Phosphorylation of 2-azabicyclo[2.2.1]hept-5-ene and 2-hydroxy-2-azabicyclo[2.2.1]hept-5-ene systems: synthesis and mechanistic study†

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The *endo* and *exo* isomers of (±)-methyl 2-hydroxy-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylates and the *in situ*-prepared *endo* and *exo* isomers of (±)-methyl 2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate were treated with diphenylphosphinic chloride ($OPClPh_2$) and chlorodiphenylphosphine ($ClPPh_2$) to afford the corresponding phosphorylated bicycles. The structure of all these compounds was unequivocally determined by NMR spectroscopy and mass spectrometry, and, based on the results obtained, a mechanistic scheme for the phosphorylation reaction of these adducts to afford the corresponding phosphorylbicycles is proposed.

Introduction

Azabicyclic compounds are important intermediates in the preparation of a large variety of compounds of chemical, biological and pharmaceutical interest.[1] Within the diverse transformations comprising cycloadditions, reactions of imine derivatives and dienes leading to monocyclic and bicyclic molecules have attracted much interest, especially those employing cyclopentadiene (CPD) as a starting material.[2] 3-Functionalized 2-azabicyclo[2.2.1]hept-5-ene-3-carboxylates and 2-hydroxy-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylates, obtained by aza-Diels–Alder reactions between imines and oximes of glyoxylates, respectively, and cyclopentadiene and its derivatives are considered as synthetic intermediates in the preparation of polyhydroxylated pyrrolidines (iminosugars),[3] therefore being useful as precursors in the preparation of nucleoside analogues.[4] In particular, *N*-functionalized azanucleoside and oxa-azanucleoside derivatives are compounds that often present biological activity.[5–8] Antiviral nucleoside analogues inhibit replication of the viral genome, whereas anticancer nucleoside analogues inhibit cellular DNA replication and repair. As stated by Chiacchio *et al.*,[6] the action of most of the nucleoside analogues possessing antiviral activities depends on phosphorylation by specific kinases in a three step phosphorylation process, the first of which is rate-limiting. These enzymes play an important role in the synthesis of nucleotides that are required for a variety of cellular metabolic processes, as well as for RNA and DNA synthesis. Nucleoside monophosphate kinases are also required for the pharmacological activation of therapeutic nucleoside and nucleotide analogues. On the other hand, phosphorylated analogues may behave as mimetics of nucleoside monophosphates and be able to bypass the initial selective enzymatic monophosphorylation step.[8] Therefore, a full understanding of non-natural phosphorylation processes allowing for the construction of N–P bonds is a challenge of major importance.

To the best of our knowledge, there are only a couple of examples of *N*-functionalized azabicycles with phosphoryl radicals, obtained from aza-Diels–Alder reactions of aryl phosphorylimines.[9] The non existence of a general method for the preparation of non-aryl phosphorylimines suggests the synthesis of *N*-phosphorylbicycles is a quite complex task. In fact, *N*-phosphorylated azanucleosides have hardly been studied, most probably due to the difficulty of their preparation. This difficulty can be rationalized by considering the chemical behaviour of phosphorus, which may adopt several coordination and oxidation states during a reaction, thus making its outcome unpredictable.

Results and discussion

(±)-Methyl 2-hydroxy-2-azabicyclo[2.2.1]hept-5-ene-3-*endo*-carboxylate (**1**) and (±)-methyl 2-hydroxy-2-azabicyclo[2.2.1]-hept-5-ene-3-*exo*-carboxylate (**2**) were prepared according to our recently described methodology.[10] Treatment of each of these adducts with an equimolar amount of $OPClPh_2$ in the presence of triethylamine (Et_3N) and a catalytic amount of 4-dimethylaminopyridine (DMAP) afforded the corresponding *O*-phosphorylated adducts, (±)-methyl 2-diphenylphosphoryloxy-2-azabicyclo[2.2.1]hept-5-ene-3-*endo*-carboxylate (**3**) and (±)-methyl 2-diphenylphosphoryloxy-2-azabicyclo[2.2.1]hept-5-ene-3-*exo*-carboxylate (**4**) (Scheme 1). The phosphorylation of **1** (*endo* isomer) has been revealed to be less effective than that of the corresponding *exo* isomer **2** (yields of 43 and 80%, respectively), even though in both cases a single compound was identified (**3** *endo* and **4** *exo*, respectively). Such

