DOI: 10.1002/ejoc.200900323

Photoswitchable Unsymmetrical Ligand for DNA Hetero-Mismatches

Chikara Dohno,[a] Tsuyoshi Yamamoto,[a] and Kazuhiko Nakatani*[a]

Keywords: DNA / Mismatch / Azobenzenes / Photoswitch / Nanostructures / Ligand design

Photoswitchable DNA-binding ligands should be useful for controlling diverse biological functions involving DNA and reversible assembly of DNA-based nanostructures. In work directed towards the development of photoswitchable ligands with various sequence specificities, we have elaborated an efficient synthesis of photoswitchable unsymmetrical ligands possessing pairs of different base recognition elements. A novel photoswitchable ligand incorporating an acylated aminonaphthyridine and an azaquinolone as its base recognition elements can bind to the CAG/CAG sequence in response to light stimuli.

Introduction

Small molecules that recognize specific DNA sequences and structures are promising therapeutic agents and molecular tools for investigation and regulation of specific gene expression.[1,2] We have developed a series of synthetic ligands that selectively bind to DNA bulges,[3] mismatch base pairs,[4] and trinucleotide repeats.[5] Integration of photochromic moieties into the ligands enables us to control the ligand binding in a reversible manner through external light stimuli.[6,7] Photoswitchable mismatch binding ligands (photoswitchable MBLs) can control DNA hybridization and secondary structure in response to light stimuli because the ligand binding alters the stability of double-stranded DNA.[6] The photoswitchable functions of such ligands

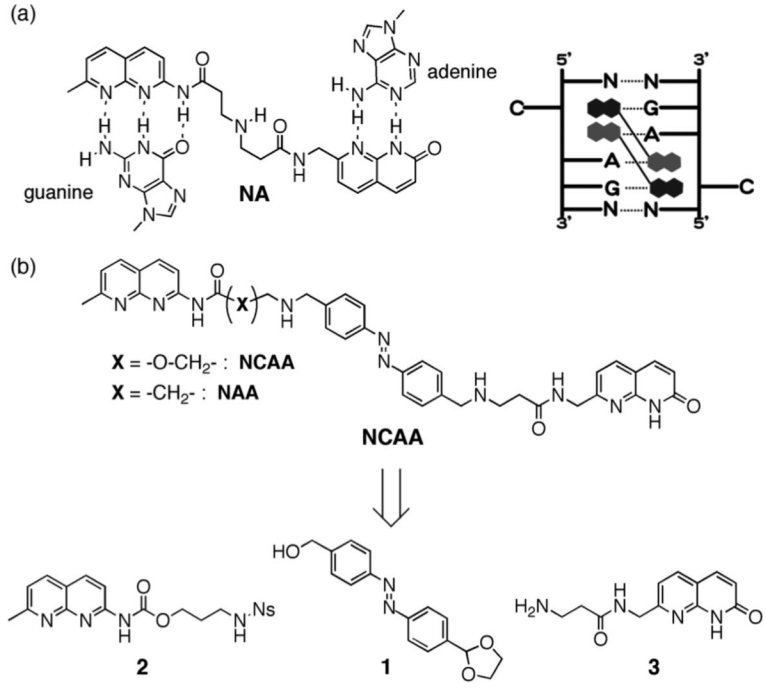


Figure 1. (a) Structure of **NA** and its mode of binding to the CAG/CAG sequence. (b) Structures of **NCAA** and **NAA** and retro-synthesis of **NCAA**. Ns denotes (2-nitrophenyl)sulfonyl.

[a] Department of Regulatory Bioorganic Chemistry, The Institute of Scientific and Industrial Research (SANKEN), Osaka University,
8-1 Mihogaoka, Ibaraki 567-0047, Japan
E-mail: nakatani@sanken.osaka-u.ac.jp

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900323.

should be useful for controlling diverse biological functions involving DNA and for the construction of DNA-based nanoarchitectures.

