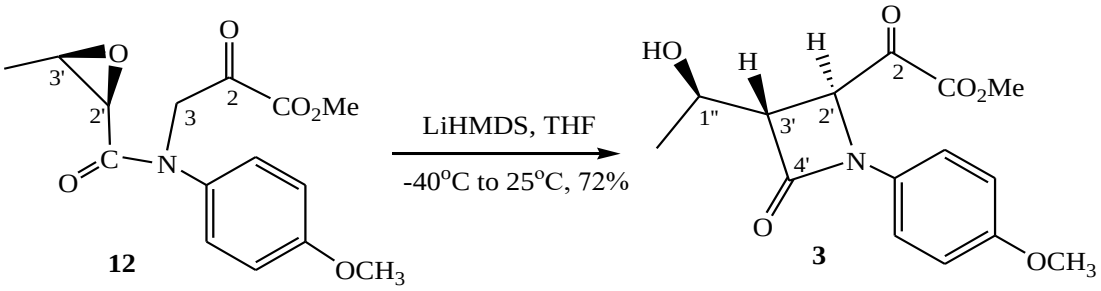
Electronic supplementary materials *Mendeleev Commun.*, 2018, **28**, 131–132

Novel azetidinones for carbapenems and fragmentation in the allylamine precursor analogue

Natalya K. Selezneva, Zuleykha R. Valiullina, Lidiya S. Khasanova, Fanuza A. Gimalova, Raisa Z. Biglova and Mansur S. Miftakhov

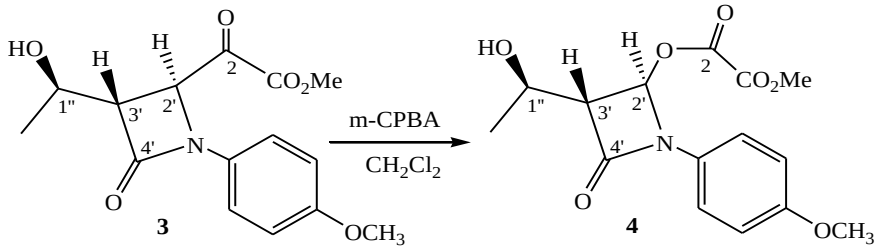
IR spectra were obtained in thin layer samples using an IR Prestige-21 Shimadzu spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE-500 spectrometer with working frequencies of 500.13 and 125.77 MHz, respectively, using TMS as the internal standard. Mass spectra were obtained on an LCMS-2010EV mass spectrometer (Shimadzu) (syringe injection, a solution of a sample in chloroform-acetonitrile, 0.1 ml min^{-1} feed rate, acetonitrile-water (95:5) as the eluent, detection of positive ions at 4.5 kV potential on a needle ionizing electrode; the temperature on the interface capillary was 250°C and the voltage on the interface capillary was 5 V). The elementary analyses of the compounds obtained were performed on a EURO EA-3000 CHNS-analyzer. The reaction was monitored by TLC on Sorbfil plates (Krasnodar, Russia). Compounds were visualized by wetting the plates with a solution of anisic aldehyde and sulfuric acid in ethanol or phosphomolybdic acid in ethanol, followed by heating at 120-150°C. The products were isolated by column chromatography on silica gel (30-60 g of the adsorbent per 1 g of the compound).

In this study we employed the equipment of the "Chemistry" User Facilities Center, Ufa Institute of Chemistry of the Russian Academy of Sciences.

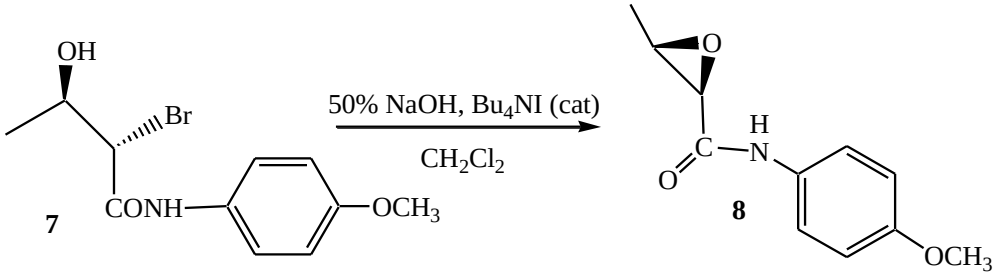


Methyl {(2*S*,3*S*)-3-[1(*R*)-hydroxyethyl]-1-(4-methoxyphenyl)-4-oxoazetidin-2-yl}-2-oxoacetate (3). A LiHMDS solution (0.24 ml, 0.24 mmol) was added dropwise at -40°C with stirring on a magnetic stirrer to a solution of amide **12** (0.05 g, 0.16 mmol) in THF (5 ml). The