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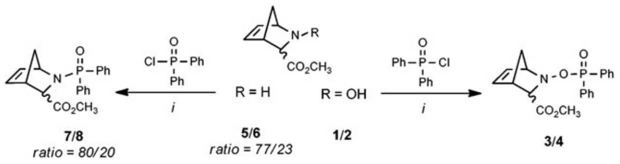
† Electronic Supplementary Information (ESI) available: special care with solvents and reagents used, spectra of mass spectrometry, NMR spectra of adducts **3**, **4**, **5**, **6**, **7**, **8** and **11**, and spectra of HPLC-MS analyses. See DOI: 10.1039/c0nj00239a

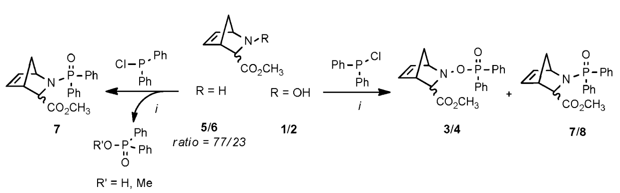


Scheme 1 Phosphorylation of adducts **1**/**2** and **5**/**6** (*endo* : *exo* ratio = 77 : 23) *via* $OPClPh_2$. (i): Et_3N, DMAP, −15 °C to room temp., 6 h under a stream of argon.

a difference may be related to the higher steric hindrance caused by the phosphoryloxy group in the bicyclic *endo* isomer.

Similarly, phosphorylation of the *in situ*-prepared mixture of *endo* and *exo* isomers of (±)-methyl 2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (**5**/**6**, ratio ≈ 4 : 1)[11] with $OPClPh_2$ in the presence of Et_3N and a catalytic amount of DMAP afforded the *endo* and *exo* isomers of the expected methyl 2-diphenylphosphoryl-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (**7**/**8**; Scheme 1) in 50% yield, the ratio of the isomers being nearly the same as in the starting materials.

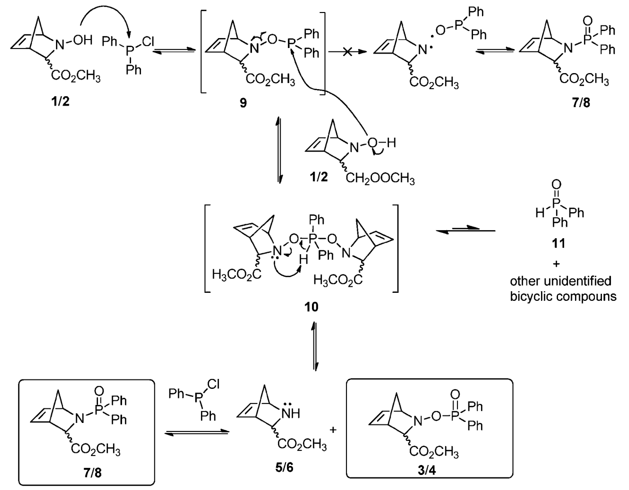
Adducts **1** and **2** were also treated with equimolar amounts of $PClPh_2$ in the presence of Et_3N. In analogy with the results obtained by Hudson *et al.*[12] with phosphinylated oximes, the formation of adducts **7** and **8** was observed, but the major products of this reaction were **3** and **4**, respectively (Scheme 2). In order to gain some insight into the reaction mechanism, phosphorylation of the mixture of isomers **5**/**6** with $PClPh_2$ was also performed. All the starting material was consumed, but the expected straightforward diphenylphosphinyl derivative could not be detected in the reaction mixture. A significant amount of by-products (methoxydiphenylphosphine oxide and diphenylphosphinic acid), as well as a small amount of **7** (*endo*), were isolated. As the reaction took place in an anhydrous environment and no extractions were made, we may conclude that the oxygen atom bonded to phosphorus in compound **7** must come from the ester group of the starting material **5**/**6**, thus explaining the formation of the by-products and the low yield of **7** obtained (≈4%, not isolated).



Scheme 2 Phosphorylation of adducts **1**/**2** and **5**/**6** (ratio = 77 : 23) *via* $PClPh_2$. (i): Et_3N, DMAP, −15 °C to room temp., 6 h under a stream of argon.

The results obtained in these experiences are listed in Table 1. The calculated yields refer to the amount of phosphorylated bicycles formed (**7** + **3** and **8** + **4**) from the starting materials **1**/**2** or **5**/**6**. Experiments realized at −60 °C or at room temperature lead to similar results.

