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SHORT COMMUNICATIONS

New Azetidinone Building Block for Carbapenems

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Abstract—A new versatile building block for the synthesis of carbapenems, (3*S*,4*R*)-3-{(*R*)-1-[*tert*-butyl(dimethyl)silyloxy]ethyl}-4-[(2*RS*)-5-(4-methoxybenzyloxy)pent-3-yn-2-yl]azetidin-2-one, has been obtained by zinc-promoted alkylation of (3*R*,4*R*)-(+)-3-{(*R*)-1-[*tert*-butyl(dimethyl)silyloxy]ethyl}-2-oxoazetidin-4-yl acetate with 1-[(4-bromopent-2-yn-1-yloxy)methyl]-4-methoxybenzene.

Keywords: carbapenems, β-lactams, azetidinone, propargyl alcohol, acetaldehyde, building block.

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Carbapenems remain among the best β-lactam antibiotics used in the treatment of infectious diseases [1, 2]. The basic bicyclic core of carbapenems **1** is shown in Scheme 1; a number of synthetic approaches to particular carbapenems have been proposed [3–7], including those implemented on an industrial scale [7–10].

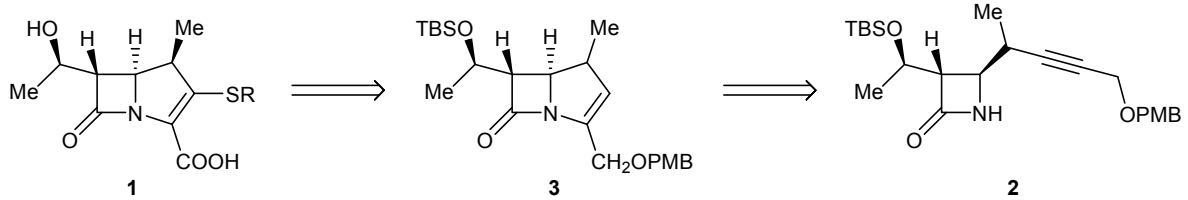
Herein we describe the synthesis of azetidine building block **2** for the development of a new approach to carbapenems **1** via intramolecular N,C-cyclization to precursors like **3**, followed by appending a required side chain. It is seen that structure **2** contains all functionalities necessary for intramolecular N,C-cyclization and "workpieces" for building up side-chain substituents.

Scheme 2 outlines the synthesis of **2**. The starting material was propargyl alcohol whose hydroxy group was protected by etherification with 4-methoxybenzyl alcohol. Ether **4** was converted to lithium derivative which was brought into condensation with acetaldehyde to obtain alcohol **5**. The hydroxy group in **5** was replaced by bromine, and bromide **6** reacted with azetidinone **7** [11, 12] in the presence of zinc. We thus isolated 56% of azetidinone **2** as a 3:2 mixture of diastereoisomers at the 4-CH chiral center. The ^{1}H NMR spectrum of **2** showed signals of the 4-H proton as doublets of doublets at δ 3.62 and 3.71 ppm with a coupling constant $J_{4,3}$ of 1.9 Hz, which indicated *trans* arrangement of 4-H and 3-H [13].

Building block **2** was used to test versions of intramolecular N,C-cyclization in order to obtain bicyclic carbapenem precursors like **3**. For this purpose, azetidinone **2** was converted into *N*-bromo derivative **8** by treatment with *N*-bromosuccinimide. However, attempts to effect 5-*endo*-dig radical cyclization of **8** by the action of tributyltin hydride were unsuccessful. Studies of other ways to accomplish intramolecular cyclization of **2** are now in progress in our laboratory.