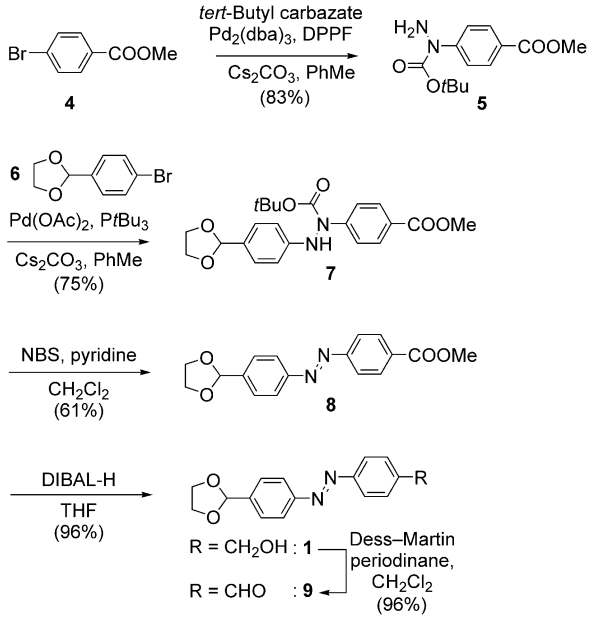
A photoswitchable MBL consists of three parts: a photochromic azobenzene group, base recognition elements, and a connecting linker between them.[6] The first photoswitchable MBL was a C_2-symmetric compound targeting the GG homo-mismatch, and was synthesized by a double reductive amination of naphthyridine units with a symmetrical azobenzene dialdehyde.[6] Here we report the synthesis, based on the coupling of two different base recognition elements onto an unsymmetrically functionalized azobenzene unit, of a photoswitchable MBL (naphthyridine-carbamate-and-azaquinolone-functionalized azobenzene, **NCAA**) designed to target a GA hetero-mismatch. The synthetic scheme described here should be useful for the preparation of libraries of photoswitchable MBLs targeting hetero-mismatches.

We have previously developed the ligand naphthyridine-azaquinolone (**NA**, Figure 1a), possessing two different base recognition elements.[5] The two heterocycles in **NA**, an acylated aminonaphthyridine and an azaquinolone, can form complementary hydrogen bonds with guanine and adenine, respectively (Figure 1a). **NA** binds to a GA mismatch,[4] and more strongly to a CAG/CAG sequence. A key intermediate for the synthesis of **NCAA** is the unsymmetrically substituted azobenzene derivative **1**, which could be modified with various combinations of recognition elements in a stepwise manner (Figure 1b). For evaluation of the linker length connecting between the base recognition groups and the photochromic azobenzene group, the photoresponsive ligand naphthyridine-azaquinolone-functionalized azobenzene (**NAA**, Figure 1b) was also synthesized.

Results and Discussion

NCAA was synthesized from three building blocks: the photochromic azobenzene unit **1**, the guanine-recognizing naphthyridine derivative **2**, and the adenine-recognizing azaquinolone derivative **3** (Figure 1b). The key azobenzene derivative **1** bears two functional groups with different oxidation states, alcohol and aldehyde, at its two *para* positions. The hydroxymethyl and formyl groups are used for coupling reactions with base recognition elements through the Fukuyama–Mitsunobu reaction[8] and reductive amination, respectively. In this synthetic scheme, the two functional groups are both eventually converted into secondary amino groups connected to the base recognition elements. Secondary amino groups are effective for DNA binding because the positive charges on the ammonium groups increase the affinity to DNAs and the solubility in water.

