First synthesis of heterocyclic allenes – benzazecine derivatives

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Supplementary Information

Experimental Section

IR spectra were registered on an Infralum FT-801 FTIR spectrometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were acquired on a JEOL JNM-ENM 600 spectrometer (600 and 150 MHz, respectively) in $CDCl_3$ for compounds **1a-c**, with solvent signal as internal standard (7.26 ppm for ^{1}H nuclei, 77.2 ppm for ^{13}C nuclei) and in DMSO-d_6 for compounds **3**, with solvent signal as internal standard (2.50 ppm for ^{1}H nuclei, 39.5 ppm for ^{13}C nuclei). Mass spectra (LC-MS) of compounds **1a-c** and **3** were acquired on an Agilent 1100/Agilent Technologies LC/MS VL LC-MS system (electrospray ionization). Elemental analysis was performed on a Euro Vector EA-3000 Elemental Analyzer. Melting points were determined on an SMP 10 apparatus in open capillaries. Sorbfil PTH-AF-A-UF plates were used for TLC, visualization in an iodine chamber. Silica gel (40–60 μm, 60 Å) was used for column chromatography for compounds **1a-c** and Al_2O_3 (150 mesh, 58Å) was used for column chromatography for compounds **3ab**, **3bb**, **3cb**.

All solvents were purified by distillation before use. Methyl propiolate **2a**, ethynyl methyl ketone **2b**, trifluoroethanol, and phenylacetylene (Acros Organics) were used without additional purification.

General procedure for the synthesis of isoquinolines 1a-c

Compounds **1a-c** were prepared following a modifier method[1]. CuI (7.1 mmol) was added with stirring under nitrogen to a solution of 1-(methyl-), 1-benzyl-6,7-dimethoxy-2-methyl-3,4-dihydro-isoquinolinium iodide (7.1 mmol) in absolute CH_2Cl_2 (30 ml). The resulting solution was poured under a nitrogen atmosphere into a solution of phenylacetylene (71 mmol) in absolute CH_2Cl_2 (10 ml). Then triethylamine (32 mmol) was added to the reaction mixture. The reaction was performed at -20 °C, monitoring the progress by TLC (eluent ethanol). The solvent was evaporated in vacuum, and the residue separated by chromatography on silica gel (compounds 7-9 were eluted with EtOAc–hexane, 1:2).

6,7-Dimethoxy-1,2-dimethyl-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline **(1a)**. Colorless crystals. Mp 115-117 °C. Yield 41%. R_f = 0.6 (1:2 EtOAc:Hex). IR spectrum, ν, $см^{-1}$: 2200 (C≡C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40–7.42 (m, 2H), 7.27–7.29 (m, 3H), 6.99 (s, 1H), 6.56 (s, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 2.94–3.02 (m, 2H), 2.84–2.87 (m, 1H), 2.68–2.72 (m, 1H), 2.63 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.8, 147.3, 132.4, 131.6, 128.1 (2C), 127.8 (2C), 125.8, 123.3, 110.9, 110.3, 91.3, 85.3, 58.1, 56.0, 55.7, 48.7, 40.0, 29.0, 27.9. *m/z*:

[1] A. M. Taylor, S. L. Schreiber, *Org. Lett.*, 2006, **8**, 143.

322 $[M+H]^+$. Anal Calcd for $C_{21}H_{23}NO_2$ (%): C 78.47, H 7.21, N 4.36. Found (%): C 78.45, H 7.23, N 4.34.

1-Benzyl-6,7-dimethoxy-2-methyl-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline **(1b)**. Colorless crystals. Mp 88-89 °C. Yield 40%. R_f = 0.6 (1:3 EtOAc:Hex). IR spectrum, ν, $см^{-1}$: 2230 (C≡C). ^1H NMR (600 MHz, $CDCl_3$) δ 7.44–7.46 (m, 2H), 7.30–7.33 (m, 3H), 7.14–7.16 (m, 3H), 6.99–7.01 (m, 2H), 6.75 (s, 1H), 6.48 (s, 1H), 3.85 (s, 3H), 3.72 (s, 3H), 3.39 (d, 1H, *J* = 13.8 Hz), 3.34 (d, 1H, *J* = 13.8 Hz), 2.87–2.95 (m, 2H), 2.74 (s, 3H), 2.60–2.68 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.5, 146.5, 137.1, 131.6 (2C), 130.9 (2C), 129.6, 128.2 (2C), 127.9, 127.2 (2C), 127.1, 126.1, 123.3, 111.8, 110.6, 91.2, 86.6, 62.6, 55.7, 55.6, 48.1, 44.9, 40.0, 28.7. *m/z*: 398 $[M+H]^+$. Anal Calcd for $C_{27}H_{27}NO_2$ (%): C 81.56, H 6.84, N 3.55. Found (%): C 81.58, H 6.85, N 3.52.

