A General Synthesis of substituted 1,2-Dihydropyridines.

David Tejedor,* Leandro Cotos, Gabriela Méndez-Abt and Fernando García-Tellado*

Departamento de Química Biológica y Biotecnología, Instituto de Productos Naturales y Agrobiología, CSIC, Astrofísico Francisco Sánchez 3, 38206 La Laguna, Tenerife, Spain.

E-mail: fgarcia@ipna.csic.es; dtejedor@ipna.csic.es

Home page: <https://www.ipna.csic.es/dept/qbb/qob/>

Topology: monocyclic/sp³-quaternized/spiro
Diversity: wide substitution pattern
Substituents: high combinatorial power

Abstract. A general and practical metal-free protocol for the synthesis of 1,2-dihydropyridines with a wide structural/functional diversity at the ring and featuring mono, double or spiro substitution at the sp³-position is described. The protocol entails a microwave-assisted domino reaction of a propargyl vinyl ether (secondary or tertiary) and a primary amine (aliphatic or aromatic) in toluene or methanol.

Keywords: 1,2-dihydropyridine, spiro compounds, domino reactions, propargyl vinyl ethers, 1-azatrienes, microwave-assisted, propargyl Claisen rearrangement, 6π-aza-electrocyclization.

Dihydropyridines (DHPs) represent a group of organic scaffolds based on the pyridine ring.¹ Among the five possible isomeric structures containing this motive, the 1,2- and the 1,4-dihydro constitute the most populated group. Whereas the 1,4-DHPs have received a great attention due to their wide variety of biological and pharmacological actions,² the biological annotation of 1,2-DHPs remains relatively unexplored,³ which converts them into a valuable candidate structure for the design of heterocyclic focused libraries. On the other hand, 1,2-DHPs have found important synthetic applications as cyclic aza-dienes in the Diels-Alder mediated

preparation of isoquinuclidines,⁴ an important structural motive present in many pharmacologically relevant natural products⁵ as the alkaloids ibogaine (**2**)⁶ and catharanthine (**3**),⁷ a chemical and biological precursor of the potent antitumor alkaloids vinblastine and vincristin⁸ (Scheme 1).

The synthesis of the 1,2-DHPs has been recently reviewed.⁹ Currently, these heterocyclic scaffolds are synthesized from activated pyridines (reduction, condensation)¹⁰ or

Scheme 1. Isoquinuclidinic alkaloids.

from the corresponding 1-azatrienes by a 6π -aza-electrocyclization process.^{11,12} Although less general, azadienes have been also used as convenient precursors.^{13,14} Moreover, the first approach suffers from a reliance on the pyridine inputs which translates to a limited degree of substitution at the DHP's ring. The second approach allows for wider degrees of substitution at the ring and it is better suited for diversity-oriented library construction. However, the key to this approach resides on the efficient access to highly functionalized 1-azatriene platforms. Currently, these platforms are formed in situ by coupling of vinylogous amides and α,β -unsaturated iminium salts or by direct condensation of a primary amines with 2,4-dienals.¹² We^{12b} and others^{12a,12c} have developed a direct protocol toward 1,2-DHPs **8** from propargyl vinyl ethers (PVEs) **4**, using the propargyl Claisen rearrangement¹⁵ to directly deliver the 2,4-dienals **6**. In the presence of a primary amine, these units condense to generate the corresponding 1-azatrienes **7** which, by a 6π -aza-electrocyclization process, construct the corresponding 1,2-DHPs **8**.

In spite of these advances, the domino synthesis of 1,2-DHPs from propargyl vinyl ethers still maintains a number of experimental limitations to become a robust, general and practical methodology with direct application in diversity-oriented synthetic programs. The main limitation is related to the grade of substitution at the sp^3 -position (for clarity, we will refer to this position as the C-2 position regardless of the other substituents on the ring). The current

a) Propargyl Claisen Rearrangement

b) Azatriene-approach to C-2 monosubstituted 1,2-dihydropyridines

Our previous work: $R^1 = \text{H, Ar, Alk}$; $R^2 = \text{H, Ar, Alk}$; $R^4 = \text{Ar, Alk}$

Structural limitation: If $R^1 = \text{Alk or Ar}$, then $R^2 = \text{Ar}$

Scheme 2. 1-Azatriene-approach to 1,2-dihydropyridines.

methodology synthesizes 1,2-DHPs bearing only one substituent at this position. The introduction of a second substituent should allow the access to quaternary or spiro motives which not only should increase the degree of structural diversity but should also provide new chemotypes with unpredictable biological (pharmaceutical) properties. The establishment of a simple and efficient access to spiro 1,2-DHPs should pave the way to the construction of chemical libraries with high value in medicinal chemistry.¹⁶ The number of reported methodologies to access quaternary/spiro 1,2-DHPs is really scarce.¹⁷ Besides this general

limitation, our own approach to these scaffolds^{12b} showed a particular structural restraint regarding internal alkynes ($R^1 \neq H$, Scheme 2a). In these cases, the reaction did not tolerate an alkyl substituent at the propargylic position ($R^2 \neq Alk$). This restriction has also been reported by Xu and col.^{12c} in their Au/Ag-catalyzed domino protocol. Interestingly, Kirsch and col.^{12a} have described an Au-catalyzed one-pot protocol which overrides this substituents restraint but poses a new structural limitation on the use of terminal alkynes. In this note we describe our advances in the development of a metal-free protocol able to deliver these important heterocyclic scaffolds with a wide structural/functional diversity at the ring and featuring mono, double or spiro substitution at the sp^3 -position. The protocol entails a microwave-assisted domino reaction involving a propargyl vinyl ether (secondary or tertiary)¹⁸ and a primary amine. The manifold constructs 1,2-DHPs featuring a wide array of topologies spanning from simple monocyclic scaffolds to spiro derivatives. The protocol tolerates a topologically diverse substitution pattern at the triene terminus of the 1-azatriene intermediate **7** which is directly delivered to the C-2 position of the final 1,2-DHP (Table 1).

We undertook this work studying the reaction of the tertiary PVE **4a**¹⁹ ($R^1 = H$, $R^2 = R^3 = Me$; Table 1) and *p*-methoxyaniline (1.1 eq) under the microwave conditions established in our previous protocol [toluene, μv (120 °C, 150 W, 1h, closed vessel)].^{12b} Under these conditions, the quaternary 1,2-DHP **8a** was cleanly obtained in an excellent 93% yield. Other tertiary PVEs also delivered the corresponding quaternary 1,2-DHPs in excellent yields. Thus, for example, the PVEs **4b** and **4c** were cleanly transformed into the corresponding products **8b** and **8c** in 92% and 94% yield respectively. The manifold was able to transform the monocyclic tertiary PVEs **4d** and **4e** into the spiro derivatives **8d** and **8e** with high efficiency (94% and 93% respectively). In our previous work,^{12b} we had performed the reaction of the secondary PVE **4f** with (*S*)-1-phenylethanamine obtaining the chiral 1,2-DHP **8f** in excellent yield (83%) but modest diastereoselectivity (75:25). However, when the tertiary PVE **4g** was submitted to the same set of reaction conditions, the chiral quaternary 1,2-DHP **8g** was obtained with the same high

Table 1. μv -Assisted domino synthesis of 1,2-dihydropyridines **8** from propargyl vinyl ethers **4**.^a

