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Reaction of 2*H*-Azirine-Phosphine Oxides and -Phosphonates with Enolates Derived from β-Keto Esters

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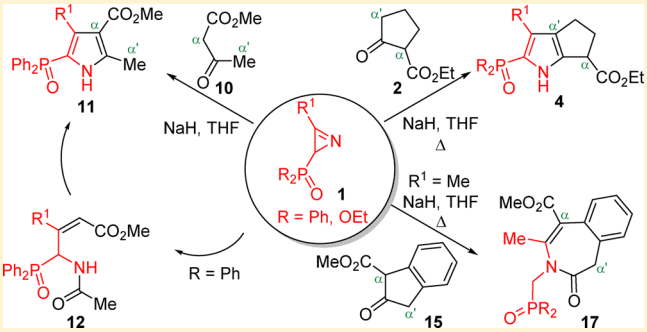
Supporting Information

ABSTRACT: Cyclopenta[*b*]-pyrrole-2-phosphine oxides **4a** and -phosphonates **4b,c** are generated by the addition of cyclic enolates derived from ethyl 2-oxo-cyclopentanecarboxylate **2** to phosphorated 2*H*-azirines **1**. However, the addition of enolate derived from acyclic 2-oxo-butanoate **10** to 2*H*-azirine phosphine oxide **1** led to vinylogous *N*-acyl-α-aminoalkyl phosphine oxides **12**, involving the carbonyl group and the Cα of the keto ester **10**. Ring closure of vinylogous derivative **12** in the presence of base afforded pyrrole-2-phosphine oxide **11**. The addition of enolates derived from indenone-carboxylate **15** to 2*H*-azirines **1** led to the formation of functionalized *N*-substituted 1*H*-benzo[*d*]azepine derivatives **17**.

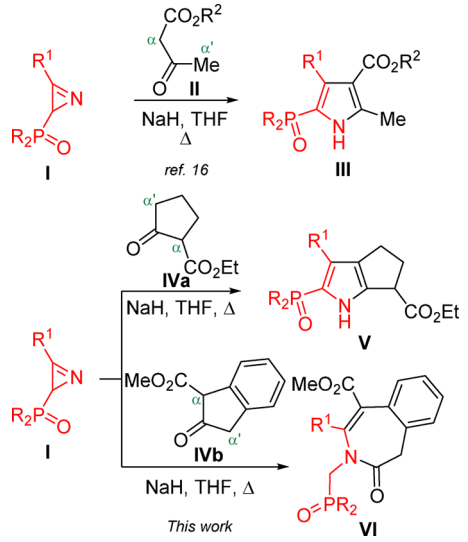


INTRODUCTION

2*H*-Azirine ring systems represent an important class of compounds because of their high reactivity[1] and because they can be used as key intermediates in organic synthesis in the preparation of heterocycles[2a−c] and acyclic functionalized amino derivatives.[2d] Moreover, pyrrole[3] is an important fragment in natural products,[4] which are widely used in material science[5] and medicinal chemistry for the preparation of biologically important molecules.[6] For these reasons, although many methods have been devised for their preparation,[7] the design and development of new methods of synthesis of substituted pyrroles continues to be a challenge.[8] The interest of azaheterocyclic phosphonates in synthetic, agrochemical, and medicinal chemistry has been well-documented[9] because it is known that phosphorus substituents regulate important biological functions[10] and that molecular modifications involving the introduction of organophosphorus functionalities in simple synthons could be very interesting because they can be useful substrates for the preparation of biologically active compounds. However, very little information is reported regarding the properties of phosphorus-substituted pyrroles[9] undoubtedly due to the fact that there are no general methods for their preparation.

We have previously described new methods for the preparation of phosphorus-substituted nitrogen heterocycles,[11] including *N*-hydroxypyrrole derivatives,[11a] and the synthetic uses of aminophosphorus derivatives as starting materials for the synthesis of acyclic compounds.[12] Likewise, we have reported the preparation[13] of 2*H*-azirine-phosphine oxides **I** (R = Ph) and -phosphonates **I** (R = OEt, Scheme 1) and their use for the synthesis of aminophosphorus derivatives,[14] as well as phosphorylated aziridines,[15a] oxazoles,[15b] pyrazines,[15c] and

Scheme 1



pyrroles **III** (Scheme 1).[16] Although the reaction of azirines, or their precursors vinyl azides, with acetylacetates is not a simple process because mixtures of pyrrole derivatives were obtained,[17] enolates derived from acetylacetates **II** (Scheme 1) were used for the preparation of pyrroles **III** from azirines **I** and the α-enolate of keto esters **II** involving its carbonyl group (C═O) and CHα in the formation of five-membered heterocycles **III**. Continuing with our interest in the chemistry

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of small strained nitrogen-containing heterocycles, such as azirines, we report here the use of α-enolates of cyclic keto esters **IV** and a new strategy for the formation of functionalized bicyclic pyrroles **V** and 1*H*-benzo[*d*]azepine derivatives **VI**. To the best of our knowledge, this strategy represents the first example of the construction of five-membered pyrroles involving 2*H*-azirines, which contributes with 3 atoms to the heterocycle, a cyclic keto ester linked to the azirines through the carbonyl group and the CHα', as well as the formal insertion of the C−N bond from the azirines **I** between the carbonyl group and the CHα of indenone-carboxylate **IVb** with the formation of seven-membered ring systems.

RESULTS AND DISCUSSION

Selective Addition of Enolates Derived from Ethyl 2-Oxo-cyclopentanecarboxylate 2 to 2*H*-Azirines 1. Because of the strain of the three-membered ring, the electrophilic character of the C−N double bond is higher than in a normal imine, and azirines react with nucleophiles at the N−C3 double bond to produce aziridines. When 2*H*-azirine-phosphine oxide **1a** (R = Ph, R^1 = Me) was treated with methyl 2-oxo-cyclopentanecarboxylate **2** in the presence of NaH in THF at 60 °C, the expected bicyclic pyrrole derivative **3** was not obtained in a similar way to that reported, as it would be expected according to previous results for acetylacetates.[16] The formation of these pyrroles **3** would involve the addition reaction of the α-enolate of the keto ester **2** to the azirine followed by intramolecular nucleophilic attack of the aziridine moiety to the carbonyl group of intermediate **5** and ring expansion of the bicyclic fused aziridine-azetidine fragment of tricyclic intermediate **6**. However, instead of pyrrole **3** a different bicyclic pyrrole derivative, the 6-ethoxycarbonyl-3-methyl-1,4,5,6-tetrahydro-cyclopenta[*b*]-pyrrol-2-yl phosphine oxide **4a** (R = Ph, R^1 = Me; Scheme 2, Table 1, entry 1) was obtained.

The ^{31}P NMR spectrum showed only one signal for the phosphine oxide group of this substituted pyrrole **4a** at δ_P = 19.8 ppm, and a doublet at δ_H = 1.78 ppm ($^4J_{PH}$ = 1.4 Hz) for the methyl group in the ^{1}H NMR spectra was observed.

Scheme 2

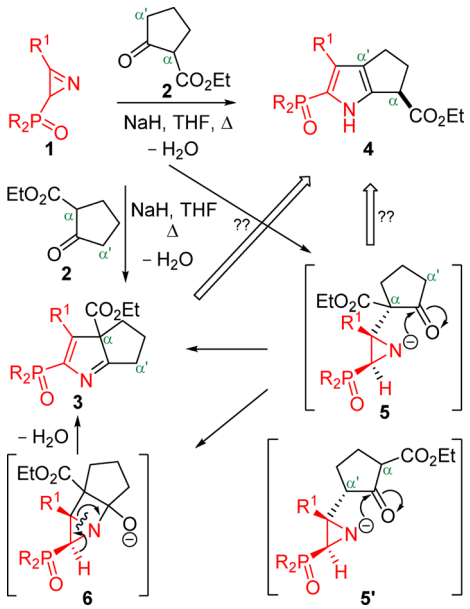

Table 1. Substituted Pyrroles 4 and Aziridines 7 Obtained

entry	compound	R	R^1	yield (%)[a]
1	**4a**	Ph	Me	87
2	**4b**	OEt	Me	81 (90)[b]
3	**4c**	OEt	Ph	75 (96)[b]
4	**7a**	OEt	Me	86
5	**7b**	OEt	Ph	88

[a]Yield of isolated purified compounds **4** and **7** from 2*H*-azirines **1**. [b]Yield from aziridines **7**.

Moreover, ^{13}C NMR spectra showed that the carboxylate group was not placed in a quaternary carbon atom as was expected in compound **3a** but was directly linked to a CH of the cyclopentane ring with signals at δ_C = 43.7 and 172.0 ppm for the 6-CH atom and the carboxylate group, respectively. X-ray diffraction structure of pyrrole **4a** undoubtedly confirms the structure of this compound (see Supporting Information).

