Functionalized *N*-propargylanabazine derivatives

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N-Propargyl derivatives of the alkaloid anabazine with carbonyl, ester, and cyano groups in the side chain were obtained by three-component condensation of anabazine hydrochloride with paraformaldehyde and appropriate terminal alkynes. Decyanoethylation and hydration of the isopropylidene double bond resulted in mono- and dihydroxy derivatives of *N*-propargylanabazines, respectively.

Key words: anabazine, the Mannich reaction, *N*-propargylanabazines, decyanoethylation.

Functionalized acetylenes are employed for the synthesis of biologically active and natural compounds (steroids, amino acids, terpenoids, polyynes, antibiotics, polymers, *etc.*) (see Refs 1—3). For instance, some alkaloid derivatives containing alkyne fragments are agonists of the nicotinic cholinergic system whose failure triggers development of neurodegenerative diseases.[4] For example, 5-ethynylnicotine is used in the treatment of Parkinson´s disease.[5] The propargylamine structural element is contained in antidepressants (pargyline, chlorgyline), cholinergics (tremorine, oxotremorine), and antihypertensive drugs (oxybutynin) (see Refs. 3, 6 and references cited therein).

Recently, we have developed a simple and convenient method for the synthesis of compounds comprising anabazine and propargylamine fragments by three-component condensation of anabazine **1** (Anb-H) with formaldehyde and terminal alkynes in the presence of copper salts.[7] This method is used in the present work for the synthesis of this kind of compounds containing the functional groups CO, OCH_2CH_2CN, COOR, and $C(OR)_2$ in the alkynyl substituents (Scheme 1).

It turned out that alkynes **2a**—**m** containing the ester and cyano groups and the double bonds C=C easily react under the conditions studied to give various *N*-propargylanabazines **4a**—**m**. Reactions with diynes **3a,b** yielded compounds **5a** and **5b** each containing two anabazine fragments. Attempted synthesis of monoadducts failed despite the use of an excess of anabazine or variation of the reaction conditions.

In these reactions, functionalized alkynes **2n**—**p** show some characteristic features. For instance, the anabazine-related ketal **4n** generated *in situ* from alkyne **2n** is transformed into the corresponding hydroxy ketone **4q** upon acid treatment of the reaction mixture. In the case of methyl propiolate **2o**, which is an active Michael acceptor, the Mannich and Michael reactions compete. As the result, the yield of product **4o** was only ~30% and its purity was ~85% (^{1}H NMR). The reaction of anabazine **1** with diethyl propargylmalonate **2p** containing an active methine group gave hydroxymethyl derivative **6a** in 67% yield.

The functional groups in the compounds obtained were transformed to produce new functionalized anabazine derivatives. For instance, alcohol **6a** was converted into acetate **6b** under the action of Ac_2O in CH_2Cl_2; *O*-cyanoethyl derivatives **4e,k** were hydrolyzed[8] with $KOBu^t$ or EtONa to the corresponding alcohols **4s,t**. In the anabazine series, this reaction was carried out for the first time and used to obtain more complex anabazine-based alcohols, *e.g.*, terpene diol **7** (Scheme 2) by room-temperature hydration of the isopropylidene C=C bond in compounds **4k,t** in the presence of 3 *M* HCl. Usually, alcohols are prepared from alkenes by hydroxymercuration or hydrolysis with stronger mineral acids.[9]

Functionalized *N*-propargylanabazines **4**—**7** are liquids with high specific rotations, $[\alpha]_D = -150—250$, which is indirect evidence for the retention of the configuration of the chiral center C(2) in the anabazine molecule upon the Mannich reaction. The structures of compounds **4**—**7** were proved by IR, ^{1}H NMR, and mass spectra (Table 1, Experimental), elemental analysis, and, in some cases, by transformation into the corresponding hydrochlorides. The ^{1}H NMR spectra of the diastereomers of anabazine derivatives **4h,k,n,q,r** with an asymmetric substituent in the side chain are similar. It should only be noted that the signals for the H(2´) and H(6´) atoms are usually broadened (δ ~0.2—1.0), probably because of the inversion of the N atom of the piperidine ring. The signals for the C(2´) and C(6´) atoms in the

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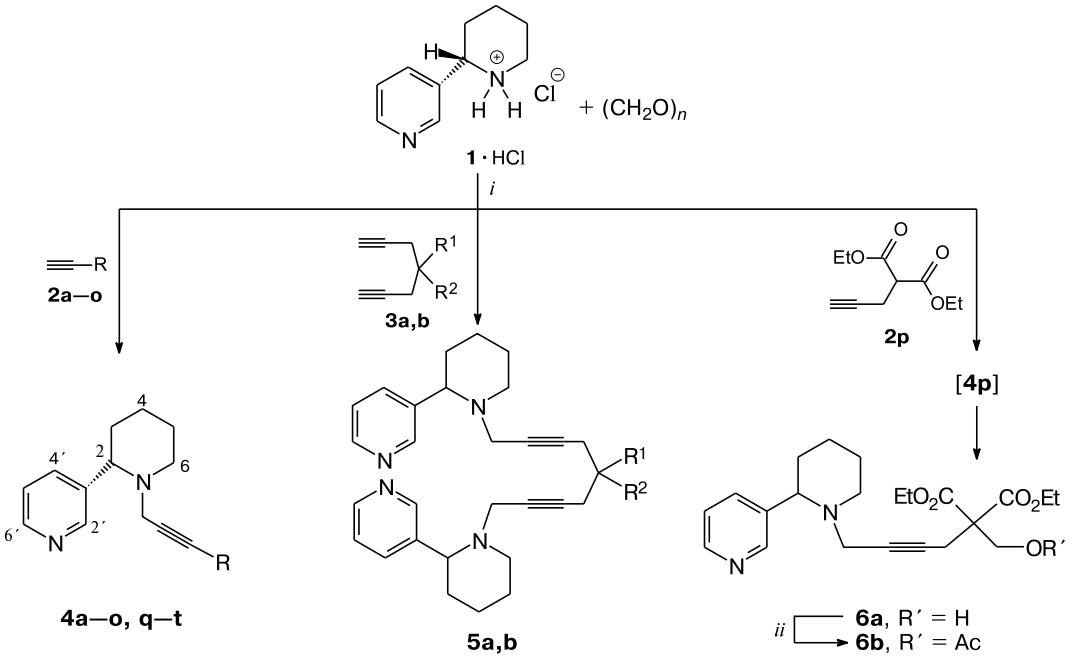
Scheme 1

