 and 3412.6 (NH_2); m/z 275 (M^+, 72.1), 260 (23.9), 246 (28.2), 138 (100), 137 (35.2) and 122 (40.0). Anal. calcd. for $C_{12}H_{22}NO_4P$ (275.28): C, 52.36, H, 8.05 and N, 5.09%. Found: C, 51.80, H, 8.30 and N, 5.10%.

Acetylation of the vinyl aminocyclohexenonealkylphosphonate 5b

Preparation of vinyl acetamidocyclohexenonealkylphosphonate **6b** A stirred solution of **5b** (1.1 mmol) in pyridine (5 ml per mmol of **5b**) was treated dropwise with acetic anhydride (1.2 mmol) at room temperature. After 6 h excess acetic anhydride was decomposed with ice and the product was extracted with ethyl acetate. The organic solution was washed with water, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography to afford *diethyl 1-(2-acetamido-3-oxocyclohex-1-enyl)ethylphosphonate* **6b**, oil, (EtOAc—acetone, 1:2 v/v) (60%); δ_H 1.30 (6H, dt, J_{HH} 1.6 and 7.1 Hz), 1.39 (3H, dd, J_{HH} 7.2 and J_{HP} 18.5 Hz), 1.88–2.06 (2H, m), 2.10 (3H, s), 2.41–2.64 (4H, m), 3.24 (1H, dq, J_{HH} 7.3 and J_{HP} 24.8 Hz), 4.08 (4H, dq, J_{HH} 7.1 and J_{HP} 11.1 Hz) and 7.40 (1H, br s); δ_C 11.7 (d, J_{CP} 6.8 Hz), 16.4 (d, J_{CP} 5.5 Hz), 21.9 (s), 22.0 (s), 27.1 (s), 36.4 (d, J_{CP} 136.2 Hz), 37.3 (s), 62.5 and 62.4 (two d, J_{CP} 7.1 and 8.0 Hz), 131.7 (d, J_{CP} 11.5 Hz), 151.4 (d, J_{CP} 8.9 Hz), 169.3 (s) and 194.0 (s); δ_P 29.2, ν_{max}/cm^{-1} ($CHCl_3$) 1259.7 (P=O), 1627.3 (C=O), 1682.4 (C=O), and 3428.9 and 3619.8 (NH); m/z 317 (M^+, 14.7), 275 (100), 138 (94.6), 136 (86.5) and 43 (37.5). Anal. calcd. For $C_{14}H_{24}NO_5P$ (317.12): C, 52.95, H, 7.62, N, 4.41%. Found: C, 52.36, H, 7.75, N, 4.28%.

Acknowledgements

Financial support from the University of Pretoria and the Foundation for Research Development is gratefully acknowledged.

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