^aPVE (1 eq), amine (1.1 eq), toluene (methanol) (5 mL). ^b 3h. ^c 3h, 150 °C. PMP = p-Methoxyphenyl

efficiency (83%) but with practically null diastereoselectivity (60:40). This decreasing in diastereoselectivity was in certain manner predictable according to the marked steric difference between a methyl group and hydrogen.²⁰ Nevertheless, the two isomers could be separated by simple flash chromatography. When we attempted to perform the reaction using tertiary PVEs armed with internal alkynes ($R^1 \neq H$), the yields considerably dropped down. This was the case of the spiro 1,2-DHP **8h** which was obtained with a modest 43% yield. Fortunately, the use of methanol as the reaction solvent²¹ reverted the reaction's efficiency back to the previous high levels, rendering the spiro derivative in 83% yield. Interestingly, the quaternary 1,2-DHP **8a** could be also obtained under these new conditions (μv , methanol) but with a significant reduction in the yield (58%). These new conditions proved to be highly tolerant with the structure of the PVE (secondary or tertiary, internal alkyne) and the electronic nature of the primary amine (aliphatic or aromatic). It is remarkable the power of this reaction to generate diversity on the nitrogen atom regardless of the structure of the PVE: quite different primary amines (aliphatic, aromatic) are able to react with tertiary PVEs armed with electronically different alkyne moieties to afford the corresponding heterocyclic core with similar overall yields. This is the case of the spiro derivatives **8h** (*p*-anisidine, 83%) and **8i** (benzylamine, 82%), or **8j** (aniline, 76%), **8k** (methylamine, 79%) and **8l** (*p*-anisidine, 77%). The reaction showed high tolerance with the electronic nature of the internal alkyne moiety of the PVE. It is remarkable the generation of the spiro 1,2-DHP **8m**. In spite of the steric congestion that a *tert*-butyl group should introduce into the 1-azatriene intermediate **7m** (Scheme 2b), this is formed and cyclized to generate **8m**, although in a 15% yield. The reduction of the steric demand from a *tert*-butyl to a methyl substituent was mirrored in a net increase of the reaction efficiency (compare **8m** with **8j-l**). The reaction manifold also accepted acyclic tertiary PVEs to generate the corresponding quaternary derivatives (e.g., **8n**, 81%). Cyclic tertiary PVEs **4o** and **4p** afforded the functionalized spiro 1,2-DHPs **8o** and **8p** in very good yields, although they need more time to be fully transformed into the final products. The extra functionalization incorporated at the spiro cycle (protected amine, masked ketone) constitutes a convenient chemical handle for further chemical access to this ring or for the generation of molecular

complexity. Finally, the reaction was also able to override the structural limitation found in our previous model: the use of secondary PVEs armed with internal alkynes and alkyl substituents at the propargylic position. The 1,2-DHPs **8q-s** are nice examples of this structural breakthrough. In these cases, the reaction needs more energy and more time (3h under 150 °C and irradiation) to be accomplished.

It is interesting to note that 1,2-DHPs **8j-l** exist in equilibrium as mixtures of the “methyl” and “methylene” tautomers (endocyclic or exocyclic double bond respectively) (see supporting information for details).

Scheme 3. Tautomeric equilibrium in 1,2-dihydropyridines.

In summary, we have enhanced the practicality and generality of our previous metal-free synthetic protocol for the access to 1,2-DHPs from propargyl vinyl ethers and primary amines. This improved version delivers these important heterocyclic scaffolds with a wider diversity at the ring and mono, double or spiro substitution at the sp^3 -position. The protocol accepts secondary and tertiary propargyl vinyl ethers bearing internal or terminal alkyne moieties and aromatic and aliphatic primary amines.

Experimental Section

General information. ^1H NMR and ^{13}C NMR spectra of CDCl_3 solutions were recorded either at 400 and 100 MHz or at 500 and 125 MHz, respectively. Microwave reactions were conducted in sealed glass vessels (capacity 10 mL) using CEM Discover

microwave reactor equipped with a surface sensor for temperature measuring of the reaction mixture. FT-IR spectra were measured in chloroform solutions using a FT-IR spectrophotometer. Mass spectra (low resolution) (EI/CI) and HRMS (EI/TOF) were obtained with a gas chromatograph/mass spectrometer. Analytical thin-layer chromatography plates used UV-active silica on aluminum. Flash column chromatography was carried out with silica gel of particle size less than 0.020 mm, using appropriate mixtures of ethyl acetate and hexanes as eluents. All reactions were performed in oven-dried glassware. All materials were obtained from commercial suppliers and used as received unless otherwise noted. When necessary, the propargyl alcohols were prepared by addition of the lithium acetylides onto the appropriate aldehydes or ketones following the standard procedures (see below for a general procedure). Products **4a**,¹⁹ **4b**,¹⁹ **4e**,¹⁹ **4n**¹⁹ and **4s**²² have been previously prepared.

General procedure for the synthesis of propargyl alcohols: A terminal alkyne (13 mmol) was dissolved in 25 mL of dry THF in a round-bottom flask. After the mixture was cooled to -40°C, a 1.6M solution of BuLi in hexanes (13 mmol) was added dropwise. The temperature was maintained for 1 hr with stirring of the solution. The ketone was then added slowly (if solid, dissolved in THF) and the stirring was continued overnight allowing the reaction mixture to warm up to room temperature slowly without additional cooling. After completion, the reaction was quenched with saturated NH₄Cl solution and extracted with CH₂Cl₂. This was followed by isolation of the corresponding product by flash column chromatography (silica gel, appropriate mixtures of *n*-hexane/EtOAc).

Representative procedure for the synthesis of propargyl vinyl ethers **4 from secondary or tertiary alcohols:** methyl propiolate (2.6 mmol) was added dropwise (time of addition 10 minutes) to a solution of 1-(phenylethynyl)cyclopentanol (2.0

mmol) and DABCO (0.20 mmol) in dry CH₂Cl₂ (5 mL). The reaction mixture was stirred for 5 min (TLC control). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (silica gel; *n*-hexane/EtOAc, 90:10) to give **4h** (512 mg, 90 %). Less reactive alcohols were synthesized in *n*-hexanes to control the competitive dimerization of methyl propiolate.¹⁹

(E)-methyl 3-(1,1-diphenylprop-2-ynoxy)acrylate (4c): This product rearranges partially (around 15%) during isolation by column chromatography. The rearranged product has a similar R_f so the mixture can be used for the synthesis of the corresponding dihydropyridine. ¹H NMR (CDCl₃, 400 MHz): δ = 2.79 (s, 1H), 3.64 (s, 3H), 5.57 (d, ³J_(H,H) = 12.1, 1H), 7.28-7.36 (m, 6H), 7.50-7.52 (m, 4H), 7.74 (d, ³J_(H,H) = 12.1, 1H).

(E)-Methyl 3-(1-ethynylcyclopentyloxy)acrylate (4d): (361 mg, 93%) colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ = 1.71-1.78 (m, 4H), 1.95-2.03 (m, 2H), 2.09-2.15 (m, 2H), 2.64 (s, 1H), 3.67 (s, 3H), 5.37 (d, ³J_(H,H) = 12.1 Hz, 1H), 7.76 (d, ³J_(H,H) = 12.1 Hz, 1H). ¹³C NMR (CDCl₃, 100 MHz): δ = 23.3 (2C), 40.4 (2C), 51.0, 75.4, 83.0, 84.2, 100.0, 158.6, 168.1. IR (CHCl₃, cm⁻¹) 3305.5, 2954.0, 2118.6, 1702.3, 1641.0, 1438.3, 1333.5, 1294.9, 1169.8. MS (70 eV): *m/z* (%): 194 (2.0) [*M*⁺], 135 (11), 103 (14), 93 (81), 92 (37), 91 (100), 77 (89), 65 (28). HRMS calculated for C₁₁H₁₄O₃ 194.0943, found 194.0945.

(E)-methyl 3-(1-(phenylethynyl)cyclopentyloxy)acrylate (4h): (512 mg, 90%) colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ = 1.80-1.84 (m, 4H), 2.05-2.12 (m, 2H), 2.19-2.23 (m, 2H), 3.69 (s, 3H), 5.41 (d, ³J_(H,H) = 12.1, 1H), 7.28-7.32 (m, 3H), 7.42-7.45 (m, 2H), 7.89 (d, ³J_(H,H) = 12.1, 1H). ¹³C NMR (CDCl₃, 100 MHz): δ = 23.5 (2C), 40.6 (2C), 51.0, 85.1, 87.2, 88.1, 99.8, 122.0, 128.3 (2C), 128.7, 131.8 (2C), 159.0, 158.2. IR (CHCl₃, cm⁻¹) 3015.49, 2953.95, 2878.33, 2230.20, 1701.20, 1638.73,

1558.93, 1540.42, 1490.37, 1438.07, 1334.77, 1294.38, 1222.25, 1209.89, 1166.91, 1135.38, 1050.74. MS (70 eV): m/z (%): 270 (1.7) [M^+], 211 (11), 169 (100), 154 (29), 141 (75), 128 (37), 115 (77), 91 (80), 77 (13), 67 (11). HRMS calculated for $C_{17}H_{18}O_3$ 270.1256, found 270.1259.