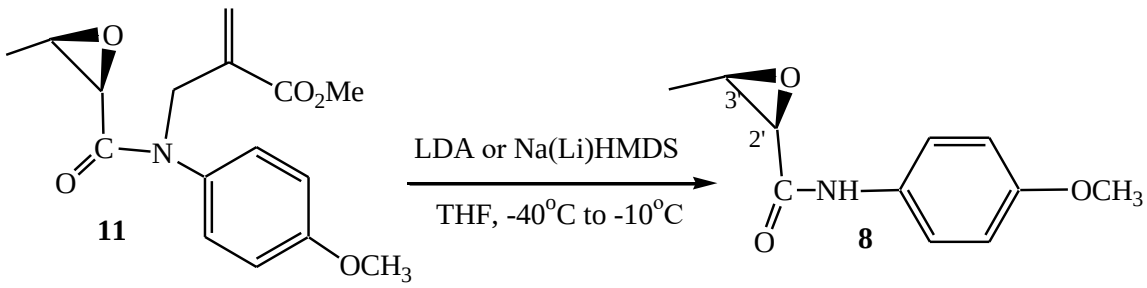
mixture was heated to 0°C and stirred for 2 h, then stirred at room temperature until the starting compound was consumed (~10 h, TLC monitoring). Saturated NH_4Cl solution (1 ml) was added, THF was evaporated, the reaction product was extracted with CH_2Cl_2 (3×5 ml), then the combined extracts were dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography on SiO_2 (petroleum ether – ethyl acetate, 1:1) to isolate 36.0 mg (72%) of azetidinone **3**. $[\alpha]_{D.}^{25}$ -204.3° (*c* 1.8, $CHCl_3$). MS (EI, *m/z*) (%): 308 $[MH]^+$ (100), 349 $[MH$+MeCN$]^+$ (75), 279 (14), 249 (14). ^{1}H NMR (500 MHz) $CDCl_3$, δ: 1.29 d (3H, CH_3, *J* 6.6 Hz), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.98 (br.s , 1H, $H^{3'}$), 4.56 (d, 1H, $H^{2'}$, *J* 2.2 Hz), 4.80 (dq, 1H, $H^{1''}$, *J* 6.6 and 2.9 Hz), 6.68 (s, 1H, OH), 6.96 (d, 2H, H_{ar}, *J* 8.9 Hz), 7.18 (d, 2H, H_{ar}, *J* 8.9 Hz). ^{13}C NMR (125 MHz) $CDCl_3$, δ: 14.15 (CH_3), 52.81 ($C^{3'}$, OCH_3), 55.53 (OCH_3), 73.30 ($C^{2'}$), 76.52 ($C^{1''}$), 114.69, 127.49, 133.18 and 159.32 (C_{ar}), 164.18 (CONH), 172.06 ($\underline{C}O_2Me$).