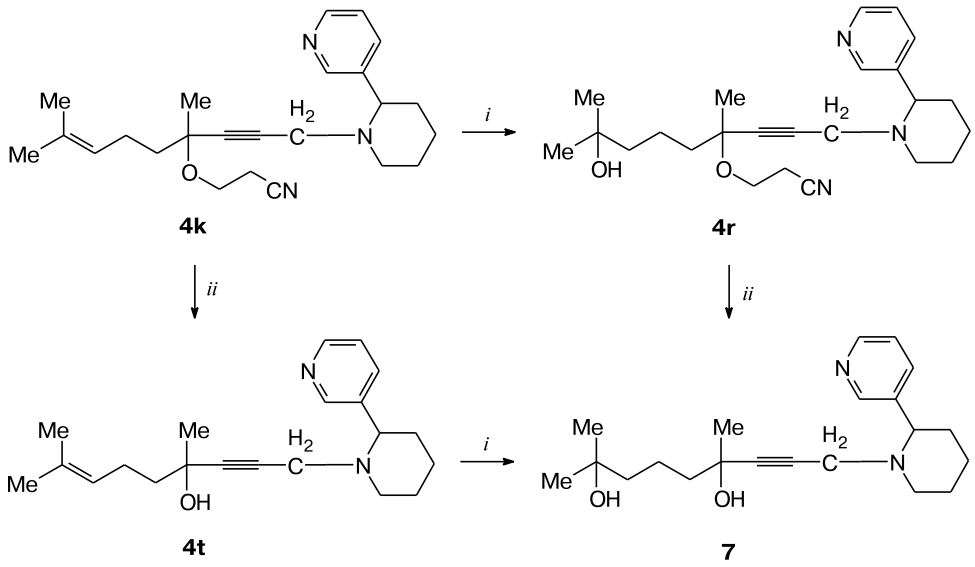


i. Cu_2Cl_2—AcONa/dioxane; *ii*. Ac_2O, NEt_3, DMAP/CH_2Cl_2

3, 5: R^1 = H, R^2 = CO_2Me (**a**), R^1 = R^2 = CO_2Et (**b**)

2, 4: R = $MeOCH_2$ (**a**), 2,6,6-trimethyltetrahydropyran-2-yl (**b**), $Bu^tOCH(Me)CH_2$ (**c**), N≡$CCH_2CH_2OCH_2$ (**d**), N≡$CCH_2CH_2OCH_2CH_2$ (**e**), N≡$CCH_2CH_2OCH(Me)CH_2$ (**f**), N≡$CCH_2CH_2OCMe_2$ (**g**), N≡$CCH_2CH_2OC(Me)Et$ (**h**), N≡$CCH_2CH_2OCEt_2$ (**i**), [*cyclo*-$(CH_2)_5C$]OCH_2CH_2C≡N (**j**), Me_2C=$CHCH_2CH_2C(Me)O$ CH_2CH_2C≡N (**k**), $MeO_2CCH_2CH_2$ (**l**), $EtO_2CCH_2CH_2$ (**m**), (*cyclo*-OCH_2CH_2O) $C(Me)CH_2C(Me)OH$ (**n**), MeO_2C (**o**), $(EtOOC)_2CHCH_2$ (**p**), O=$C(Me)CH_2C(Me)OH$ (**q**), $Me_2C(OH)CH_2CH_2CH_2C(Me)OCH_2CH_2C$≡N (**r**), $HOCH_2CH_2$ (**s**), Me_2C=$CHCH_2CH_2C(Me)OH$ (**t**).

Scheme 2



i: 3 *M* HCl, 20 °C, 5 h *ii*: EtONa/EtOH, 80 °C, 7 h.

Table 1. ^{1}H NMR spectra (DMSO-d_6, δ, *J*/Hz)[a] of compounds **4**, **6**, and **7**