(E)-Methyl 3-(1-(prop-1-ynyl)cyclohexyloxy)acrylate (4j): (435 mg, 98%) colorless oil. Repeated on 20 mmol scale obtaining the same yield. 1H NMR ($CDCl_3$, 400 MHz): δ = 1.23-1.33 (m, 1H), 1.44-1.57 (m, 3H), 1.59-1.70 (m, 4H), 1.83-1.87 (m, 2H), 1.87 (s, 3H), 3.67 (s, 3H), 5.35 (d, $^3J_{(H,H)} = 12.1$ Hz, 1H), 7.92 (d, $^3J_{(H,H)} = 12.1$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 3.6, 22.5 (2C), 24.8, 37.9 (2C), 50.9, 78.5, 79.0, 84.6, 98.7, 158.8, 168.5. IR ($CHCl_3$, cm^{-1}) 2942.6, 2860.5, 2241.6, 1701.5, 1636.9, 1438.3, 1334.4, 1305.5, 1231.5, 1133.1. MS (70 eV): m/z (%): 222 (2.6) [M^+], 179 (3.8), 163 (5.6), 121 (100), 105 (12), 93 (29), 91 (14), 79 (14). HRMS calculated for $C_{13}H_{18}O_3$ 222.1256, found 222.1250.

(E)-methyl 3-(1-(3,3-dimethylbut-1-ynyl)cyclohexyloxy)acrylate (4m): (486 mg, 92%) colorless oil. 1H NMR ($CDCl_3$, 400 MHz): δ = 1.21-1.34 (m, 1H), 1.26 (s, 9H), 1.51-1.60 (m, 3H), 1.65-1.70 (m, 4H), 1.88-1.92 (m, 2H), 3.71 (s, 3H), 5.38 (d, $^3J_{(H,H)} = 12.1$ Hz, 1H), 8.00 (d, $^3J_{(H,H)} = 12.1$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.8 (2C), 24.9, 27.5, 30.9 (3C), 38.1 (2C), 50.8, 77.7, 79.3, 98.3, 98.5, 158.9, 168.5. IR ($CHCl_3$, cm^{-1}) 2971.8, 2942.2, 2863.6, 2231.0, 1702.1, 1636.3, 1438.4, 1334.4, 1191.6. MS (70 eV): m/z (%): 264 (0.9) [M^+], 163 (100), 121 (30), 107 (46), 95 (37), 93 (29), 91 (24), 81 (25). HRMS calculated for $C_{16}H_{24}O_3$ 264.1725, found 264.1729.

(E)-methyl 3-(8-(phenylethynyl)-1,4-dioxaspiro[4.5]decan-8-yloxy)acrylate (4o). (671 mg, 98%) colorless oil: 1H NMR ($CDCl_3$, 400 MHz): δ = 1.77–1.83 (m, 4H), 2.13 (pseudo t, $^3J_{(H,H)} = 6.3$, 4H), 3.67 (s, 3H), 3.93 (s, 4H), 5.44 (d, $^3J_{(H,H)} = 12.1$, 1H), 7.27-7.35 (m, 3H), 7.42-7.44 (m, 2H), 7.97 (d, $^3J_{(H,H)} = 12.1$, 1H). ^{13}C NMR ($CDCl_3$, 100

MHz): δ = 30.8 (2C), 35.2 (2C), 50.9, 64.4 (2C), 77.4, 87.2, 88.2, 99.8, 107.3, 121.7, 128.3 (2C), 128.9, 131.8 (2C), 158.1, 168.1. IR (CHCl₃, cm⁻¹) 2955.69, 2887.50, 2226.76, 1703.49, 1639.32, 1490.25, 1438.38, 1374.26, 1335.76, 1293.65. MS (70 eV): m/z (%): 342 (1.1) [M^+], 241 (100), 197 (23), 179 (34), 141 (11), 127 (12), 115 (12), 99 (21), 86 (13). HRMS calculated for C₂₀H₂₂O₅ 342.1467, found 342.1469.

(E)-methyl 3-(1-benzyl-4-(phenylethynyl)piperidin-4-yloxy)acrylate (4p): (735 mg, 98%) colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ = 2.01–2.13 (m, 4H), 2.48–2.52 (m, 2H), 2.63–2.67 (m, 2H), 3.53 (s, 2H), 3.69 (s, 3H), 5.47 (d, ³ $J_{(H,H)}$ = 12.1, 1H), 7.25–7.27 (m, 1H), 7.25–7.27 (m, 1H), 7.31–7.33 (m, 7H), 7.44–7.46 (m, 2H), 7.99 (d, ³ $J_{(H,H)}$ = 12.1, 1H). ¹³C NMR (CDCl₃, 100 MHz): δ = 37.3 (2C), 49.5 (2C), 50.9, 62.6, 77.1, 87.3, 89.0, 99.8, 121.7, 127.1, 128.2 (2C), 128.3 (2C), 128.91, 128.93 (2C), 131.8 (2C), 138.4, 158.1, 168.1. IR (CHCl₃, cm⁻¹) 3028.72, 2952.64, 2814.99, 2226.76, 1705.38, 1639.61, 1490.58, 1438.29. MS (70 eV): m/z (%): 375 (4.9) [M^+], 347 (10), 274 (75), 182 (8.2), 146 (6.7), 155 (6.4), 91 (100). HRMS calculated for C₂₄H₂₅NO₃ 375.1834, found 375.1848.

(E)-Methyl 3-((1-phenylhept-6-en-1-yn-3-yl)oxy)acrylate (4q): (569 mg, 97%) colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ = 1.87–2.02 (m, 2H), 2.19–2.25 (m, 2H), 3.62 (s, 3H), 4.71 (t, ³ $J_{(H,H)}$ = 6.6, 1H), 4.95–5.03 (m, 2H), 5.35 (d, ³ $J_{(H,H)}$ = 12.6, 1H), 5.70–5.80 (m, 1H), 7.21–7.27 (m, 3H), 7.35–7.37 (m, 2H), 7.60 (d, ³ $J_{(H,H)}$ = 12.6, 1H). ¹³C NMR (CDCl₃, 100 MHz): δ = 29.1, 34.5, 51.1, 71.4, 85.1, 88.1, 98.6, 115.9, 121.8, 128.3, 128.9, 131.8, 136.7, 160.6, 168.1. IR (CHCl₃, cm⁻¹) 3082.8, 3063.5, 3026.7, 3013.5, 2953.7, 2850.1, 2229.4, 2205.1, 1706.1, 1642.8, 1624.2, 1491.2, 1438.6, 1416.9, 1333.8, 1292.9, 1222.7, 1209.5, 1191.8, 1141.8, 1070.6, 1050.0. HRMS (ESI) m/z calculated for C₁₇H₁₈O₃Na [$M + Na$]⁺ 293.1154, found 293.1158.

(E)-Methyl 3-(1-cyclohexyl-3-phenylprop-2-ynoxy)acrylate (4r): (584 mg, 98%) yellowish oil. ^1H NMR (CDCl_3 , 400 MHz): δ = 1.10-1.34 (m, 5H), 1.68-1.70 (m, 1H), 1.73-1.84 (m, 3H), 1.88-1.93 (m, 2H), 3.69 (s, 3H), 4.55 (d, $^3J_{(\text{H,H})}$ = 6.1, 1H), 5.42 (d, $^3J_{(\text{H,H})}$ = 12.5, 1H), 7.28-7.33 (m, 3H), 7.41-7.46 (m, 2H), 7.69 (d, $^3J_{(\text{H,H})}$ = 12.6, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 25.69, 25.70, 26.2, 28.2, 28.6, 42.6, 51.0, 76.9, 84.5, 88.6, 98.2, 122.0, 128.3 (2C), 128.8, 131.8 (2C), 161.0, 168.2. IR (CHCl_3 , cm^{-1}) 3025.7, 2933.3, 2856.9, 2227.4, 1704.3, 1641.6, 1623.4, 1490.8, 1438.5, 1322.2, 1294.3, 1231.6, 1136.1. ES (70 eV): m/z (%): 298 (0.9) [M^+], 197 (86), 155 (30), 141 (29), 129 (29), 117 (46), 115 (100), 91(40). HRMS calculated for $\text{C}_{19}\text{H}_{22}\text{O}_3$ 298.1569, found 298.1575.

