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Bicyclo[1.1.1]pentane-Derived Building Blocks for Click Chemistry

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Abstract: Syntheses of bicyclo[1.1.1]pentane-derived azides and terminal alkynes – interesting substrates for click reactions – are described. With a few exceptions, the title compounds were prepared in two or three steps starting from common synthetic intermediates – the corresponding carboxylic acids. The key step in the synthesis of 1-azidobicyclo[1.1.1]pentanes was a copper-catalyzed diazo transfer reaction with imidazole-1-sulfonyl azide. The preparation of bicyclo[1.1.1]pentyl-substituted alkynes relied on Seyferth – Gilbert homologation with dimethyl 1-diazo-2-oxopropyl-phosphonate (Ohira – Bestmann reagent). It was shown that target compounds of both types are suitable substrates for click reactions, therefore they are promising building blocks for medicinal, combinatorial and bioconjugate chemistry. A practically important side result of this study is a multigram preparation of Boc-monoprotected 1,3-diaminobicyclo[1.1.1]pentane – a representative of bicyclic conformationally restricted diamine derivatives.

Introduction

Bicyclo[1.1.1]pentane derivatives have given rise to a considerable interest in recent years. While initially these bicyclic compounds could be found in purely academic studies as the products obtained from an unusual hydrocarbon possessing inverted carbon atoms – [1.1.1]propellane (**1**) (Figure 1),[1–4] currently they are attracting more and more attention in various areas of science as rigid structural elements to link molecular fragments in a linear fashion.[5–7] 1,3-Disubstituted bicyclo[1.1.1]-pentane has geometric parameters similar to those of a 1,4-diphenylene motif[5,8] and is therefore considered as an effective isosteric replacement for this fragment currently occurring in drug discovery. Such replacement increases three-dimensionality of the molecules and improves DMPK-related properties such as solubility, hydrophilicity, and membrane permeability.[8,9]

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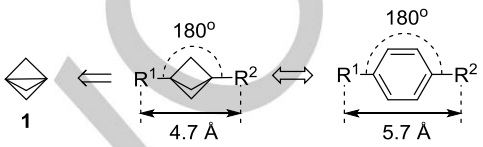
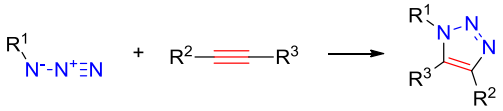


Figure 1. Bicyclo[1.1.1]pentane as an isostere of benzene

Click chemistry is another design concept which has gained momentum in recent decades. While being initially introduced by Sharpless as a catch phrase for any powerful, highly reliable, and selective reaction for the rapid synthesis of useful new compounds,[10] at the moment this term usually refers to the copper-catalyzed or strain-promoted reaction of azides and alkynes to produce 1,2,3-triazoles (Scheme 1).[11,12] The method allows for the preparation of combinatorial libraries of 1,2,3-triazoles which are attractive chemotypes for drug discovery.[13,14] Another important aspect of the click reaction is its use as a bioorthogonal transformation for bioconjugation.[15–17] Both these areas can potentially benefit from using bicyclo[1.1.1]pentane-derived building blocks. In particular, introducing a bicyclo[1.1.1]pentane motif into the 1,2,3-triazole ring complies well with recent design concepts of medicinal chemistry such as lead-oriented synthesis, *i. e.* shifting towards more sp^3-rich, three-dimensional, low-molecular-weight, hydrophilic compounds as the starting points for drug discovery projects.[18] On the other hand, bicyclo[1.1.1]pentane can serve as a rigid but sterically undemanding linear spacer allowing conjugation of the molecules in a well-defined manner, which can make the bioconjugate design more controllable.



Scheme 1. The click reaction of azides and alkynes.

Herein, we describe an approach to the gram-scale synthesis of bicyclo[1.1.1]pentane-derived azides (**2**) and alkynes (**3**) and demonstrate their use as substrates for the click reaction (Figure 2). To increase the potential for successful application of **2** and **3** and the products derived from them in medicinal, combinatorial and bioconjugate chemistry, the focus was made on fluorinated and bifunctional building blocks. In particular, the following

classes of bicyclo[1.1.1]pentane-derived azides/alkynes were planned to be made: (a) monofunctional building blocks to be used as decorating reagents, *e. g.* to introduce isosteres of *tert*-butyl[9] or larger lipophilic groups (R^1 = H, Ph) or their fluorinated analogues (R^1 = F, CF_3); (b) azides/alkynes with additional protected functional groups (R^1 = CO_2Me, NHBoc, NHCBz) to be used as *p*-phenylene isosteres or linear linkers (*i. e.* bifunctional building blocks), possibly under parallel synthesis conditions.[19]

