Domino Ring-Closing Enyne-Metathesis–Cross-Metathesis Approach to 1-Phosphonylated Benzazepines

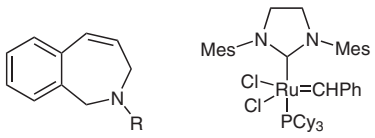
Nicolai Dieltiens, Christian V. Stevens*

Research Group SynBioc, Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, 9000 Ghent, Belgium
Fax +32(9)2646243; E-mail: chris.stevens@UGent.be
Received 8 August 2006

Abstract: A short approach was developed towards phosphonylated benzazepines. Aminophosphonates containing an 'yne' and an 'ene' moiety were synthesised via phosphonylation of the corresponding imines. The key step in the reaction sequence is a domino enyne-metathesis–cross-metathesis.

Key words: domino reactions, enynes, fused-ring systems, metathesis, phosphorus

Benzo-fused seven-membered-ring systems have received a lot of attention over the years because of their ubiquitous appearance in natural products and modern pharmaceuticals.[1] 2,3-Dihydro-1*H*-benzo[*c*]azepines **1** have previously been prepared by electrocyclisation reactions[2] and ring-closing metathesis[3–5] using the second-generation Grubbs' catalyst **2** (Figure 1).[6]

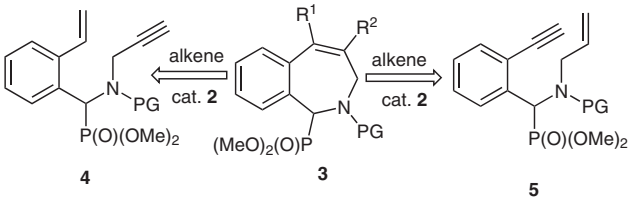


1 2

Figure 1

Only a few papers, however, have been published in the field of seven-membered aza-heterocyclic phosphonates,[7] although some of these compounds show interesting biological properties, such as bone-resorption inhibitory activity.[8] To the best of our knowledge, the ring expansion of nitro-substituted naphthalenes upon reaction with dimethyl phosphite under basic conditions is the only synthesis of 1*H*-2-benzazepine-1-ylphosphonates reported in the literature.[9] During our ongoing program to evaluate ring-closing metathesis for the synthesis of aza-heterocyclic phosphonates,[10] we became interested in ring-closing enyne metathesis for the construction of new 1*H*-2-benzazepine-1-ylphosphonates.[11] Not only is ring-closing enyne metathesis more atom-efficient than normal ring-closing metathesis, it also provides the possibility of immediately functionalising the intermediate diene by cross-metathesis with an alkene.[12]

Scheme 1 shows the retrosynthetic analysis of the envisaged structures **3**. Depending on the position of the alkene and alkyne moieties, an alkenyl group (R^1 or R^2) is introduced at a different position. Starting from aminophosphonates **4** leads to derivatives **3** with a substituent at the 4-position (R^1 = H) whereas starting from compounds **5** should lead to benzazepines bearing a substituent at the 5-position (R^2 = H). The main advantage of this strategy is that the synthesis of the two pivotal compounds **4** and **5** provides access to a wide variety of benzazepines **3**. Aminophosphonate **4** was synthesised in four steps starting from α-bromobenzaldehyde **6** (Scheme 2). In the first step the aldehyde was converted into an alkene via a Wittig reaction in good yield. Compound **7** was treated with 1.05 equivalents of BuLi at –78 °C and after stirring for one hour 1.1 equivalents of DMF was added. Aldehyde **8** was converted into the imine upon treatment with propargylamine and $MgSO_4$ in CH_2Cl_2, subsequently phosphonylated using dimethylphosphite in MeOH and isolated using an acid-base extraction.[13] The N-atom was protected using an appropriate electrophile and K_2CO_3 as a solid base in refluxing acetone.