This process could also be extended to 2*H*-azirines derived from phosphonates **1** (R = OEt). Treatment of 3-methyl-**1b** (R = OEt, R^1 = Me) and 3-phenyl-2*H*-azirine **1c** (R = OEt, R^1 = Ph) with the enolate derived from ethyl 2-oxo-cyclopentane-carboxylate **2** in the presence of NaH in THF gave cyclopenta[*b*]pyrrol-2-yl phosphonates **4b**,**c** (Scheme 2, Table 1, entries 2 and 3). The formation of compound **4** does not seem simple; it may be explained by, among others reasons, (i) by direct addition of the α'-enolate of the keto ester **2**, involving the carbonyl group and the CHα', to azirine **1** to give intermediate **5′** followed by intramolecular nucleophilic addition of intermediate **5′**; (ii) by formation of expected bicyclic pyrrole derivative **3** and subsequent [1,3] rearrangement of the carboxylic group and/or; (iii) by direct addition of the α-enolate of keto ester **2**, involving the carbonyl group and the CHα, to azirine **1** to give intermediate **5** and formation of the corresponding bicyclic pyrrole derivative **4** through a new process involving new intermediates. These different alternatives may be consistent with the synthesis of different kinds of pyrrole derivatives[17] reported from acetylacetates and vinyl azides by ring expansion of 3-vinyl 2*H*-azirines[18] or by the reaction of azirines or imines with functionalized acetylenes.[19] However, our strategy describes, as far as we know, the first synthesis of bicyclic cyclopenta[*b*]pyrrole compounds containing a phosphonate or a phosphine oxide group.

To explain the mechanism of formation of pyrroles **4**, we tried to trap or isolate intermediates of the process. Initially, we explored whether the α'-enolate (dianion) of keto ester **2** might be involved in the nucleophilic addition to azirine **1** to give **4** by means of intramolecular nucleophilic addition of intermediate **5′** in a similar way to that reported in the reaction of 1,3-dicarbonyl dianions with α-azido ketones.[20] However, the treatment of 2*H*-azirine phosphine oxide **1a** (R = Ph, R^1 = Me) or of 2*H*-azirine phosphonate **1b** (R = OEt, R^1 = Me) with ethyl 2-oxo-cyclopentanecarboxylate **2** in the presence of 2 equiv of LDA in THF at −78 °C did not give pyrroles **4**, as the starting materials were isolated (Scheme 3). When the temperature was raised to rt and 60 °C, a complex mixture of products was obtained.

Next, the reaction of **1** and **2** was explored in the presence of NaH in THF but at 0 °C instead of heating at 60 °C. When 2*H*-azirine-phosphine oxide **1a** (R = Ph, R^1 = Me) was used, no intermediates could be isolated, and pyrrole **4a** was obtained (Scheme 3). However, the reaction of 2*H*-azirine-phosphonate **1b** (R = OEt, R^1 = Me) or 2*H*-azirine-phosphonate **1c** (R =

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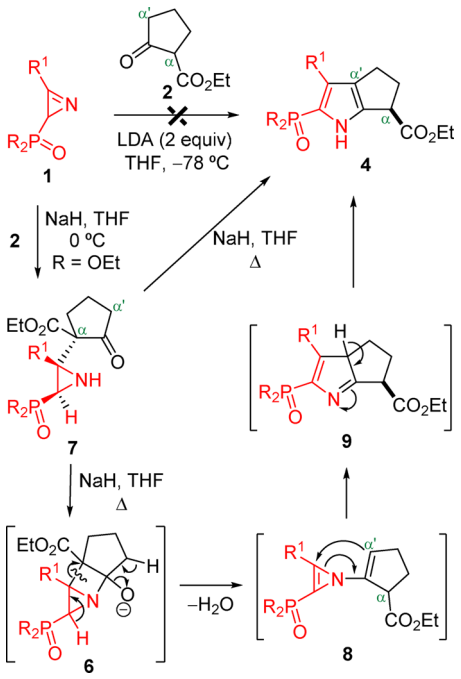
Scheme 3



OEt, R^1 = Ph) with ethyl 2-oxo-cyclopentanecarboxylate **2** in the presence of NaH in THF at 0 °C afforded the functionalized aziridines ethyl 3-(diethoxyphosphoryl)-2-azir-idin-2-yl-2-oxocyclopentane-1-carboxylates **7a** (R = OEt, R^1 = Me) and **7b** (R = OEt, R^1 = Ph) (Scheme 3, Table 1, entries 4, 5). ^{31}P NMR spectrum of the phosphonate group of aziridine **7a** resonated at δ_P = 23.8 ppm, whereas a well resolved doublet at δ_H = 1.54 ppm ($^2J_{PH}$ = 12.9 Hz) for H3 in the ^{1}H NMR spectrum, as well as at δ_C = 32.0 ppm ($^1J_{PC}$ = 201.4 Hz), and a singlet at δ_C = 41.6 ppm for C3 and C2 in the ^{13}C NMR spectrum were observed. Thermal treatment of aziridine-phosphonates **7a** and **7b** with NaH in refluxing THF led to the formation of the corresponding 1,4,5,6-tetrahydro-cyclopenta[*b*]-pyrrol-2-yl phosphonates **4b** and **4c** in excellent yields (Scheme 3, Table 1, entries 2, 3).

These results showed that functionalized aziridines **7** are involved in the formation of cyclopenta[*b*]-pyrrole derivatives **4** and that in the presence of a base (NaH) the intermediate **5** (*α*-enolate) and not **5′** (*α′*-enolate) is involved in the process (see Scheme 2). Therefore, the formation of bicyclic pyrrole derivatives **4** may be explained as shown in Scheme 3 through addition of the *α*-enolate of *β*-keto ester **2**, instead of the *α′*-enolate, to the 2*H*-azirine with generation of aziridine derivatives **7**. Even in the case of phosphonates (R = OEt), the aziridines **7a** and **7b** were isolated. The treatment of aziridines **7** with a base (NaH) may give tricyclic intermediate **6** generated by intramolecular nucleophilic attack of the aziridine moiety to the carbonyl group in a similar way to that reported for acetyl acetates.[16] Ring expansion of this intermediate as described before[16] would give pyrroles **3** (see Scheme 2). However, formation of pyrroles **4** must involve a different path, and the formation of an unstable *N*-cyclopentenyl-1*H*-azirine **8** followed by ring expansion to bicyclic pyrrole derivatives **9** and [1,3] prototropic rearrangement may afford pyrroles **4**. 1*H*-Azirine ring systems are antiaromatic with high ring strain and high reactivity.[21] For this reason, they are very unstable and, as has been recently demonstrated by Prof. Banert et al.,[22] 1*H*-azirines "are very short lived intermediates, which can be detected only at very low temperature with the help of the noble gas matrix isolation technique", although they are reported as very short-lived intermediates in the formation of nitrogen heterocycles.[23]

Selective Addition of Enolate Derived from Methyl 2-Oxo-butanoate 10 to 2*H*-Azirines 1. We reported the reaction of 2*H*-azirine-phosphine oxides **1** with methyl 2-oxo-butanoate **10** in the presence of NaH in refluxing THF to give 1*H*-pyrrol-2-yl phosphine oxides **11**.[16] New results observed with the enolates derived from keto ester **2** led us to update this process, and we attempted to isolate intermediates to illustrate the mechanism of the formation of the corresponding functionalized pyrroles **11**. For this reason, we explored if it would be possible to trap an intermediate of the process when the reaction was performed at 0 °C. Reaction of 2*H*-azirine-phosphine oxide **1a** (R^1 = Me) with methyl 2-oxo-butanoate **10** and NaH in THF at 0 °C led to the formation of methyl 5-(diphenylphosphoryl)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate **11a** (R^1 = Me) together with a new compound **12a**[24] in a ratio of 55:45 (Scheme 4, Table 2, entry 1). Unfortunately, this new

Scheme 4

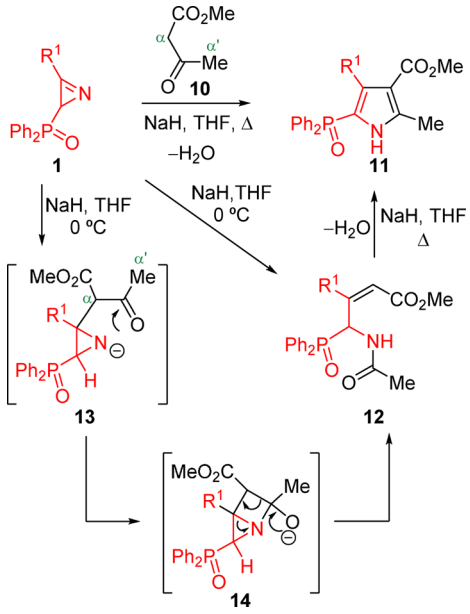


Table 2. Compounds 11, 12, 16, and 17 Obtained

entry	compounds	R	ratio	R^1	yield (%)[a]
1	**11a/12a**	Ph	55:45[b]	Me	85
2	**11b/12b**	Ph	70:30[b]	Et	83
3	**11a**	Ph		Me	(90)[c]
4	**11b**	Ph		Et	(80)[c] (84)[d]
5	**16a**	Ph	60:40[e]		68
6	**16b**	OEt	55:45[e]		70
7	**17a**	Ph			62 (86)[f]
8	**17b**	OEt			58 (88)[f]

[a]Yield of compounds from azirines **1**. [b]Both compounds **11** and **12** were obtained. [c]Yield of isolated purified compounds **11** from a mixture of **11**/**12**. [d]Yield of isolated purified compounds **11** from **12**. [e]Both isomers *E* and *Z* were obtained. [f]Yield of isolated purified compounds **17** from aziridines **16**.