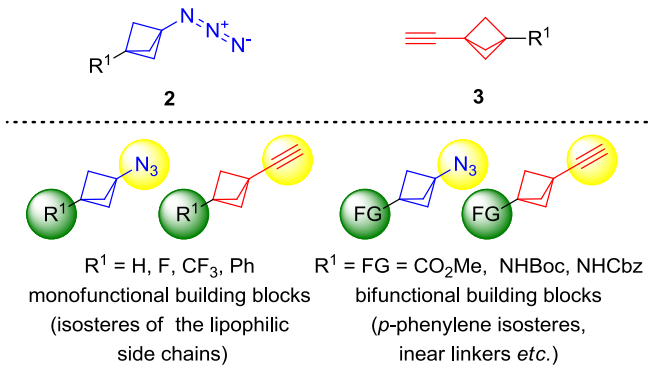
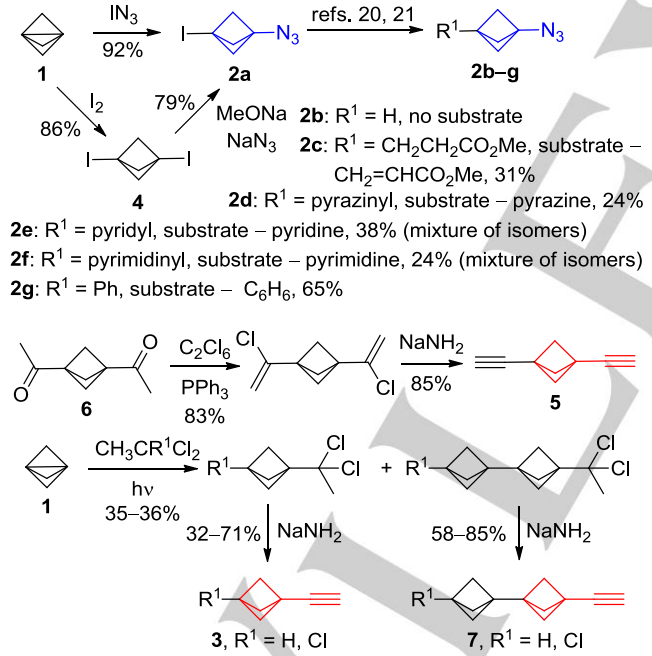


Figure 2. The target molecules of this study.

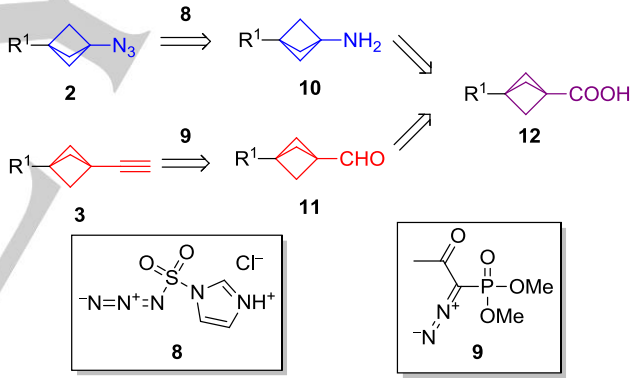


Scheme 2. Syntheses of azides **2** and alkynes **3** reported in the literature.

It should be noted that to date, only a few papers described syntheses of azides **2**; they were prepared *via* a common synthetic intermediate **2a** (R^1 = I).[20,21] In turn, compound **2a** was obtained by reaction of propellane (**1**) with IN_3[22] or *via* 1,3-diiodopropellane (**4**)[23,24] (Scheme 2). A number of works described synthesis and some selective reactions (*e. g.* Sonogashira coupling or silylation) of 1,3-diethynyl[1.1.1]-bicyclopentane (**5**); it was prepared in two steps from 1,3-diacetylbicyclo[1.1.1]pentane (**6**).[25–30] Apart from that, alkynes **3** and **7** (R^1 = H, Cl) were prepared using a similar method.[31]

Results and Discussion

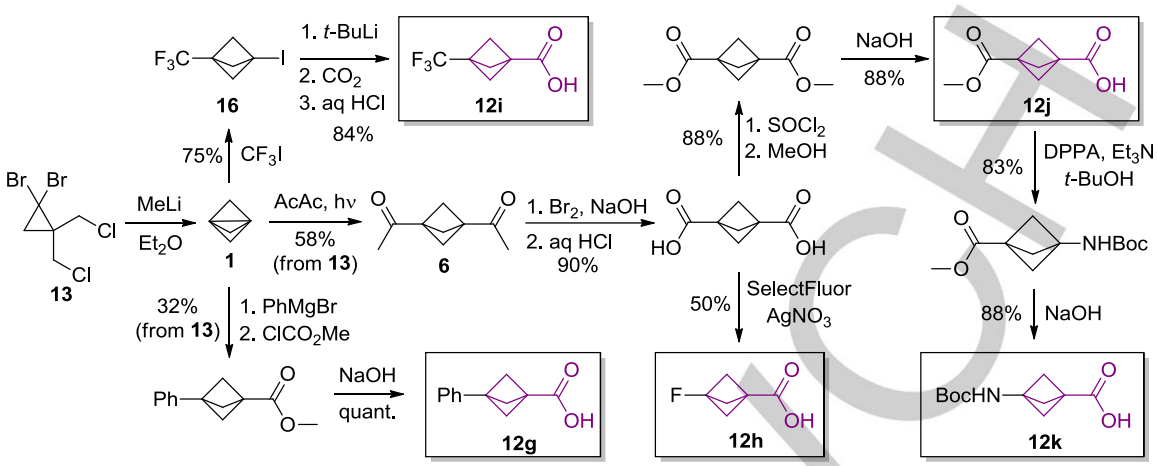
The literature methods for the preparation of azides **2** and alkynes **3** shown in Scheme 2 have limited substrate scope and are not applicable to the preparation of functionalized substrates. Therefore, we have looked for more appropriate key intermediates which could be used for the synthesis of all the target building blocks. In the case of azides **2**, we have turned our attention to the method of Goddard-Borger and Stick, who described imidazole-1-sulfonyl azide hydrochloride (**8**) as a convenient shelf-stable diazo transfer reagent for primary amines (Scheme 3).[32] For the synthesis of alkynes **3**, we envisaged the use of the Ohira – Bestmann reagent (**9**) which is known to convert aldehydes into terminal acetylenes.[33] Both primary amines **10** and aldehydes **11** could be obtained from the bicyclo[1.1.1]pentane-derived carboxylic acids **12**, which are known and accessible compounds for most of the substituents R^1 planned in this study.[34–39]