Compound	H(2′) (br.s)	H(4′) (d, *J* = 7.4)	H(5′) (dd, *J* = 7.4, *J* = 4.3)	H(6′) (d, *J* = 4.3)	H(2) (*J* = 10.8)	C(3,4,5)H_2 (2 m, 1 H, 5 H)	H(6e) (br.d)	H(6a) (t)	CH_2(7) (two d, 1 H each)	H—R (*J* = 6.3—7.5)
							J = 10.6			
4a	8.51	7.70	7.22	8.46	3.29 dd[b]	1.32—1.76	2.92	2.46	3.23, 2.96	3.28 (s, 3 H), 4.13 (s, 2 H)
4b	8.46	7.64	7.25	8.42	3.30 d	1.25—1.84[c]	2.91	2.55	3.10, 3.01	1.13, 1.40 (both s, 3 H and 6 H), 1.25—1.84[c], 1.96 (both m, 5 H and 1 H)
4c	8.42[d]	7.64	7.24	8.39	3.30 d	1.27, 1.50—1.78	2.94[c]	—[e]	3.05, 2.94	1.18 (s, 9 H), 1.19 (d, 3 H), 2.19, 2.27 (both d, 1 H each), 3.69 (br.s, 1 H)
4d	8.50	7.69	7.36	8.47	3.30[c]	1.32, 1.44—1.77	2.92	2.41	3.22, 2.93	2.63, 3.65 (both t, 2 H each), 4.25 (s, 2 H)
4e	8.49	7.64	7.28	8.39	3.28 dd[b]	1.34, 1.45—1.78	2.98	—[e]	3.09, 2.89	2.48 (m, 2 H), 2.78, 3.56, 3.64 (all t, 2 H each)
4f	8.49	7.70	7.34	8.46	3.31 d	1.34, 1.44—1.76	2.88	—[e]	3.10, 2.96	1.31 (d, 3 H), 2.35—2.55 (m, 2 H), 2.60, 3.74 (both t, 2 H each), 3.64 (br.s, 1 H)
4g	8.49	7.70	7.36	8.46	3.28 d	1.32, 1.46—1.77	2.88	—[e]	3.18, 2.96	1.43, 1.44 (both s, 3 H each), 2.48, 3.54 (both t, 2 H each)
4h	8.49	7.70	7.36	8.46	3.31 d	1.32, 1.42—1.82[c]	2.88	—[e]	3.22, 3.01	0.97 (t, 3 H), 1.37, 1.38 (both s, 1.5 H each), 1.80[c] (m, 2 H), 2.73, 3.71 (both m, 2 H each)
4i	8.49	7.69	7.37	8.45	3.32 d	1.25—1.82[c]	2.85	—[e]	3.25, 3.02	0.81—0.92 (m, 6 H), 1.64[c] (m, 4 H), 2.75, 3.70 (both t, 2 H each)
4j	8.49	7.69	7.36	8.46	3.32 d	1.31—1.88[c]	2.9	—[e]	3.24, 3.02	1.31—1.88[c] (m, 10 H), 2.75, 3.70 (both t, 2 H each)
4k	—[f]	7.69	7.38	—[f]	3.32 d	1.24—1.88[c]	2.93	2.58[c]	3.12, 3.19	1.24—1.88[c] (m, 2 H), 1.42, 1.64, 1.73 (all s, 3 H each), 2.19 (m, 2 H), 2.58[c], 3.74 (both m, 2 H each), 5.12 (t, 1 H)
4l	8.67[d]	7.68	7.24	8.51	3.29 d	1.32, 1.54—1.86	2.9	—[e]	3.12, 3.02	2.54 (t, 2 H), 2.60—2.74 (m, 2 H), 3.74, 3.77, 3.78 (all s, 3 H total)
4m	8.49	7.68	7.35	8.48	3.25 dd[b]	1.32, 1.50—1.76	2.84	—[e]	3.08, 2.85	1.21 (3 H, s), 2.42—2.68 (m, 4 H), 4.12 (q, 2 H)
4n	—[f]	7.82	7.34[g]	—[f]	3.32 d	1.20—1.89	3.02[c]	2.56[g]	3.13, 3.09	1.43, 1.49, 1.50 (all s, 6 H total), 1.98, 2.16 (both m, 1 H each), 3.94 (s, 4 H), 4.40 (br.s, 1 H)
4q	8.5[a]	7.71	7.37	8.46	~3.32 d	1.31, 1.44—1.78	2.83	2.46	3.21, 2.86	1.42, 2.19 (both s, 3 H each), 2.67—2.76 (m, 2 H), 5.02 (s, OH)
4r	8.58	7.81	7.26	8.49	3.21 d	1.18—1.92[c]	2.91	2.51[c]	3.16, 3.08	1.18—1.92[c] (m, 6 H), 1.21, 1.25, 1.26, 1.39, 1.48 (all s, 9 H total), 2.51—2.70[c] (m, 2 H), 3.76 (m, 2 H)
6a	8.47	7.68	7.35	8.46	3.24 d	1.28, 1.44—1.78	2.82	2.46[c]	3.11, ~2.87	1.22, 1.24 (both t, 3 H each), 2.82 (s, 2 H), 3.96 (dd, 2 H), 4.11—4.22 (m, 4 H), 5.22 (t, OH)
6b	8.51	7.62	7.19	8.43[f]	3.22 dd[b]	1.08—1.82	—[e]	2.47[e]	3.06, ~2.92	1.21 (t, 6 H), 2.02 (s, 3 H) 2.81 (br.s, 2 H), 4.18 (q, 4 H), 4.63 (s, 2 H)
7	—[f]	7.69	7.32	—[f]	3.31 d	1.08—1.92[c]	2.88[c]	2.52	3.09, 2.92	1.11, 1.36 (both br.s, 6 H, 3 H), 1.08—1.92[c] (m, 6 H), 4.08, 5.09 (both br.s, 1 H each)

[a] The ^{1}H NMR spectra of compounds **4k,n,r** were recorded on a Bruker AM-300 instrument (300 MHz, $CDCl_3$). The averaged coupling constants (±0.3 Hz) are given.

[b] *J* = 11.8 Hz, *J* = 2.4 Hz.

[c] Overlap of the signals.

[d] The doublet with *J* = 1.8 Hz.

[e] The signal for the H(6a) atom (δ ≈ 2.50) is masked by the signal for the solvent.