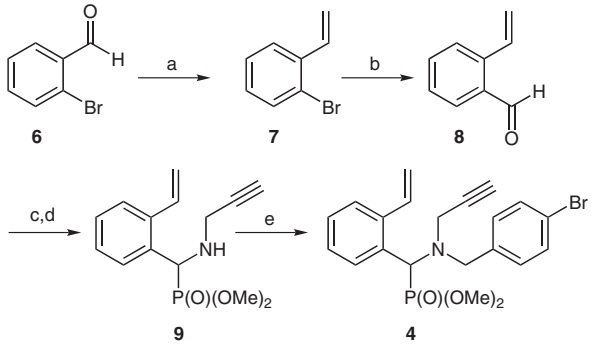


Scheme 1 Retrosynthetic analysis of 1*H*-2-benzazepine-1-ylphosphonates **3**

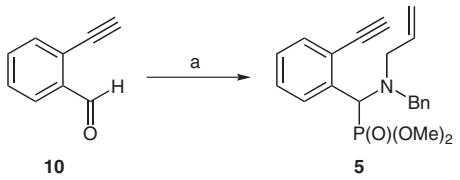
The synthesis of the second building block, aminophosphonate **5**, started from the commercially available aldehyde **10** (Scheme 3). It was observed, however, that treating this aldehyde with allylamine and $MgSO_4$ in CH_2Cl_2, in order to synthesise the imine, resulted in the formation of a complex reaction mixture. Therefore, aldehyde **10** was converted into the desired aminophosphonate by a one-pot three-component coupling mediated by $LiClO_4$ and was further purified by column chromatography.[14]

Upon evaluation of the enyne-metathesis–cross-metathesis sequence between **5** and five equivalents of styrene (Scheme 4) by ^{31}P NMR spectroscopy, it was found that after 30 minutes the starting compound was completely

SYNLETT 2006, No. 17, pp 2771–2776
Advanced online publication: 09.10.2006
DOI: 10.1055/s-2006-950262; Art ID: G26506ST



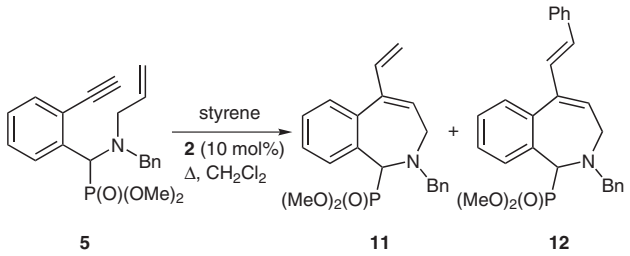
Scheme 2 *Reagents and conditions*: (a) Ph_3PCH_3Br, *t*-BuOK, THF, 24 h (**6**, 91%); (b) BuLi, DMF, THF, –78 °C (**7**, 73%); (c) propargylamine, $MgSO_4$, CH_2Cl_2; (d) $HP(O)(OMe)_2$, MeOH (**9**, 82%); (e) *p*-bromobenzylbromide, K_2CO_3, acetone (**4**, 69%).



Scheme 3 *Reagents and conditions*: (a) $LiClO_4$, allylbenzylamine, $P(OMe)_3$, Et_2O (**5**, 68%).

consumed. At this point, most of the product present was compound **11** (**11**/**12** = 60:40). Following the course of the reaction further revealed that conversion of **11** to **12** proceeds very slowly. The addition of an extra five equivalents of styrene, however, had a very positive effect on the conversion rate (Figure 2). This can be explained by looking at the complete reaction cycle of this conversion (Scheme 5). In the first step vinylic carbene **13** is formed. When working under Mori's conditions,[15] this carbene would react with ethylene to produce **11**.[16] In the absence of ethylene, however, **13** can react with the alkene in two different ways: with the R group pointing away from the metallic centre (**14**) or with the R group towards the metallic centre (**15**).

In the first case the desired end product **12** is produced after the cycloreversion. In the second case the unwanted