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compound could not be isolated. However, thermal treatment of the mixture **11a**/**12a** with NaH in refluxing THF led to the formation of pyrrole-phosphine oxide **11a** (Scheme 4, Table 2, entry 3).

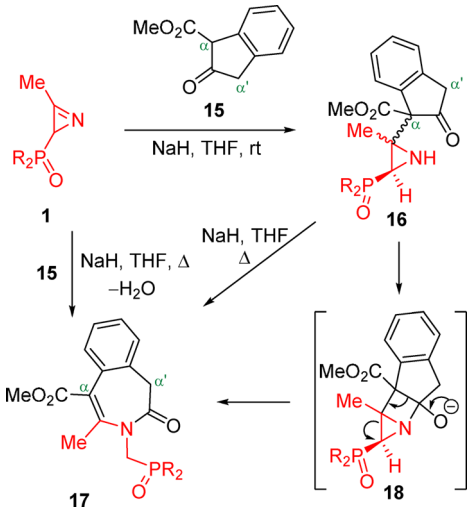
The reaction was extended to 2*H*-azirine-phosphine oxide **1d** (R^1 = Et) with methyl 2-oxo-butanoate **10** and NaH in THF at 0 °C to give a mixture of methyl 5-(diphenylphosphoryl)-4-ethyl-2-methyl-1*H*-pyrrole-3-carboxylate **11b** (R^1 = Et) together with new compound **12b** (R^1 = Et) in a ratio of 70:30 (Scheme 4, Table 2, entry 2). In this case, the vinylogous *α*-aminoalkyl-phosphine oxide **12b** could be isolated by flash-chromatography. Spectroscopic data were in agreement with the assigned structure for **12b**, and the X-ray diffraction spectrum of vinylogous *α*-aminoalkyl-phosphine oxide **12b** confirms the structure of this compound (see the Supporting Information).

As described above, thermal treatment of the mixture **11b**/**12b** with NaH in refluxing THF led to the formation of pyrrole-phosphine oxide **11b** (Scheme 4, Table 2, entry 4). Likewise, thermal treatment of vinylogous *α*-aminoalkyl-phosphine oxide **12b** in similar reaction conditions afforded pyrrole-phosphine oxide **11b** (Scheme 4, Table 2, entry 4). The formation of vinylogous *α*-aminoalkyl-phosphine oxide **12** suggests the selective addition of the enolate derived from acetyl acetate **10** to the imine bond of cyclic azirine **1** with the formation of intermediate **13** followed by nucleophilic addition of the aziridine to the carbonyl group to generate bicyclic-fused aziridine-azetidine intermediate **14** and ring opening of the C−N bond of the aziridine moiety of **14**. The cyclocondensation of **12** in the presence of a base (NaH) with the loss of water may give pyrrole **11**.

Selective Addition of Enolate Derived from Indenone-Carboxylate 15 to 2*H*-Azirines 1. To study the reaction of enolates derived from *β*-keto esters of indanone-carboxylate, the methyl 2-oxo-2,3-dihydro-1*H*-indeno-1-carboxylate **15** to 2*H*-azirines was also studied to test if this nucleophile could give a new entry to substituted polycyclic phosphorylated pyrrole derivatives, and/or if the presence of a benzene ring fused to the cyclopentanone may modify the mechanism. For this reason, we explored the reaction of 2*H*-azirine-phosphine oxide **1a** and -phosphonate **1b** with the enolate derived from indenone-carboxylate **15**. Reaction of 2*H*-azirine-phosphine oxide **1a** (R = Ph) with indenone-carboxylate ester **15** and NaH in THF at rt led to the formation of functionalized aziridine-phosphine oxides **16a** (R = Ph; Scheme 5, Table 2, entry 5) as an inseparable mixture of both isomers in a ratio of 60:40. The process was extended to 2*H*-azirine-phosphonate **1b** (R = OEt) with indenone-carboxylate ester **15** and NaH to afford aziridine-phosphonate **16b** (R = OEt; Scheme 5, Table 2, entry 6) in a ratio of 55:45, as confirmed by the ^{31}P NMR spectrum of the phosphonate group of aziridines **16b**, which resonated at δ_P = 23.3 and 25.3 ppm.

Thermal treatment of aziridine-phosphine oxide **16a** (R = Ph) or -phosphonate **16b** (R = OEt) with NaH in THF led to the formation of functionalized *N*-substituted 2-oxo-2,3-dihydro-1*H*-benzo[*d*]azepines **17** with good yields (Scheme 5, Table 2, entries 7 and 8). These bicyclic 1*H*-benzo[*d*]-azepines containing a phosphine oxide **17a** or a phosphonate group **17b** may also be directly obtained from 2*H*-azirine-phosphine oxide **1a** (R = Ph) and 2*H*-azirine-phosphonate **1b** (R = OEt) with *β*-keto ester **15** in the presence of NaH in refluxing THF (Scheme 5, Table 2, entries 7 and 8). Spectroscopic data were in agreement with the assigned

Scheme 5



structure for **17**, and the assignment of derivative **17a** was based on NOESY 1D experiments. Irradiation of one of the diastereotopic CH_2 protons directly linked to the phosphine oxide group ($C\underline{H}$-$POPh_2$) at 5.23 ppm showed an enhancement (2.29 and 1.95%) of the aromatic ring protons signal from the phenyl rings linked to the phosphorus atom, whereas the irradiation of the second diastereotopic CH_2 proton at 3.92 ppm showed an enhancement (5.93%) of the methyl protons signal at C4 of the 1*H*-benzo[*d*]azepine ring. Likewise, irradiation of the benzylic protons linked to the amido group ($C\underline{H}_2$-CON) at 3.37 ppm showed an interaction (4.03%) with the *ortho*-aromatic ring proton. X-ray diffraction structure of 1*H*-benzo[*d*]azepine **17a** confirms the structure of this compound (see the Supporting Information).

The formation of functionalized 1*H*-benzo[*d*]azepines **17** may be explained as illustrated in Scheme 5. Thermal treatment of aziridines **16** in the presence of the base (NaH) may give polycyclic intermediate **18** by intramolecular nucleophilic addition of the aziridine moiety to the carbonyl group. Ring expansion of the fused polycyclic aziridine-azetidine **18** involving not only the C−C bond cleavage of the fused cyclopenta-azetidine fragment but also the concomitant ring opening of the aziridine moiety with the cleavage of its C−C bond may explain the formation of functionalized bicyclic heterocycles **17**. 1*H*-Benzo[*d*]azepines constitute the skeleton of therapeutic substrates[25] and are disclosed as 5HT2C receptor agonists[26a] as well as NMDA[26b] and dopamine D(1) receptor[26c] activities. As far as we know, this process represents the first synthesis of bicyclic 1*H*-benzo[*d*]azepine derivatives containing a phosphonate or a phosphine oxide group.

CONCLUSIONS

In conclusion, this account describes a simple convenient strategy for the selective synthesis of bicyclic cyclopenta[*b*]-pyrroles **4** containing a phosphine oxide or a phosphonate group in the 2-position by addition of enolates derived from a cyclic *β*-keto ester **2** to 2*H*-azirine-phosphine oxide **1a** or -phosphonate **1b**. An unstable *N*-cyclopentenyl-1*H*-azirine **8** may explain the formation of bicyclic pyrrole derivatives **4**. However, vinylogous *α*-aminoalkyl-phosphine oxides **12** may be obtained from azirines **1** and the enolate derived from methyl 2-oxo-butanoate **10**. Basic cyclocondensation of these substrates **12** in the presence of a base (NaH) gives pyrroles **11**.