1,2-Dimethyl-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline **(1c)**. Yellow oil. Yield 90%. R_f = 0.55 (1:3 EtOAc:Hex). IR spectrum, ν, $см^{-1}$: 2225 (C≡C). ^1H NMR (600 MHz, $CDCl_3$) δ 7.57–7.58 (m, 1H), 7.44–7.45 (m, 2H), 7.29–7.31 (m, 3H), 7.25 (t, 1H, *J* = 7.3 Hz), 7.20 (t, 1H, *J* = 7.3 Hz), 7.12–7.13 (m, 1H), 3.08–3.13 (m, 1H), 2.99–3.03 (m, 1H), 2.88–2.91 (m, 1H), 2.80–2.84 (m, 1H), 2.67 (s, 3H), 1.84 (c, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.5, 133.4, 131.6 (2C), 128.7, 128.1 (2C), 127.8, 127.4, 126.3, 125.9, 123.3, 91.2, 85.4, 58.4, 48.6, 40.0, 29.5, 27.9. Масс-спектр, m/z: 262 $[M+H]^+$. Anal Calcd for $C_{19}H_{19}N$ (%): C 87.31, H 7.33, N 5.36. Found (%): C 87.35, H 7.37, N 5.38.

General procedure for the synthesis of benzazecines with allenic fragment 3

The solution of tetrahydroisoquinolines **1a-c** (1.1 mmol, 1 equiv) and terminal alkynes (1.2 mmol, 1.05 equiv) in trifluoroethanol (7 ml) was kept at +7 ° C for 1 day, monitoring the reaction progress by TLC (eluent EtOAc–hexane, 1:2). The solvent was evaporated in vacuum. Adducts with methyl propiolate **3aa**, **3ba**, **3ca** recrystallized from EtOAc–hexane mixture, and adducts with ethynyl methyl ketone **3ab**, **3bb**, **3cb** were isolated by chromatography on Al_2O_3. Compounds **3ab**, **3bb**, **3cb** were eluted with EtOAc–hexane, 1:20.

Methyl 10,11-dimethoxy-3,8-dimethyl-6-phenyl-benzo[d]-3-aza-deca-4,6,7-trien-5-carboxylate **(3aa)**. Colorless crystals. Mp 150-152 °C. Yield 84%. R_f = 0.75 (1:2 EtOAc:Hex). IR spectrum, ν, $см^{-1}$: 1072, 1937 (C=C=C), 1674 (C=O). ^1H NMR (600 MHz, DMSO-d_6) δ 7.55 (s, 1H), 7.24–7.27 (m, 2H), 7.12–7.17 (m, 3H), 6.97 (s, 1H), 6.82 (s, 1H), 3.78 (s, 3H), 3.76–3.80 (m, 1H), 3.71 (s, 3H), 3.49 (s, 3H), 3.25–3.29 (m, 1H), 3.14 (s, 3H), 2.93–2.98 (m, 1H), 2.82–2.86

(m, 1H), 2.20 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.1, 168.7, 147.7, 147.6, 147.5, 138.6, 129.1, 128.4 (2C), 127.9, 126.4, 125.8 (2C), 113.9, 110.9, 101.2, 99.4, 93.9, 55.7, 55.50, 50.9, 50.7, 44.7, 30.3, 18.6. *m/z*: 406 $[M+H]^+$. Anal Calcd for $C_{25}H_{27}NO_4$ (%): C 74.05, H 6.71, N 3.45. Found (%): C 74.04, H 6.73, N 3.41.