Scheme 3. Our retrosynthetic approach to **2** and **3**.

Therefore, our synthesis of **2** and **3** started with preparation of the carboxylic acids **12g–k** following the literature procedures (Scheme 4). A modified Curtius reaction of **12g–j** gave the known amines **10g–j**,[21,39–41] isolated as hydrochlorides in 65–84% yield (Table 1). For the synthesis of novel monoprotected diamines **10k,l**, carboxylic acid **12k** was transformed into unsymmetrical bis-carbamate **14** (85% yield), which was deprotected selectively to give either **12k** (99% yield) or **12l** (93% yield) (Scheme 5). Finally, amine **10b** was prepared as a hydrochloride using a previously reported reaction sequence (Scheme 6).[42]

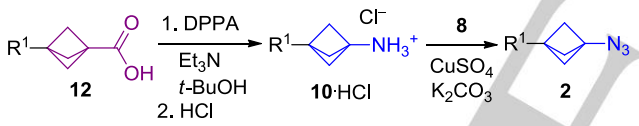
It should be noted that despite the synthesis of the amine **12k** included nine steps, it was performed successfully on up to 86 g scale. Therefore, this building block, a representative of monoprotected bicyclic conformationally restricted diamine deri-



Scheme 4. Synthesis of carboxylic acids **12**.

vatives,[43] can be considered now as readily available for drug discovery and other areas of potential application. It is a far more convenient reagent for selective modification than the free 1,3-diaminobicyclo[1.1.1]pentane reported previously.[44,45]

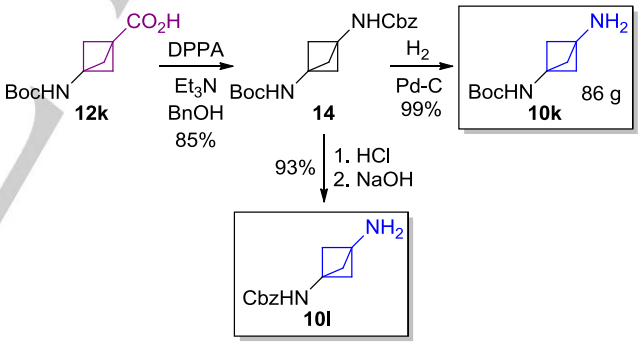
Table 1. Synthesis of azides **2**



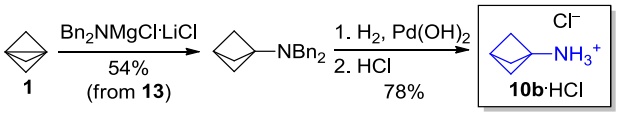
#	R^1	Amine or salt (yield, %)	Azide (yield, %)
1	H	**10b**·HCl (see Scheme 7)	**2b** (84)[a]
2	Ph	**10g**·HCl (65)	**2g** (63)
3	F	**10h**·HCl (79)	**2h** (67)[a]
4	CF_3	**10i**·HCl (70)	**2i** (76)[a]
5	CO_2Me	**10j**·HCl (84)	**2j** (78)
6	NHBoc	**10k** (see Scheme 6)	**2k** (82)
7	NHCbz	**10l** (see Scheme 6)	**2l** (61)

[a] Obtained as a methanolic solution; the yield was calculated from ^{1}H NMR data.

Reactions of amines **10** with imidazole-1-sulfonyl azide hydrochloride (**8**) in the presence of $CuSO_4$ and K_2CO_3 gave the target azides **2** in 61–84% yields (Table 1). It should be noted that whereas for azides **2g** and **2j–l**, standard work-up of the reaction mixture (including extraction and chromatographic purification) could be used, in the case of **2b**, **2h** and **2i**, the product was distilled from the crude reaction mixture together with the solvent. Therefore, the latter volatile azides were obtained as methanolic solutions which were used in further transformations without isolation.



Scheme 5. Synthesis of amines **10k** and **10l**.