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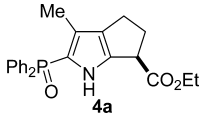
What is more, the addition of enolates derived from indenone-carboxylate **15** to azirines **1** gave functionalized aziridines **16**, although ring expansion of these three-membered heterocycles **16** leads to the formation of functionalized 1*H*-benzo[*d*]-azepines **17**. Substituted pyrroles[3−8] and 1*H*-benzo[*d*]-azepines[26] are important building blocks in organic synthesis, and phosphorus substituents regulate important biological functions.[10] Thus, molecular modifications involving the introduction of organophosphorus functionalities into pyrrole and/or 1*H*-benzo[*d*]azepine derivatives could be interesting because these new substituted five- and seven-membered heterocycles may be useful substrates for the preparation of biologically active compounds of interest in medicinal chemistry.[6,9,25]

EXPERIMENTAL SECTION

General Methods. Solvents for extraction and chromatography were of technical grade. All solvents used in reactions were freshly distilled and dried over 70 Å molecular sieves. All other solvents and reagents were obtained from commercial sources and used without further purification. All reactions were performed under an atmosphere of dry nitrogen. Melting points are uncorrected. IR spectra were measured on an FT-IR spectrometer, and absorbance frequencies are given at maximum of intensity in cm^{-1}. High resolution mass spectra (HRMS) were obtained using an electron spray ionization (ESI) method with a time-of-flight Q-TOF system. ^{1}H (300 MHz), ^{13}C (75 MHz), and ^{31}P NMR (120 MHz) spectra were recorded on a 300 MHz spectrometer in $CDCl_3$ as specified below. Chemical shifts (δ_H) are reported in parts per million (ppm) relative to TMS as internal standard. Chemical shifts (δ_C) are reported in parts per million (ppm), relative to $CDCl_3$, as internal standard in broad band decoupled mode. The abbreviations used are as follows: s, singlet; d, doublet; dd, double-doublet; t, triplet; q, quartet; m, multiplet. Flash-column chromatography was carried out using commercial grades of silica gel finer than 230 mesh. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} plates, and spot visualization was accomplished by UV light (254 nm) or $KMnO_4$ solution. Azirines **1** were prepared according to a literature procedure.[13b]

General Procedure for the Synthesis of Substituted Pyrroles 4 from Azirines 1. To a solution of NaH (6.0 mmol) in dry THF (15 mL) under nitrogen atmosphere was added a solution of ethyl 2-oxocyclopentane-1-carboxylate **2** (6.0 mmol). The mixture was stirred at 0 °C for 1 h. Then, a solution of 2*H*-azirine-phosphine oxides **1** (R = Ph) or -phosphonates (R = OEt) (5.0 mmol) was slowly added in dry THF (6 mL) under a nitrogen atmosphere. The mixture was stirred in refluxing THF for 4−6 h until TLC showed the disappearance of azirine **1**. The remaining NaH was neutralized with a saturated solution of NH_4Cl, and the solvent was evaporated under vacuum. The crude reaction mixture was dissolved in CH_2Cl_2 (25 mL) and washed with water (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated under vacuum. The crude product was purified by chromatography using silica-gel (hexane/ethyl acetate) to yield compounds **4**.

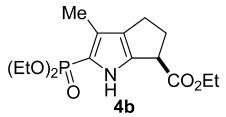
*Ethyl (R)-2-(Diphenylphosphoryl)-3-methyl-1,4,5,6-tetrahydrocyclopenta[b]pyrrole-6-carboxylate (**4a**).* Compound **4a** was ob-



4a

tained as a white solid (1711 mg, 87%) from 2*H*-azirine **1a** as described in the general procedure. Mp 184−185 °C; ^{1}H NMR ($CDCl_3$) δ 1.19 (t, $^{3}J_{HH}$ = 7.2 Hz, 3H, CH_3), 1.78 (d, $^{4}J_{PH}$ = 1.4 Hz, 3H, CH_3), 2.48−2.82 (m, 4H, CH_2), 3.88 (t, $^{3}J_{PH}$ = 5.5 Hz, 1H, CH-C=O), 4.12 (q, $^{3}J_{HH}$ = 7.2 Hz, 2H, OCH_2), 7.28−7.80 (m, 10H, CH-arom), 8.51 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 11.3, 14.1, 22.8, 32.6, 43.7, 61.0, 120.4 (d, $^{1}J_{PC}$ = 129.9 Hz), 123.9 (d, $^{2}J_{PC}$ = 13.6 Hz), 128.1−132.3, 133.5 (d, $^{3}J_{PC}$ = 12.1 Hz), 137.6 (d, $^{3}J_{PC}$ = 9.1 Hz), 172.0; ^{31}P NMR ($CDCl_3$) δ 19.8; IR (neat) ν_{max} 3452, 3150, 3056, 2972, 2932, 1730, 1432, 1178 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{25}NO_3P$ $[M + H]^+$ 394.1572, found 394.1567.

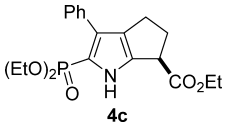
*Ethyl (R)-2-(Diethoxyphosphoryl)-3-methyl-1,4,5,6-tetrahydrocyclopenta[b]pyrrole-6-carboxylate (**4b**).* Compound **4b** was ob-



4b

tained as a yellow oil (1333 mg, 81%) from 2*H*-azirine **1b** as described in the general procedure. R_f = 0.47 (AcOEt); ^{1}H NMR ($CDCl_3$) δ 1.32 (t, $^{3}J_{HH}$ = 7.1 Hz, 9H, CH_3), 2.14 (s, H, CH_3), 2.34−2.75 (m, 4H, CH_2), 3.90 (t, $^{3}J_{HH}$ = 6.9 Hz, 1H, CH−CO_2Et), 4.00−4.22 (m, 6H, OCH_2), 8.65 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 10.7, 14.3, 16.2, 22.8, 32.7, 43.7, 61.1, 61.7, 117.3 (d, $^{1}J_{PC}$ = 223.7 Hz), 124.1 (d, $^{3}J_{PC}$ = 17.1 Hz), 130.4 (d, $^{3}J_{PC}$ = 15.3 Hz), 137.7 (d, $^{2}J_{PC}$ = 12.2 Hz), 172.1; ^{31}P NMR ($CDCl_3$) δ 11.8; IR (neat) ν_{max} 3212, 2976, 2945, 1739, 1232, 1018 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{25}NO_5P$ $[M + H]^+$ 330.1470, found 330.1475.

*Ethyl (R)-2-(Diethoxyphosphoryl)-3-phenyl-1,4,5,6-tetrahydrocyclopenta[b]pyrrole-6-carboxylate (**4c**).* Compound **4c** was ob-

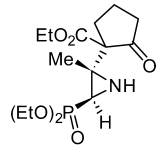


4c

tained as a white solid (1467 mg, 75%) from 2*H*-azirine **1c** as described in the general procedure. Mp 116−117 °C; ^{1}H NMR ($CDCl_3$) δ 1.07 (t, $^{3}J_{HH}$ = 7.0 Hz, 3H, CH_3), 1.25 (t, $^{3}J_{HH}$ = 7.2 Hz, 6H, CH_3), 2.69 (m, 4H, CH_2), 3.84−4.02 (m, 4H, OCH_2), 3.97 (t, $^{3}J_{HH}$ = 7.0 Hz, 1H, CH−CO_2Et), 4.16 (q, $^{3}J_{HH}$ = 7.0 Hz, 2H, OCH_2), 7.13−7.49 (m, 5H, CH-arom), 9.04 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.3, 15.9, 24.3, 32.8, 43.6, 61.2, 62.1, 116.6 (d, $^{1}J_{PC}$ = 221.1 Hz), 126.6−128.4, 128.6, 134.4, 138.2 (d, $^{2}J_{PC}$ = 12.1 Hz), 172.0; ^{31}P NMR ($CDCl_3$) δ 11.3; IR (neat) $_{max}$ 3185, 3056, 2985, 2927, 1734, 1445, 1241, 1018 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{27}NO_5P$ $[M + H]^+$ 392.1627, found 392.1630.

General Procedure for the Synthesis of Substituted Aziridines 7 from Azirines 1. To a solution of NaH (5.5 mmol) in dry THF (15 mL) under nitrogen atmosphere was added a solution of ethyl 2-oxocyclopentane-1-carboxylate **2** (5.5 mmol). The mixture was stirred at 0 °C for 1 h. Then, a solution of 2*H*-azirine-phosphonates **1b** or **1c** (5.0 mmol) in dry THF (6 mL) was slowly added under a nitrogen atmosphere. The mixture was stirred at 0 °C for 4−5 h until TLC showed the disappearance of azirine. The remaining NaH was neutralized with a saturated solution of NH_4Cl, and the solvent was evaporated under vacuum. The crude reaction mixture was dissolved in CH_2Cl_2 (25 mL) and washed with water (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated under vacuum. The crude product was purified by chromatography using silica-gel (hexane/ethyl acetate) to yield compounds **7**.