Scheme 4 Conversion of aminophosphonate **5** into **11** and **12**

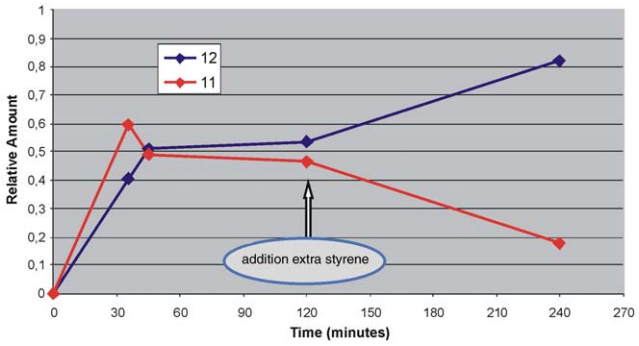


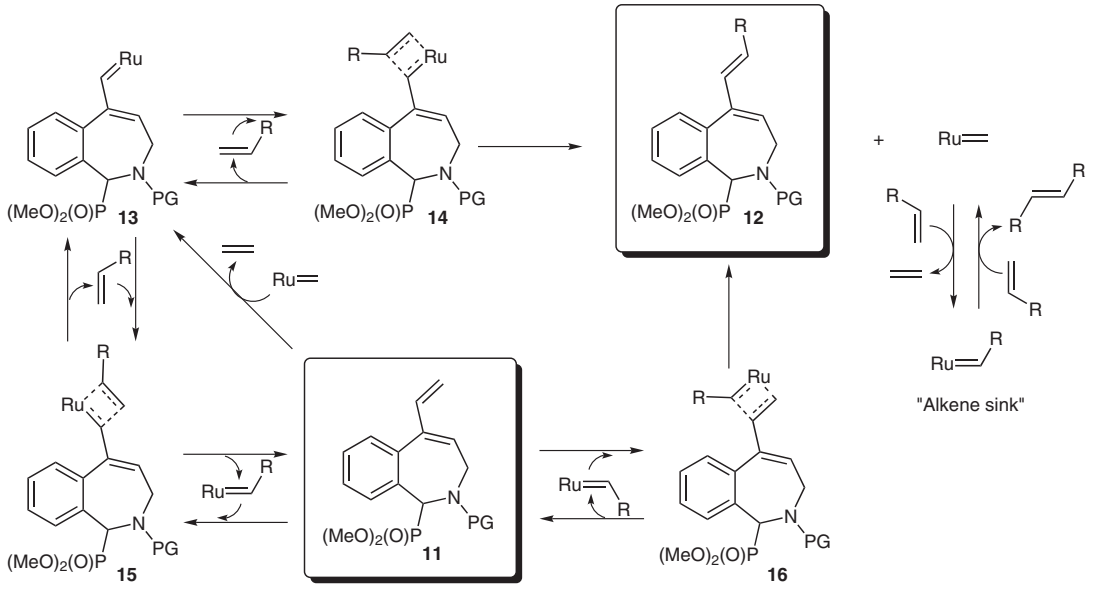
Figure 2 Conversion of aminophosphonate **5** into **11** and **12** as followed by ^{31}P NMR spectroscopy

by-product **11** is formed after cycloreversion which can react in three different ways: 1) conversion to **13** via **15**; 2) conversion to **13** by reaction with the methylidene carbene and production of ethylene or 3) conversion to **12** after reaction with the alkylidene carbene via **16**. During the course of the reaction, the alkene is consumed in two different ways. The first is incorporation in the end product. The second, the alkene sink (Scheme 5), is an unproductive pathway in which the alkene is dimerised with regeneration of the methylidene carbene and production of ethylene. This explains the fact that adding an extra amount of alkene speeds up the conversion of **11** to **12** since the dimerised alkene remains relatively inert in the reaction mixture.[17] In all cases, however, about 10% of **11** remained present which was removed by flash chromatography.

Upon evaluation of the enyne-metathesis–cross-metathesis sequence between **4** and styrene, it was found that in this case it is not necessary to add an extra amount of alkene. This seems to prove that in this case the formation of metallacyclobutanes of type **14** are favoured, immediately leading to the final products.

Table 1 provides an overview of the synthesised 2-benzazepine-1-ylphosphonates.[18] In only two cases an *E*/*Z* mixture was observed (Table 1, entries 2 and 3), in all other cases the *E*-form was obtained exclusively. With both substrates the reaction failed using allyl cyanide, which is probably due to the fact that this is a quite electron-poor alkene.[12a]

In summary we have developed a new and efficient entry to an interesting class of benzo-fused phosphonoazepines. The reaction sequence starts with the synthesis of imines, which are phosphonylated using dimethylphosphite in MeOH. Using a domino enyne-metathesis–cross-metathesis, these substrates are cyclised and functionalised in the presence of a terminal alkene under the action of the second-generation Grubbs catalyst.



Scheme 5

Table 1 Overview of the Synthesised 1*H*-2-Benzazepine-1-ylphosphonates[18]

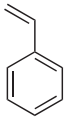
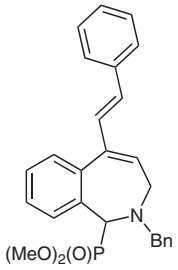
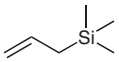
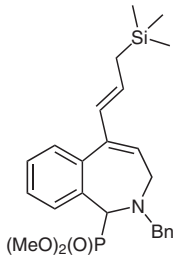
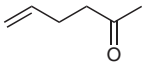
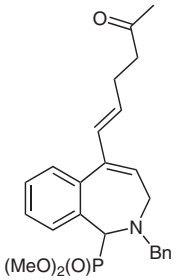
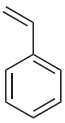
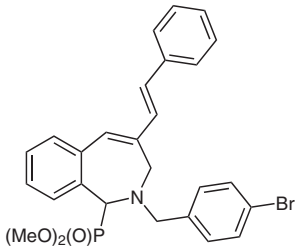
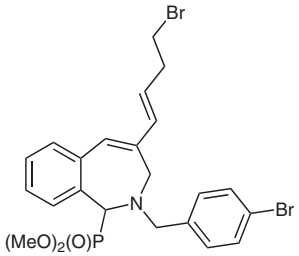
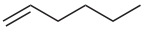
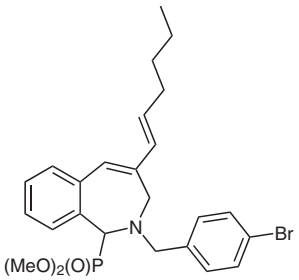
Entry	Enyne	Alkene	Product	Yield (%) (*E*/*Z*)
1	**5**			78 (100:0)
2	**5**			74 (66:34)
3	**5**			68 (67:33)