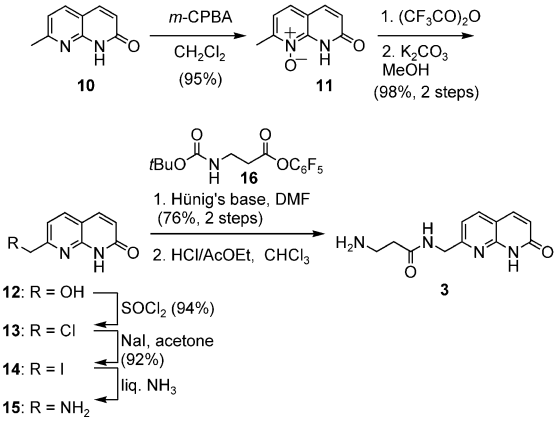
The azobenzene derivative **1** was synthesized from commercially available methyl *p*-bromobenzoate (**4**, Scheme 1). The aryl hydrazide **5** was obtained through a Pd-catalyzed amidation reaction with *tert*-butyl carbazate.[9] Coupling between **5** and the bromobenzene derivative **6** was accomplished by use of $Pd(OAc)_2/P(tBu)_3$ as catalyst in 75% yield,[9] and the resulting diarylhydrazide **7** was oxidized with NBS to the corresponding azobenzene derivative **8**. Reduction of the ester moiety **8** then gave the azobenzene derivative **1**. The doubly functionalized azobenzene unit **1** can be further converted into the unsymmetrically functionalized dialdehyde equivalent **9**. Compound **9** is also a useful intermediate for the synthesis of photoresponsive heterodimeric ligands.



Scheme 1. Synthesis of the azobenzene unit.

For the adenine recognition element we had previously synthesized the 7-aminomethyl-8-azaquinolone derivative **15** (Scheme 2) through bromination of the 7-methyl-8-azaquinolone **10**, but the bromination of **10** was poor in terms both of chemical yield and reproducibility.[10] An improved synthesis of **15** is shown in Scheme 2. The key step is the rearrangement of the *N*-oxide **11** to the corresponding hydroxymethyl derivative **12**.[11] The azaquinolone *N*-oxide **11** was readily prepared by oxidation of **10** with *m*-CPBA. The [3,3] sigmatropic rearrangement resulting in the oxidation of the C7-methyl group was conducted with trifluoroacetic anhydride and subsequent hydrolysis of the trifluoroacetyl group to provide the alcohol **12** in 98% yield over two steps. The alcohol **12** was converted into the iodide **14** in two steps. Nucleophilic substitution of the iodide **14** with liquid ammonia gave **15**. The desired azaquinolone building block **3** was obtained by coupling of **15** with β-alanine derivative **16**, in which the carboxyl group was activated as a pentafluorophenyl ester. The synthesis of the naphthyridine derivative **2**, possessing a 2-nitrobenzenesulfonamide (nosyl amide) moiety, from 2-amino-7-methyl-1,8-naphthyridine is straightforward.[6]

Coupling of the first base-recognition element **2** onto the azobenzene unit was carried out through a Fukuyama–Mitsunobu reaction (Scheme 3).[8] The naphthyridine carbamate derivative **2**, containing a nosyl-protected/activated amine, underwent efficient monoalkylation with **1** under Mitsunobu conditions to give **18** in 91% yield. The *N*,*N*-



Scheme 2. Synthesis of the azaquinolone building block.

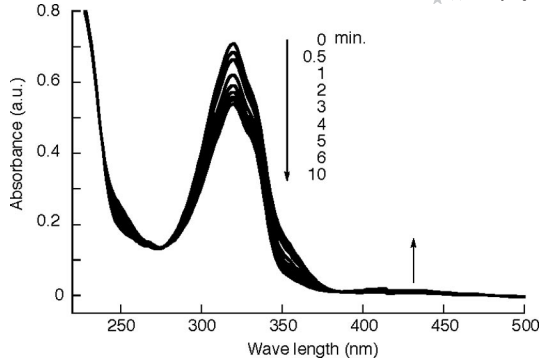


Figure 2. UV/Vis spectra of **NCAA** (30 μM) in sodium cacodylate (pH = 7.0, 10 mM) and NaCl (100 mM). The sample was irradiated with 360 nm light for the indicated periods.

disubstituted sulfonamide was removed, and the resulting secondary amine was protected with a *t*Boc group to give **20**. The acetal of **20** was readily removed by treatment with *p*TsOH to give the aldehyde **21**.