*Ethyl (R)-1-((2S,3S)-3-(Diethoxyphosphoryl)-2-methylaziridin-2-yl)-2-oxocyclopentane-1-carboxylate (**7a**).* Compound **7a** was



7a

obtained as a yellow oil (1493 mg, 86%) from 2*H*-azirine **1b** as described in the general procedure. R_f = 0.36 (AcOEt); ^{1}H NMR ($CDCl_3$) δ 1.22 (t, $^{3}J_{HH}$ = 7.0 Hz, 3H, CH_3), 1.27 (t, $^{3}J_{HH}$ = 7.0 Hz, 6H, CH_3), 1.47 (s, 3H, CH_3) 1.54 (d, $^{2}J_{PH}$ = 12.9 Hz, 1H, CH-P),

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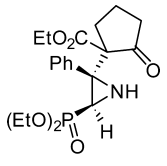
1.82−2.10 (m, 2H, CH_2), 2.19−2.40 (m, 4H, CH_2), 4.05−4.18 (m, 6H, OCH_2); ^{13}C NMR ($CDCl_3$) δ 13.9, 16.6, 17.2, 19.1, 30.1, 32.0 (d, $^1J_{PC}$ = 201.4 Hz), 32.4, 38.9, 41.6, 61.9−62.3, 63.3, 169.0, 212.4; ^{31}P NMR ($CDCl_3$) δ 23.8; IR (neat) ν_{max} 3466, 3274, 2980, 2927, 2900, 1748, 1721, 1227, 1009 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{27}NO_6P$ $[M + H]^+$ 348.1576, found 348.1571.

*Ethyl (1R)-1-((3S)-3-(Diethoxyphosphoryl)-2-phenylaziridin-2-yl)-2-oxocyclopentane-1-carboxylate (**7b**).* Compound **7b** was obtained

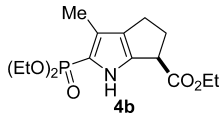


7b

as a white solid (1800 mg, 88%) from 2*H*-azirine **1c** as described in the general procedure. Mp 95−96 °C; ^1H NMR ($CDCl_3$) δ 0.90 (t, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3), 1.20 (t, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3), 1.26 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CH_3), 2.00 (d, $^2J_{PH}$ = 14.6 Hz, 1H, CH-P), 2.43 (t, $^3J_{HH}$ = 7.0 Hz, 2H, CH_2), 3.26 (t, $^3J_{HH}$ = 7.0 Hz, 2H, CH_2), 3.64 (m, 2H, CH_2), 4.00 (q, $^3J_{HH}$ = 7.1 Hz, 2H, OCH_2), 4.10 (q, $^3J_{HH}$ = 7.0 Hz, 4H, OCH_2), 7.29−7.51 (m, 5H, H-arom); ^{13}C NMR ($CDCl_3$) δ 13.7 (CH_3), 15.7, 15.9, 19.0, 33.6 (d, $^1J_{PC}$ = 213.0 Hz), 34.3, 39.3, 48.3, 61.7, 61.8, 64.3, 124.00−129.7, 135.8, 166.6, 212.2; ^{31}P NMR ($CDCl_3$) δ 20.4; IR (neat) ν_{max} 3283, 2980, 2927, 1720, 1712, 1232, 1022 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{29}NO_6P$ $[M + H]^+$, 410.1732, found 410.1735.

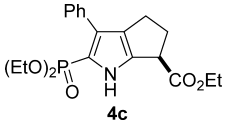
General Procedure for the Synthesis of Substituted Pyrroles 4 from Aziridines 7. To a solution of NaH (5.5 mmol) in dry THF (15 mL) under nitrogen atmosphere was added a solution of the corresponding aziridine **7** (5.0 mmol). The mixture was stirred in refluxing THF for 3−4 h until TLC showed the disappearance of aziridine **7**. The remaining NaH was neutralized with a saturated solution of NH_4Cl, and the solvent was evaporated under vacuum. The crude reaction mixture was dissolved in CH_2Cl_2 (25 mL) and washed with water (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated under vacuum. The crude product was purified by chromatography using silica-gel (hexane/ethyl acetate) to yield compounds **4**.

*Ethyl (R)-2-(Diethoxyphosphoryl)-3-methyl-1,4,5,6-tetrahydrocyclopenta[b]pyrrole-6-carboxylate (**4b**).* Compound **4b** was obtained as yellow oil (1481 mg, 90%) from aziridine **7a** as described in the general procedure. For experimental data see above.



4b

*Ethyl (R)-2-(diethoxyphosphoryl)-3-phenyl-1,4,5,6-tetrahydrocyclopenta[b]pyrrole-6-carboxylate (**4c**).* Compound **4c** was obtained as a white solid (1878 mg, 96%) from aziridine **7b** as described in the general procedure. For experimental data see above.



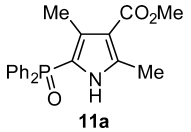
4c

General Procedure for the Synthesis of Substituted Pyrroles 11 and α-Aminoalkyl-phosphine Oxides 12 from Azirines 1. To a 0 °C solution of NaH (5.5 mmol) in dry THF (15 mL) under nitrogen atmosphere was added a solution of methyl 2-oxobutanoate **10** (5.5 mmol). The mixture was stirred at the same temperature for 1 h. Then, a solution of 2*H*-azirine-phosphine oxides **1a** or **1d** (5.0 mmol) in dry THF (6 mL) was slowly added at 0 °C under a nitrogen atmosphere. The mixture was stirred in refluxing THF for 4−5 h until TLC showed the disappearance of azirine **1**. The remaining NaH was neutralized with a saturated solution of NH_4Cl, and the solvent was evaporated under vacuum. The crude reaction mixture was dissolved in CH_2Cl_2 (25 mL) and washed with water (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated under vacuum. The crude product was purified by chromatography using silica-gel (hexane/ethyl acetate) to yield compounds **11** and **12**.

General Procedure for the Synthesis of Substituted Pyrroles 11 from a Mixture of 11/12. To a solution of NaH (5.5 mmol) in dry THF (15 mL) under a nitrogen atmosphere was added a solution of a mixture of compounds **11** and **12** (5.5 mmol). The mixture was stirred in refluxing THF for 2 h until TLC showed the disappearance of **12**. The remaining NaH was neutralized with a saturated solution of NH_4Cl, and the solvent was evaporated under vacuum. The crude reaction mixture was dissolved in CH_2Cl_2 (25 mL) and washed with water (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated under vacuum. The crude product was purified by chromatography using silica-gel (hexane/ethyl acetate) to yield compounds **11**.

General Procedure for the Synthesis of Substituted Pyrrole 11b from α-Aminoalkyl-phosphine Oxide 12b. To a solution of NaH (5.5 mmol) in dry THF (15 mL) under a nitrogen atmosphere was added a solution of the α-aminoalkyl-phosphine oxide **12b** (5.0 mmol). The mixture was stirred at 0 °C in THF for 3 h until TLC showed the disappearance of compound **12b**. The remaining NaH was neutralized with a saturated solution of NH_4Cl, and the solvent was evaporated under vacuum. The crude reaction mixture was dissolved in CH_2Cl_2 (25 mL) and washed with water (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated under vacuum. The crude product was purified by chromatography using silica-gel (hexane/ethyl acetate) to yield compound **11b**.

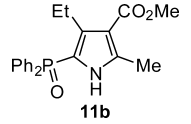
*Methyl 5-(Diphenylphosphoryl)-2,4-dimethyl-1H-pyrrole-3-carboxylate (**11a**).* Compound **11a** was obtained as a white solid



11a

(1589 mg, 90%) from a mixture of **11a**/**12a**. Mp 236−237 °C; ^1H NMR ($CDCl_3$) δ 1.89 (d, $^4J_{PH}$ = 1.5 Hz, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 7.36−7.69 (m, 10H, H-arom), 10.41 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 12.8, 13.9, 50.6, 113.3 (d, $^3J_{PC}$ = 11.1 Hz), 115.4 (d, $^1J_{PC}$ = 133.0 Hz), 128.4−133.2, 130.7 (d, $^2J_{PC}$ = 14.6 Hz), 141.0 (d, $^3J_{PC}$ = 8.1 Hz), 166.1; ^{31}P NMR ($CDCl_3$) δ 21.9; IR (neat) ν_{max} 3154, 3081, 3037, 2958, 1698, 1438, 1169, 1125 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{21}NO_3P$ $[M + H]^+$ 354.1254, found 354.1253.