Representative procedure for the microwave-assisted reaction of propargyl vinyl ethers 4 with primary amines: propargyl vinyl ether **4a** (1.0 mmol) and *p*-anisidine (1.10 mmol) in toluene (1 mL) were placed in a microwave-special closed vial and the solution was irradiated for 1 hour in a single-mode microwave oven (150 Watt, 120 °C). After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, n-hexane/EtOAc 85/15) to yield **8a** (254 mg, 93%).

Methyl 1-(4-methoxyphenyl)-6,6-dimethyl-1,6-dihydropyridine-3-carboxylate (8a): (254 mg, 93%) yellowish oil. ^1H NMR (CDCl_3 , 400 MHz): δ = 1.23 (s, 6H), 3.64 (s, 3H), 3.78 (s, 3H), 4.88 (d, $^3J_{(\text{H,H})}$ = 9.9 Hz, 1H), 6.34 (d, $^3J_{(\text{H,H})}$ = 9.9 Hz, 1H), 6.84 (d, $^3J_{(\text{H,H})}$ = 8.8 Hz, 2H), 7.12 (d, $^3J_{(\text{H,H})}$ = 8.8 Hz, 2H), 7.25 (s, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 29.1 (2C), 50.6, 55.4, 58.4, 98.4, 114.0 (2C), 199.9, 120.6, 130.2 (2C), 136.1, 146.7, 158.9, 167.0. IR (CHCl_3 , cm^{-1}) 2964.1, 2842.0, 1683.0, 1640.6, 1557.4, 1507.7, 1437.9, 1264.2, 1219.0, 1096.0. MS (70 eV): m/z (%): 273 (3.5) [M^+], 259 (17), 258 (100), 242 (3.6), 214 (3.5), 188 (2.7), 134 (4.7), 77 (7.1). HRMS calculated for $\text{C}_{16}\text{H}_{19}\text{NO}_3$ 273.1365, found 273.1369.

Methyl 1-(4-methoxyphenyl)-6-methyl-6-phenyl-1,6-dihydropyridine-3-carboxylate (8b): (308 mg, 92%) amorphous pale yellow solid. ^1H NMR (CDCl_3 , 400 MHz): δ = 1.65 (s, 3H), 3.70 (s, 3H), 3.73 (s, 3H), 4.99 (d, $^3J_{(\text{H,H})}$ = 9.9 Hz, 1H), 6.44 (dd, $^3J_{(\text{H,H})}$ = 9.9 and 1.5 Hz, 1H), 6.64-6.70 (m, 4H), 7.24-7.28 (m, 1H), 7.29-7.31 (m, 2H), 7.35 (s, 1H), 7.41-7.47 (m, 2H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 26.8, 50.7, 55.4, 63.9, 97.4, 113.7 (2C), 118.1, 121.4, 126.7 (2C), 127.6, 128.3 (2C), 128.9 (2C), 136.6, 146.0, 146.8, 158.5, 167.1. IR (CHCl_3 , cm^{-1}) 2975.6, 2947.2, 1678.9, 1645.5, 1547.4, 1509.1, 1440.7, 1288.0, 1250.9, 1185.9, 1099.3. MS (70 eV): m/z (%): 335 (7.8) [M^+], 321 (25), 320 (100), 276 (16), 258 (59), 149 (11), 115 (11), 77 (25). HRMS calculated for $\text{C}_{21}\text{H}_{21}\text{NO}_3$ 335.1521, found 335.1519.

Methyl 1-(4-methoxyphenyl)-6,6-diphenyl-1,6-dihydropyridine-3-carboxylate (8c): (373 mg, 94%) amorphous orange solid. ^1H NMR (CDCl_3 , 400 MHz): δ = 3.62 (s, 3H), 3.67 (s, 3H), 5.34 (d, $^3J_{(\text{H,H})}$ = 9.6 Hz, 1H), 6.45-6.49 (m, 3H), 6.76 (d, $^3J_{(\text{H,H})}$ = 9.1 Hz, 2H), 7.15-7.18 (m, 2H), 7.21-7.24 (m, 4H), 7.31-7.33 (m, 4H), 7.61 (s, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 50.8, 55.3, 72.5, 100.3, 113.4 (2C), 118.0, 121.5, 127.2 (2C), 127.8 (4C), 128.1 (2C), 128.7 (4C), 137.9, 143.6 (2C), 144.1, 157.7, 167.0. IR (CHCl_3 , cm^{-1}) 3009.8, 2952.8, 1683.8, 1635.7, 1560.2, 1509.2, 1441.7, 1266.2, 1233.3, 1109.2. MS (70 eV): m/z (%): 397 (36) [M^+], 339 (23), 338 (100), 320 (62), 203 (13), 202 (23), 165 (23), 77 (24). HRMS calculated for $\text{C}_{26}\text{H}_{23}\text{NO}_3$ 397.1678, found 397.1667.

Methyl 6-(4-methoxyphenyl)-6-azaspiro[4.5]deca-7,9-diene-8-carboxylate (8d): (281 mg, 94%) amorphous brown solid. ^1H NMR (CDCl_3 , 400 MHz): δ = 1.36-1.45 (m, 2H), 1.53-1.63 (m, 2H), 1.70-1.76 (m, 2H), 1.79-1.86 (m, 2H), 3.65 (s, 3H), 3.80 (s, 3H), 5.06 (d, $^3J_{(\text{H,H})}$ = 9.9 Hz, 1H), 6.36 (dd, $^3J_{(\text{H,H})}$ = 9.9 and 1.5 Hz, 1H), 6.85 (d, $^3J_{(\text{H,H})}$ = 9.1 Hz, 2H), 7.14 (d, $^3J_{(\text{H,H})}$ = 9.1 Hz, 2H), 7.32 (d, $^3J_{(\text{H,H})}$ = 1.5 Hz, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 22.3 (2C), 40.0 (2C), 50.6, 55.4, 68.5, 98.5, 114.1 (2C),

119.0, 119.9, 130.5 (2C), 136.3, 147.6, 158.9, 167.0. IR (CHCl₃, cm⁻¹) 3010.4, 2953.0, 1675.7, 1635.5, 1560.9, 1510.0, 1441.7, 1278.8, 1212.2. MS (70 eV): *m/z* (%): 299 (34) [*M*⁺], 271 (27), 270 (100), 207 (32), 175 (32), 160 (19), 121 (39). HRMS calculated for C₁₈H₂₁NO₃ 299.1521, found 299.1513.

Methyl 1-(4-methoxyphenyl)-1-azaspiro[5.5]undeca-2,4-diene-3-carboxylate (8e):

(291 mg, 93%) dark red oil. ¹H NMR (CDCl₃, 400 MHz): δ = 0.89-0.99 (m, 1H), 1.28-1.35 (m, 2H), 1.49-1.58 (m, 5H), 1.98-2.01 (m, 2H), 3.66 (s, 3H), 3.80 (s, 3H), 5.35 (d, ³*J*_(H,H) = 9.9 Hz, 1H), 6.48 (d, ³*J*_(H,H) = 9.9 Hz, 1H), 6.85 (d, ³*J*_(H,H) = 8.8 Hz, 2H), 7.11 (d, ³*J*_(H,H) = 8.8 Hz, 2H), 7.32 (d, ³*J*_(H,H) = 1.5 Hz, 1H). ¹³C NMR (CDCl₃, 100 MHz): δ = 21.3 (2C), 25.3, 36.0 (2C), 50.6, 55.5, 60.8, 99.1, 114.0 (2C), 115.7, 121.0, 130.9 (2C), 135.7, 147.3, 159.0, 167.1. IR (CHCl₃, cm⁻¹) 2937.9, 2854.3, 1683.3, 1627.2, 1554.4, 1508.0, 1440.7, 1222.2. MS (70 eV): *m/z* (%): 313 (31) [*M*⁺], 271 (28), 270 (100), 257 (22), 256 (39), 242 (10), 134 (10), 123 (16), 121 (19). HRMS calculated for C₁₉H₂₃NO₃ 313.1678, found 313.1683.