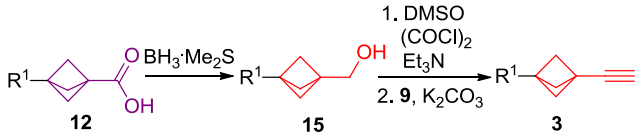


Scheme 6. Synthesis of amine **10b** (as hydrochloride)

For the synthesis of alkynes **3**, carboxylic acids **12** were reduced first to alcohols **15** using the BH_3·Me_2S complex (91–94% yield, Table 2). In the case of alcohol **15j**, this method followed the literature procedures for its preparation.[7,40] To transform **15** into aldehydes **11**, we have initially used the Dess – Martin reagent; it was shown, however, that Swern oxidation gave much better

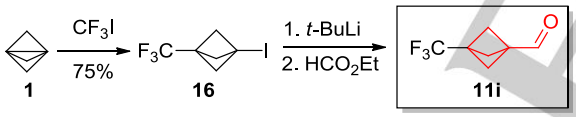
yields and purer products. To obtain aldehyde **11i**, the shorter literature method was used (Scheme 7).[46] Compounds **11** were not purified but subjected to the next step (*i. e.* the Seyferth – Gilbert reaction with the Ohira – Bestmann reagent (**9**)) to give the target alkynes **3g** and **3i–k** (43–88% yields over two steps). The volatile acetylene **3i** was obtained as a CH_2Cl_2 solution.

Table 2. Synthesis of alkynes **3**



#	R^1	Alcohol (yield, %)	Alkyne (yield, %)
1	Ph	**15g** (91)	**3g** (88)
2	CF_3	–	**3i** (50)[a]
3	CO_2Me	**15j** (92)	**3j** (43)
4	NHBoc	**15k** (94)	**3k** (55)

[a] Obtained *via* aldehyde **11i** (see Scheme 8); yield from **16**, detected by ^{1}H NMR



Scheme 7. Synthesis of adehyde **11i**

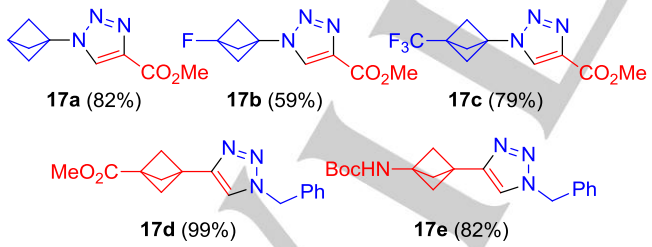


Figure 3. The products of click reactions with **2** and **3**

To demonstrate applicability of the products obtained for the click chemistry, as well as for characterization purposes in the case of the volatile substrates, we have performed their click reactions with methyl propiolate or benzyl azide. The products **17a–e** were obtained in 59–95% yields (Figure 3). It should be noted that unlike **17a–c**,[20,21] triazoles **17d** and **17e** represent a novel type of the bicyclo[1.1.1]pentane and 1,2,3-triazole scaffolds combination.

Conclusions

Bicyclo[1.1.1]pentane-derived building blocks are interesting structural motifs for the click reaction. Both azides **2** and alkynes **3** containing the bicyclo[1.1.1]pentane moiety can be prepared from common synthetic intermediates – the corresponding carboxylic acids **12** (although in some cases, alternative pathways are more convenient). In particular, modified Curtius rearrangement followed by diazo transfer reaction with imidazole-1-sulfonyl azide hydrochloride (**8**) is a convenient approach to 1-azidobicyclo[1.1.1]pentanes, which are obtained in 41–69% yields (from **12**). Bicyclo[1.1.1]pentyl-substituted terminal acetylenes **3** are prepared from **12** *via* reduction with borane, Swern oxidation, and Seyferth – Gilbert reaction with the Ohira – Bestmann reagent in 40–80% overall yield. Both **2** and **3** are appropriate substrates for click reactions, which give the corresponding 1,2,3-triazoles in 59–99% yields. An important side result of this study is the preparation of Boc-monoprotected 1,3-diaminobicyclo[1.1.1]pentane **10k**, which has been performed on up to 86 g scale. The novel compounds described herein are promising building blocks for medicinal, combinatorial and bioconjugate chemistry, which can be used either as decorating reagents to replace lipophilic side chains or as linkers and benzene isosteres.

Experimental Section

General. The solvents were purified according to the standard procedures.[47] Carboxylic acids **12g**[35,39] and **12j**,[39] hydrochlorides **10b**·HCl[42] and **10g–j**·HCl,[21,39–41] alcohol **15j**,[7] and aldehyde **11i**[46] were obtained using the reported procedures (see also the main text). All other starting materials were purchased from commercial sources. Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 499.9 MHz for Protons and 124.9 MHz for Carbon-13) and Varian Unity Plus 400 spectrometer (at 400.4 MHz for protons and 100.7 MHz for Carbon-13). Chemical shifts are reported in ppm downfield from TMS as an internal standard. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, National Taras Shevchenko University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI), electrospray ionization (ESI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)).