Whilst the formation of adducts **3**/**4** from **1**/**2**, and **7**/**8** from **5**/**6**, using $OPClPh_2$ may easily be explained by a nucleophilic displacement at phosphorus, the outcome of the reactions



Scheme 3 A proposed mechanism for the reaction of adducts **1**/**2** with $PClPh_2$, affording phosphorylbicycles **3**/**4** and **7**/**8**.

of **1**/**2** and **5**/**6** with $PClPh_2$ is not so straightforward. The full/partial identification of some of the trace by-products was crucial for the establishment of a plausible mechanism that fully explained the results obtained. In Scheme 3, such a mechanism for the phosphorylation of adducts **1** and **2** with $PClPh_2$ affording phosphorylbicycles **3**/**7** and **4**/**8**, respectively, is proposed.

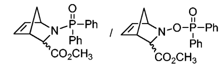
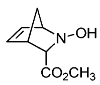
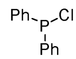
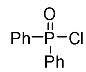
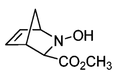
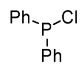
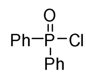
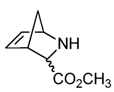
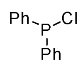
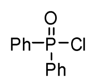
On the contrary to the results obtained by Hudson *et al.*[12] in the phosphorylation of phosphinylated oximes, adducts **7**/**8** did not result from a homolytic thermal $P^{III} \rightarrow P^{V}$ rearrangement of non-stable and non-isolable intermediate **9** (diphenylphosphinyloxiamine). If it were so, a concentration of $PClPh_2$ higher than that of the adduct (**1** or **2**) should lead to an increase in the percentage of **7** or **8** in the reaction mixture. To verify this assumption, a reaction was performed by slowly (4 h) adding a highly dilute solution of the adduct (**1** or **2**) in CH_2Cl_2 (0.009 M) to a more concentrated solution of $PClPh_2$ in CH_2Cl_2 (0.2 M, thus ensuring an excess of PPh_2Cl at any given time during the reaction) using the reaction conditions described in Scheme 2.

After work-up (elimination of the solvent, addition of AcOEt, filtration to remove Et_3NHCl and evaporation of the solvent), a ^{31}P NMR analysis of the mixture showed no significant difference between the ratios of the products obtained, **3**/**7** or **4**/**8**, respectively, when compared to the results of the same reactions under normal conditions.

Furthermore, when the reaction was performed using 2.0 equiv. of **2**, 1.0 equiv. of $PClPh_2$ and 1.0 equiv. of Et_3N, no traces of compound **8** were detected by ^{31}P NMR in a sample of the reaction mixture, while compound **4** was obtained in 73% yield (see the ESI, Fig. 23†).

As already referred to, the presence of the additional oxygen bonded to phosphorus (O=P) in adducts **3** and **4** can be explained if we assume that two molecules of starting adduct (**1** or **2**) react with one molecule of $PClPh_2$, probably through the formation of intermediate **9**, to give the corresponding intermediate **10** (*endo* or *exo*), detected by ESI-MS [peaks (M + 1) = 523.20 and (M + 23) = 545.20, see the ESI†].

Table 1 Yields (η) and ratios of phosphorylated adducts from the reactions between adducts **1**/**2** or **5**/**6** and the phosphorus reagents (according to Scheme 3 and Scheme 4)

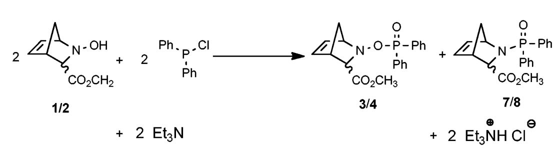
Starting compound	Phosphorous reagent	η (%)[a]	Product (%)[c]  **7/8** / **3/4**
 **1**		30[b]–35[c]	**7/3** (15/85)
		43	**7/3** (0/100)
 **2**		25[b]–30[c]	**8/4** (15/85)
		80	**8/4** (0/100)
 **5/6** (77:23)[d]		4[e]	**7/3** (100/0)
		50	**7/8** / — (80/20) / —

[a] Combined yield of the two adducts. [b] Yield after chromatographic purification. [c] Values determined by ^{31}P NMR from the crude of the reaction by using an internal standard for quantification (diethylphosphoramidate—see supporting information). [d] Values determined by ^{1}H NMR from the crude of the reaction (see supporting information). [e] Value estimated by ^{1}H NMR (not isolated, **8** was not detected probably due to its very low concentration).