[f] δ 8.5—9.5 (2 H, degenerate br.s).

[g] The broadened singlet.

^{13}C NMR spectra are strongly broadened; in the case of **4k**, they appear at elevated temperature (70 °C). The characteristic peaks in the mass spectra of the compounds obtained correspond to the intense fragmentation ions $[M - C_5H_4N]^+$, 199 $[AnbCH_2C{\equiv}C]^+$, and 161 $[Anb]^+$ (Anb is the anabazine moiety).

Thus, three-component condensation of anabazine with paraformaldehyde and functionalized terminal alkynes afforded functionalized *N*-propargylanabazines, useful precursors of new biologically active anabazine-based compounds.

Experimental

IR spectra were recorded on a Specord M-80 instrument in thin films for oils and in KBr pellets for solids. ^1H NMR spectra were recorded on Bruker DRX-500 and Bruker AM-300 spectrometers in DMSO-d_6 and $CDCl_3$ with $SiMe_4$ as the internal standard. Mass spectra were measured on a Finnigan MAT 112S INCOS 50 instrument (EI, 70 eV, direct inlet probe). Specific rotation ($[\alpha]_D$/deg mL (g dm)$^{-1}$) was determined on a PU-07 polarimeter (Russian Federation) at 20—23 °C for solutions in chloroform (*C*/g (100 mL)$^{-1}$). Elemental analysis data were obtained on a Perkin-Elmer CHN 2004 instrument.

The reaction products were purified by flash chromatography or dry column chromatography on Merck 60 silica gel (70—230 mesh). The course of the reactions was monitored by TLC on Silufol UV-254 plates in the solvent system chloroform—methanol—ethyl acetate (9 : 1 : 1, v/v) saturated with NH_4OH. Spots were visualized in the iodine vapor.

Anabazine hydrochloride (**1** • HCl), m.p. 220—222 °C, >99% purity, (S)-base, $[\alpha]_D$ −82.5 (*c* 0.6, EtOH), R_f 0.17. Ethanol was distilled over metallic Mg; THF was distilled from sodium benzophenone ketyl.

Compounds **2a,o**,[10] **2b**,[11] **2c**,[12] **2d—k**,[13] **2l**,[14] **2m,p**, **3a,b**,[15] and **2n**[16] were prepared as described earlier.

3-(2-Cyanoethoxy)-3,7-dimethyloct-6-en-1-yne (2k). Yield 66%, b.p. 160 °C (bath)/0.5 Torr, n_D^{20} 1.4630. Found (%): N, 8.49. $C_{10}H_{19}NO$. Calculated (%): N, 8.28. IR, ν/cm^{-1}: 3288, 2112 (—C≡CH); 2256 (C≡N). ^1H NMR ($CDCl_3$, 300 MHz), δ: 1.38, 1.59, 1.67 (all s, 3 H each, 3 Me); 1.62, 2.12 (both m, 2 H each, CH_2CH_2); 2.49 (s, ≡CH); 2.64, 3.74 (both m, 2 H each, CH_2CH_2); 5.12 (t, 1 H, =CH, *J* = 6.4 Hz).

N*-Propargylanabazines 4, 5, and 6 (general procedure).** Anabazine hydrochloride **1** • HCl (1.12 g, 5 mmol) was added in one portion at 60—65 °C to a mixture of alkyne **2** or **3** (8—10 mmol), paraformaldehyde (0.48 g, 16 mmol), Cu_2Cl_2 (0.5 g), and AcONa (1.0 g) in dry dioxane (30 mL). The reaction mixture was vigorously stirred for 5—8 h (TLC) and then at 85—90 °C for an additional 2—4 h. The mixture was passed hot through a short column with SiO_2 and concentrated under reduced pressure. The residue was refluxed in light petroleum (15—20 mL) for 7—10 min, the solvent was decanted, and the product was purified by method ***A or ***B***.

Method A. The crude product was dissolved in CH_2Cl_2 (0.3 mL) and chromatographed on silica gel (25—30 g, column 40×2.5 cm). Light petroleum and then MeOH (0—10%)—NH_4OH (0—1%) in CH_2Cl_2 (stepwise gradient) were used as eluents. This procedure was used to isolate compounds **4c,k,t** and **6a**.

Method B. The crude product was dissolved in benzene (60 mL) and extracted with 2 *M* HCl (2×15 mL). The aqueous layer was alkalified with K_2CO_3 to pH 10 and the product was extracted with Et_2O (3×30 mL) (for **4a—j**) or benzene—ethyl acetate (4 : 1). The combined extracts were washed with water and brine, dried with $MgSO_4$, concentrated, and chromatographed as described above (see method *A*). This procedure was used to isolate compounds **4a—j,e,m,o,q,r** and **5a,b**.

Compounds **4c,o,q,r**, **5a,b**, and **6a** were rechromatographed on SiO_2 with CH_2Cl_2—MeOH as an eluent (gradient elution from 0 to 20% MeOH).

(*S*)-*N*-(4-Methoxybut-2-ynyl)anabazine (4a). Yield 83%, oil, $[\alpha]_D$ −229.3 (*c* 0.60). IR, ν/cm^{-1}: 2916, 1592, 1576, 1428, 1088, 908, 720. For ^1H NMR data, see Table 1. MS, *m/z* (I_{rel} (%)): 244 $[M]^+$ (37); 213 (39); 199 (17); 166 $[M - C_5H_4N]^+$ (100); 161 (25); 119 (25); 105 (41); 92 (25); 77 (26). Found (%): N, 11.24. $C_{15}H_{20}N_2O$. Calculated (%): N, 11.47.