Benzyl *tert*-butyl bicyclo[1.1.1]pentane-1,3-diyldicarbamate (14). Diphenylphosphoroyl azide (67.0 g, 0.244 mol) was added dropwise to a solution of carboxylic acid **12k** (51.5 g, 0.212 mol) and triethylamine (25.7 g, 35.4 mL, 0.254 mol) in benzene (0.64 L) at rt. The solution was heated under reflux for 3 h. Then benzyl alcohol (27.5 g, 0.254 mol) was added dropwise, and the solution was heated at reflux for 24 h. The mixture was cooled, and *t*-BuOMe (1.2 L) was added. The solution was washed with 2 M aq NaOH (400 mL), brine (400 mL), dried with Na_2SO_4

and concentrated under reduced pressure. The residue was crystallized from CH_2Cl_2 – hexanes to give **14**. Yield 60.0 g, 85%. Colorless solid. Mp 157–159 °C. Anal. Calcd. for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 65.3; H, 7.67; N, 8.70. MS (CI): 355 (MNa^+), 233 ($MH^+–CO_2–C_4H_8$), 189, 91 ($C_7H_7^+$). ^{1}H NMR (400 MHz, DMSO) δ = 7.93 (s, 1H), 7.48 (s, 1H), 7.33 (s, 5H), 4.98 (s, 2H), 2.04 (s, 6H), 1.36 (s, 9H) ppm. ^{13}C NMR (101 MHz, DMSO) δ = 155.5, 155.0, 137.5, 128.8, 128.3, 128.3, 78.2, 65.9, 54.5, 44.9, 44.6, 28.7 ppm.

***tert*-Butyl (3-aminobicyclo[1.1.1]pent-1-yl)carbamate (10k).** To a stirred solution of carbamate **14** (145.0 g, 0.436 mol) in MeOH – THF (1:1, 3.0 L), 10% *wt*. palladium on charcoal (24.0 g) was added. Hydrogen gas was bubbled through the mixture at rt until the ^{1}H NMR showed completion of the reaction (18 – 48 h). The mixture was filtered and evaporated under reduced pressure to give amine **10m** pure enough for further transformations. An analytical sample could be obtained by recrystallization from methanol. Yield 86.0 g, 99%. Colorless solid. Mp 118–120 °C. Anal. Calcd. for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.21; H, 9.18; N, 14.48. MS (CI): 199 (MH^+), 143 ($MH^+–C_4H_8$), 126. ^{1}H NMR (500 MHz, DMSO) δ = 4.99 (s, 1H), 2.01 (s, 6H), 1.69 (s, 2H), 1.43 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 154.9, 79.4, 55.4, 47.6, 42.7, 28.4 ppm.

Benzyl (3-aminobicyclo[1.1.1]pent-1-yl)carbamate (10l). To a stirred solution of carbamate **14** (1.42 g, 4.27 mmol) in MeOH (10 mL), 4 M HCl in dioxane (10 mL, 40 mmol) was added at 0 °C. The mixture was stirred overnight at rt. Then it was concentrated under reduced pressure. The residue was treated with 2 M aq NaOH (25 mL) and extracted with *t*-BuOMe (3×25 mL). The organic layer was dried with Na_2SO_4 and evaporated under reduced pressure to give amine **10n**. Yield 0.92 g, 93%. Colorless solid. Mp 92–94 °C. Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.98; H, 6.73; N, 11.83. MS (CI): 233 (MH^+), 172, 91 ($C_7H_7^+$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 (s, 5H), 5.47 (s, 1H), 5.05 (s, 2H), 2.03 (s, 6H), 1.69 (s, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 155.4, 136.4, 128.5, 128.1, 128.1, 66.4, 55.4, 47.6, 42.8 ppm.

General procedure for the synthesis of azides 2b, 2h, and 2i. To a suspension of hydrochloride **10** (8.36 mmol), K_2CO_3 (3.11 g, 22.6 mmol), and $CuSO_4·5H_2O$ (0.02 g, 0.08 mmol) in methanol (40 mL), imidazole-1-sulfonyl azide hydrochloride (**8**) (2.10 g, 10.0 mmol) was added at rt. The mixture was stirred until the ^{1}H NMR showed completion of the reaction (12-18 h). Then all the volatiles were transferred into a trap kept at –20 °C by careful heating of the reaction mixture in a 60 °C bath at *ca.* 20 mmHg. (CAUTION! Safety shield must be used!) The trap content proved to be a methanol solution of azide **2** and was used without further purification.

1-Azidobicyclo[1.1.1]pentane (2b). Yield 0.77 g (30.5 g of methanolic solution), 84%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.26 (s, 1H), 1.73 (s, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 51.7, 30.8, 21.7 ppm.

1-Azido-3-fluorobicyclo[1.1.1]pentane (2h). Yield 0.43 g (16.8 g of methanolic solution), 67%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.90 (s, 6H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ = –175.02 ppm.

1-Azido-3-(trifluoromethyl)bicyclo[1.1.1]pentane (2i). Yield 0.43 g (12.5 g of methanolic solution), 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.12 (s, 6H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ = –71.79 ppm.

General procedure for the synthesis of azides 2g, 2j–l. To a suspension of amine **10** or hydrochloride **10**·HCl (5.11 mmol) in methanol (25 mL), K_2CO_3 (1.90 g, 13.8 mmol (for **10g**·HCl and **10j**·HCl) or 1.19 g, 8.68 mmol (for **10k** and **10l**)), $CuSO_4·5H_2O$ (0.01 g, 0.04 mmol), and imidazole-1-sulfonyl azide hydrochloride (**8**) (1.28 g, 6.13 mmol) were added subsequently at rt. The mixture was stirred until the ^{1}H NMR showed completion of the reaction (*ca*. 18-48 h). The mixture was concentrated under reduced pressure, water (25 mL) was added to the residue acidified with conc. aq HCl (for **10g**·HCl and **10j**·HCl) or 1 M aq $NaHSO_4$ (for **10k** and **10l**) to pH = 3, and extracted with EtOAc (3×50 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography to give azide **2**.