Intermediate **10** may rearrange (to a small extent), as shown in Scheme 3, giving rise to diphenylphosphine oxide (**11**; identified by ^{1}H NMR) and to a few unidentified bicyclic compounds. Even though only traces of these compounds were obtained, their detection (particularly of **11**) is important because it confirms the formation of intermediate **10** and, consequently, corroborates the proposed mechanism. However, rearrangement of intermediate **10** (*endo* or *exo*) will give essentially compounds **3** (or **4**) and **5** (or **6**). The latter one reacts with another molecule of $PClPh_2$, yielding **7** or **8** according to Scheme 3.

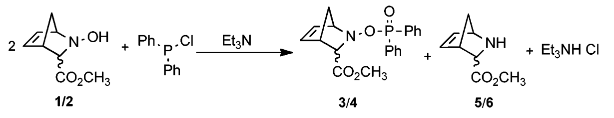
In order to identify as many species as possible and confirm the proposed mechanism, a HPLC-MS analysis of a 30 min reaction mixture (after the Et_3NHCl had been filtered off and the solvent evaporated) was performed. High intensity mass peaks corresponding to compounds **1**/**2**, **3**/**4**, **5**/**6** and **7**/**8** were observed. Peaks corresponding to by-products, such as diphenylphosphinic acid, diphenylphosphine oxide and methoxy-diphenylphosphine oxide, were also detected (see the ESI†). The minor percentage of adducts **7**/**8** relative to adducts **3**/**4** is in accordance with the low yield of the reaction between **5**/**6** and $PClPh_2$ (4%, see Table 1), thus justifying the low yield of the overall reaction.

Taking into consideration the consistency of the reaction outcome when some of the parameters were changed (reaction temperature, order of addition of the reagents, reaction time and time of addition of the reagents) and the small quantity of by-products formed, the overall reaction may be described by the chemical equation represented in Scheme 4.



Scheme 4 A chemical equation that represents the overall reaction of the phosphorylation of adducts **1**/**2** *via* $PClPh_2$ through the mechanism presented in Scheme 3.

The yields of this reaction, reported in Table 1, refer to the sum of phosphorylated products obtained in each reaction, considering the stoichiometry as represented in Scheme 4.



Scheme 5 A chemical equation representing the overall reaction of the phosphorylation of adducts **1**/**2** *via* $PClPh_2$ considering a 2 : 1 stoichiometry.

However, if we consider that compounds **7** or **8** result from a side reaction, which is reasonable in view of their low yields, then we can rewrite the chemical equation of the phosphorylation reaction as represented in Scheme 5.

According to this equation, the stoichiometry of the reagents is 2 : 1, and a recalculation of the yields of the phosphorylation reaction leads to values in the order of 51%. These values are relatively close to those obtained when the reaction was performed with 2 equiv. of **2** and 1 equiv. of $PClPh_2$ (73%), the difference probably arising from the scale on which the experiments were performed (Table 1—large scale experiments).

Concerning the identification of the phosphorylated compounds formed, bicycles **7**/**8** and **3**/**4** were not easy to distinguish by NMR analysis. In order to find characteristic patterns that would help in their discrimination, ^{15}N and ^{31}P NMR analyses were performed. Table 2 presents ^{15}N NMR and ^{31}P NMR data for the four synthesized phosphorylbicycles.

As can be seen from Table 2, the ^{31}P chemical shifts of compounds **3** and **4** (N–O–P bonds) are slightly higher than those of **7** and **8** (N–P). In the case of the ^{15}N NMR chemical shifts, the difference between these values for compounds **3**/**4** and **7**/**8** is much more pronounced, reflecting the greater deprotection caused by the directly bonded oxygen atom in compounds **3**/**4**. The discrepancy observed for the ^{15}N NMR chemical shifts of **3** and **4** (*endo* and *exo* isomers) may be related to steric effects, which may affect the N–O bond stability. Further studies are being performed in our laboratories in order to clarify this issue. Concerning the N–P coupling constants, they are smaller in **3** and **4** (N–O–P bonds) due to the longer distance between the P and N atoms in these adducts. The different compounds also exhibit characteristic splitting patterns in the region of the aromatic protons of their ^{1}H NMR spectra, as illustrated in Fig. 1.

These features easily allow the distinction between N–O–P and N–P bonds in the adducts. In fact, the *ortho*-hydrogens of both phenyl rings are sufficiently different to give rise to two distinct signals. The chemical shift difference between these two signals is more significant in the diphenylphosphorylazabicycles (**7** and **8**, N–P bond) than in the diphenylphosphoryloxyazabicycles (**3** and **4**, N–O–P bond).

Table 2 ^{31}P NMR and ^{15}N NMR chemical shifts and coupling constants of the phosphorylbicycles.