Methyl 6-methyl-6-phenyl-1-((S)-1-phenylethyl)-1,6-dihydropyridine-3-carboxylate (8g):

(277 mg, 83%) orange oil. 2 Diastereomers separated by flash chromatography (60:40 of less polar:more polar). Major isomer: ¹H NMR (CDCl₃, 400 MHz): δ = 1.31 (d, ³*J*_(H,H) = 7.1 Hz, 3H), 1.56 (s, 3H), 3.72 (s, 3H), 4.23 (q, ³*J*_(H,H) = 7.1 Hz, 1H), 4.81 (d, ³*J*_(H,H) = 10.1 Hz, 1H), 6.38 (dd, ³*J*_(H,H) = 10.1 and 1.5 Hz, 1H), 7.24-7.27 (m, 3H), 7.30-7.35 (m, 3H), 7.39-7.42 (m, 2H), 7.54-7.56 (m, 2H), 7.74 (s, 1H). ¹³C NMR (CDCl₃, 100 MHz): δ = 23.4, 27.1, 50.6, 56.9, 64.7, 95.1, 117.7, 121.0, 125.8 (2C), 127.0 (2C), 127.2, 127.7, 128.4 (2C), 128.8 (2C), 143.2, 144.1, 146.4, 167.1. Minor isomer: ¹H NMR (CDCl₃, 400 MHz): δ = 1.65 (d, ³*J*_(H,H) = 7.1 Hz, 3H), 1.83 (s, 3H), 3.68 (s, 3H), 4.28 (q, ³*J*_(H,H) = 7.1 Hz, 1H), 4.81 (d, ³*J*_(H,H) = 10.1 Hz, 1H), 6.41 (dd, ³*J*_(H,H) = 10.1 and 1.5 Hz, 1H), 6.61 (dd, ³*J*_(H,H) = 7.3 and 1.5 Hz, 2H), 7.06-7.10 (m, 3H),

7.22-7.27 (m, 3H), 7.44-7.46 (m, 2H), 7.58 (s, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 23.4, 25.5, 50.6, 56.1, 64.2, 95.5, 118.3, 120.1, 126.5 (2C), 127.2, 127.7, 128.0 (2C), 128.2 (2C), 128.3 (2C), 141.4, 142.4, 145.3, 167.0. IR (major isomer) (CHCl_3 , cm^{-1}) 3009.9, 2950.4, 1671.6, 1638.3, 1563.0, 1434.7, 1321.2, 1254.3, 1128.2. MS (70 eV): m/z (%): 333 (65) [M^+], 318 (77), 302 (15), 274 (32), 256 (23), 215 (17), 214 (100), 105 (76). HRMS calculated for $\text{C}_{22}\text{H}_{23}\text{NO}_2$ 333.1729, found 333.1740.

Methyl 6-(4-methoxyphenyl)-9-phenyl-6-azaspiro[4.5]deca-7,9-diene-8-carboxylate (8h): (311 mg, 83%) amorphous brown solid. ^1H NMR (CDCl_3 , 400 MHz): δ = 1.47-1.55 (m, 2H), 1.62-1.71 (m, 2H), 1.80-1.90 (m, 4H), 3.49 (s, 3H), 3.83 (s, 3H), 4.99 (s, 1H), 6.90 (d, $^3J_{(\text{H,H})}$ = 8.8 Hz, 2H), 7.20 (d, $^3J_{(\text{H,H})}$ = 8.8 Hz, 2H), 7.24-7.32 (m, 5H), 7.61 (s, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 22.0 (2C), 38.6 (2C), 50.3, 55.5, 68.8, 100.0, 114.2 (2C), 120.9, 126.6, 127.4 (2C), 127.6 (2C), 130.2 (2C), 134.6, 136.0, 141.3, 149.4, 158.9, 166.6. IR (CHCl_3 , cm^{-1}) 3011.1, 2953.0, 1683.1, 1618.3, 1554.3, 1509.5, 1438.5, 1283.6, 1240.4. MS (70 eV): m/z (%): 375 (59) [M^+], 374 (19), 347 (40), 346 (100), 332 (19), 123 (45), 121 (44). HRMS calculated for $\text{C}_{24}\text{H}_{25}\text{NO}_3$ 375.1834, found 375.1836.

Methyl 6-benzyl-9-phenyl-6-azaspiro[4.5]deca-7,9-diene-8-carboxylate (8i): (295 mg, 82%) reddish oil. ^1H NMR (CDCl_3 , 400 MHz): δ = 1.61-1.70 (m, 4H), 1.76-1.82 (m, 2H), 1.85-1.92 (m, 2H), 3.46 (s, 3H), 4.49 (s, 2H), 4.90 (s, 1H), 7.21-7.30 (m, 8H), 7.32-7.50 (m, 2H), 7.55 (s, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 23.1 (2C), 39.3 (2C), 50.2, 53.7, 68.1, 98.9, 121.0, 126.3 (2C), 126.5, 127.3 (2C), 127.5, 127.6 (2C), 128.8 (2C), 134.2, 138.6, 141.3, 149.9, 166.4. IR (CHCl_3 , cm^{-1}) 3011.6, 2957.3, 2873.7, 1678.5, 1623.7, 1562.4, 1495.7, 1438.2, 1395.7, 1354.8, 1324.1, 1298.8, 1225.2, 1188.7, 1148.4, 1091.3. MS (70 eV): m/z (%): 359 (33) [M^+], 331 (26), 330 (64), 317

(35), 316 (18), 240 (20), 91 (100). HRMS calculated for $C_{24}H_{25}NO_2$ 359.1885, found 359.1875.

Methyl 4-methyl-1-phenyl-1-azaspiro[5.5]undeca-2,4-diene-3-carboxylate (8j): (226 mg, 76%) amorphous pale solid. Major tautomer ("4-methyl" group) 1H NMR ($CDCl_3$, 400 MHz): δ = 0.88-1.01 (m, 1H), 1.26-1.40 (m, 2H), 1.49-1.67 (m, 5H), 1.99 (d, $^3J_{(H,H)} = 11.1$ Hz, 2H), 2.13 (s, 3H), 3.63 (s, 3H), 5.09 (s, 1H), 7.18-7.22 (m, 2H), 7.30-7.38 (m, 3H), 7.45 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.4, 21.5 (2C), 25.3, 35.7 (2C), 50.3, 60.9, 100.7, 114.6, 127.6, 128.9 (2C), 129.8 (2C), 130.3, 142.9, 148.1, 167.2. Minor tautomer ("4-methylene" group) 1H NMR ($CDCl_3$, 400 MHz): δ = 0.88-1.01 (m, 1H), 1.26-1.40 (m, 2H), 1.49-1.67 (m, 5H), 1.74 (d, $^3J_{(H,H)} = 11.1$ Hz, 2H), 2.59 (s, 2H), 3.66 (s, 3H), 4.79 (d, $^3J_{(H,H)} = 2.5$ Hz, 1H), 5.73 (d, $^3J_{(H,H)} = 2.5$ Hz, 1H), 7.12-7.15 (m, 2H), 7.30-7.38 (m, 3H), 7.46 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.7 (2C), 25.3, 33.6 (2C), 40.1, 50.5, 60.0, 98.3, 108.8, 127.7, 128.9 (2C), 129.4 (2C), 133.7, 143.1, 147.3, 167.4. IR ($CHCl_3$, cm^{-1}) 3011.9, 2943.2, 2860.0, 1733.1, 1678.3, 1625.6, 1573.7, 1494.0, 1438.1, 1292.2, 1232.0, 1093.1. MS (70 eV): m/z (%): 297 (30) [M^+], 255 (20), 254 (100), 241 (11), 240 (30), 93 (16), 77 (13). HRMS calculated for $C_{19}H_{23}NO_2$ 297.1729, found 297.1726.