X-ray structure determination. The crystal of **3aa** ($C_{25}H_{27}NO_4$, M = 405.47) is monoclinic, space group $P2_1/c$, at T = 100 K: a = 8.4800(17) Å, b = 25.563(5) Å, c = 9.970(2) Å, β = 99.16(3)°, V = 2133.7(8) Å^3, Z = 4, d_{calc} = 1.262 g/cm^3, $F(000)$ = 864, μ = 0.177 mm^{-1}. The X-ray diffraction data were collected on the 'Belok' beamline of the Kurchatov Synchrotron Radiation Source (National Research Center 'Kurchatov Institute', Moscow, Russian Federation) using a Rayonix SX165 CCD detector at λ = 0.96990 Å. A total of 360 images (32673 reflections, 4042 independent reflections, R_{int} = 0.044) were collected using an oscillation range of 1.0° and φ scan mode ($2\theta_{max}$ = 76.84°). The data were indexed and integrated using the utility iMOSFLM from the CCP4 program suite[2] and then scaled and corrected for absorption using the Scala program (T_{min} = 0.940; T_{max} = 0.980).[3] The structure was determined by direct methods and refined by full-matrix least squares technique on F^2 with anisotropic displacement parameters for non-hydrogen atoms. The hydrogen atoms were placed in calculated positions and refined within riding model with fixed isotropic displacement parameters [U_{iso}(H) = 1.5U_{eq}(C) for the CH_3-groups and 1.2U_{eq}(C) for the other groups]. The final divergence factors were R_1 = 0.048 for 3298 independent reflections with $I > 2\sigma(I)$ and wR_2 = 0.134 for all independent reflections, S = 1.055. All calculations were carried out using the SHELXTL program.[4]

Crystallographic data for compound **3aa** have been deposited with the Cambridge Crystallographic Data Center, CCDC 1507230. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).

[2] T. G. G. Battye, L. Kontogiannis, O. Johnson, H. R. Powell, A. G. W. Leslie, *Acta Crystallogr.* 2011, **D67**, 271.
[3] P. R. Evans, *Acta Crystallogr.* 2006, **D62**, 72.
[4] G. M. Sheldrick, *Acta Crystallogr.* 2015, **C71**, 3.