Phosphorylated adduct	^{15}N/ppm	J_{N-P}/Hz	^{31}P/ppm
3	99.1	3.1	31.8
4	177.5	5.7	33.8
7	72.1	8.6	27.4
8	74.5	10.3	26.0

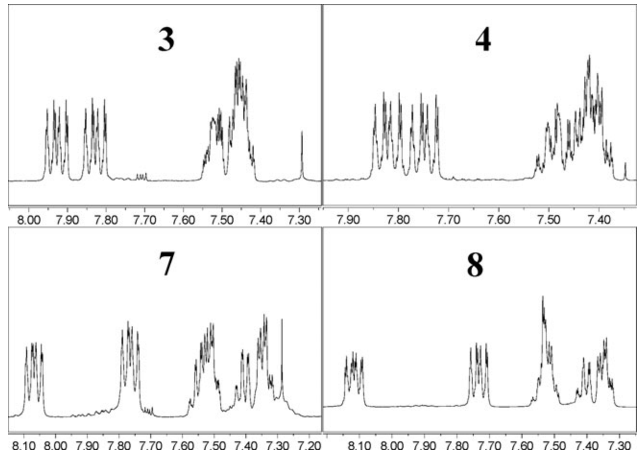


Fig. 1 ^{1}H NMR spectra of the aromatic region of phosphorylbicycles **3**, **4**, **7** and **8**, respectively.

Conclusions

(±)-Methyl 2-diphenylphosphoryloxy-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylates (**3**/**4**) are easily obtained by nucleophilic substitution between (±)-2-hydroxy-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylates (**1**/**2**) and diphenylphosphinic chloride ($OPClPh_2$).

The same diphenylphosphoryloxy adducts (**3**/**4**) can also be obtained from **1**/**2** *via* phosphinoylation (with $PClPh_2$), although in moderate yields. In addition to these adducts, (±)-methyl 2-diphenylphosphoryl-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylates (**7**/**8**) are formed as by-products (low yield) if $PClPh_2$ and **1**/**2** are used in equimolar amounts.

On the other hand, (±)-methyl 2-diphenylphosphoryl-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylates (**7**/**8**) can be obtained by the phosphorylation of a mixture of (±)-2-azabicyclo-[2.2.1]hept-5-ene-3-carboxylates (**5**/**6**). However, these bicyclic amines are unstable and must be synthesized *in situ* or immediately before the phosphorylation and used without purification. Separation of the final products yields the *endo* and *exo* isomers of the phosphorylated bicyclic amines, the *endo* isomer (**7**) being the major product.

Experimental section

This experimental section contains the procedures for the synthesis of adducts **5**/**6** and procedures for the phosphorylation of adducts **1**/**2** and **5**/**6**, as well as analytical data for the phosphorylated adducts **3**, **4**, **7** and **8**. NMR analyses were performed using a Bruker Avance III 400, with TMS as the internal standard for ^{1}H and ^{13}C, H_3PO_4 85% for ^{31}P and NH_3 for ^{15}N nuclei. ESI-MS analyses were performed on a liquid chromatography Finnigan Surveyor equipment coupled to a mass detector Finnigan LQC DECA XP MX with an API and an ESI interface. LC-MS analyses were performed on an Applied Biosystems Q TRAP LC/MS/MS System (ESI) coupled to an Agilent Technologies HPLC 1200 instrument. The samples were analyzed with a C18 reverse phase Agilent column (ZORBAX Eclipse XDB-C18 4.6 × 150 mm 5-micron) and an ACE 5 C18 3 mm pre-column.

Syntheses

(±)-Methyl 2-diphenylphosphoryloxy-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylates (3/4). A solution of 2-hydroxy-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate[10] (0.56 g, 3.3 mmol), Et_3N (0.98 mL, 7.0 mmol) and a catalytic amount of DMAP (5.0 mg, 0.04 mmol) in dry CH_2Cl_2 (5 mL) was stirred under an argon atmosphere at −5 °C for 5 min, before the dropwise addition of $OPClPh_2$ (0.63 mL, 3.31 mmol). The mixture was left to react for 2 h at −5 °C and then allowed to reach room temperature, reacting during a further 2 h. The solvent was evaporated under low pressure and the residue filtered through a funnel with cotton using ethyl acetate. After removal of the solvent, the residue was purified by flash chromatography (SiO_2, CH_2Cl_2–Et_2O 1 : 1). (R_f: **3**, 0.23; **4**, 0.50).