Table 1 Overview of the Synthesised 1*H*-2-Benzazepine-1-ylphosphonates[18] (continued)

Entry	Enyne	Alkene	Product	Yield (%) (*E*/*Z*)
4	**4**			69 (100:0)
5	**4**			50 (100:0)
6	**4**			70 (100:0)

Acknowledgment

Financial support from the BOF (Bijzonder Onderzoeksfonds Universiteit Gent, Research Fund Ghent University) is gratefully acknowledged. The authors thank their fellow researchers of the Synbioc group for their fine-tuning of this manuscript.

References and Notes

(1) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.
(2) (a) Arany, A.; Groundwater, P. W.; Nyerges, M. *Tetrahedron Lett.* **1998**, *39*, 3267. (b) Arany, A.; Bendell, D.; Groundwater, P. W.; Garnett, I.; Nyerges, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2605. (c) Gerdes, K.; Sagar, P.; Fröhlich, R.; Wibbeling, B.; Würthwein, E.-U. *Eur. J. Org. Chem.* **2004**, 3465. (d) Sajitz, M.; Fröhlich, R.; Salorinne, K.; Würthwein, E.-U. *Synthesis* **2006**, 2183.
(3) (a) Van Otterlo, W. A. L.; Pathak, R.; de Koning, C. B. *Synlett* **2003**, 1859. (b) Toda, N.; Tago, K.; Marumoto, S.; Takami, K.; Ori, M.; Yamada, N.; Koyama, K.; Naruto, S.; Abe, K.; Yamazaki, R.; Hara, T.; Aoyagi, A.; Abe, Y.; Kaneko, T.; Kogen, H. *Bioorg. Med. Chem.* **2003**, *11*, 4389.
(4) For recent reviews on ring-closing metathesis, see: (a) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592. (b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. (c) Deiters, A.; Martin, F. *Chem. Rev.* **2004**, *104*, 2199. (d) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4490. (e) Dragutan, I.; Dragutan, V.; Filip, P. *Arkivoc* **2005**, *(x)*, 105.
(5) For a review on the use of Fisher carbene complexes for heterocyclisation, see: Barluenga, J.; Martinez, S. *Arkivoc* **2006**, *(vii)*, 129.
(6) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
(7) Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177.
(8) Gaffar, A. US 5753633, **1998**; *Chem. Abstr.* **1998**, *129*, 8161.
(9) Danikiewicz, W.; Makosza, M. *J. Org. Chem.* **1991**, *56*, 1283.
(10) (a) Dieltiens, N.; Stevens, C. V.; De Vos, D.; Allaert, B.; Drozdzak, R.; Verpoort, F. *Tetrahedron Lett.* **2004**, *45*, 8995. (b) Dieltiens, N.; Stevens, C. V.; Allaert, B.; Verpoort, F. *Arkivoc* **2005**, *(i)*, 92. (c) Moonen, K.; Dieltiens, N.; Stevens, C. V. *J. Org. Chem.* **2006**, *71*, 4006. (d) Dieltiens, N.; Moonen, K.; Stevens, C. V. *Chem. Eur. J.* **2006**, in press.
(11) For recent reviews on enyne metathesis, see: (a) Poulson, C. S.; Madson, R. *Synthesis* **2003**, 1. (b) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317. (c) Maifeld, S. V.; Lee, D. *Chem. Eur. J.* **2005**, *11*, 6118.
(12) (a) Royer, F.; Vilain, C.; Elkaïm, L.; Grimaud, L. *Org. Lett.* **2003**, *5*, 2007. (b) Lee, H.-Y.; Kim, H. Y.; Tae, H.; Kim, B. G.; Lee, J. *Org. Lett.* **2003**, *5*, 3439. (c) Imhof, S.; Blechert, S. *Synlett* **2003**, 609. (d) Kitamura, T.; Sato, Y.; Mori, M. *Tetrahedron* **2004**, *60*, 9649.
(13) Van Meenen, E.; Moonen, K.; Acke, D.; Stevens, C. V. *Arkivoc* **2006**, *(i)*, 31.
(14) Azizi, N.; Saidi, M. R. *Tetrahedron* **2003**, *59*, 5329.
(15) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082.

