Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

Primary Amine-Specific Lactamization of ω-Amino Acids by Artificial Cyclotransferase Based on 18-Crown-6

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Experimental details including synthesis and characterization of 1, 2, 3b, 3c, and 5.

General methods. ^{1}H and spectra were recorded on a Bruker DPX 400 spectrometer. Chemical shifts are reported as δ values relative to tetramethylsilane as internal standard. Infrared spectra were recorded on a Nicolet FT-IR AVATER 360 spectrometer. Mass spectra were measured on a Waters Micromass ZQ2000 spectrometer (ESI-MS), and a JEOL The MStation JMS-700 (FAB-MS). HPLC analyses were performed on a Intersil ODS-3 (GL Sciences). Preparative thin-layer chromatography (PTLC) was performed on Merck precoated silica gel plates. *N*-Methyl-5-aminovaleric acid (**3b**),[1] *N*-isopropyl-5-aminovaleric acid (**3c**), 1-isopropyl-2-piperidone (**4c**),[2] and *N*-cyclohexylmorpholine[3] were prepared according to methods in the literature. Other chemicals were obtained from commercial sources and used as received unless otherwise noted.

***N*-Methyl-5-aminovaleric acid (3b)**: colorless crystals. mp 124°C. IR (KBr): 3417, 2958, 1560 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.63-1.80 (m, 4 H), 2.24 (t, J = 6.0 Hz, 2 H), 2.59 (s, 3 H), 2.87 (t, J = 7.0 Hz, 2 H); ESI-MS *m/z* 132 [$(M+H)^+$]; HRMS (FAB) *m/z* calcd for $C_6H_{14}NO_2$ [$(M+H)^+$]: 132.1024; found: 132.1030.

***N*-Isopropyl-5-aminovaleric acid (3c)**: colorless crystals. mp 170-171°C. IR (KBr): 3406, 2951, 1626, 1523 cm^{-1}; ^{1}H NMR (CD_3OD): δ 1.33 (d, J = 6.6 Hz, 6 H), 1.60-1.78 (m, 4 H), 2.21 (t, J = 6.0 Hz, 2 H), 2.83 (t, J = 7.2 Hz, 2 H), 3.22 (septet, J=6.6 Hz, 1 H); ESI-MS *m/z* 160 [$(M+H)^+$];

HRMS (FAB) *m/z* calcd for $C_8H_{18}NO_2$ [$(M+H)^+$]: 160.1338; found: 160.1328.

Preparation of

2-[2-(*N,N*-Dimethylamino)acetoxymethyl]-1,4,7,10,13,16-hexaoxacyclooctadecane (1)

To a suspension of *N,N*-dimethylglycine hydrochloride (683 mg, 4.9 mmol), 2-(hydoroxymethyl)-18-crown-6 (960 mg, 3.3 mmol), *N*-methylmorpholine (495 mg, 4.9 mmol), and *N,N*-dimethylaminopyridine (399 mg, 3.3 mmol) in dry dichloromethane (26 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.25 g, 6.5 mmol) under nitrogen atmosphere. After being stirred for 20 h at room temperature, the reaction mixture was poured into aqueous ammonium chloride, and extracted. The organic layer was washed successively with $NaHCO_3$, water, and brine, and then dried over $MgSO_4$. The crude mixture was purified by silica gel column chromatography ($CHCl_3$: MeOH = 9 : 1) to give **1** (798 mg, 65% yield) . Colorless liquid, IR (neat): 2938, 2870, 2775, 1748, 1453, 1352, 1123 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.36 (s, 6 H), 3.12 (s, 2 H), 3.59-3.73 (m, 20 H), 3.77-3.86 (m, 3 H), 4.17 (A part of AB, dd, J_{AB} = 11.6 Hz, J = 5.6 Hz, 1 H), 4.30 (B part of AB, dd, J_{AB} = 11.6 Hz, J = 4.3 Hz, 1 H); ESI-MS *m/z* 380 [$(M+H)^+$]; HRMS *m/z* calcd for $C_{17}H_{33}NO_8$ [M^+]: 379.2206; found: 379.2219. *Anal*. Calcd for $C_{17}H_{33}NO_8$: C, 53.81; H, 8.77. Found C, 54.01; H, 8.53.

Preparation of

2-{2-[*N*-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-*N,N*-dimethylammonio]acetoxymethyl}-1,4,7,10,13,16-hexaoxacyclooctadecane triflate (2)

To a solution of 2-hydroxy-4,6-dimethoxy-1,3,5-triazine (HO-DMT; 1.77 g, 11.3 mmol) in dry CH_2Cl_2 (44 mL) was added trifluoromethanesulfonic anhydride (3.50 g, 12.4 mmol) and *N,N*-diisopropylethylamine (1.46 mg, 11.3 mmol) under nitrogen atmosphere. After being stirred for 1.5 h, the solvent was removed *in vacuo*, and the residue was dissolved in ether. The organic layer was washed successively with water (two times) and brine, dried ($MgSO_4$), and then concentrated. The resulting reside was dissolved in dry THF (20 mL), and then, **1** (1.71 g, 4.50 mmol) in THF (10 mL) was added. After being stirred for 1.5 h, the solvent was removed *in vacuo*, and the residue was purified by recrystallization (THF-ether) to give **2** (2.44 g, 81% yield). Colorless crystals; mp 48-50°C IR (KBr): 2904, 1752, 1622, 1529, 1482, 1378, 1260, 1107, 1032, 640 cm^{-1}; ^1H NMR (CD_3OD): δ 3.54-3.73 (m, 28 H), 3.79-3.85 (m, 1 H), 4.17 (s, 6 H), 4.25 (A part of AB, dd, J_{AB} = 11.7 Hz, J = 5.1 Hz, 1 H), 4.43 (B part of AB, dd, J_{AB} = 11.7 Hz, J = 3.6 Hz, 1 H), 5.07 (2H, s); HRMS (FAB) *m/z* calcd for $C_{22}H_{39}N_4O_{10}$ [$(M - CF_3SO_3)^+$]: 519.2666; found: 519.2674.

***N*-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-*N,N*-dimethyl-*N*-(ethyloxycarbonylmethyl)ammonium triflate (5:** 67% yield).

Colorless crystal; mp 77-78°C. IR (KBr): 2971, 1741, 1630 cm^{-1}; ^1H NMR (CD_3OD): δ 1.27 (t, *J*=7.1 Hz, 3 H), 3.68 (s, 6 H), 4.16 (s, 6 H), 4.24 (q, *J* = 7.1 Hz, 2 H), 5.01 (s, 2 H). ESI-MS *m/z* 271[$(M - CF_3SO_3)^+$]. *Anal.* Calcd for $C_{12}H_{19}F_3N_4O_7S$: C, 34.29; H, 4.56; N, 13.33. Found : C, 34.35; H, 4.45; N, 13.26.

References

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