Analytical data for **3**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.89 (m, 2H, ArH_{ortho}), 7.86–7.79 (m, 2H, ArH_{ortho}), 7.55–7.41 (m, 6H, ArH), 6.25 (t, 1H, J = 3.3 Hz, 6-H), 6.18 (d, 1H, J = 3.7 Hz, 5-H), 4.96 (ddd, 1H, J = 12.9, 5.8, 2.5 Hz, 1-H), 3.92 (s, 1 H, 3-H), 3.69 (s, 3H, $OC\underline{H}_3$), 3.32 (t, 1 H, J = 2.9 Hz, 2-H), 1.99 (dt, 1 H, J = 12.5, 2.8 Hz, 7_{syn}-H), 1.91 (dd, 1H, J = 12.5, 5.8 Hz, 7_{anti}-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.97 ($\underline{C}O_2CH_3$), 140.31 (C-6), 134.51 (C-5), 132.27 (d, $J_{C–P}$ = 2.9 Hz, C_{para}), 132.22 (d, $J_{C–P}$ = 2.9 Hz, C_{para}), 132.06 (d, $J_{C–P}$ = 94.1 Hz, C_{ipso}), 132.05 (d, $J_{C–P}$ = 10.5 Hz, 2 × C_{ortho}), 131.38 (d, $J_{C–P}$ = 10.3 Hz, 2 × C_{ortho}), 130.70 (d, $J_{C–P}$ = 87.7 Hz, C_{ipso}), 128.51 (d, $J_{C–P}$ = 13.3, 2 C_{meta}), 128.48 (d, $J_{C–P}$ = 13.3, 2 C_{meta}), 89.54 (d, $J_{C–P}$ = 5.5 Hz, C-3), 75.64 (C-1), 52.10 ($O\underline{C}H_3$), 43.46 (C-4), 35.77 (d, $J_{C–P}$ = 3.3 Hz, C-7 = $\underline{C}H_2$); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 31.78; ^{15}N NMR (40 MHz, $CDCl_3$): δ = 99.09 (d, $J_{P–N}$ = 3.1 Hz); ESI-MS: calculated for $[C_{20}H_{20}NO_4P + H]^+$ (M + H^+) 370.11, found 370.13.

Analytical data for **4**. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86–7.79 (m, 2 H, ArH_{ortho}), 7.78–7.71 (m, 2 H, ArH_{ortho}), 7.53–7.37 (m, 6 H, ArH), 6.62 (ddd, 1 H, J = 5.5, 3.2, 1.1 Hz, 6-H), 6.32 (dd, 1 H, J = 5.6, 2.1 Hz, 5-H), 4.59 (m, 1 H, 1-H), 3.39 (s, 3 H, $OC\underline{H}_3$), 3.07 (d, 1 H, J = 2.1 Hz, 3-H), 3.06 (brs, 1 H, 4-H), 1.95 (d, 1 H, J = 9.5, 7_{syn}-H), 1.91 (ddd, 1H, J = 9.5, 3.5, 2.0 Hz, 7_{anti}-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.37 ($\underline{C}O_2CH_3$), 138.51 (C-6), 133.28 (C-5), 132.44 (d, $J_{C–P}$ = 10.0 Hz, 2 × C_{ortho}), 132.09 (d, $J_{C–P}$ = 2.6 Hz, C_{para}), 131.95 (d, $J_{C–P}$ = 2.8 Hz, C_{para}), 131.57 (d, $J_{C–P}$ = 9.7 Hz, 2 × C_{ortho}), 131.50 (d, $J_{C–P}$ = 39.8 Hz, C_{ipso}), 130.16 (d, $J_{C–P}$ = 39.0 Hz, C_{ipso}), 128.32 (d, $J_{C–P}$ = 10.7, 2 × C_{meta}), 128.19 (d, $J_{C–P}$ = 11.0, 2 × C_{meta}), 70.31 (d, $J_{C–P}$ = 2.3 Hz, C-3), 69.22 (d, $J_{C–P}$ = 4.5 Hz, C-1), 51.90 ($O\underline{C}H_3$), 47.96 (C-4), 44.39 (d, $J_{C–P}$ = 3.3 Hz, C-7 = $\underline{C}H_2$); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 33.84; ^{15}N NMR (40 MHz, $CDCl_3$): δ = 177.48 (d, $J_{P–N}$ = 5.7 Hz); ESI-MS: calculated for $[C_{20}H_{20}NO_4P + H]^+$ (M + H^+) 370.11, found 370.20.