Hydrochloride 4a • HCl. M.p. 135—137 °C, $[\alpha]_D$ −100.5 (*c* 0.48). ^1H NMR, δ: 3.19 (t, 1 H, H(6e), *J* = 13.0 Hz); 3.29 (s, 2 H, MeO); 3.67 (d, 1 H, H(6e), *J* = 13.0 Hz); 3.79, 4.00 (both d, 1 H each, $\equiv CCH_2N$, *J* = 17.4 Hz); 4.21 (br.s, 2 H, CH_2O); 4.64 (d, 1 H, H(2), *J* = 13.0 Hz); 8.03 (t, 1 H, H(5′), *J* = 7.6 Hz); 8.91, 8.92 (s, 1 H each, H(4′), H(6′)); 9.20 (br.s, 1 H, H(2′)). Found (%): Cl, 13.46. $C_{15}H_{20}N_2O$ • HCl. Calculated (%): Cl, 12.98.

(*S*)-*N*-[3-(2,6,6-Trimethyltetrahydropyran-2-yl)prop-2-ynyl]anabazine (4b). Yield 86%, light oil, $[\alpha]_D$ −194.1 (*c* 0.46). IR, ν/cm^{-1}: 2936, 1592, 1576, 1428, 1220, 1076, 988, 716. For ^1H NMR data, see Table 1. MS, *m/z* (I_{rel} (%)): 326 $[M]^+$ (30); 248 $[M - C_5H_4N]^+$ (100); 199 (14); 161 (32); 92 (12); 43 (26). Found (%): N, 8.47. $C_{21}H_{30}N_2O$. Calculated (%): N, 8.58.

Mixture of mono- and dihydrochlorides (20—30%), m.p. 155—157 °C, $[\alpha]_D$ −85.0 (*c* 0.43). ^1H NMR, δ: 1.08, 1.31, 1.32, 1.41 (all s, 3 H, 1.5 H, 1.5 H, 3 H, Me); 1.17—1.65, 1.76—1.97, 2.15 (all m, 5 H, 5 H, 2 H, CH_2); 3.04 (br.s, 1 H, H(6a)); 3.71 (dd, 2 H, $\equiv CCH_2N$, H(6e), *J* =16.0 Hz, *J* = 9.0 Hz); 3.86 (d, 1 H, $\equiv CCH_2N$, *J* = 16.0 Hz); 4.35 (t, 1 H, H(2), *J* = 9.0 Hz); 7.39 (br.t, 1 H, H(5′), *J* = 7.8 Hz); 8.58 (br.s, 1 H, H(4′)); 8.79 (d, 1 H, H(6′), *J* = 4.8 Hz); 8.96 (br.s, 1 H, H(2′)); 12.60 (br.s, NH).

(*S*)-*N*-(5-*tert*-Butoxyhex-2-ynyl)anabazine (4c). Yield 62%, dark oil (unstable on storage), $[\alpha]_D$ −189.0 (*c* 0.70). IR, ν/cm^{-1}: 2928, 1592, 1576, 1428, 1082, 720. For ^1H NMR data, see Table 1. MS, *m/z* (I_{rel} (%)): 314 $[M]^+$ (49); 236 $[M - C_5H_4N]^+$ (100); 213 (60); 199 (19); 161 (Anb, 33); 84 (17); 57 (77); 41 (23).

(*S*)-*N*-[4-(2-Cyanoethoxy)but-2-ynyl]anabazine (4d). Yield 84%, oil, $[\alpha]_D$ −196.2 (*c* 0.58). IR, ν/cm^{-1}: 2932, 2256 (C≡N), 1592, 1580, 1428, 1108, 716. For ^1H NMR data, see Table 1. MS, *m/z* (I_{rel} (%)): 283 $[M]^+$ (14); 213 (21); 205 $[M - C_4H_4N]^+$ (100); 161 (32); 77 (17). Found (%): N, 14.64. $C_{17}H_{21}N_3O$. Calculated (%): N, 14.83.

(*S*)-*N*-[5-(2-Cyanoethoxy)pent-2-ynyl]anabazine (4e). Yield 82%, oil, $[\alpha]_D$ −195.1 (*c* 0.74). IR, ν/cm^{-1}: 2936, 2256 (C≡N), 1592, 1576, 1428, 1120, 720. For ^1H NMR data, see Table 1. MS, *m/z* (I_{rel} (%)): 297 $[M]^+$ (22); 227 (24); 219 $[M - C_5H_4N]^+$ (100); 161 (29); 77 (16). Found (%): N, 14.26. $C_{18}H_{23}N_3O$. Calculated (%): N, 14.13.

(*S*)-*N*-[5-(2-Cyanoethoxy)hex-2-ynyl]anabazine (4f). Yield 73%, oil, $[\alpha]_D$ −190 (*c* 0.45). IR, ν/cm^{-1}: 2932, 2256 (C≡N), 1428, 1108, 716. For ^1H NMR data, see Table 1. MS, *m/z* (I_{rel} (%)): 311 $[M]^+$ (13); 241 (18); 233 $[M - C_5H_4N]^+$ (100);

161 (24); 105 (20); 98 (35); 77 (18); 54 (49); 45 (66). Found (%): N, 13.21. $C_{19}H_{25}N_3O$. Calculated (%): N, 13.49.