*Methyl 5-(Diphenylphosphoryl)-4-ethyl-2-methyl-1H-pyrrole-3-carboxylate (**11b**).* Compound **11b** was obtained as a white solid



11b

(1469 mg, 80%) from a mixture of **11b**/**12b** (1542 mg, 84%) from α-aminoalkyl-phosphine oxide **12b**. Mp 245−246 °C; ^1H NMR ($CDCl_3$) δ 0.57 (t, $^3J_{HH}$ = 7.3 Hz, 3H, CH_3), 2.37 (q, $^3J_{HH}$ = 7.3 Hz, 2H, CH_2), 2.49 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 7.40−7.68 (m, 10H, CH-arom), 11.21 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.6, 19.9, 50.5, 112,1 (d, $^3J_{PC}$ = 11.1 Hz), 114.5 (d, $^1J_{PC}$ = 133.0 Hz), 128.4−133.5, 137.2 (d, $^2J_{PC}$ = 15.1 Hz), 141.7 (d, $^3J_{PC}$ = 8.6 Hz), 168.8; ^{31}P NMR ($CDCl_3$) δ 22.4; IR (neat) ν_{max} 3155, 3082, 2958, 1698, 1438, 1169, 1125 cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{23}NO_3P$ $[M + H]^+$ 368.1416, found 368.1418.

*Methyl (Z)-4-Acetamido-4-(diphenylphosphoryl)-3-methylbut-2-enoate (**12a**).*[24] ^1H NMR ($CDCl_3$) δ 1.70 (d, $^2J_{PH}$ = 14.0 Hz, 1H, CH-P), 2.10 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 3.52 (s, 3H, OCH_3),

DOI: 10.1021/acs.joc.5b02347
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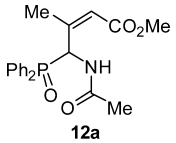
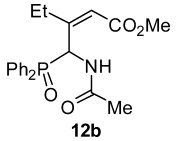


12a

5.22 (s, 1H, NH), 5.75 (s, 1H, CH), 7.29−7.74 (m, 8H, CH-arom), 8.11−8.27 (m, 2H, CH-arom); ^{31}P NMR ($CDCl_3$) δ 35.0 ppm.

*Methyl (Z)-3-Acetamido-4-(diphenylphosphoryl)methyl)pent-2-enoate (**12b**).* Compound **12b** was obtained as a white solid (481

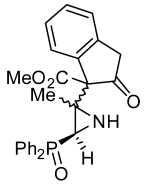


12b

mg, 25%) from 2*H*-azirine **1a** as described in the general procedure. Mp 218−219 °C ;^{1}H NMR ($CDCl_3$) δ 0.96 (t, $^3J_{HH}$ = 7.3, 3H, CH_3), 1.89 (d, $^2J_{PH}$ = 18.0 Hz, 1H, CH-P), 1.92 (s, 3H, CH_3), 2.42 (dq, $^4J_{PH}$ = 19.8 Hz, $^3J_{HH}$ = 7.3 Hz, 2H, CH_2), 2.5 (s, 1H, NH), 3.57 (s, 3H, CH_3), 5.53 (d, $^4J_{PH}$ = 1.5 Hz, 1H, CH), 7.27−7.69 (m, 8H, CH-arom), 8.01−8.08 (m, 2H, CH-arom); ^{13}C NMR ($CDCl_3$) δ 11.3, 22.9, 26.9, 49.6 (d, $^1J_{PC}$ = 71.5 Hz), 117.2 (d, $^3J_{PC}$ = 8.1 Hz), 127.7−132.4, 156.9 (d, $^2J_{PC}$ = 2.0 Hz), 166.4, 169.6; ^{31}P NMR ($CDCl_3$) δ 35.8; IR (neat) ν_{max} 3256, 3190, 2979, 2923, 1703, 1672, 1432, 1165 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $NaC_{21}H_{24}NO_4P$ [M + Na]$^+$ 408.1341, found 408.1353.

General Procedure for the Synthesis of Substituted Aziridines 16 from Azirines 1. To a solution of NaH (6.0 mmol) in dry THF (15 mL) under a nitrogen atmosphere was added a solution of methyl 2-oxo-2,3-dihydro-1*H*-indene-1-carboxylate **15** (6.0 mmol). The mixture was stirred at room temperature for 1 h. Then, a solution of 2*H*-azirine-phosphine oxide **1a** (R = Ph) or -phosphonate **1b** (R = OEt) (5.0 mmol) in dry THF (6 mL) was slowly added under a nitrogen atmosphere. The mixture was stirred at room temperature for 14 h until TLC showed the disappearance of azirine **1**. The remaining NaH was neutralized with a saturated solution of NH_4Cl, and the solvent was evaporated under vacuum. The crude reaction mixture was dissolved in CH_2Cl_2 (25 mL) and washed with water (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated under vacuum. The crude product was purified by chromatography using silica-gel (hexane/ethyl acetate) to yield isomeric compounds **16**.

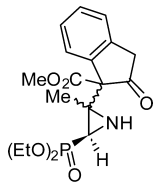
*Methyl 2-(3-(Diphenylphosphoryl)-2-methylaziridin-2-yl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**16a**).* The general procedure



16a

was applied using 2*H*-azirine **1a**, affording a mixture (60/40) of isomers **16a** as a white solid (1513.5 mg, 68%). ^{1}H NMR ($CDCl_3$) **16a**$_{major}$ δ 1.55 (s, 3H, CH_3), 2.44 (d, $^2J_{PH}$ = 22.3 Hz, 1H, CH-P), 3.47 (s, 3H, CH_3), 4.11 (d, $^2J_{HH}$ = 19.8 Hz, 2H, CH_2), 7.01−7.54 (m, 11H, H-arom), 7.73−7.97 (m, 3H, H-arom); **16a**$_{minor}$ δ 1.37 (s, 3H, CH_3), 3.14 (d, $^2J_{PH}$ = 20.9 Hz, 1H, CH-P), 3.51 (s, 3H, OCH_3), 3.85 (d, $^2J_{HH}$ = 19.7 Hz, 2H, CH_2), 7.01−7.54 (m, 11H, H-arom), 7.73−7.97 (m, 3H, H-arom); ^{13}C NMR ($CDCl_3$) **16a**$_{major}$ δ 15.6 (d, $^3J_{PC}$ = 1.8 Hz), 34.6 (d, $^1J_{PC}$ = 91.6 Hz), 42.9, 49.7 (d, $^2J_{PC}$ = 3.4 Hz), 52.2, 68.1, 124.7−137.5, 168.2, 208.1; **16a**$_{minor}$ δ 13.8, 43.3, 44.1 (d, $^1J_{PC}$ = 101.3 Hz), 51.7, 53.1, 59.8, 124.7−137.5, 169.1, 181.6; ^{31}P NMR ($CDCl_3$) **16a**$_{major}$ δ 27.9; **16a**$_{minor}$ δ 24.1; IR (neat) ν_{max} 3439, 3246, 3053, 2986, 2948, 1764, 1732, 1688, 1264, 1188 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{25}NO_4P$ [M + H]$^+$ 446.1521, found 446.1526.

*Methyl (2-(3-(Diethoxyphosphoryl)-2-methylaziridin-2-yl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**16b**).* The general procedure



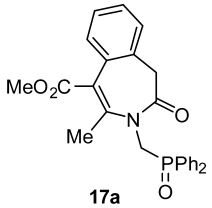
16b

was applied using 2*H*-azirine **1b**, affording a mixture (55:45) of isomers **16b** as a yellow oil (1334 mg, 70%). ^{1}H NMR ($CDCl_3$) **16b**$_{major}$ δ 1.24 (t, $^3J_{HH}$ = 7.0 Hz, 6H, CH_3), 1.49 (s, 3H, CH_3), 3.03 (d, $^2J_{PH}$ = 23.0 Hz, 1H, CH-P), 3.20 (d, $^2J_{HH}$ = 7.2 Hz, 2H, CH_2), 3.65 (s, 3H, OCH_3), 3.87 (d, $^3J_{PH}$ = 16.5 Hz, 1H, NH), 4.05 (q, $^3J_{HH}$ = 7.0 Hz, 4H, OCH_2), 7.23−7.66 (m, 4H, H-arom); **16b**$_{minor}$ δ 1.27 (t, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3), 1.34 (t, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3), 1.65 (s, 3H, CH_3), 2.83 (d, $^2J_{PH}$ = 10.7 Hz, 1H, CH-P), 3.40 (d, $^2J_{HH}$ = 17.2 Hz, 1H, CH), 3.77 (d, $^2J_{HH}$ = 17.2 Hz, 1H, CH), 3.65 (s, 3H, OCH_3), 4.06 (q, $^3J_{HH}$ = 7.0 Hz, 2H, OCH_2), 4.17 (q, $^3J_{HH}$ = 7.0 Hz, 2H, OCH_2), 7.27−7.65 (m, 4H, H-arom); ^{13}C NMR ($CDCl_3$) **16b**$_{major}$ δ 16.3 (d, $^3J_{PC}$ = 6.1 Hz), 18.0, 31.3 (d, $^1J_{PC}$ = 208.1 Hz), 32.7, 42.7, 53.2, 62.2 (d, $^2J_{PC}$ = 6.4 Hz), 63.7 (d, $^3J_{PC}$ = 2.1 Hz), 124.8−136.2, 152.9, 168.7, 198.8; **16b**$_{minor}$ δ 16.4 (d, $^3J_{PC}$ = 5.2 Hz), 18.2 (d, $^3J_{PC}$ = 2.7 Hz), 32.2 (d, $^1J_{PC}$ = 183.4 Hz), 36.2, 42.3, 52.9, 62.3 (d, $^2J_{PC}$ = 6.4 Hz), 64.2, 124.8−135.5, 135.1, 152.7, 169.6, 198.2; ^{31}P NMR ($CDCl_3$) **16b**$_{major}$ δ 23.3; **16b**$_{minor}$ δ 25.3; IR (neat) ν_{max} 3474, 3284, 2983, 2901, 1742, 1704, 1245, 1023 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{25}NO_6P$ [M + H]$^+$ 382.1419, found 382.1418.