(±)-Methyl 2-diphenylphosphoryl-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (7/8). To a stirred solution of ammonium chloride (NH_4Cl) (1.50 g, 28.0 mmol) and methyl 2-hydroxy-2-methoxyacetate (methyl hemiacetal of methyl glyoxylate) (1.20 g, 9.99 mmol) in water (15 mL) at room temperature was added CPD (0.60 mL, 7.5 mmol). After 2.5 h, additional CPD (0.60 mL, 7.5 mmol) was added and the reaction left to react for a further 18 h. The reaction mixture was extracted once with hexane to remove excess CPD and the organic layer discarded. The aqueous phase was adjusted to pH 9 with an aqueous saturated solution of $NaHCO_3$ and/or NaOH 1 M, and extracted with AcOEt until no compound remained in the aqueous phase (TLC). The organic extract was dried and the solvent evaporated, affording an orange-coloured oil, identified as methyl 2-azabicyclo[2.2.1]hept-5-ene-3-carboxylates (**5**/**6**) (60% yield, not purified). The oil was dissolved in dry CH_2Cl_2 (15 mL), and Et_3N (2.00 mL, 14.3 mmol) and a catalytic amount of DMAP (10 mg, 0.08 mmol) were added. The mixture was stirred at −15 °C under an argon atmosphere for 5 min before the dropwise addition of $OPClPh_2$ (1.40 mL, 7.35 mmol). The mixture was stirred for 2 h at −15 °C and then allowed to reach room temperature, reacting during a further 4 h. The solvent was evaporated under low pressure and the residue filtered through a funnel with cotton using AcOEt. After removal of the solvent, the residue was purified by flash chromatography (SiO_2, AcOEt). (R_f: [0.27–0.30]).

Analytical data for **5**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.33–6.28 (m, 1 H, 6-H), 5.90–5.85 (m, 1 H, 5-H), 4.01 (s, 1 H, 1-H), 3.94 (d, 1 H, J = 3.0 Hz, 3-H), 3.68 (s, $OC\underline{H}_3$), 3.44 (brs, 1 H, 4-H), 2.05 (brs, 1 H, $N\underline{H}$), 1.64 (d, 1 H, J = 8.3 Hz, 7_{syn}-H), 1.44 (d, 1 H, J = 8.3 Hz, 7_{anti}-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.08 ($\underline{C}O_2CH_3$), 137.38 (C-6), 130.82 (C-5), 61.79 ($O\underline{C}H_3$), 57.91 (C-3), 52.80 (C-1), 50.35 (C-7 = CH_2), 48.80 (C-4); ^{15}N NMR (40 MHz, $CDCl_3$): δ = 43.5; ESI-MS: calculated for $[C_8H_{11}NO_2 + H]^+$ (M + H^+) 154.08, found 154.53.

Analytical data for **6**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.33–6.28 (m, 2 H, 6-H, 5-H), 4.09 (brs, 1 H, 1-H), 3.78 (s, 3 H, $OC\underline{H}_3$), 3.29 (brs, 1 H, 3-H), 2.97 (brs, 1 H, 4-H), 2.05 (brs, 1 H, $N\underline{H}$), 1.66–1.61 (m, 1 H, 7_{syn}-H), 1.38 (d, 1 H, J = 8.5 Hz, 7_{anti}-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.79 ($\underline{C}O_2CH_3$), 137.53 (C-6), 136.58 (C-7), 61.18 ($O\underline{C}H_3$), 58.36 (C-3), 52.99 (C-1), 48.98 (C-4), 46.54 (C-7 = CH_2); ^{15}N NMR (40 MHz, $CDCl_3$): δ = 45.8.