(*S*)-*N*-[4-(2-Cyanoethoxy)-4-methylpent-2-ynyl]anabazine (4g). Yield 78%, oil, $[\alpha]_D$ −193.3 (*c* 0.55). IR, ν/cm^{-1}: 2936, 2256 (C≡N), 1584, 1560, 1428, 1244, 1156, 1096, 720. For ^{1}H NMR data, see Table 1. MS, *m/z* (I_{rel} (%)): 311 $[M]^+$ (16); 241 (25); 233 $[M - C_5H_4N]^+$ (100); 213 (16); 162 (21); 161 (36); 106 (17); 79 (16); 45 (17). Found (%): N, 13.52. $C_{19}H_{25}N_3O$. Calculated (%): N, 13.49.

(*S*)-*N*-[4-(2-Cyanoethoxy)-4-methylhex-2-ynyl]anabazine (4h). Yield 76%, oil, $[\alpha]_D$ −181.0 (*c* 0.74). IR, ν/cm^{-1}: 2936, 2256 (C≡N), 1592, 1576, 1428, 1124, 1096, 720. For ^{1}H NMR data, see Table 1. MS, *m/z* (I_{rel} (%)): 325 $[M]^+$ (11); 247 $[M - C_5H_4N]^+$ (100); 161 (30); 105 (21); 77 (24); 55 (18). Found (%): N, 13.04. $C_{20}H_{27}N_3O$. Calculated (%): N, 12.91.

(*S*)-*N*-[4-(2-Cyanoethoxy)-4-ethylhex-2-ynyl]anabazine (4i). Yield 81%, oil, $[\alpha]_D$ −155.6 (*c* 0.53). IR, ν/cm^{-1}: 2932, 2256 (C≡N), 1592, 1576, 1428, 1096, 720. For ^{1}H NMR data, see Table 1. MS, *m/z* (I_{rel} (%)): 339 $[M]^+$ (12); 261 $[M - C_5H_4N]^+$ (100); 161 (40); 105 (16); 77 (19); 54 (16). Found (%): N, 12.19. $C_{21}H_{29}N_3O$. Calculated (%): N, 12.38.

(*S*)-*N*-{3-[1-(2-Cyanoethoxy)cyclohexyl]prop-2-ynyl}-anabazine (4j). Yield 89%, oil, $[\alpha]_D$ −166.8 (*c* 0.46). IR, ν/cm^{-1}: 2936, 2256 (C≡N), 1592, 1580, 1428, 1172, 1096, 716. For ^{1}H NMR data, see Table 1. MS, *m/z* (I_{rel} (%)): 351 $[M]^+$ (13); 273 $[M - C_5H_4N]^+$ (100); 161 (63); 105 (24); 91 (39); 77(31); 55 (37); 41 (44). Found (%): N, 11.83. $C_{22}H_{29}N_3O$. Calculated (%): N, 11.96.

(*S*)-*N*-[4-(2-Cyanoethoxy)-4,8-dimethylnon-7-en-2-ynyl]-anabazine (4k). Yield 58%, oil, R_f 0.79, $[\alpha]_D$ −181.2 (*c* 0.93). IR, ν/cm^{-1}: 2256, 1656, 1600, 1580, 1436, 1100, 708. For ^{1}H NMR data, see Table 1. ^{13}C NMR (DMSO-d_6, 75 MHz, 70 °C), δ: 148.4, 148.1, 134.2, 130.6, 123.5, 118.4, 85.9, 79.8, 73.0, 62.3, 58.6, 52.1, 43.2, 41.0, 40.3, 38.6, 35.0, 26.0, 25.2, 24.9, 24.0, 22.5, 18.4, 17.0. MS, *m/z* (I_{rel} (%)): 379 $[M]^+$ (4); 309 (26); 301 $[M - C_5H_4N]^+$ (47); 199 (29); 162 (78); 161 (100); 160 (48); 131 (81); 119 (80); 105 (89); 92 (70); 82 (42); 79 (65); 69 (83); 59 (76); 55 (72). Found (%): N, 10.72. $C_{24}H_{33}N_3O$. Calculated (%): N, 11.07.

(*S*)-*N*-(5-Methoxycarbonylpent-2-ynyl)anabazine (4l). Yield 84%, oil, $[\alpha]_D$ −205.2 (*c* 0.91). IR, ν/cm^{-1}: 2936, 1744 (COOMe), 1592, 1580, 1436, 1208, 1172, 720. For ^{1}H NMR data, see Table 1. MS, *m/z* (I_{rel} (%)): 286 $[M]^+$ (17); 208 $[M - C_5H_4N]^+$ (100); 199 (16); 161 (33); 105 (14); 92 (14); 65 (22); 55 (21). Found (%): N, 9.47. $C_{17}H_{22}N_2O_2$. Calculated (%): N, 9.78.

(*S*)-*N*-(5-Ethoxycarbonylpent-2-ynyl)anabazine (4m). Yield 84%, oil, $[\alpha]_D$ −210.1 (*c* 0.43). IR, ν/cm^{-1}: 2936, 1740, 1592, 1576, 1428, 1172, 720. For ^{1}H NMR data, see Table 1. MS, *m/z* (I_{rel} (%)): 300 $[M]^+$ (15); 255 (17); 222 $[M - C_5H_4N]^+$ (100); 199 (18); 161 (38); 105 (15); 92 (15); 65 (21); 55 (20). Found (%): N, 9.18. $C_{18}H_{24}N_2O_2$. Calculated (%): N, 9.33.