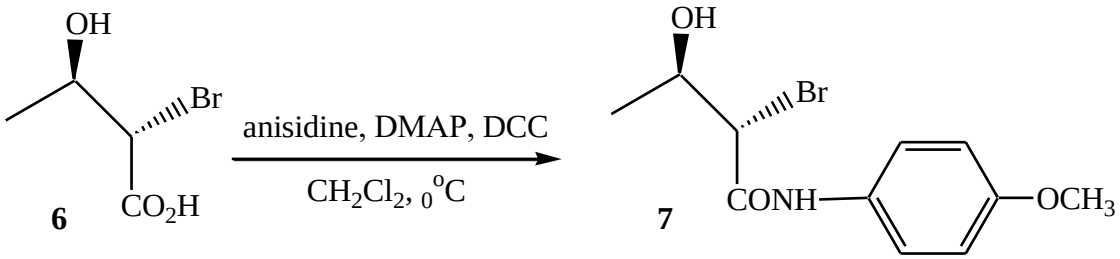
Methyl (2*R*,3*R*)-3-[(1*R*)-1-hydroxyethyl]-1-(4-methoxyphenyl)-4-oxoazetidin-2-yl oxalate (4). m-Chloroperoxybenzoic acid (0.05 g, 0.19 mmol) was added at -78°C with stirring to a mixture of compound **3** (0.05 g, 0.16 mmol) in anhydrous dichloromethane (5 ml). The mixture was stirred for 30 min at –78°C, then warmed to room temperature and stirred for more 12 h. The mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography on SiO_2 (ethyl acetate – petroleum ether, 1:2, then 1:1) to give 0.015 g (30%) product **4** as an oil $[\alpha]_{D.}^{25}$ +19.7° (*c* 0.6, $CHCl_3$). MS (EI, *m/z*) (%): 324 $[MH]^+$ (100). ^{1}H NMR (500 MHz) $CDCl_3$, δ: 1.41 (d, 3H, CH_3, *J* 6.4 Hz), 3.80 and 3.87 (s, 6H, OCH_3), 4.03 (q, 1H, $H^{1''}$, *J* 6.4 Hz), 4.53 (d, 1H, $H^{3'}$, *J* 0.8 Hz), 5.50 (d, 1H, $H^{2'}$, *J* 0.8 Hz), 6.00 (br.s, 1H, OH), 6.80 (dd, 2H, *J* 9.9 and 0.7 Hz) and 7.18 (dd, 2H, H_{ar}, *J* 9.0 and 0.7 Hz). ^{13}C NMR (125 MHz) $CDCl_3$, δ: 16.54 (CH_3), 53.05 and 55.51 (OCH_3), 70.98 ($C^{3'}$), 74.93 ($C^{1''}$), 85.50 ($C^{2'}$), 114.26, 126.18, 133.27 and 158.24 (C_{ar}), 167.66 (CONH), 168.10 ($\underline{C}O_2$).



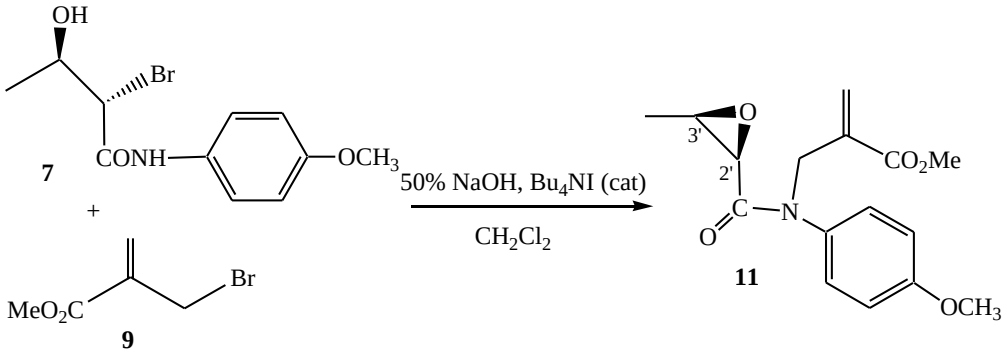
(2*R*,3*R*)-*N*-(4-Methoxyphenyl)-3-methyloxirane-2-carboxamide (8). Sodium hydroxide solution (50%, 5 ml) and Bu_4N^+I (3 mg) were added to a solution of bromide **7** (0.3 g) in CH_2Cl_2 (10 ml), and the mixture was stirred for 10 h (TLC monitoring). Saturated NaCl solution (5 ml) was added, the organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (3×5 ml). The combined extracts were dried with $MgSO_4$, the solvent was evaporated, and the residue was purified by column chromatography on SiO_2 (petroleum ether – ethyl acetate, 1:1). Yield 0.2 g (97%). Colourless crystals, m.p. 196-198°C. $[\alpha]_{D.}^{25}$ +314° (*c* 0.86, $CHCl_3$). Found, %: C 63.55, H 6.24, N 6.87. Calc. for $C_{11}H_{13}NO_3$, %: C 63.76, H 6.32, N 6.76. ^{1}H NMR (500 MHz) $CDCl_3$, δ: 1.39 (d, 3H, CH_3, *J* 5.5 Hz), 3.36 (m, 1H, H^3, *J* 5.3 Hz), 3.60 (d, 1H, H^2, *J* 4.4 Hz), 3.78 (s, 3H, OCH_3), 6.87 (d, 2H, H_{ar}, *J* 8.9 Hz), 7.45 (d, 2H, H_{ar}, *J* 8.9 Hz). ^{13}C NMR (125 MHz) $CDCl_3$, δ: 12.70 (CH_3), 53.54 (C^3), 54.23 (C^2), 55.49 (OCH_3), 114.72, 129.08, 131.00 and 159.44 (C_{ar}), 166.98 (CONH).