(16) Lloyd-Jones, G. C.; Margue, R. G.; de Vries, J. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 7442.
(17) For a general model for selectivity in cross-metathesis, see: Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
(18) **Synthesis of Derivatives 3 from 4; General Procedure**
To a solution of **4** (1 equiv) in anhyd CH_2Cl_2 (15 mL) was added the alkene (5 equiv). This mixture was refluxed under N_2 atmosphere and the second-generation Grubbs' catalyst **2** (10 mol%) was added. The resulting solution was refluxed for 4 h. The residue was adsorbed onto silica gel and purified by flash chromatography.
Synthesis of Derivatives 3 from 5; General Procedure
To a solution of **5** (1 equiv) in anhyd CH_2Cl_2 (15 mL) was added the alkene (5 equiv). This mixture was refluxed under N_2 atmosphere and the second-generation Grubbs' catalyst **2** (10 mol%) was added. An additional amount of alkene (5 equiv) was added after 2 h and refluxing was continued for an additional 4 h. The residue was adsorbed onto silica gel and purified by flash chromatography.
Dimethyl 2-Benzyl-5-[(*E*)-2-phenylvinyl]-2,3-dihydro-1*H*-2-benzazepin-1-ylphosphonate: R_f = 0.27 (EtOAc–MeCN, 8:2). IR: 1031 (PO), 1057 (PO), 1247 (P=O), 1600 (C=C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.79 (dd, *J* = 7.2 Hz, *J* = 11.6 Hz, 1 H, NCH_AH_BCH), 3.04 (dd, *J* = 7.2 Hz, *J* = 11.6 Hz, 1 H, NCH_AH_BCH), 3.50 (d, *J* = 10.5 Hz, 3 H, OCH_3), 3.62 (d, *J* = 12.6 Hz, 1 H, NCH_AH_BPh), 3.62 (d, *J* = 10.7 Hz, 3 H, OCH_3), 4.06 (d, *J* = 12.6 Hz, 1 H, NCH_AH_BPh), 4.35 (d, *J* = 25.0 Hz, 1 H, CHP), 6.30 (t, *J* = 7.2 Hz, 1 H, NCH_2CH), 6.67 (d, *J* = 16.2 Hz, 1 H, HC=C*H*Ph), 7.00 (d, *J* = 16.2 Hz, 1 H, *H*C=CHPh), 7.16–7.47 (m, 13 H, 13 × ArCH), 7.53 (d, *J* = 7.2 Hz, 1 H, ArCH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 50.14 (d, *J* = 5.8 Hz), 53.04 (d, *J* = 10.4 Hz), 61.48 (d, *J* = 11.5 Hz), 64.71 (d, *J* = 171.9 Hz), 126.58, 127.42, 127.96, 128.05, 128.32, 128.43, 128.69, 129.42, 129.50, 129.76, 131.44, 131.61 (d, *J* = 10.4 Hz), 133.13, 137.45, 138.14 (d, *J* = 6.9 Hz), 138.63, 143.58. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 26.30. MS (ESI): *m*/*z* (%) = 446.3 ($M + H^+$, 100), 336.2 [$M^+ - P(O)(OMe)_2$, 50].
Dimethyl 2-Benzyl-5-(3-trimethylsilanyl-propenyl)-2,3-dihydro-1*H*-2-benzazepin-1-ylphosphonate: *E*/*Z*, 66:34. R_f = 0.47 (hexane–EtOAc, 2:8). IR: 1033 (PO), 1059 (PO), 1248 (P=O), 1636 (C=C) cm^{-1}. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 127.28, 127.45, 127.67, 127.80, 127.93, 128.35, 129.21, 129.30, 129.39, 129.45, 129.91, 130.86; where it was possible to assign the chemical shift to a specific isomer, the assignments are given below. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 26.33, 26.36. MS (ESI): *m*/*z* (%) = 456.2 ($M + H^+$, 100), 346.3 [$M^+ - P(O)(OMe)_2$, 53].
E-Isomer: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.03 [s, 9 H, $Si(CH_3)_3$], 1.59 (d, *J* = 8.3 Hz, 2 H, CH_2Si), 2.75 (dd, *J* = 7.0 Hz, *J* = 11.7 Hz, 1 H, NCH_AH_BCH), 2.86 (dd, *J* = 7.0 Hz, *J* = 11.7 Hz, 1 H, NCH_AH_BCH), 3.49 (d, *J* = 10.5 Hz, 3 H, OCH_3), 3.54 (d, *J* = 13.2 Hz, 1 H, NCH_AH_BPh), 3.63 (d, *J* = 10.7 Hz, 3 H, OCH_3), 4.08 (d, *J* = 13.2 Hz, 1 H, NCH_AH_BPh), 4.29 (d, *J* = 25.0 Hz, 1 H, CHP), 5.81 (dt, *J* = 8.3 Hz, *J* = 15.5 Hz, 1 H, HC=C*H*CH_2), 5.99 (t, *J* = 7.0 Hz, 1 H, NCH_2CH), 6.09 (d, *J* = 15.5 Hz, 1 H, *H*C=$CHCH_2$), 7.25–7.46 (m, 18 H, 18 × ArCH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –1.67, 24.03, 50.12 (d, *J* = 6.9 Hz), 53.00 (d, *J* = 5.8 Hz), 53.07 (d, *J* = 5.8 Hz), 61.19 (d, *J* = 9.2 Hz), 64.41 (d, *J* = 168.4 Hz), 123.97, 131.04, 131.30 (d, *J* = 9.2 Hz), 132.92 (d, *J* = 2.3 Hz), 133.09 (d, *J* = 2.3 Hz), 138.83, 139.11 (d, *J* = 8.1 Hz), 139.79, 144.03.