(*S*)-*N*-(6,6-Ethylenedioxy-4-hydroxy-4-methylhept-2-ynyl)-anabazine (4n). Yield 67%, oil, $[\alpha]_D$ −182.7 (*c* 0.83). IR, ν/cm^{-1}: 3480, 2936, 1600, 1584, 1432, 1380, 1216, 1044, 736, 708. For ^{1}H NMR data, see Table 1. MS, *m/z* (I_{rel} (%)): 344 $[M]^+$ (11); 302 (27); 266 $[M - C_5H_4N]^+$ (27); 199 (22); 164 (21); 133 (25); 131 (38); 122 (37); 105 (40); 101 (92); 87 (100); 82 (42); 78 (28). Found (%): N, 8.02. $C_{20}H_{28}N_2O_3$. Calculated (%): N, 8.13.

(*S*)-*N*-(3-Methoxycarbonylpropargyl)anabazine (4o) was purified by repeated column chromatography. Yield ~30%, unstable dark oil (~85% purity). IR, ν/cm^{-1}: 2232 (C≡C), 1720 (COOMe), 1624, 1436, 1252, 720. Partial ^{1}H NMR ($CDCl_3$), δ: 1.34, 1.45—1.79 (both m, 1 H, 5 H, CH_2); 2.44 (t, H(6a), *J* = 12.5 Hz); 2.96 (br.d, 1 H, H(6e), *J* = 12.4 Hz); 3.15, 3.43 (both d, 1 H each, ≡CCH_2N, *J* = 18.0 Hz); 3.27 (dd, 1 H, H(2), *J* = 12.8 Hz, *J* = 1.8 Hz); 3.73 (s, MeO); 7.40 (dd, 1 H, H(5′), *J* = 7.8 Hz, *J* = 4.6 Hz); 7.70 (d, 1 H, H(4′), *J* = 7.8 Hz); 8.49, 8.50 (both s, 1 H each, H(4′), H(6′)).

(*S*)-*N*-(4-Hydroxy-4-methyl-6-oxohept-2-ynyl)anabazine (4q). Yield 77%, oil, $[\alpha]_D$ −172.0 (*c* 0.61). IR, ν/cm^{-1}: 3400—3200, 2936, 1708, 1590, 1580, 1428, 1364, 1328, 1216, 1100, 776. For ^{1}H NMR data, see Table 1. MS, *m/z* (I_{rel} (%)): 300 $[M]^+$ (8); 222 $[M - C_5H_4N]^+$ (55); 199 (17); 164 (60); 161 (61); 105 (20); 58 (15); 43 [MeCO] (100). Found (%): N, 9.19. $C_{18}H_{24}N_2O_2$. Calculated (%): N, 9.33.

(*S*)-*N*-[4-(2-Cyanoethoxy)-8-hydroxy-4,8-dimethylnon-2-ynyl]anabazine (4r) was obtained by aminomethylation of anabazine according to general method ***B***. Yield 52%, oil, R_f 0.63, $[\alpha]_D$ −183.4 (*c* 0.91). IR, ν/cm^{-1}: 3400, 2256, 1592, 1580, 1432, 1172, 1100, 716. For ^{1}H NMR data, see Table 1. ^{13}C NMR ($CDCl_3$), δ: 19.2, 24.4, 25.6, 26.2, 28.9, 29.3, 35.0, 42.0, 43.7, 44.0, 52.9, 58.7, 62.7, 65.6, 69.9, 74.0 and 79.6 (C≡C), 86.1, 117.8 (C≡N), 123.6, 134.9, 138.6, 148.4, 149.0. MS, *m/z* (I_{rel} (%)): 397 $[M^+]$ (1); 301 (7); 199 (13); 161 (59); 136 (29); 131 (74); 122 (61); 124 (62); 106 (31); 69 (57); 59 [Me_2COH] (100); 54 (78). Found (%): N, 10.30. $C_{24}H_{35}N_3O_2$. Calculated (%): N, 10.57.

Method C. A mixture of compound **4k** (0.4 g, 1.0 mmol) and 3 *M* HCl (25 mL) was stirred at 20 °C for 5 h, neutralized with NH_4OH, and, after work-up (see method ***B***), chromatographed on SiO_2. The resulting alcohol **4r** (0.34 g, 68%) is spectroscopically identical with the product obtained according to method ***B***.

(*S*)-*N*-(5-Hydroxypent-2-ynyl)anabazine (4s). Potassium *tert*-butoxide (0.6 g) was added to a solution of compound **4e** (0.30 g, 1 mmol) in anhydrous THF (10 mL). The reaction mixture was refluxed for 7 h. The excess of the base was neutralized with the KU-2 cation-exchange resin (H^+). The solvent was removed and the residue was chromatographed on SiO_2 to give alcohol **4s** (175 mg, 72%). Its ^{1}H NMR and IR spectra are identical with those of an authentic sample.[7]

(*S*)-*N*-(4-Hydroxy-4,8-dimethylnon-7-en-2-ynyl)anabazine (4t). Compound **4k** (0.30 g, 1 mmol) was refluxed in a 2% solution of EtONa in EtOH (10 mL) for 7 h and, after work-up, chromatographed. The yield of alcohol **4t** was 172 mg (62%). Its ^{1}H NMR and IR spectra are identical with those of an authentic sample.[7]

***N,N′*-(5-Methoxycarbonylnona-2,7-diyne-1,9-diyl)di-(*S*)-anabazine (5a).** Yield 61%, oil, $[\alpha]_D$ −232.2 (*c* 0.57). IR, ν/cm^{-1}: 1736, 1592, 1576, 1428, 1128, 756, 716. ^{1}H NMR, δ: 1.28 (m, 2 H); 1.44—1.77 (m, 10 H); 2.47 (overlap, 2 H, H(6a)); 2.56—2.68 (br.s, 4 H, CH_2C≡); 2.81—2.94 (m, 5 H, H(6e), CH, ≡CCH_2N); 3.13 (d, 2 H, ≡CH_2N, *J* = 17.0 Hz); 3.29 (br.d, 2 H, H(2), *J* = 12.0 Hz); 3.71 (s, 3 H, MeO); 7.35 (dd, 2 H, H(5′), *J* = 7.8 Hz, *J* = 4.6 Hz); 7.69 (br.d, 2 H, H(4′), *J* = 7.8 Hz); 8.48 (br.d, 2 H, H(6′), *J* = 4.6 Hz); 8.51 (br.s, 2 H, H(2′)). Found (%): N, 10.96. $C_{31}H_{38}N_4O_2$. Calculated (%): N, 11.24.