General Procedure for the Synthesis of 1*H*-Benzo[*d*]azepine Derivatives 17 from Azirines 1. To a solution of NaH (6.0 mmol) in dry THF (15 mL) under a nitrogen atmosphere was added a solution of methyl 2-oxo-2,3-dihydro-1*H*-indene-1-carboxylate **15** (6.0 mmol). The mixture was stirred at room temperature for 1 h. Then, a solution of 2*H*-azirine-phosphine oxide **1a** (R = Ph) or -phosphonate **1b** (R = OEt) (5.0 mmol) in dry THF (6 mL) was slowly added under a nitrogen atmosphere. The mixture was stirred at room temperature for 14 h until TLC showed the disappearance of azirine **1**. The remaining NaH was neutralized with a saturated solution of NH_4Cl, and the solvent was evaporated under vacuum. The crude reaction mixture was dissolved in CH_2Cl_2 (25 mL) and washed with water (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated under vacuum. The crude product was purified by chromatography using silica-gel (hexane/ethyl acetate) to yield compounds **17**.

General Procedure for the Synthesis of 1*H*-Benzo[*d*]azepine Derivatives 17 from Aziridines 16. To a solution of NaH (5.5 mmol) in dry THF (15 mL) under a nitrogen atmosphere was added a solution of substituted aziridines **16** (5.5 mmol). The mixture was stirred in refluxing THF for 6 h until TLC showed the disappearance of aziridine. The crude reaction mixture was washed with water (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated under vacuum. The crude product was purified by chromatography using silica-gel (hexane/ethyl acetate) to yield compounds **17**.

*Methyl 3-((Diphenylphosphoryl)methyl)-4-methyl-2-oxo-2,3-dihydro-1H-benzo[d]azepine-5-carboxylate (**17a**).* Compound **17a**



17a

was obtained as a white solid (1463 mg, 62%) from 2*H*-azirine **1a** (1811 mg, 86%) from aziridine **16a**. Mp 97−98 °C; ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H, CH_3), 3.31 (d, $^2J_{HH}$ = 12.4 Hz, 1H, CH_2), 3.43

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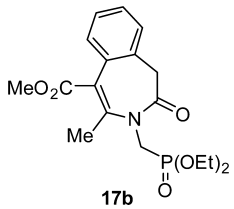
(d, $^2J_{HH}$ = 12.4 Hz, 1H, CH_2), 3.92 (dd, $^2J_{PH}$ = 16.0 Hz, $^4J_{HH}$ = 7.9 Hz, 1H, CH_2–P), 5.23 (dd, $^2J_{PH}$ = 16.0 Hz, $^4J_{HH}$ = 4.1 Hz, 1H, CH_2–P), 6.88–7.70 (m, 14H, H-arom); ^{13}C NMR ($CDCl_3$) δ 19.9, 42.3, 43.6 (d, $^1J_{PC}$ = 76.0 Hz), 57.2, 126.2, 127.2–132.4, 129.6, 131.6, 133.6 (d, $^2J_{PC}$ = 1.1 Hz), 139.9, 169.0 ($^3J_{PC}$ = 2.1 Hz), 169.4; ^{31}P NMR ($CDCl_3$) δ 28.3; IR (neat) ν_{max} 3056, 3024, 2989, 2955, 1720, 1669, 1435, 1216, 1121, 1093 cm^{-1}; HRMS (ESI) m/z calcd for $C_{26}H_{25}NO_4P$ $[M + H]^+$ 446.1521, found 446.1541.

*Methyl 3-((Diethoxyphosphoryl)methyl)-4-methyl-2-oxo-2,3-dihydro-1H-benzo[d]azepine-5-carboxylate (**17b**).* Compound **17b**



17b

was obtained as a yellow oil (1164 mg, 58%) from 2*H*-azirine **1b** (1606 mg, 88%) from aziridine **16b**. R_f (AcOEt) = 0.64; ^{1}H NMR ($CDCl_3$) δ 0.83 (t, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3), 1.11 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_3), 2.22 (s, 3H, CH_3), 3.47 (d, $^2J_{HH}$ = 14.0 Hz, 1H, CH_2), 3.51 (q, $^3J_{HH}$ = 7.2 Hz, 2H, OCH_2), 3.63 (q, $^3J_{HH}$ = 7.0 Hz, 2H, OCH_2), 3.65 (q, $^3J_{HH}$ = 14.0 Hz, 1H, CH_2), 3.74 (s, 3H, OCH_3), 4.65 (dd, $^2J_{PH}$ = 16.2 Hz, $^2J_{HH}$ = 13.1 Hz, 2H, CH_2–P), 7.19–7.28 (m, 4H, H-arom); ^{13}C NMR ($CDCl_3$) δ 14.3, 24.7, 29.6, 31.2 (d, $^1J_{PC}$ = 145.5 Hz), 53.7, 62.1, 127.1, 125.0–128.0, 128.5, 135.4, 135.8 (d, $^2J_{PC}$ = 22.9 Hz), 153.8, 169.8; ^{31}P NMR ($CDCl_3$) δ 20.7; IR (neat) ν_{max} 2964, 2923, 2853, 1726, 1675, 1258, 1096, 1030 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{25}NO_6P$ $[M + H]^+$ 382.1419, found 382.1423.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02347.

^{1}H NMR and ^{13}C NMR spectra of all new compounds (PDF)

Crystallographic data for **4a** (CIF) (ZIP)

Crystallographic data for **12b** (CIF) (ZIP)

Crystallographic data for **17a** (CIF) (ZIP)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews on azirines, see: (a) Huang, C.-Y.; Doyle, A. G. *Chem. Rev.* **2014**, *114*, 8153–8198. (b) Khlebnikov, A. F.; Novikov, M. S. *Tetrahedron* **2013**, *69*, 3363–3401. (c) Padwa, A. *Adv. Heterocycl. Chem.* **2010**, *99*, 1–31. (d) Padwa, A. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K., Eds; Elsevier: Oxford, UK, 2008; Vol *1A*, pp 1–104. (e) Pinho e Melo, T. M. V. D.; d'A Rocha Gonsalves, A. M. *Curr. Org. Synth.* **2004**, *1*, 275–292. (f) Gilchrist, T. L. *Aldrichimica Acta* **2001**, *34*, 51–55. (g) Palacios, F.; Ochoa de Retana, A. M.; Martínez de Marigorta, E.; de los Santos, J. M. *Eur. J. Org. Chem.* **2001**, *2001*, 2401–2414.

(2) For recent contributions, see: (a) Luo, J.; Chen, W.; Shao, J.; Liu, X.; Shu, K.; Tang, P.; Yu, Y. *RSC Adv.* **2015**, *5*, 55808–55811. (b) Pawar, S. K.; Sahani, R. L.; Liu, R.-S. *Chem. - Eur. J.* **2015**, *21*, 10843–10850. (c) Jin, L.; Wu, Y.; Zhao, X. *J. Org. Chem.* **2015**, *80*, 3547–3555. (d) Stoykova, S. A.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2012**, *95*, 1325–1351.