Z-Isomer: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.02 [s, 9 H, $Si(CH_3)_3$], 1.64 (d, *J* = 9.0 Hz, 2 H, CH_2Si), 3.07 (dd, *J* = 6.4 Hz, *J* = 13.9 Hz, 1 H, NCH_AH_BCH), 3.17 (dd, *J* = 6.4 Hz, *J* = 13.9 Hz, 1 H, NCH_AH_BCH), 3.54 (d, *J* = 13.4 Hz, 1 H, NCH_AH_BPh), 3.54 (d, *J* = 10.4 Hz, 3 H, OCH_3), 3.69 (d, *J* = 10.5 Hz, 3 H, OCH_3), 4.04 (d, *J* = 13.4 Hz, 1 H, NCH_AH_BPh), 4.36 (d, *J* = 24.8 Hz, 1 H, CHP), 5.74 (dt, *J* = 9.0 Hz, *J* = 12.2 Hz, 1 H, HC=C*H*CH_2), 6.01 (t, *J* = 6.4 Hz, 1 H, NCH_2CH), 6.01 (d, *J* = 12.2 Hz, 1 H, *H*C=$CHCH_2$), 7.25–7.46 (m, 18 H, 18 × ArCH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –1.40, 19.67, 51.27 (d, *J* = 8.1 Hz), 52.96 (d, *J* = 6.9 Hz), 53.34 (d, *J* = 6.9 Hz), 60.30 (d, *J* = 8.1 Hz), 64.84 (d, *J* = 166.1 Hz), 130.91 (d, *J* = 8.1 Hz), 138.87, 139.95 (d, *J* = 8.1 Hz).
Dimethyl 2-Benzyl-5-[(1*E*)-5-oxohex-1-enyl]-2,3-dihydro-1*H*-2-benzazepin-1-ylphosphonate: R_f = 0.27 (EtOAc–MeCN, 8:2). IR: 1031 (PO), 1057 (PO), 1249 (P=O), 1713 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.15 (s, 3 H, C=OCH_3), 2.42 (dt, *J* = 6.8 Hz, *J* = 6.8 Hz, 2 H, CH_2CH_2C=O), 2.56 (t, *J* = 6.8 Hz, 2 H, CH_2CH_2C=O), 2.73 (dd, *J* = 7.1 Hz, *J* = 11.9 Hz, 1 H, NCH_AH_BCH), 2.98 (dd, *J* = 7.1 Hz, *J* = 11.9 Hz, 1 H, NCH_AH_BCH), 3.47 (d, *J* = 10.5 Hz, 3 H, OCH_3), 3.59 (d, *J* = 13.1 Hz, 1 H, NCH_AH_BPh), 3.66 (d, *J* = 10.5 Hz, 3 H, OCH_3), 4.01 (d, *J* = 13.1 Hz, 1 H, NCH_AH_BPh), 4.29 (d, *J* = 25.0 Hz, 1 H, CHP), 5.79 (dt, *J* = 6.8 Hz, *J* = 15.5 Hz, 1 H, HC=C*H*CH_2), 6.08 (t, *J* = 7.1 Hz, 1 H, NCH_2CH), 6.26 (d, *J* = 15.5 Hz, 1 H, *H*C=$CHCH_2$), 7.23–7.41 (m, 9 H, 9 × ArCH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.16, 30.06, 43.17, 50.07 (d, *J* = 5.8 Hz), 52.92 (d, *J* = 6.9 Hz), 53.07 (d, *J* = 8.1 Hz), 61.41 (d, *J* = 10.4 Hz), 64.91 (d, *J* = 171.9 Hz), 126.38, 127.35, 127.82, 128.37, 129.16, 129.45, 131.47, 131.53 (d, *J* = 9.2 Hz), 131.76, 132.98, 138.49 (d, *J* = 6.9 Hz), 138.69, 143.06, 208.13. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 26.22. MS (ESI): *m*/*z* (%) = 439.7 ($M + H^+$, 10), 330 [$M^+ - P(O)(OMe)_2$, 100].
Dimethyl 2-Benzyl-5-[(1*Z*)-5-oxohex-1-enyl]-2,3-dihydro-1*H*-2-benzazepin-1-ylphosphonate:
R_f = 0.27 (EtOAc–MeCN, 8:2). IR: 1030 (PO), 1058 (PO), 1252 (P=O), 1714 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.10 (s, 3 H, C=OCH_3), 2.34–2.53 (m, 4 H, CH_2CH_2C=O), 3.01 (dd, *J* = 6.1 Hz, *J* = 13.8 Hz, 1 H, NCH_AH_BCH), 3.29 (dd, *J* = 6.1 Hz, *J* = 13.8 Hz, 1 H, NCH_AH_BCH), 3.53 (d, *J* = 10.5 Hz, 3 H, OCH_3), 3.66 (d, *J* = 13.2 Hz, 1 H, NCH_AH_BPh), 3.71 (d, *J* = 10.4 Hz, 3 H, OCH_3), 3.94 (d, *J* = 13.2 Hz, 1 H, NCH_AH_BPh), 4.36 (d, *J* = 24.8 Hz, 1 H, CHP), 5.61 (dt, *J* = 7.0 Hz, *J* = 11.4 Hz, 1 H, HC=C*H*CH_2), 6.00 (t, *J* = 6.1 Hz, 1 H, NCH_2CH), 6.13 (d, *J* = 11.4 Hz, 1 H, *H*C=$CHCH_2$), 7.26–7.38 (m, 9 H, 9 × ArCH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.28, 29.90, 43.68, 50.87 (d, *J* = 6.9 Hz, 52.97 (d, *J* = 6.9 Hz, 53.29 (d, *J* = 8.1 Hz), 61.02 (d, *J* = 9.2 Hz), 65.75 (d, *J* = 167.3 Hz), 127.33, 127.70, 128.02, 128.37, 128.81, 129.16, 129.39, 131.16, 131.41 (d, *J* = 9.2 Hz), 131.59, 133.10, 138.74, 139.22 (d, *J* = 8.1 Hz), 139.53, 208.25. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 25.89. MS (ESI): *m*/*z* (%) = 439.7 ($M + H^+$, 13), 330 [$M^+ - P(O)(OMe)_2$, 100].
Dimethyl 2-(4-Bromobenzyl)-4-[(1*E*)-4-fenylvinyl]-2,3-dihydro-1*H*-2-benzazepin-1-ylphosphonate: R_f = 0.20 (hexane–EtOAc, 4:6). IR: 1031 (PO), 1057 (PO), 1250 (P=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.52 (d, *J* = 13.6 Hz, 1 H, NCH_AH_BPh), 3.65 (d, *J* = 10.7 Hz, 3 H, OCH_3), 3.68 (d, *J* = 11.0 Hz, 3 H, OCH_3), 3.75 (d, *J* = 13.5 Hz, 1 H, NCH_AH_BPh), 3.95 (d, *J* = 18.4 Hz, 1 H, NCH_AH_BC), 4.37 (d, *J* = 18.4 Hz, 1 H, NCH_AH_BC), 4.47 (d, *J* = 27.5 Hz, 1 H, CHP), 6.46 (d, *J* = 16.4 Hz, 1 H, HC=C*H*Ph), 6.68 (s, 1 H, C=CHC), 6.89 (d, *J* = 16.4 Hz, 1 H, *H*C=CHPh), 7.10–7.42 (m, 13 H, 13 × ArCH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.08 (d, *J* = 6.9 Hz), 53.65 (d, *J* = 4.6 Hz), 53.72 (d, *J* = 6.9 Hz), 57.07, 64.14 (d, *J* = 155.8 Hz), 121.25, 126.46, 127.33, 127.68, 128.06, 128.09,