***N,N′*-(5,5-Diethoxycarbonylnona-2,7-diyne-1,9-diyl)di-(*S*)-anabazine (5b).** Yield 57%, oil, $[\alpha]_D$ −249.3 (*c* 0.49). IR, ν/cm^{-1}: 1736, 1600, 1592, 1428, 1124, 716. ^{1}H NMR (DMSO-d_6, 300 MHz), δ: 1.09—1.84 (m, 12 H); 1.22 (br.t, 6 H); 2.50 (td, 2 H, H(6A), *J* = 11.8 Hz, *J* = 2.4 Hz); 2.72—3.14 (m, 10 H, H(6e), CH_2C≡CCH_2); 3.23 (br.d, 2 H, H(2), *J* = 12.0 Hz); 4.18

(q, 4 H, CH_2O); 7.20 (br.s, 2 H, H(5′)); 7.62 (d, 2 H, H(4′), J = 7.6 Hz); 8.3—8.7 (br.s, 4 H, H(2′), H(6′)). MS, m/z (I_{rel} (%)): 584 $[M]^+$ (7); 423 (21); 409 (14); 349 (21); 248 (42); 214 (46); 213 (42); 199 (47); 187 (33); 175 (43); 161 (100); 131 (79); 119 (74); 106 (78); 92 (69); 84 (96); 59 (91); 55 (54). Found (%): N, 9.31. $C_{35}H_{44}N_4O_4$. Calculated (%): N, 9.58.

(*S*)-*N*-(5,5-Diethoxycarbonyl-6-hydroxyhex-2-ynyl)anabazine (6a). Yield 67%, m.p. 64—65 °C, $[\alpha]_D$ −153.0 (*c* 0.33). IR, ν/cm^{-1}: 1732, 1598, 1590, 1426, 1120, 716. For ^{1}H NMR data, see Table 1. MS, m/z (I_{rel} (%)): 402 $[M]^+$ (15); 324 $[M - C_5H_4N]^+$ (85); 294 (29); 214 (26); 213 (60); 199 [AnbCH$_2$C≡] (27); 161 [Anb] (100); 119 (20); 105 (24); 92 (29); 77 (23); 65 (45); 55 (33). Found (%): N, 6.84. $C_{22}H_{30}N_2O_5$. Calculated (%): N, 6.96.

(*S*)-*N*-[6-Acetoxy-5,5-di(ethoxycarbonyl)hex-2-ynyl]anabazine (6b) was obtained by acetylation of alcohol **6a** with acetic anhydride in CH_2Cl_2 in the presence of DMAP and triethylamine at 20 °C for 48 h. Yield 87%, oil, $[\alpha]_D$ −148.1 (*c* 0.41). IR, ν/cm^{-1}: 1752, 1736, 1592, 1576, 1428, 1212, 1100, 1040, 720. For ^{1}H NMR data, see Table 1. MS, m/z (I_{rel} (%)): 444 $[M]^+$ (10); 416 (14); 367 (16); 366 $[M - C_5H_4N]^+$ (100); 213 (17); 199 (12); 161 (17); 105 (16); 77 (19); 55 (27); 43 (23). Found (%): N, 6.36. $C_{24}H_{32}N_2O_6$. Calculated (%): N, 6.30.

(*S*)-*N*-(4,8-Dihydroxy-4,8-dimethylnon-2-ynyl)anabazine (7). ***Method A.*** Nitrile **4r** (0.40 g) was heated at 80 °C in a 2% solution of EtONa in EtOH (10 mL) for 7 h. The yield of diol **7** was 0.23 g (68%), glass, R_f 0.45, $[\alpha]_D$ −176.4 (*c* 0.92). IR, ν/cm^{-1}: 3390 (br.s, OH), 1590, 1584, 1432, 1172, 1116, 1100, 756, 516. For ^{1}H NMR data, see Table 1. ^{13}C NMR ($CDCl_3$), δ: 19.7, 24.4, 25.6, 28.9, 29.3,30.2,34.9, 42.9, 43.8, 44.2, 52.9, 62.8, 67.5, 70.3, 76.2, 90.5, 123.6, 135.3, 138.9, 148.1, 149.0. MS, m/z (I_{rel} (%)): 344 $[M]^+$ (13); 328 (26); 312 (59); 268 (53); 250 (90); 245 (58); 226 (50); 200 (66); 162 (100); 161 (31); 123 (96); 85 (86); 77 (60); 69 (50); 55 (52). Found (%): N, 8.37. $C_{21}H_{32}N_2O_2$. Calculated (%): N, 8.13.

Method D. A mixture of compound **4t** (0.24 g) and 3 *M* HCl (15 mL) was stirred at 20 °C for 5 h and alkalified with NH_4OH to pH 10. The product was isolated as described above (see method ***B***). The yield of diol **7** was 0.15 g (60%). Its spectroscopic characteristics are identical with those of the product obtained according to method ***A***.

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