Methyl 1,4-dimethyl-1-azaspiro[5.5]undeca-2,4-diene-3-carboxylate (8k): (186 mg, 79%) yellowish oil. Major tautomer ("4-methyl" group) 1H NMR ($CDCl_3$, 400 MHz): δ = 1.03-1.25 (m, 1H), 1.44-1.70 (m, 7H), 1.78-1.88 (m, 2H), 2.04 (s, 3H), 2.96 (s, 3H), 3.63 (s, 3H), 4.89 (s, 1H), 7.36 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.3 (2C), 21.4, 25.5, 33.4, 37.3 (2C), 50.1, 59.2, 98.4, 112.4, 130.5, 150.0, 167.2. Minor tautomer ("4-methylene" group) 1H NMR ($CDCl_3$, 400 MHz): δ = 1.03-1.25 (m, 1H), 1.44-1.70 (m, 7H), 1.78-1.88 (m, 2H), 2.42 (s, 2H), 2.95 (s, 3H), 3.67 (s, 3H), 4.65 (d, $^3J_{(H,H)} = 2.5$ Hz, 1H), 5.57 (d, $^3J_{(H,H)} = 2.5$ Hz, 1H), 7.36 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ =

21.5 (2C), 25.5, 31.3, 37.2 (2C), 39.6, 50.3, 58.0, 107.2, 133.8, 149.1, 167.5. IR (CHCl₃, cm⁻¹) 3010.0, 2941.1, 2858.6, 1670.4, 1623.9, 1588.3, 1572.0, 1439.3, 1298.1, 1154.2, 1068.7. MS (70 eV): *m/z* (%): 235 (21) [*M*⁺], 206 (8.7), 204 (7.3), 193 (18), 192 (100), 179 (37). HRMS calculated for C₁₄H₂₁NO₂ 235.1572, found 235.1567.

Methyl 1-(4-methoxyphenyl)-4-methyl-1-azaspiro[5.5]undeca-2,4-diene-3-carboxylate (8l): (252 mg, 77%) amorphous pale brown solid. Major tautomer ("4-methyl" group) ¹H NMR (CDCl₃, 400 MHz): δ = 0.90-0.98 (m, 1H), 1.23-1.36 (m, 2H), 1.45-1.60 (m, 5H), 1.96 (d, ³*J*_(H,H) = 11.1 Hz, 2H), 2.13 (s, 3H), 3.63 (s, 3H), 3.81 (s, 3H), 5.06 (s, 1H), 6.86 (d, ³*J*_(H,H) = 8.8 Hz, 2H), 7.12 (d, ³*J*_(H,H) = 8.8 Hz, 2H), 7.42 (s, 1H). ¹³C NMR (CDCl₃, 100 MHz): δ = 21.4, 21.5 (2C), 25.3, 35.7 (2C), 50.2, 55.4, 60.8, 100.2, 113.95 (2C), 114.0, 130.3, 130.8 (2C), 135.6, 145.6, 158.9, 167.2. Minor tautomer ("4-methylene" group) ¹H NMR (CDCl₃, 400 MHz): δ = 0.90-0.98 (m, 1H), 1.23-1.36 (m, 2H), 1.45-1.60 (m, 5H), 1.71 (d, ³*J*_(H,H) = 11.6 Hz, 2H), 2.58 (s, 2H), 3.66 (s, 3H), 3.81 (s, 3H), 4.78 (d, ³*J*_(H,H) = 2.5 Hz, 1H), 5.71 (d, ³*J*_(H,H) = 2.5 Hz, 1H), 6.86 (d, ³*J*_(H,H) = 8.8 Hz, 2H), 7.05 (d, ³*J*_(H,H) = 8.8 Hz, 2H), 7.43 (s, 1H). ¹³C NMR (CDCl₃, 100 MHz): δ = 21.7 (2C), 25.3, 33.5 (2C), 40.1, 50.4, 55.4, 59.9, 97.8, 108.5, 114.4 (2C), 130.5 (2C), 130.8, 135.8, 147.8, 158.9, 167.4. IR (CHCl₃, cm⁻¹) 3011.7, 2941.8, 2859.8, 1677.8, 1625.2, 1573.9, 1509.5, 1438.4, 1292.3, 1249.2, 1170.2, 1093.3. MS (70 eV): *m/z* (%): 327 (32) [*M*⁺], 285 (21), 284 (100), 271 (13), 270 (24), 123 (15). HRMS calculated for C₂₀H₂₅NO₃ 327.1834, found 327.1828.

Methyl 4-tert-butyl-1-(4-methoxyphenyl)-1-azaspiro[5.5]undeca-2,4-diene-3-carboxylate (8m): (56 mg, 15%) amorphous pale brown solid. ¹H NMR (CDCl₃, 400 MHz): δ = 1.20-1.27 (m, 2H), 1.29 (s, 9H), 1.45-1.58 (m, 6H), 1.96-1.99 (m, 2H), 3.63 (s, 3H), 3.81 (s, 3H), 5.22 (s, 1H), 6.85 (d, ³*J*_(H,H) = 9.1 Hz, 2H), 7.11 (d, ³*J*_(H,H) = 9.1 Hz,

2H), 7.44 (s, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 21.9 (2C), 25.5, 30.6 (3C), 34.7 (2C), 34.9, 50.5, 55.5, 59.9, 101.9, 113.3, 113.9 (2C), 130.6 (2C), 135.8, 142.5, 149.1, 158.8, 167.9. IR (CHCl_3 , cm^{-1}) 2940.6, 1686.4, 1618.6, 1508.9, 1435.9, 1362.4, 1289.6, 1247.9. MS (70 eV): m/z (%): 369 (16) [M^+], 327 (24), 326 (100), 313 (16), 312 (24), 296 (7.4), 282 (6.3). HRMS calculated for $\text{C}_{23}\text{H}_{31}\text{NO}_3$ 369.2304, found 369.2298.

Methyl 6-butyl-1-(4-methoxyphenyl)-4,6-diphenyl-1,6-dihydropyridine-3-carboxylate (8n): (367 mg, 81%) reddish oil. ^1H NMR (CDCl_3 , 400 MHz): δ = 0.84 (t, $^3J_{(\text{H,H})}$ = 7.3 Hz, 3H), 1.21-1.34 (m, 2H), 1.48-1.67 (m, 2H), 1.75-1.82 (m, 1H), 2.08-2.16 (m, 1H), 3.50 (s, 3H), 3.74 (s, 3H), 4.80 (s, 1H), 6.68 (d, $^3J_{(\text{H,H})}$ = 8.8 Hz, 2H), 6.74 (d, $^3J_{(\text{H,H})}$ = 8.8 Hz, 2H), 7.24-7.30 (m, 6H), 7.34 (t, $^3J_{(\text{H,H})}$ = 7.3 Hz, 2H), 7.51 (d, $^3J_{(\text{H,H})}$ = 7.3 Hz, 2H), 7.65 (s, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 14.0, 22.9, 26.6, 36.9, 50.4, 55.4, 67.8, 98.1, 113.7 (2C), 121.5, 126.5, 126.9 (2C), 127.3 (2C), 127.6 (2C), 127.7, 128.2 (2C), 128.4 (2C), 133.9, 136.4, 141.4, 146.7, 148.4, 158.3, 166.6. IR (CHCl_3 , cm^{-1}) 2958.8, 1681.9, 1630.7, 1560.5, 1509.4, 1438.2, 1280.9, 1237.0, 1182.3, 1099.8. MS (70 eV): m/z (%): 453 (12) [M^+], 397 (37), 396 (100), 394 (31), 320 (36), 123 (23). HRMS calculated for $\text{C}_{30}\text{H}_{31}\text{NO}_3$ 453.2304, found 453.2292.

Methyl 1-(4-methoxyphenyl)-9-oxo-4-phenyl-1-azaspiro[5.5]undeca-2,4-diene-3-carboxylate ethylene ketal (8o): (327 mg, 73%) amorphous brown solid. ^1H NMR (CDCl_3 , 400 MHz): δ = 1.58-1.64 (m, 2H), 1.71-1.78 (m, 2H), 1.89-1.97 (m, 2H), 2.04-2.07 (m, 2H), 3.50 (s, 3H), 3.82 (s, 3H), 3.84-3.93 (m, 4H), 5.22 (s, 1H), 6.89 (d, $^3J_{(\text{H,H})}$ = 8.8 Hz, 2H), 7.18 (d, $^3J_{(\text{H,H})}$ = 8.8 Hz, 2H), 7.26-7.33 (m, 5H), 7.61 (s, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ = 30.4 (2C), 31.9 (2C), 50.4, 55.5, 60.2, 64.2, 64.3, 100.8, 107.7, 114.2 (2C), 115.4, 126.9, 127.5 (2C), 127.7 (2C), 130.3 (2C), 135.3, 136.9, 141.2, 148.8, 159.0, 166.6. IR (CHCl_3 , cm^{-1}) 3011.7, 2952.6, 1682.7, 1548.8, 1509.6, 1438.5, 1368.7, 1281.2, 1236.2, 1172.3, 1105.7. MS (70 eV): m/z (%): 447 (8.9) [M^+],

404 (10), 388 (9.1), 347 (32), 346 (100), 332 (21), 123 (21). HRMS calculated for $C_{27}H_{29}NO_5$ 447.2046, found 447.2037.