(3) For reviews, see: (a) Khaghaninejad, S.; Heravi, M. M. *Adv. Heterocycl. Chem.* **2014**, *111*, 95–146. (b) Lopchuk, J. M. *Prog. Heterocycl. Chem.* **2013**, *25*, 137–182. (c) Russel, J. S.; Pelkey, E. T.; Yoon-Miller, S. J. P. *Prog. Heterocycl. Chem.* **2011**, *22*, 143–180. (d) Trofimov, B. A.; Mikhaleva, A. I.; Schmidt, E.; Yu; Sobenina, L. N. *Adv. Heterocycl. Chem.* **2010**, *99*, 209–254. (e) Balme, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238–6241. (f) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*; Blackwell Science: Oxford, 2000. (g) *Pyrroles*; Jones, R. A., Ed.; The Chemistry of Heterocyclic Compounds; Wiley: New York, 1996, Vol. *48*, Part. I. (h) Gossauer, A. *Pyrrole*; Houben-Weyl: Thieme: Stuttgart, 1994; Vol. *E6a/1*, p 556.

(4) (a) Nisha, K. K.; Kumar, V. *RSC Adv.* **2015**, *5*, 10899–10920. (b) Clive, D. L. J.; Cheng, P. *Tetrahedron* **2013**, *69*, 5067–5078. (c) Donohoe, T. J.; Pullin, R. D. C. *Chem. Commun.* **2012**, *48*, 11924–11938. (d) Young, I. S.; Thornton, P. D.; Thompson, A. *Nat. Prod. Rep.* **2010**, *27*, 1801–1839.

(5) (a) Kim, D. S.; Sessler, J. L. *Chem. Soc. Rev.* **2015**, *44*, 532–546. (b) Koifman, O. I.; Ageeva, T. A. *Polym. Sci., Ser. C* **2014**, *56*, 84–103. (c) Pareek, Y.; Ravikanth, M.; Chandrashekar, T. K. *Acc. Chem. Res.* **2012**, *45*, 1801–1816. (d) Hagfeldt, A.; Boschloo, G.; Sun, L.; Kloo, L.; Pettersson, H. *Chem. Rev.* **2010**, *110*, 6595–6663.

(6) (a) Bailly, C. *Mar. Drugs* **2015**, *13*, 1105–1123. (b) Bhardwaj, V.; Gumber, D.; Abbot, V.; Dhiman, S.; Sharma, P. *RSC Adv.* **2015**, *5*, 15233–15266. (c) Li, J. J. In *Heterocyclic Chemistry in Drug Discovery*, Li, J. J., Ed; Wiley: Chichester, 2013; pp 18–53. (d) Su, T.-L.; Lee, T.-C.; Kakadiya, R. *Eur. J. Med. Chem.* **2013**, *69*, 609–621.

(7) For reviews on these procedures see: (a) Estevez, V.; Villacampa, M.; Menendez, J. C. *Chem. Soc. Rev.* **2014**, *43*, 4633–4657. (b) Joshi, S. D.; More, U. A.; Kulkarni, V. H.; Aminabhavi, T. M. *Curr. Org. Chem.* **2013**, *17*, 2279–2304. (c) Estevez, V.; Villacampa, M.; Menendez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402–4421.

(8) (a) Ryu, T.; Baek, Y.; Lee, P. H. *J. Org. Chem.* **2015**, *80*, 2376–2383. (b) Zhu, L.; Yu, Y.; Mao, Z.; Huang, X. *Org. Lett.* **2015**, *17*, 30–33. (c) Li, T.; Xin, X.; Wang, C.; Wang, D.; Wu, F.; Li, X.; Wan, B. *Org. Lett.* **2014**, *16*, 4806–4809.

(9) (a) Van der Jeught, K.; Stevens, C. V. *Chem. Rev.* **2009**, *109*, 2672–2702. (b) Moneen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177–6215.

(10) For reviews, see: (a) Engel, R. In *Handbook of Organophosphorus Chemistry*; Dekker, M., Inc.: New York, 1992. (b) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193–215. (c) Hoagland, R. E. In *Biologically Active Natural Products*; Culter, H. G., Ed; ACS Symposium Series 380. American Chemical Society: Washington DC, 1988; p 182. (d) Toy, A. D. F.; Walsh, E. N. In *Phosphorus Chemistry in Everyday Living*; American Chemical Society: Washington DC, 1987; p 333.

(11) (a) de los Santos, J. M.; Ignacio, R.; Aparicio, D.; Palacios, F.; Ezpeleta, J. M. *J. Org. Chem.* **2009**, *74*, 3444–3448. (b) Vicario, J.; Aparicio, D.; Palacios, F. *J. Org. Chem.* **2009**, *74*, 452–455.

(12) Palacios, F.; Ochoa de Retana, A. M.; Fernández de Trocóniz, G.; Pascual, S.; Ezpeleta, J. M. *Eur. J. Org. Chem.* **2010**, *2010*, 6618–6626.

(13) (a) Palacios, F.; Aparicio, D.; Ochoa de Retana, A. M.; de los Santos, J. M.; Gil, J. I.; Alonso, J. M. *J. Org. Chem.* **2002**, *67*, 7283–7288. (b) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; Ezpeleta, J. M. *J. Org. Chem.* **2000**, *65*, 3213–3217.

DOI: 10.1021/acs.joc.5b02347
J. Org. Chem. 2016, 81, 100–108

(14) Palacios, F.; Ochoa de Retana, A. M.; Alonso, J. M. *J. Org. Chem.* **2006**, *71*, 6141−6148.
(15) (a) Palacios, F.; Ochoa de Retana, A. M.; Alonso, J. M. *J. Org. Chem.* **2005**, *70*, 8895−8901. (b) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; Alonso, J. M. *Tetrahedron* **2004**, *60*, 8937−8947. (c) Palacios, F.; Ochoa de Retana, A. M.; Gil, J. I.; López de Munáin, R. *Org. Lett.* **2002**, *4*, 2405−2408.
(16) Palacios, F.; Ochoa de Retana, A. M.; Vélez del Burgo, A. *J. Org. Chem.* **2011**, *76*, 9472−9477.
(17) (a) Ng, E. P. J.; Wang, Y.-F.; Hui, B. W.-Q.; Lapointe, G.; Chiba, S. *Tetrahedron* **2011**, *67*, 7728−7737. (b) Chiba, S.; Wang, Y.-F.; Lapointe, G.; Narasaka, K. *Org. Lett.* **2008**, *10*, 313−316. (c) Chiba, S.; Wang, Y.-F.; Lapointe, G.; Narasaka, K. *Org. Lett.* **2008**, *10*, 313−316.
(18) Padwa, A.; Stengel, T. *Tetrahedron Lett.* **2004**, *45*, 5991−5993.
(19) Palacios, F.; Ochoa de Retana, A. M.; Martinez de Marigorta, E.; Rodriguez, M.; Pagalday, J. *Tetrahedron* **2003**, *59*, 2617−2623.
(20) (a) Freifeld, I.; Shojaei, H.; Dede, R.; Langer, P. *J. Org. Chem.* **2006**, *71*, 6165−6170. (b) Freifeld, I.; Shojaei, H.; Langer, P. *J. Org. Chem.* **2006**, *71*, 4965−4968. (c) Langer, P.; Freifeld, I. *Chem. Commun.* **2002**, 2668−2669.
(21) (a) Csaszar, A. G.; Demaison, J.; Rudolph, H. D. *J. Phys. Chem. A* **2015**, *119*, 1731−1746. (b) Zeller, K.-P. *Sci. Synt.* **2002**, *9*, 67−83.
(22) Banert, K.; Bochmann, S.; Hagedorn, M.; Richter, F. *Tetrahedron Lett.* **2013**, *54*, 6185−6188 and references cited therein.
(23) (a) Banert, K.; Hagedorn, M.; Peisker, H. *Synlett* **2012**, *23*, 2943−2946. (b) Banert, K. *Tetrahedron Lett.* **2012**, *53*, 6443−6445. (c) Mitchell, G.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1987**, 413−422. (d) Mitchell, G.; Rees, C. W. *J. Chem. Soc., Chem. Commun.* **1986**, 399−4017. (e) Gilchrist, T. L.; Gymer, G. E.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1−8. (f) Huisgen, R.; Blaschke, H. *Chem. Ber.* **1965**, *98*, 2985−2997.
(24) The structure of new compound **12a** (R^1 = Me) was elucidated from ^{1}H NMR data of the mixture **11a**/**12a** and by comparison with compound **12b** (R^1 = Et).
(25) For a review, see: Lee, S.-M.; Yang, Y.; Mailman, R. B. *J. Pharmacol. Exp. Ther.* **2014**, *351*, 9−17.
(26) (a) Fish, P. V.; Brown, A. D.; Evrard, E.; Roberts, L. R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1871−1875. (b) Sarkar, S.; Husain, S. M.; Schepmann, D.; Frohlich, R.; Wunsch, B. *Tetrahedron* **2012**, *68*, 2687−2695. (c) Zhang, J.; Chen, X.; Yu, L.; Zhen, X.; Zhang, A. *Bioorg. Med. Chem.* **2008**, *16*, 9425−9431.

DOI: 10.1021/acs.joc.5b02347
J. Org. Chem. 2016, 81, 100−108