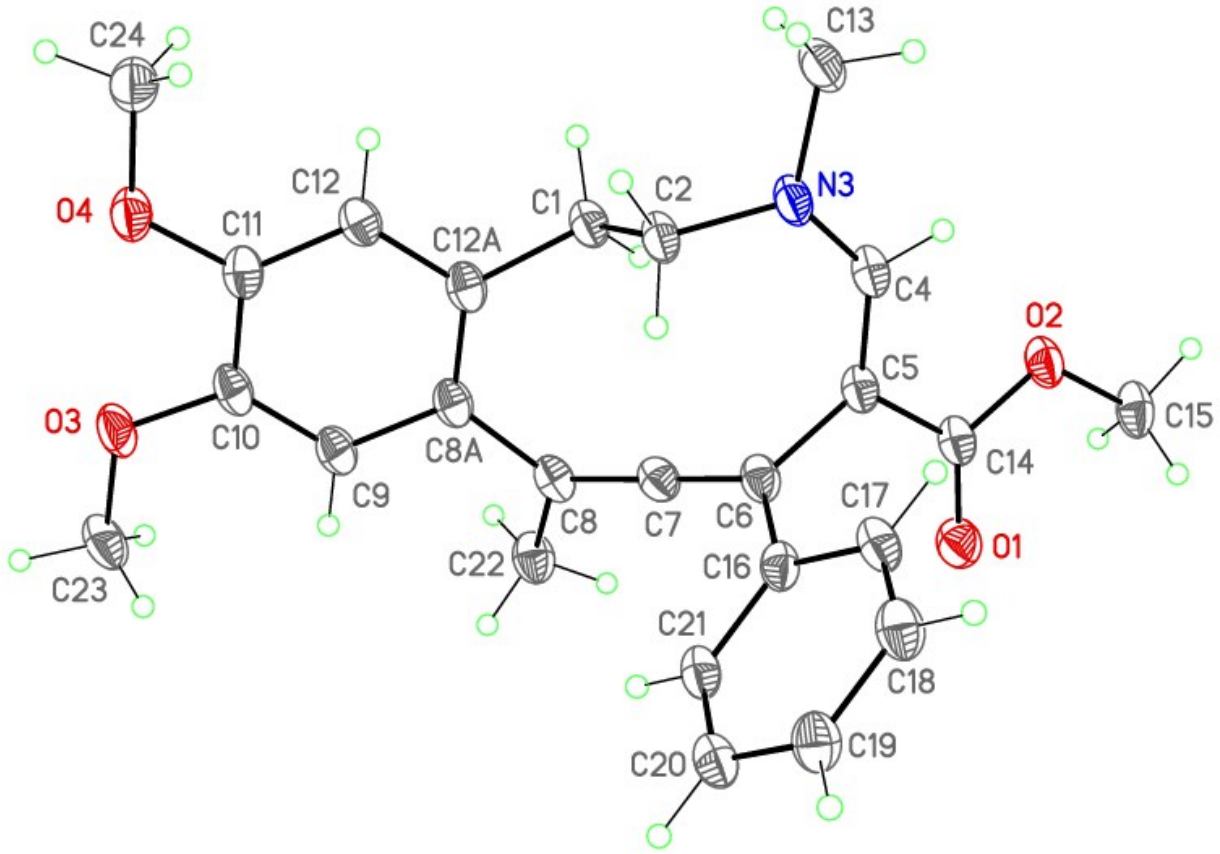

Figure 1S. Molecular structure of **3aa**.

1-(10,11-Dimethoxy-3,8-dimethyl-6-phenyl-benzo[d]-3-aza-deca-4,6,7-trien-5-yl)ethanone **(3ab)**. Yellow oil. Yield 90%. R_f = 0.75 (1:2 EtOAc:Hex). IR spectrum, ν, см$^{-1}$: 1054, 1934 (C=C=C), 1650 (C=O). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.55 (s, 1H), 7.29–7.30 (m, 2H), 7.24–7.26 (m, 2H), 7.14–7.17 (m, 1H), 6.87 (s, 1H), 6.57 (s, 1H), 4.08–4.13 (m, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.48–3.52 (m, 1H), 3.20 (s, 3H), 2.70–2.82 (m, 2H), 2.26 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.6, 193.5, 147.7, 147.4, 138.4, 129.1, 128.5 (2C), 127.9, 126.6, 125.8 (3C), 114.0, 110.5, 102.3, 99.2, 93.8, 55.7, 55.5, 51.0, 44.9, 30.4, 26.3, 18.2. Масс-спектр, *m/z*: 390 $[M+H]^+$. Anal Calcd for $C_{25}H_{27}NO_3$ (%): C 74.07, H 6.97, N 3.61. Found (%): C 74.09, H 6.99, N 3.60.

Methyl 8-Benzyl-10,11-dimethoxy-3-methyl-6-phenyl-benzo[d]-3-aza-deca-4,6,7-trien-5-carboxylate **(3ba)**. Colorless crystals. Mp 181-183 °C. Yield 85%. R_f = 0.75 (1:2 EtOAc:Hex). IR spectrum, ν, см$^{-1}$: 1062, 1935 (C=C=C), 1682 (C=O). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.53 (s, 1H), 7.21 – 7.27 (m, 6H), 7.12–7.17 (m, 4H), 7.08 (s, 1H), 6.75 (s, 1H), 4.01 (d, 1H, *J* = 14.0 Hz), 3.89 (d, 1H, *J* = 14.0 Hz), 3.79–3.82 (m, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 3.41 (s, 3H), 3.21–3.25 (m, 1H), 3.13 (s, 3H), 2.91–2.97 (m, 1H), 2.73–2.79 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$)

δ 207.6, 168.7, 147.6, 147.5, 147.4, 139.2, 138.3, 128.7 (2C), 128.4 (2C), 128.2 (2C), 127.8, 126.5, 126.0, 125.7, 113.8 (2C), 110.9, 103.8, 102.1, 94.0, 59.3, 59.1, 55.8, 55.4, 50.7, 44.6, 38.2, 30.1. *m/z*: 482 $[M+H]^+$. Anal Calcd for $C_{31}H_{31}NO_4$ (%): C 77.30, H 6.48, N 2.90. Found (%): C 77.31, H 6.49, N 2.91.