Methyl 9-benzyl-1-(4-methoxyphenyl)-4-phenyl-1,9-diazaspiro[5.5]undeca-2,4-diene-3-carboxylate (8p): (360 mg, 75%) amorphous pale orange solid. 1H NMR ($CDCl_3$, 400 MHz): δ = 1.73-1.78 (m, 2H), 1.98-2.04 (m, 2H), 2.32-2.37 (m, 2H), 2.70-2.72 (m, 2H), 3.50 (s, 3H), 3.50 (s, 2H), 3.83 (s, 3H), 5.19 (s, 1H), 6.88-6.90 (m, 2H), 7.16-7.18 (m, 2H), 7.25-7.32 (m, 10H), 7.64 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 34.7 (2C), 49.1 (2C), 50.4, 55.5, 59.5, 62.9, 100.8, 114.2 (2C), 116.2, 126.8, 127.0, 127.5 (2C), 127.7 (2C), 128.2 (2C), 129.0 (2C), 130.6 (2C), 135.1, 136.3, 138.4, 141.3, 148.9, 159.1, 166.6. IR ($CHCl_3$, cm^{-1}) 2927.7, 1683.9, 1616.7, 1549.8, 1509.0, 1438.4, 1364.3, 1294.0, 1222.0, 1105.0. MS (70 eV): m/z (%): 480 (10) [M^+], 451 (9.0), 389 (15), 347 (34), 346 (65), 332 (34), 91 (100). HRMS calculated for $C_{31}H_{32}N_2O_3$ 480.2413, found 480.2418.

Methyl 6-(but-3-en-1-yl)-1-(4-methoxyphenyl)-4-phenyl-1,6-dihydropyridine-3-carboxylate (8q): (252 mg, 67%) dark brown oil. 1H NMR (400 MHz, $CDCl_3$): δ = 1.62-1.71 (m, 1H), 2.00-2.08 (m, 1H), 2.16-2.30 (m, 2H), 3.53 (s, 3H), 3.80 (s, 3H), 4.59-4.64 (m, 1H), 4.99-5.08 (m, 2H), 5.19 (d, $^3J_{(H,H)} = 6.3$ Hz, 1H), 5.78-5.90 (m, 1H), 6.90-6.92 (m, 2H), 7.12-7.14 (m, 2H), 7.22-7.31 (m, 5H), 7.80 (d, $^3J_{(H,H)} = 1.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.9, 32.6, 50.9, 56.0, 58.2, 104.4, 114.2, 115.2 (2C), 115.8, 121.4 (2C), 127.2, 127.9 (2C), 128.0 (2C), 137.0, 138.1, 138.3, 141.4, 143.2, 157.3, 167.0; IR ($CHCl_3$, cm^{-1}) 3009.0, 2950.2, 2840.0, 2360.3, 1684.5, 1618.3, 1557.7, 1511.0, 1437.6, 1231.3, 1037.0. MS (70 eV): m/z (%): 375 (1.3) [M^+], 321 (22), 320 (100), 277 (9.2), 217 (4.2), 154 (2.7), 128 (4.1), 115 (4.9), 92 (4.1); HRMS: calculated for $C_{24}H_{25}NO_3$: 375.1834, found: 375.1832.

Methyl 6-cyclohexyl-1-(4-methoxyphenyl)-4-phenyl-1,6-dihydropyridine-3-carboxylate (8r): (133 mg, 33%) dark brown oil. ^1H NMR (400 MHz, CDCl_3): δ = 0.99-1.13 (m, 5H), 1.40-1.49 (m, 3H), 1.50-1.59 (m, 2H), 1.76-1.79 (m, 1H), 3.37 (s, 3H), 3.67 (s, 3H), 4.40-4.43 (m, 1H), 4.95 (d, $^3J_{(\text{H,H})} = 6.1$ Hz, 1H), 6.74-6.78 (m, 2H), 7.02-7.04 (m, 2H), 7.08-7.17 (m, 5H), 7.70 (d, $^3J_{(\text{H,H})} = 1.3$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ = 26.0, 26.3, 26.4, 27.2, 28.5, 43.3, 50.5, 55.6, 63.8, 106.3, 113.1, 114.8 (2C), 122.0 (2C), 126.7, 127.4 (2C), 127.5 (2C), 137.0, 138.7, 141.4, 144.3, 156.9, 166.6; IR (CHCl_3 , cm^{-1}) 3005.6, 2931.0, 2855.1, 2360.4, 1684.2, 1617.3, 1559.8, 1511.1, 1438.1, 1231.7. MS (70 eV): m/z (%): 403 (1.0) [M^+], 332 (3.8), 321 (28), 320 (100), 277 (8.5), 217 (3.0), 123 (2.6), 115 (3.8), 92 (3.6); HRMS: calculated for $\text{C}_{26}\text{H}_{29}\text{NO}_3$: 403.2147, found: 403.2133.

Methyl 1-(4-methoxyphenyl)-4-phenyl-6-propyl-1,6-dihydropyridine-3-carboxylate (8s): (244 mg, 67%) dark brown oil. ^1H NMR (400 MHz, CDCl_3): δ = 0.96 (t, $^3J_{(\text{H,H})} = 6.9$ Hz, 3H), 1.52-1.55 (m, 4H), 3.53 (s, 3H), 3.81 (s, 3H), 4.57-4.61 (m, 1H), 5.20 (d, $^3J_{(\text{H,H})} = 6.3$ Hz, 1H), 6.90-6.92 (m, 2H), 7.13-7.15 (m, 2H), 7.27-7.31 (m, 5H), 7.80 (d, $^3J_{(\text{H,H})} = 1.5$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ = 14.1, 17.6, 35.5, 50.5, 55.6, 58.3, 106.3, 114.4, 114.8 (2C), 121.0 (2C), 126.8, 127.5 (2C), 127.6 (2C), 136.3, 138.0, 141.1, 142.8, 156.8, 166.6; IR (CHCl_3 , cm^{-1}) 3009.0, 2960.3, 2839.8, 2360.5, 1684.4, 1621.8, 1557.8, 1511.0, 1437.5, 1230.9, 1036.2. MS (70 eV): m/z (%): 363 (1.3) [M^+], 321 (25), 320 (100), 277 (8.1), 217 (3.1), 131 (4.0), 115 (3.0); HRMS: calculated for $\text{C}_{23}\text{H}_{25}\text{NO}_3$: 363.1834, found: 363.1836.

Supporting Information

Copies of ^1H and ^{13}C NMR spectra of the new compounds are available in the Supporting Information.

Acknowledgements

This research was supported by the Spanish Ministerio de Economía y Competitividad (MICINN) and the European Regional Development Fund (CTQ2011-28417-C02-02).

L.C. and G.M.A thank Spanish MEC for a FPI and a FPU grant respectively.