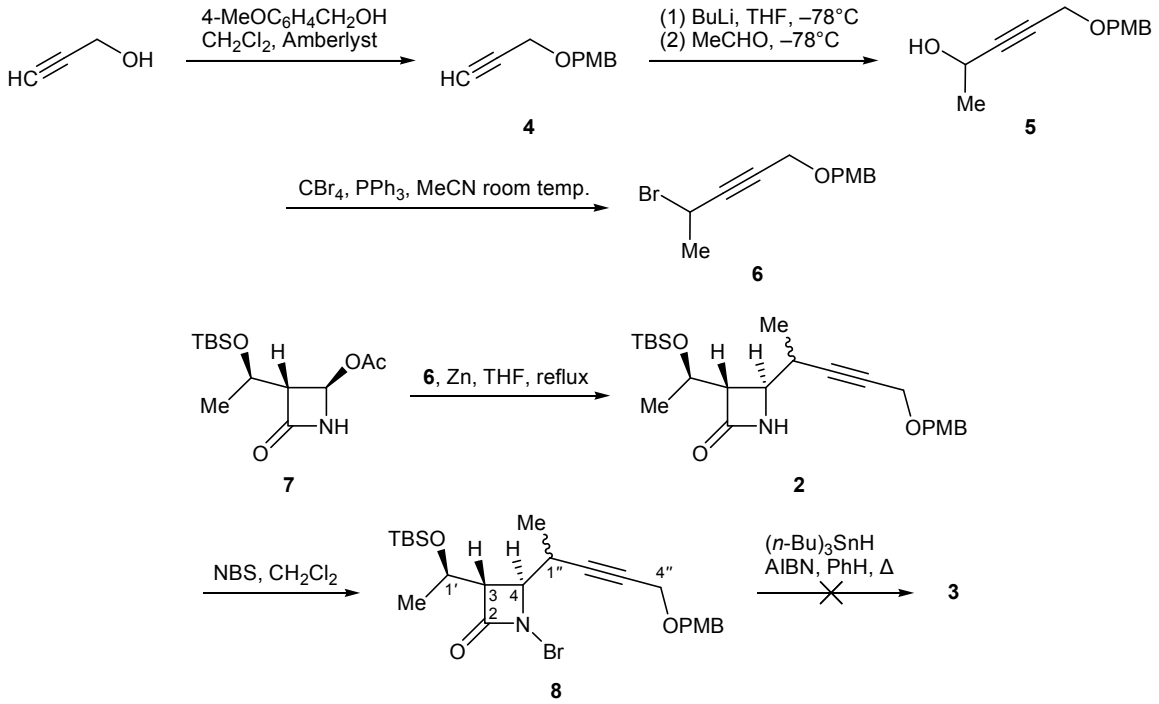
Thus, we have demonstrated the possibility of substitution of the acetoxy group in azetidinone **7** by secondary propargyl bromide **6** despite its tendency to isomerize into allene structure.

Scheme 1.



TBS = *t*-BuMe$_2$Si; PMB = 4-MeOC$_6$H$_4$CH$_2$.

Scheme 2.



PMB = 4-$MeOC_6H_4CH_2$.

5-(4-Methoxybenzyloxy)pent-3-yn-2-ol (5). A solution of 0.5 g (2.8 mmol) of compound **4** in 10 mL of anhydrous THF was cooled to –78°C, 3.2 mL (3.4 mmol) of a 1.1 M solution of butyllithium in hexane was added with stirring, and the mixture was stirred for 35–40 min at that temperature. A solution of 0.19 mL (3.4 mmol) of acetaldehyde in 5 mL of THF was then added dropwise, and the mixture was stirred for 1 h at –78°C and quenched by adding 3–4 mL of a saturated aqueous solution of ammonium chloride. Tetrahydrofuran was distilled off, the residue was extracted with methylene chloride (3 × 10 mL), the combined extracts were dried over $MgSO_4$ and evaporated, and the residue was purified by column chromatography on silica gel. Yield 0.30 g (40%), colorless oil, R_f 0.59 (petroleum ether–ethyl acetate, 2:1). ^{1}H NMR spectrum ($CDCl_3$, 500 MHz), δ, ppm: 1.47 d (3H, CH_3, J = 6.6 Hz), 2.04 br.s (1H, OH), 3.80 s (3H, OCH_3), 4.16 d (2H, OCH_2, J = 1.2 Hz), 4.52 s (2H, OCH_2), 4.59 m (1H, OCH), 6.89 d (2H, H_{arom}, J = 8.6 Hz), 7.28 d (2H, H_{arom}, J = 8.6 Hz). ^{13}C NMR spectrum ($CDCl_3$, 125 MHz), δ_C, ppm: 24.34 (CH_3), 55.26 (OCH_3), 56.96 (OCH_2), 58.29 (C^2), 71.26 (OCH_2), 79.91 and 88.39 (C^3, C^4), 118.80 (C_{arom}), 129.33 (C_{arom}), 129.75 (C_{arom}), 159.34 (C_{arom}). Mass spectrum, m/z (I_{rel}, %): 238 $[M + H_2O]^+$ (33), 121 $[CH_2C_6H_4OCH_3]^+$ (100).