1-(8-Benzyl-10,11-dimethoxy-3-methyl-6-phenyl-benzo[d]-3-aza-deca-4,6,7-trien-5-yl)ethanone **(3bb)**. Yellow oil. Yield 80%. R_f = 0.75 (1:2 EtOAc:Hex). IR spectrum, ν, $см^{-1}$: 1026, 1935 (C=C=C), 1648 (C=O). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.71 (s, 1H), 7.31–7.32 (m, 2H), 7.28–7.29 (s, 3H), 7.25–7.27 (m, 3H), 7.16–7.18 (m, 2H), 6.98 (s, 1H), 6.58 (s, 1H), 4.06–4.10 (m, 1H), 4.05 (d, 1H, *J* = 15.3 Hz), 3.91 (s, 3H), 3.84 (s, 3H), 3.78 (d, 1H, *J* = 15.3 Hz), 3.46–3.50 (m, 1H), 3.19 (s, 3H), 2.70–2.82 (m, 2H), 1.52 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.7, 194.4, 153.1, 148.2, 148.0, 139.9, 138.8, 129.5 (2C), 129.2 (2C), 128.9 (2C), 128.8, 128.6, 127.4, 126.7, 126.3 (2C), 114.4, 111.5, 105.5, 104.5, 63.2, 56.4, 55.9, 51.6, 45.4, 38.7, 30.8, 26.8. *m/z*: 466 $[M+H]^+$. Anal Calcd for $C_{31}H_{31}NO_3$ (%): C 79.95, H 6.70, N 3.03. Found (%): C 79.97, H 6.71, N 3.01.

Methyl 3,8-dimethyl-6-phenyl-benzo[d]-3-aza-deca-4,6,7-trien-5-carboxylate (**3ca**). Colorless crystals. Mp 166-168 °C. Yield 72%. R_f = 0.54 (1:3 EtOAc:Hex). IR spectrum, ν, $см^{-1}$: 1069, 1920 (C=C=C), 1681 (C=O). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.56 (s, 1H), 7.43–7.45 (m, 1H), 7.24–7.27 (m, 3H), 7.12–7.20 (m, 5H), 3.77–3.82 (m, 1H), 3.50 (s, 3H), 3.30–3.34 (m, 1H), 3.15 (s, 3H), 2.88–2.97 (m, 2H), 2.21 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.2, 168.6, 147.5, 138.3, 137.3, 135.4, 130.4, 128.4 (2C), 126.8, 126.7, 126.5, 125.7 (2C), 101.5, 99.4, 99.2, 93.5, 50.8, 50.7, 44.6, 30.8, 18.4. Масс-спектр, *m/z*: 346 $[M+H]^+$. Found (%): C 79.95, H 6.73, N 4.07. Anal Calcd for $C_{23}H_{23}NO_2$ (%): C 79.97, H 6.71, N 4.05.

1-(3,8-Dimethyl-6-phenyl-benzo[d]-3-aza-deca-4,6,7-trien-5-yl)ethanone (**3cb**). Yellow oil. Yield 84%. R_f = 0.52 (1:3 EtOAc:Hex). IR spectrum, ν, $см^{-1}$: 1043, 1934 (C=C=C), 1648 (C=O). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.59 (s, 1H), 7.44–7.45 (m, 1H), 7.25–7.28 (m, 3H), 7.13–7.20 (m, 5H), 3.80–3.84 (m, 1H), 3.27–3.31 (m, 1H), 3.20 (s, 3H), 2.88–2.98 (m, 2H), 2.22 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.7, 193.5, 148.1, 138.1, 137.2, 135.3, 130.4, 128.6, 127.0, 126.7 (3C), 126.6, 125.8 (3C), 102.6, 99.1, 50.9, 44.9, 30.9, 26.3, 18.1. *m/z*: 330 $[M+H]^+$. Anal Calcd for $C_{23}H_{23}NO$ (%): C 83.85, H 7.04, N 4.86. Found (%): C 83.87, H 7.09, N 4.82.