Reaction of amide 11 with LiHMDS. A solution of LiHMDS (1 *M*, 0.16 ml, 0.16 mmol) was added dropwise at -40°C on stirring to a solution of compound **11** (0.04 g, 0.13 mmol) in THF (3 ml), and the mixture was stirred for 1 h. The mixture was warmed to -10°C, saturated NH_4Cl solution (1 ml) was added dropwise, THF was evaporated, the reaction product was extracted with CH_2Cl_2 (3×5 ml), the combined extracts were dried with $MgSO_4$ and concentrated by evaporation. The residue was purified by column chromatography on SiO_2 (petroleum ether – ethyl acetate, 2:1) to isolate 16.0 mg (60%) of product **8**.

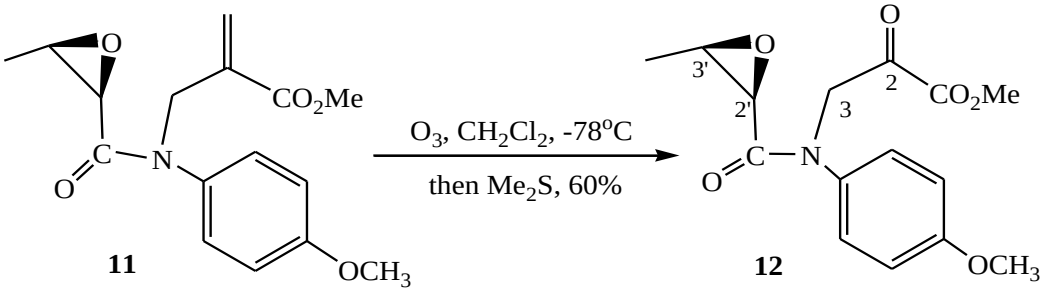


(2*S*,3*R*)-2-Bromo-3-hydroxy-*N*-(4-methoxyphenyl)butanamide (7). Anisidine (0.33 g, 2.68 mmol) and DMAP (0.08 g, 0.66 mmol) were added under argon with stirring to a solution of bromo hydroxy acid **6** (0.5 g, 2.73 mmol) in CH_2Cl_2 (8 ml). The mixture was cooled to 0°C, then dicyclohexylcarbodiimide (DCC) (0.61 g, 2.96 mmol) in CH_2Cl_2 (3 ml) was added dropwise. The mixture was warmed to room temperature and stirred for 8 h. The mixture was filtered on a Schott filter and the filter cake was washed 3-4 times with small portions of CH_2Cl_2. The combined filtrates were washed with 5% HCl solution, then with saturated $NaHCO_3$ solution and water, dried with $MgSO_4$, and concentrated. The residue was purified by column chromatography on SiO_2 (petroleum ether – ethyl acetate) to isolate 0.5 g (63%) of product **7** as a white crystalline compound. M.p. 106-108°C. $[\alpha]_{D.}^{25}$ -17.9° (*c* 1.005, $CHCl_3$). ^{1}H NMR (500 MHz) $CDCl_3$, δ: 1.33 (d, 3H, CH_3, *J* 6.2 Hz), 3.45 (br.s, 1H, OH), 3.77 (s, 3H, OCH_3), 4.18 (m, 1H, H^2, *J* 2.2 and 5.8 Hz), 4.40 (d, 1H, H^3, *J* 2.6 Hz), 6.84 (d, 2H, H_{ar}, *J* 8.7 Hz), 7.40 (d, 2H, H_{ar}, *J* 8.7 Hz), 8.60 (s, 1H, NH). ^{13}C NMR (125 MHz) $CDCl_3$, δ: 20.92 (CH_3), 55.44 (OCH_3), 56.62 (C^2), 67.40 (C^3), 114.13, 122.21, 129.93 and 156.93 (C_{ar}), 166.82 (CONH).