128.92, 130.55, 130.92, 131.54, 132.31 (d, J = 4.6 Hz), 132.52, 132.83, 133.74, 136.28 (d, J = 8.1 Hz), 136.57, 137.33, 137.71, 139.27. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 25.29. MS (ESI): m/z (%) = 524.03/526.3 ($M + H^+$, 60), 414.2/416.2 [$M^+ - P(O)(OMe)_2$, 100].

Dimethyl 2-(4-Bromobenzyl)-4-[(1*E*)-4-bromobut-1-enyl]-2,3-dihydro-1*H*-2-benzazepin-1-ylphosphonate: R_f = 0.29 (hexane–EtOAc, 4:6). IR: 1031 (PO), 1058 (PO), 1252 (P=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.67 (q, J = 7.0 Hz, 2 H, CH_2CH_2Br), 3.40 (t, J = 7.0 Hz, 2 H, CH_2Br), 3.46 (d, J = 13.5 Hz, 1 H, NCH_AH_BPh), 3.63 (d, J = 10.7 Hz, 3 H, OCH_3), 3.68 (d, J = 10.8 Hz, 3 H, OCH_3), 3.71 (d, J = 13.5 Hz, 1 H, NCH_AH_BPh), 3.79 (d, J = 18.6 Hz, 1 H, NCH_AH_BC), 4.22 (d, J = 18.6 Hz, 1 H, NCH_AH_BC), 4.38 (d, J = 27.8 Hz, 1 H, CHP), 5.54 (dt, J = 7.0 Hz, J = 15.8 Hz, 1 H, $HC{=}CHCH_2$), 6.23 (d, J = 15.8 Hz, 1 H, $HC{=}CHCH_2$), 6.49 (s, 1 H, C=CHC), 7.10–7.46 (m, 8 H, 8 × ArCH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.39, 36.61, 53.07 (d, J = 6.9 Hz), 53.68 (d, J = 5.8 Hz), 53.68, 57.01, 63.98 (d, J = 154.6 Hz), 121.19, 125.74, 127.21, 128.02, 130.48, 130.89, 131.50, 132.67, 133.62 (d, J = 2.3 Hz), 136.20 (d, J = 6.9 Hz), 136.57, 137.68, 138.67. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 25.24. MS (ESI): m/z (%) = 554.0/556.0/558.0 ($M + H^+$, 35), 444.0/446.0/448.0 [$M^+ - P(O)(OMe)_2$, 100].