1-[(4-Bromopent-2-yn-1-yloxy)methyl]-4-methoxybenzene (6). Carbon tetrabromide, 0.62 g (1.90 mmol), was added in portions to a solution of 0.38 g (1.70 mmol) of compound **5** and 0.50 g (1.90 mmol) of triphenylphosphine in 10 mL of anhydrous acetonitrile under stirring at room temperature. The mixture was stirred for 12 h at room temperature, the solvent was evaporated, and the product was isolated from the residue by column chromatography on silica gel (ethyl acetate–petroleum ether, 1:4). Yield 0.31 g (61%), oily material, R_f 0.43 (petroleum ether–ethyl acetate, 4:1). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: 1.93 d (3H, CH_3, J = 6.9 Hz), 3.81 s (3H, OCH_3), 4.19 d (2H, OCH_2, J = 1.7 Hz), 4.56 s (2H, OCH_2), 4.68 m (1H, CHBr), 6.89 d (2H, H_{arom}, J = 8.6 Hz), 7.29 d (2H, H_{arom}, J = 8.5 Hz). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ_C, ppm: 27.30 (CH_3), 30.89 (CHBr), 55.26 (OCH_3), 56.90 (OCH_2), 71.27 (OCH_2), 82.25 and 86.41 ($C^{2'}$, $C^{3'}$), 113.83 (C_{arom}), 129.24 (C_{arom}), 129.64 (C_{arom}), 159.40 (C_{arom}). Found, %: C 55.53; H 5.12; Br 28.48. $C_{13}H_{15}BrO_2$. Calculated, %: C 55.14; H 5.34; Br 28.22.

(3*S*,4*R*)-3-{(*R*)-1-[*tert*-Butyl(dimethyl)silyloxy]-ethyl}-4-[5-(4-methoxybenzyloxy)pent-3-yn-2-yl]-azetidin-2-one (2). A mixture of 0.12 g (0.42 mmol) of azetidinone **7**, 0.35 g (1.20 mmol) of bromide **6**, and 0.19 g (2.9 mmol) of zinc in 10 mL of anhydrous THF

was refluxed for 30 min (until compound **6** disappeared according to the TLC data). The mixture was filtered, the filtrate was evaporated, and the residue was purified by column chromatography on silica gel (petroleum ether–ethyl acetate, 4:1). Yield 0.11 g (56%), colorless oil, R_f 0.54 (petroleum ether–ethyl acetate, 4:1), diastereoisomer mixture at a ratio of 3:2 (according to the ^{1}H NMR data). IR spectrum, ν, cm^{-1}: 3244, 2955, 2931, 2856, 1734, 1613, 1514, 1444, 1374, 1360, 1303, 1249, 1174, 1143, 1095, 1078, 1036, 1011, 988, 959, 834, 812, 777, 726. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm: major isomer: 0.12 s (6H, $SiCH_3$), 0.94 s (9H, *t*-Bu), 1.29 d (3H, CH_3, J = 7.4 Hz), 1.30 d (3H, CH_3, J = 6.1 Hz), 2.69 q (1H, 1″-H, J = 7.1 Hz), 2.89 d.d (1H, 3-H, J = 3.5, 1.4 Hz), 3.62 d.d (1H, 4-H, J = 7.5, 1.9 Hz), 3.85 s (3H, OCH_3), 4.18 d (2H, OCH_2, J = 1.8 Hz), 4.23 q (1H, 1′-H, J = 5.5 Hz), 4.56 s (2H, OCH_2), 6.20 s (1H, NH), 6.94 d (2H, H_{arom}, J = 8.7 Hz), 7.33 d (2H, H_{arom}, J = 8.5 Hz); minor isomer: 0.13 s (6H, $SiCH_3$), 0.94 s (9H, *t*-Bu), 1.28 d (3H, CH_3, J = 7.4 Hz), 1.30 d (3H, CH_3, J = 6.1 Hz), 2.81 q (1H, 1″-H, J = 6.7 Hz), 3.04 m (1H, 3-H), 3.71 d.d (1H, 4-H, J = 6.3, 1.9 Hz), 3.85 s (3H, OCH_3), 4.16 d (2H, OCH_2, J = 1.8 Hz), 4.28 d.d (1H, 1′-H, J = 3.9, 6.3 Hz), 4.55 s (2H, OCH_2), 6.19 s (1H, NH), 6.93 d (2H, H_{arom}, J = 8.9 Hz), 7.33 d (2H, H_{arom}, J = 8.5 Hz). ^{13}C NMR spectrum (500 MHz, $CDCl_3$), δ_C, ppm: major isomer: –4.35 ($SiCH_3$), 17.79 (CH_3), 17.90 (Me_3**C**Si), 22.81 (CH_3), 25.73 [C(**C**H_3)$_3$], 31.21 (C$^{1''}$), 54.59 (C^3), 55.22 (OCH_3), 57.08 (OCH_2), 62.12 (C^4), 65.32 (C$^{1'}$), 71.20 (OCH_2), 78.44 and 86.79 (C$^{2''}$, C$^{3''}$), 113.77 (C^o), 129.44 (C^i), 129.68 (C^m), 159.30 (C^p), 168.11 (C=O); minor isomer: –4.99 ($SiCH_3$), 17.73 (CH_3), 17.90 (Me_3**C**Si), 22.88 (CH_3), 25.73 [C(**C**H_3)$_3$], 30.43 (C$^{1''}$), 55.22 (OCH_3), 53.61 (C^3), 57.08 (OCH_2), 62.92 (C^4), 64.73 (C$^{1'}$), 71.13 (OCH_2), 78.62 and 86.59 (C$^{2''}$, C$^{3''}$), 113.80 (C^o), 129.38 (C^i), 129.70 (C^m), 159.30 (C^p), 168.72 (C=O). Mass spectrum, m/z (I_{rel}, %): 432 (100) [M + H]$^+$, 312 (21) [M + H – $CHC_6H_4OCH_3$]$^+$, 241 (29), 121 (71) [$CH_2C_6H_4OCH_3$]$^+$.