Analytical data for **7**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10–8.04 (m, 2 H, ArH_{ortho}), 7.80–7.74 (m, 2 H, ArH_{ortho}), 7.58–7.48 (m, 3 H, ArH), 7.44–7.31 (m, 3 H, ArH), 6.52 (dd, 1 H, J = 5.5, 2.6 Hz, 6-H), 6.11 (dd, 1 H, J = 5.5, 2.7 Hz, 5-H), 4.37 (brs, 1 H, 1-H), 4.22 (dd, 1 H, J = 11.9, 3.4 Hz, 3-H), 3.50 (brs, 1 H, 4-H), 3.35 (s, $OC\underline{H}_3$), 1.96 (d, 1 H, J = 8.3 Hz, 7_{syn}-H), 1.63 (d, 1 H, J = 8.3 Hz, 7_{anti}-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.16 (d, $J_{C–P}$ = 2.5 Hz, $\underline{C}O_2CH_3$), 137.37 (d, $J_{C–P}$ = 7.6 Hz, C-6), 135.26 (C-5), 133.09 (d, $J_{C–P}$ = 9.2 Hz, 2 × C_{ortho}), 132.71 (d, $J_{C–P}$ = 44.1 Hz, C_{ipso}), 132.37 (d, $J_{C–P}$ = 9.9 Hz, 2 × $C_{ortho.}$), 132.06 (d, $J_{C–P}$ = 2.7 Hz, C_{para}), 131.67 (d, $J_{C–P}$ = 2.7 Hz, C_{para}), 131.42 (d, $J_{C–P}$ = 35.1 Hz, C_{ipso}), 128.63 (d, $J_{C–P}$ = 12.7, 2 × C_{meta}), 127.99 (d, $J_{C–P}$ = 12.7, 2 × C_{meta}), 63.91 (d, $J_{C–P}$ = 1.6 Hz, C-1), 57.48 (d, $J_{C–P}$ = 2.4 Hz, C-3), 51.51 ($O\underline{C}H_3$), 50.51 (d, $J_{C–P}$ = 2.9 Hz, C-7 = CH_2), 48.63 (C-4); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 27.44; ^{15}N NMR (40 MHz, $CDCl_3$): δ = 72.06 (d, $J_{P–N}$ = 8.6 Hz); ESI-MS: calculated for $[C_{20}H_{20}NO_3P + H]^+$ ($M + H^+$) 354.12, found 354.67.

Analytical data for **8**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15–8.08 (m, 2 H, ArH_{ortho}), 7.69–7.77 (m, 2 H, ArH_{ortho}), 7.57–7.48 (m, 3 H, ArH), 7.44–7.31 (m, 3 H, ArH), 6.52 (dd, 1 H, J = 3.4, 2.2 Hz, 6-H), 6.33–6.28 (m, 1 H, 5-H), 4.25 (brs, 1 H, 1-H), 3.39 (s, $OC\underline{H}_3$), 3.31 (d, 1 H, J = 10.1 Hz, 3-H), 3.22 (brs, 1 H, 4-H), 2.19 (d, 1 H, J = 8.4 Hz, 7_{syn}-H), 1.40–1.34 (m, 1 H, 7_{anti}-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.14 (d, J_{C-P} = 1.7 Hz, $\underline{C}O_2CH_3$), 138.05 (d, J_{C-P} = 1.7 Hz, C-6), 134.66 (C-5), 132.89 (d, J_{C-P} = 9.3 Hz, 2 × C_{ortho}), 132.25 (d, J_{C-P} = 26.0 Hz, C_{ipso}), 132.05 (d, J_{C-P} = 9.8 Hz, 2 × C_{ortho}), 131.92 (d, J_{C-P} = 2.7 Hz, C_{para}), 131.54 (d, J_{C-P} = 2.7 Hz, C_{para}), 130.96 (d, J_{C-P} = 17.5 Hz, C_{ipso}), 128.55 (d, J_{C-P} = 12.6, 2 × C_{meta}), 127.92 (d, J_{C-P} = 12.6, 2 × C_{meta}), 62.74 (C-1), 58.94 (d, J_{C-P} = 1.9 Hz, C-3), 51.68 ($O\underline{C}H_3$), 50.18 (d, J_{C-P} = 5.3 Hz, C-4), 45.31 (d, J_{C-P} = 8.7 Hz, C-7 = CH_2); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 25.95; ^{15}N NMR (40 MHz, $CDCl_3$): δ = 74.51 (d, J_{P-N} = 10.3 Hz); ESI-MS: calculated for $[C_{20}H_{20}NO_3P + H]^+$ (M + H^+) 354.12, found 354.63.

Adducts 3, 4, 7 and 8 from (±)-2-hydroxy-2-azabicyclo[2.2.1]-hept-5-ene-3-carboxylates. A solution of methyl 2-hydroxy-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (**1** or **2**)[12] (2.06 g, 12.2 mmol), Et_3N (3.30 mL, 23.8 mmol) and a catalytic amount of DMAP (20 mg, 0.16 mmol) in dry CH_2Cl_2 (25 mL) at −15 °C was stirred under an argon atmosphere for 5 min. Then, $PClPh_2$ (2.10 mL, 12.0 mmol) was added dropwise and the mixture left to react for 4 h at −15 °C and for an additional 2 h at room temperature. The solvent was removed under low pressure, and the residue taken up in AcOEt and filtered through a funnel with a cotton plug. After removal of the solvent, the compounds formed were isolated by column chromatography (SiO_2, CH_2Cl_2–Et_2O 1 : 1 and/or AcOEt).

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