1-Azido-3-phenylbicyclo[1.1.1]pentane (2g).[21] Yield 0.60 g, 63%. Colorless oil. R_f 0.62 (hexanes – EtOAc (19:1)). Anal. Calcd. for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.61; H, 5.63; N, 22.73. MS (EI): 157 ($M^+–N_2$), 141, 159, 115, 103, 91, 77, 65, 51, 39. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.33 (t, *J*=7.3, 2H), 7.29 – 7.18 (m, 3H), 2.29 (s, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 138.1, 128.4, 127.1, 126.5, 54.5, 51.0, 37.6 ppm.

Methyl 3-azidobicyclo[1.1.1]pentane-1-carboxylate (2j). Yield 0.73 g, 78%. Colorless oil. R_f 0.55 (hexanes – EtOAc (5:1)). Anal. Calcd. for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.20; H, 5.57; N, 25.31. MS (EI): 136 (M^+–OMe), 124, 108 ($M^+–CO_2Me$), 96, 80, 69, 59, 53, 45, 39. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.69 (s, 1H), 2.26 (s, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 169.2, 54.0, 51.9, 51.1, 33.6 ppm.

***tert*-Butyl (3-azidobicyclo[1.1.1]pent-1-yl)carbamate (2k)**. Yield 0.27 g, 82%. White solid. Mp 79–80 °C. R_f 0.51 (hexanes – EtOAc (4:1)). Anal. Calcd. for $C_{10}H_{16}N_4O_2$: C, 53.56; H, 7.19; N, 24.98. Found: C, 53.95; H, 7.12; N, 24.62. MS (CI): 197 ($MH^+–N_2$), 169 ($MH^+–C_4H_8$), 141 ($MH^+–N_2–C_4H_8$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.05 (br s, 1H), 2.21 (s, 6H), 1.43 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 154.7, 80.0, 54.5, 50.2, 43.4, 28.3 ppm.

Benzyl (3-azidobicyclo[1.1.1]pent-1-yl)carbamate (2l). Yield 0.47 g, 61%. Colorless solid. Mp 64–65 °C. R_f 0.45 (hexanes – EtOAc (4:1)). Anal. Calcd. for $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.69. Found: C, 60.56; H, 5.08; N, 21.37. MS (CI): 281 (MNa^+), 231 ($MH^+–N_2$), 158, 91 ($C_7H_7^+$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 (s, 5H), 5.29 (s, 1H), 5.09 (s, 2H), 2.26 (s, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 155.2, 136.2, 128.6, 128.2, 128.1, 66.8, 54.6, 50.1, 43.5 ppm.

(3-Phenylbicyclo[1.1.1]pent-1-yl)methanol (15g). Carboxylic acid **12g** (0.50 g, 2.66 mmol) was dissolved in THF (5 mL). The solution was cooled to 0 °C, and $BH_3·Me_2S$ (0.31 mL, 3.10 mmol, 10 M in Me_2S) was added dropwise. The mixture was stirred at 0 °C for 1 h and then overnight at rt. Excess of borane was quenched by careful addition of MeOH (5 mL), and the mixture was concentrated under reduced pressure. Saturated aq K_2CO_3 (20 mL) was added to the residue, and the mixture was extracted with *t*-BuOMe (3×30 mL). The organic phases were dried over Na_2SO_4, and evaporated to give alcohol **15g**. Yield 0.42 g, 91%. Yellowish oil. Anal. Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.88; H, 7.86. MS (CI): 157 ($MH^+–H_2O$). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.53 – 7.02 (m, 5H), 3.72 (s, 2H), 1.96 (s, 6H), 1.37 (br s, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 141.0, 128.3, 126.6, 126.1, 63.4, 50.7, 42.2, 39.2 ppm.

***tert*-Butyl (3-(hydroxymethyl)bicyclo[1.1.1]pent-1-yl)carbamate (15k).** Carboxylic acid **12k** (10.0 g, 44.0 mmol) was dissolved in Et_2O (200 mL). The solution was cooled to 0 °C, and $BH_3·Me_2S$ (5.2 mL, 52 mmol, 10 M in Me_2S) was added dropwise. The mixture was stirred at 0 °C for 1 h and then overnight at rt. Excess of borane was quenched by careful addition of MeOH (50 mL), and the mixture was concentrated under

reduced pressure. Saturated aq K_2CO_3 (200 mL) was added to the residue, and the mixture was extracted with CH_2Cl_2 (3×300 mL). The organic phases were dried over Na_2SO_4, and evaporated to give alcohol **15**. Yield 8.86 g, 94%. Colorless solid. Mp 134–135 °C. Anal. Calcd. for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 62.23; H, 9.28; N, 6.63. MS (CI): 236 (MNa^+), 158 (MH^+–C_4H_8). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.01 (br s, 1H), 3.65 (s, 2H), 1.89 (s, 6H), 1.70 (br s, 1H), 1.40 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.9, 79.5, 62.0, 51.2, 46.1, 37.2, 28.4 ppm.