(3*S*,4*R*)-1-Bromo-3-{(*R*)-1-[*tert*-butyl(dimethyl)-silyloxy]ethyl}-4-[5-(4-methoxybenzyloxy)pent-3-yn-2-yl]azetidin-2-one (8). *N*-Bromosuccinimide, 32 mg (0.18 mmol), was added to a solution of 50 mg (0.12 mmol) of compound **2** in 10 mL of anhydrous methylene chloride, and the mixture was stirred until the initial compound disappeared (TLC). The solvent was evaporated, and the residue was purified by flash chromatography on silica gel (petroleum ether–ethyl acetate, 4:1). Yield 45.5 mg (77%), colorless oil. ^{1}H NMR spectrum (300 MHz, $CDCl_3$) δ, ppm: 0.08 s (6H, $SiCH_3$), 0.88 s (9H, *t*-Bu), 1.22 d (3H, J = 6.2 Hz, CH_3), 1.27 d (3H, CH_3, J = 7.4 Hz), 2.83 m (1H, 1″-H), 3.28 m (1H, 3-H), 3.96 m (1H, 4-H), 3.79 s (3H, OCH_3), 4.11 s (2H, OCH_2), 4.19 m (1H, 1′-H), 4.49 s (2H, OCH_2), 6.86 d (2H, H_{arom}, J = 7.8 Hz), 7.26 d (2H, H_{arom}, J = 8.0 Hz).

The IR spectra were recorded from thin films on a Shimadzu IR Prestige-21 spectrometer. The ^{1}H and ^{13}C NMR spectra were measured on Bruker AM-300 (300.13 and 75.47 MHz, respectively) and Bruker Avance-500 spectrometers (500.13 and 125.77 MHz) using tetramethylsilane as internal standard. The mass spectra were obtained on a Shimadzu LCMS-2010EV instrument (syringe injection of a solution in chloroform–acetonitrile; eluent acetonitrile–water, 95:5, flow rate 0.1 mL/min; positive ion detection; needle voltage 4.5 kV; interface capillary voltage 5 V, temperature 250°C). The elemental compositions were determined with a Euro EA-2000 CHNS analyzer. The progress of reactions was monitored by TLC on *Sorbfil* plates (Russia); spots were visualized by treatment with a solution of 4-methoxybenzaldehyde in ethanol acidified with sulfuric acid, followed by heating at 120–150°C. The products were isolated by column chromatography on silica gel using 30–60 g of the sorbent per gram of substrate.

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CONFLICT OF INTERESTS

The authors declare the absence of conflict of interests.

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