Dimethyl 2-(4-Bromobenzyl)-4-[(1*E*)-hex-1-enyl]-2,3-dihydro-1*H*-2-benzazepin-1-ylphosphonate: R_f = 0.27 (hexane–EtOAc, 4:6). IR: 1031 (PO), 1058 (PO), 1253 (P=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, J = 7.0 Hz, 3 H, CH_3), 1.25–1.43 (m, 4 H, $CH_2CH_2CH_3$), 2.11 (q, J = 6.9 Hz, 2 H, $HC{=}CHCH_2$), 3.46 (d, J = 12.4 Hz, 1 H, NCH_AH_BPh), 3.64 (d, J = 10.7 Hz, 3 H, OCH_3), 3.68 (d, J = 12.1 Hz, 3 H, OCH_3), 3.72 (d, J = 12.4 Hz, 1 H, NCH_AH_BPh), 3.80 (d, J = 18.4 Hz, 1 H, NCH_AH_BC), 4.19 (d, J = 18.4 Hz, 1 H, NCH_AH_BC), 4.39 (d, J = 27.5 Hz, 1 H, CHP), 5.60 (dt, J = 6.9 Hz, J = 16.0 Hz, 1 H, $HC{=}CHCH_2$), 6.13 (d, J = 16.0 Hz, 1 H, $HC{=}CHCH_2$), 6.44 (s, 1 H, C=CHC), 7.11–7.40 (m, 8 H, 8 × ArCH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.06, 22.35, 31.63, 33.08, 53.00 (d, J = 6.9 Hz), 53.73 (d, J = 8.1 Hz), 53.83 (d, J = 6.9 Hz), 56.80, 63.97 (d, J = 155.8 Hz), 121.18, 126.83, 127.97, 129.85, 130.52, 130.98, 131.45, 133.22, 132.38, 133.64, 136.54 (d, J = 6.9 Hz), 137.76, 139.32. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 25.29. MS (ESI): m/z (%) =504.6/506.2 ($M + H^+$, 60), 394.2/396.3 [$M^+ - P(O)(OMe)_2$, 100].