General procedure for the preparation of alkynes 3g and 3i–k. To a solution of oxalyl chloride (0.94 g, 7.46 mmol) in CH_2Cl_2 (15 mL) cooled to −60 °C, a solution of DMSO (1.17 g, 14.9 mmol) in CH_2Cl_2 (3 mL) was added dropwise. After 15 min, a solution of **15** (5.74 mmol) in CH_2Cl_2 (5.7 mL) was added. The reaction mixture was stirred at −60 °C for 30 min, and Et_3N (4.8 mL, 34.4 mmol) was added dropwise. After 30 min at −60 °C, the mixture was warmed to rt. H_2O (30 mL) was added, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (30 mL). The combined organic layers were washed with 1 M aq $NaHSO_4$ (50 mL), saturated aq NaCl (50 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give crude **11.** Aldehydes **11g** (99%) and **11j** (63%)[48] were obtained as colorless oils which were immediately used in the next step. The crude product **11k** was purified by flash chromatography (toluene – EtOAc (1:1)) (78%). Aldehyde **11i** was prepared from iodide **16** (14.7 g, 15.9 mmol) using the reported procedure.[46]

Aldehyde **11** (15.9 mmol) was dissolved in MeOH (75 mL), and K_2CO_3 (6.58 g, 47.7 mmol) and dimethyl 1-diazo-2-oxopropylphosphonate (**9**) (4.59 g, 23.9 mmol) were added at rt. The reaction mixture was stirred at rt overnight, and then H_2O (150 mL) and Et_2O (75 mL) were added. The layers were separated, and the aqueous phase was extracted with Et_2O (3×50 mL). The combined organic extracts were washed with H_2O (3×30 mL), and dried over $MgSO_4$. The solution was concentrated at atmospheric pressure, and the residue was purified by column chromatography.

1-Ethynyl-3-phenylbicyclo[1.1.1]pentane (3g). Yield 0.81 g, 88%. Colorless solid. Mp 33–35 °C. Anal. Calcd. for $C_{13}H_{12}$: C, 92.81; H, 7.19. Found: C, 92.87; H, 7.53. MS (EI): 167 (M^+–H), 152, 141, 128, 115, 103, 91, 77 ($C_6H_5^+$), 63, 51, 39. ^{1}H NMR ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.33 – 7.14 (m, 5H), 2.35 (s, 6H), 2.15 (s, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 139.9, 128.3, 126.9, 126.1, 83.4, 68.2, 56.4, 44.1, 27.2 ppm.

1-Ethynyl-3-(trifluoromethyl)bicyclo[1.1.1]pentane (3i). Yield 1.27 g (155 g of CH_2Cl_2 solution), 50%. (^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.24 (s, 6H), 2.15 (s, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 122.2 (q, $^1J_{C,F}$ = 274.9 Hz), 80.8, 69.2, 52.6, 38.5 (q, $J_{C,F}$ = 38.7 Hz), 27.2 (q, $J_{C,F}$ = 106.6 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ = –73.97 ppm.

Methyl 3-ethynylbicyclo[1.1.1]pentane-1-carboxylate (3j). Yield 0.72 g, 43%. Colorless solid. Mp 65–66 °C. Anal. Calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.67; H, 6.88. MS (EI): 149 (M^+–H), 135, 119 (M^+–OMe), 107, 91, 77, 65, 59, 51, 39. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.65 (s, 3H), 2.31 (s, 6H), 2.11 (s, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 169.5, 82.0, 68.7, 55.6, 51.7, 39.5, 28.0 ppm.

***tert*-Butyl (3-ethynylbicyclo[1.1.1]pent-1-yl)carbamate (3k).** Yield 0.8 g, 55%. Colorless solid. Mp 107–108 °C. R_f 0.63 (hexanes – EtOAc (4:1)) Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.86; H, 8.43; N, 7.07. MS (EI): 206 (M^+–H, <1%), 161, 151 (M^+–C_4H_8), 132, 120, 106, 91, 79, 65, 57 (t-$C_4H_9^+$), 51, 41. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.08 (br s, 1H), 2.26 (s, 6H), 2.14 (s, 1H), 1.41 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 154.7, 81.7, 79.7, 69.4, 56.9, 46.7, 28.4, 25.3 ppm.

General procedure for the preparation of triazoles 17a–c. To a methanolic solution of azide **2** (4.13 mmol in 20.0 g of the solution), methyl propiolate (0.52 g, 6.15 mmol) and $Cu(OAc)_2$ (0.037 g, 0.2 mmol) were added. The mixture was stirred at rt for 72 h, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (gradient hexanes – EtOAc (2:1 to 1:1)) to give triazole **17**.

Methyl 1-(bicyclo[1.1.1]pent-1-yl)-1*H*-1,2,3-triazole-4-carboxylate (17a). Yield 0.65 g, 82%. Colorless solid. Mp 92–93 °C. Anal. Calcd. for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.98; H, 5.67; N, 21.89. MS (CI): 194 (MH^+), 162 (MH^+–MeOH), 128, 94. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.06 (s, 1H), 3.92 (s, 3H), 2.73 (s, 1H), 2.41 (s, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 161.3, 139.7, 126.0, 53.3, 52.2, 52.1, 23.5 ppm.