References

1. (a) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141-1156. (b) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, 72, 1-42.
2. Edraki, N.; Mehdipour, A. R.; Khoshneviszadeh, M.; Miri, R. *Drug Discovery Today* **2009**, 14, 1058-1066.
3. For some selected examples, see: (a) Salama, I.; Abdel-Fattah, M.A.O.; Hany, M.S.; El-Sharif, S.A.; El-Naggar, M.A.M.; Rashied, R.M.H.; Piazza, G.A.; Abadi, A.H. *Med. Chem.* **2012**, 8, 372-383. (b) Al-Said, M. S.; Bashandy, M. S.; Al-qasoumi, S. I.; Ghorab, M. M. *Eur. J. Med. Chem.* **2011**, 46, 137-141. (c) Schroeder, G. M.; An, Y. M.; Cai, Z. W.; Chen, X. T.; Clark, C.; Cornelius, L. A. M.; Dai, J.; Gullo-Brown, J.; Gupta, A.; Henley, B.; Hunt, J. T.; Jeyaseelan, R.; Kamath, A.; Kim, K.; Lippy, J.; Lombardo, L. J.; Manne, V.; Oppenheimer, S.; Sack, J. S.; Schmidt, R. J.; Shen, G. X.; Stefanski, K.; Tokarski, J. S.; Trainor, G. L.; Wautlet, B. S.; Wei, D. N.; Williams, D. K.; Zhang, Y. R.; Zhang, Y. P.; Fargnoli, J.; Borzilleri, R. M. *J. Med. Chem.* **2009**, 52, 1251-1254. (d) Domány, G.; Matúz, J.; Sághy, K.; Ezer, E. *Eur. J. Med. Chem.* **1993**, 28, 633-636.
4. For recent selected examples, see: (a) Sellstedt, M.; The Dang, H.; Prasad, G. K.; Sauer, U.; Almqvist, F. *Eur. J. Org. Chem.* **2013**, 7476-7479. (b) Martin, R. M.; Bergman, R. G.; Ellman, J. A. *Org Lett.* **2012**, 15, 444-447. (c) Oshima, K.;

- Ohmura, T.; Suginome, M. *J. Am. Chem. Soc.* **2012**, *134*, 3699-3702. (d) Nakano, H.; Osone, K.; Takeshita, M.; Kwon, E.; Seki, C.; Matsuyama, H.; Takano, N.; Koharia, Y. *Chem. Commun.* **2010**, *46*, 4827-4829. (e) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 5734-5736. (f) Songis, O.; Didierjean, C.; Laurent, C.; Martinez, J.; Calmé, M. *Eur. J. Org. Chem.* **2007**, 3166-3172. (g) Krow, G. R.; Huang, Q.; Szczepanski, S. W.; Hausheer, F. H.; Carroll, P. J. *J. Org. Chem.* **2007**, *72*, 3458-3466.
5. Khan, M. O. F.; Levi, M. S.; Clark, C. R.; Ablordeppey, S. Y.; Law, S.-L.; Wilson, N. H.; Borne, R. F. *Stud. Nat. Prod. Chem.* **2008**, *34*, 753-787.
6. (a) Ishikura, M.; Abe, T.; Choshib, T.; Hibino, S. *Nat. Prod. Rep.* **2013**, *30*, 694-752. (b) Kumar Jana, G.; Paul, S.; Sinha, S. *Org. Prep. Proc. Int.* **2011**, *43*, 541-573. (c) Alper, K. R. *Alkaloids Chem. Biol.* **2001**, *56*, 1-38.
7. Roussi, F.; Gueritte, F.; Fahy, J. in *The Vinca alkaloids. Anticancer Agents from Natural Products*; Gragg, G. M., Kingston, D. G. I., Newman, D. J., Eds; Taylor and Francis: Boca Raton, **2012**; pp 177-198.
8. Moisan, L.; Thuéry, P.; Nicolas, M.; Doris, E.; Rousseau, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 5334-5336.
9. Silva, E. M. P.; Varandas, P. A. M. M.; Silva, A. M. S. *Synthesis* **2013**, *45*, 3053-3089.
10. (a) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642-2713. (b) For a recent example of the catalytic reduction of an unactivated pyridine to 1,2-DHP, see: Oshima, K.; Ohmura, T.; Suginome, M. *J. Am. Chem. Soc.* **2012**, *134*, 3699-3702.

11. For selected reviews, see: (a) Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. *Eur. J. Org. Chem.* **2005**, 23-44. (b) Harrity, J. P. A.; Provoost, O. *Org. Biomol. Chem.* **2005**, 3, 1349-1358.
12. (a) Harschneck, T.; Kirsch, S. F. *J. Org. Chem.* **2011**, 76, 2145-2156. (b) Tejedor, D.; Méndez-Abt, G.; García-Tellado, F. *Chem. Eur. J.* **2010**, 16, 428-431. (c) Wei, H.; Wang, Y.; Yue, B.; Xu, P.-F. *Adv. Synth. Catal.* **2010**, 352, 2450-2454. For seminal papers, see: (d) De Lera, A. R.; Reischl, W.; Okamura, W. H. *J. Am. Chem. Soc.* **1989**, 111, 4051-4063. (e) Tanaka, K.; Mori, H.; Yamamoto, M.; Katsumura, S. *J. Org. Chem.* **2001**, 66, 3099-3110.
13. For the synthesis of 1,2-DHPs by cycloaddition reaction of azadienes and enamines, see: (a) Palacios, F.; Alonso, C.; Rubiales, G.; Ezpeleta, J. M. *Eur. J. Org. Chem.* **2001**, 2115-2122. For the synthesis of 1,2-DHPs from cycloaddition reaction of azadienes and N-vinyl phosphazenes: (b) Palacios, F.; Herrán, E.; Rubiales, G. *J. Org. Chem.* **1999**, 64, 6239-6246.
14. For the synthesis of 1,2-DHPs by metal-catalyzed cycloaddition reaction of azadienes and alkynes, see: (a) Ischay, M. A.; Takase, M. K.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2013**, 135, 2478-2481. (b) Yamakawa, T.; Yoshikai, N. *Org. Lett.* **2013**, 15, 196-199.
15. (a) Tejedor, D.; Méndez-Abt, G.; Cotos, L.; García-Tellado, F. *Chem. Soc. Rev.* **2013**, 42, 458-471. (b) Zhu, Z.-B.; Kirsch, S. F. *Chem. Commun.* **2013**, 49, 2272-2283.
16. The value of the spiro motive in medicinal chemistry is well established: (a) Beghyn, T.; Deprez-Poulain, R.; Willand, N.; Folleas, B.; Deprez, B. *Chem. Biol. Drug. Des.* **2008**, 72, 3-15. (b) Pradhan, R.; Patra, M.; Behera, A. K.; Mishra, B. K.; Behera, R. K. *Tetrahedron* **2006**, 62, 779-828.

17. For selected examples of the synthesis of quaternized 1,2-DHPs from pyridines, see: (a) Pérez-Vázquez, J.; Veiga, A. X.; Prado, G.; Sardina, F. J.; Paleo, M. R. *Eur. J. Org. Chem.* **2012**, 975-987. (b) Nadeau, C.; Aly, S.; Belyk, K. *J. Am. Chem. Soc.* **2011**, *133*, 2878-2880. (c) From enamines and propargylic alcohols: Shao, Y.; Zhu, K.; Qin, Z.; Li, E.; Li, Y. *J. Org. Chem.* **2013**, *78*, 5731-5736. (d) For other examples of quaternized 1,2-DHPs, see reference [10a] and references cited therein. (e) For spiro1,2-DHPs, see: Hsung, R. P.; Wei, L.-L.; Sklenicka, H. M.; Douglas, C. J.; McLaughlin, M. J.; Mulder, J. A.; Yao, L. J. *Org. Lett.* **1999**, *1*, 509-512.
18. We refer to secondary PVEs to those PVEs bearing one substituent at the propargylic position; tertiary PVEs bear two substituents at this position.
19. Tertiary PVEs were synthesized in two steps from the corresponding ketones: 1) alkynylation and 2) DABCO-catalyzed addition of the resulting tertiary propargylic alcohol onto methyl propiolate. Tejedor, D.; Álvarez-Méndez, S. J.; López-Soria, J. M.; Martín, V. S.; García-Tellado, F. *Eur. J. Org. Chem.* **2014**, 198-205.
20. Harper, K. C.; Bess, E. N.; Sigman, M. S. *Nat. Chem.* **2012**, *4*, 366-374.
21. For a recent example of a favoured imine formation by microwave irradiation in methanol, see: Kraus, G. A.; Guo, H. *Org. Lett.* **2008**, *14*, 3061-3063.
22. Tejedor, D.; Méndez-Abt, G.; Cotos, L.; Ramírez, M. A.; García-Tellado, F. *Chem. Eur. J.* **2011**, *17*, 3318-3321.