Methyl (2*R*,3*R*)-*N*-(4-methoxyphenyl)-*N*-(3-methoxy-2-methylidene-3-oxopropyl)-3-methyloxirane-2-carboxamide (11). A 50% solution of NaOH (5 ml) and $Me_3BnN^+Cl^-$ (5 mg) were added with stirring at 0°C to a solution of bromo hydroxy amide **7** (40 mg, 0.14 mmol) and bromide **9** (70 mg, 0.39 mmol) in CH_2Cl_2 (5 ml). The mixture was warmed to room temperature and stirred for 8 h. A saturated NaCl solution (2 ml) was added, the organic layer was separated, and the aqueous one was extracted with CH_2Cl_2 (3×5 ml). The combined extracts were washed with saturated NaCl solution and dried with $MgSO_4$, then concentrated. The residue was purified by column chromatography on SiO_2 (petroleum ether – ethyl acetate) to isolate 20 mg (49%) of

amide **11** as a 1:1 mixture of rotamers (~1:1). $[\alpha]_{D.}^{25}$ +236.5° (*c* 1.051, $CHCl_3$). Mass spectrum, *m/z* (*I*, %): 306 $[MH]^+$ (100), 288 (14), 256 (18), 230 (8). ^{1}H NMR (300 MHz) $CDCl_3$, δ: 1.38 (1.39) (d, 3H, CH_3, *J* 5.4 Hz), 3.01 (q.d 1H, $H^{3'}$, *J* 5.4 and 4.4 Hz), 3.23 (3.24) (d, 1H, $H^{2'}$, *J* 4.4 Hz), 3.68 (3.681) (s, 3H, OCH_3), 3.80 (3.81) (s, 3H, OCH_3), 4.47 (d, 1H, CH_2, *J* 5.8 Hz), 4.74 (d, 1H, CH_2, *J* 5.8 Hz), 5.71 (d, 1H, $=CH_2$), 6.30 (s, 1H, $=CH_2$), 6.89 (dd, 2H, H_{ar}, *J* 8.8 and 1.0 Hz), 7.06 (dd, 2H, H_{ar}, *J* 8.7 and 0.8 Hz). ^{13}C NMR (125 MHz) $CDCl_3$, δ: 13.14 (CH_3), 49.91 (CH_2), 51.91 ($C^{3'}$), 53.52 (OCH_3), 54.30 (OCH_3), 55.43 ($C^{2'}$), 127.69 ($=CH_2$), 114.85, 128.97, 135.18 and 159.31 (C_{ar}), 132.98 (=C), 166.28 and 166.58 ($\underline{C}O_2Me$, CONH).



Methyl (2*R*,3*R*)-*N*-(4-methoxyphenyl)-*N*-(3-methoxy-2,3-dioxopropyl)-3-methyl-oxirane-2-carboxamide (12). An ozone-oxygen mixture was passed at -78°C with stirring through a solution of compound **11** (0.18 g, 0.59 mmol) in anhydrous CH_2Cl_2 (10 ml) until the mixture turned blue. The excess O_3 was removed by passing argon, then Me_2S (1 ml) was added. The mixture was stirred for 30 min at –60°C, then for 6 h at room temperature. The mixture was washed with saturated NaCl solution. The organic layer was separated, dried with $MgSO_4$ and concentrated. Purification on SiO_2 (ethyl acetate – petroleum ether, 1:1) gave 0.11 g (60%) of product **12** (1:1 mixture of rotamers), oil. ^{1}H NMR (500 MHz) $CDCl_3$, δ: 1.37 (1.38) (d, 3H, CH_3, *J* 5.4 Hz), 3.03 (m, 1H, $H^{3'}$, *J* 5.4 and 4.4 Hz), 3.27 (3.28) (d, 1H, $H^{2'}$, *J* 4.5 Hz), 3.78 (3.79) (s, 3H, OCH_3), 3.83 (3.84) (s, 3H, OCH_3), 4.63 (d, 1H, CH_2, *J* 8.7 Hz), 5.14 (5.15) (d, 1H, CH_2, *J* 8.6 Hz), 6.89 (dd, 2H, H_{ar}, *J* 8.8 and 1.4 Hz), 7.23 (dd, 2H, H_{ar}, *J* 8.7 and 1.3 Hz). ^{13}C NMR (125 MHz) $CDCl_3$, δ: 12.98 (CH_3), 53.12 ($C^{3'}$), 53.70 (OCH_3), 53.95 (OCH_3), 55.47 ($C^{2'}$), 57.20 (CH_2), 115.03, 129.13, 133.00 and 159.67 (C_{ar}), 159.95 (CONH), 168.21 ($\underline{C}O_2Me$), 187.26 (CO).