Methyl 1-(3-fluorobicyclo[1.1.1]pent-1-yl)-1*H*-1,2,3-triazole-4-carboxylate (17b). Yield 0.11 g, 59%. Colorless solid. Mp 142–144 °C. Anal. Calcd. for $C_9H_{10}FN_3O_2$: C, 51.18; H, 4.77; N, 19.90. Found: C, 51.34; H, 4.38; N, 20.07. MS (CI): 212 (MH^+), 180 (MH^+–MeOH), 128, 100. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.74 (s, 1H), 3.55 (s, 3H), 2.21 (s, 1H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ = 160.9, 139.5, 129.8, 76.5 (d, $^1J_{C,F}$ = 319.2 Hz), 56.7 (d, $^2J_{C,F}$=21.4 Hz), 52.4, 44.8 (d, $^3J_{C,F}$ = 76.0 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ = –173.73 ppm.

Methyl 1-(3-(trifluoromethyl)bicyclo[1.1.1]pent-1-yl)-1*H*-1,2,3-triazole-4-carboxylate (17c). Yield 0.50 g, 79%. Colorless solid. Mp 169–171 °C. Anal. Calcd. for $C_{10}H_{10}F_3N_3O_2$: C, 45.98; H, 3.86; N, 16.09. Found: C, 46.15; H, 4.11; N, 16.06. MS (CI): 262 (MH^+), 230 (MH^+–MeOH), 128. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.13 (s, 1H), 3.93 (s, 3H), 2.65 (s, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 160.9, 140.3, 126.3, 122.8 (q, $^1J_{C,F}$ = 274 Hz), 52.5, 52.3, 49.4, 34.7 (q, $^2J_{C,F}$ = 41 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ = –71.56 ppm.

General procedure for the preparation of triazoles 17d and 17e. To a solution of benzyl azide (0.55 mL, 1.1 mmol, 2.0 M in CH_2Cl_2) alkyne **3** (0.15 g, 1.0 mmol) and $Cu(OAc)_2$ (0.005 g, 0.036 mmol) were added. The mixture was stirred at rt for 24–72 h, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography ($CHCl_3$ – MeOH (98:2) as eluent) to give triazole **17**.

Methyl 3-(1-benzyl-1*H*-1,2,3-triazol-4-yl)bicyclo[1.1.1]pentane-1-carboxylate (17d). Yield 0.28 g, 99%. Colorless solid. Mp 110–112 °C. Anal. Calcd. for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83. Found: C, 67.69; H, 5.67; N, 14.73. MS (CI): 284 (MH^+), 91 ($C_7H_7^+$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 – 7.31 (m, 3H), 7.31 – 7.17 (m, 3H), 5.49 (s, 2H), 3.70 (s, 3H), 2.39 (s, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 170.0, 146.7, 134.6, 129.1, 128.7, 128.1, 120.7, 54.1, 53.9, 51.6, 38.7, 34.3 ppm.

***tert*-Butyl (3-(1-benzyl-1*H*-1,2,3-triazol-4-yl)bicyclo[1.1.1]pent-1-yl)-carbamate (17e).** Yield 0.28 g, 82%. Colorless solid. Mp 170–171 °C. Anal. Calcd. for $C_{19}H_{24}N_4O_2$: C, 67.04; H, 7.11; N, 16.46. Found: C, 66.7; H, 7.09; N, 16.25. MS (CI): 341 (MH^+), 285 (MH^+–C_4H_8). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35 (s, 5H), 7.25 (s, 1H), 5.46 (s, 2H), 5.14 (br s, 1H), 2.31 (s, 6H), 1.43 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.9, 146.3, 134.7, 129.1, 128.7, 128.1, 120.6, 79.5, 55.1, 54.1, 46.4, 31.5, 28.4 ppm.

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Keywords: Alkynes • Azides • Nitrogen heterocycles • Click chemistry • Propellane

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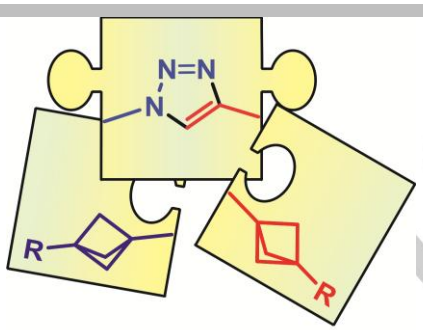
Entry for the Table of Contents

FULL PAPER

Syntheses of mono- and bifunctional bicyclo[1.1.1]pentane-derived azides and terminal alkynes – promising building blocks for medicinal, combinatorial and bioconjugate chemistry – are described. Utility of the title products as substrates for the copper-catalyzed click reactions is also demonstrated.



R = H, F, CF_3, Ph, CO_2Me, NHBoc, NHCbz

Click chemistry

*Serhii O. Kokhan, Yevheniia B. Valter, Andriy V. Tymtsunik, Igor V. Komarov, Oleksandr O. Grygorenko**

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Bicyclo[1.1.1]pentane-derived building blocks for click chemistry