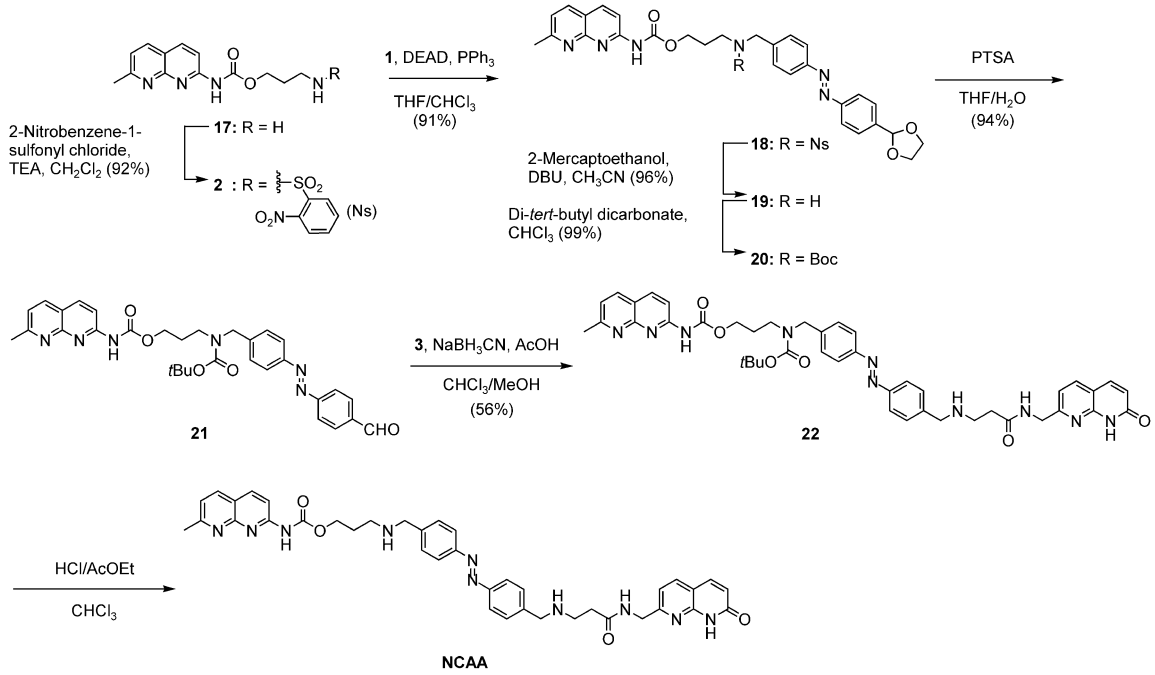
Coupling of the second base-recognition element **3** was carried out by reductive amination between **21** and **3** with use of $NaBH_3CN$. Removal of the *t*Boc group in **22** gave the target compound **NCAA** as a hydrochloride salt.

NAA was synthesized similarly by use of the azobenzene unit **9**.[12]

Photoisomerization of **NCAA** in aqueous sodium cacodylate buffer (pH = 7.0, 10 mM) and NaCl (100 mM) was monitored by UV/Vis absorption spectroscopy (Figure 2).

An absorption band observed at around 320 nm before photoirradiation represents the summation of the absorption bands of an azobenzene π–π* transition and two heterocycles. Upon exposure to 360 nm light, the band intensity at 320 nm decreased and the absorbance at around 430 nm increased concurrently, with isosbestic points at 277 and 385 nm. These spectral changes are characteristic of *trans* to *cis* photoisomerization of azobenzenes.

Photoisomerization of **NCAA** was further analyzed by HPLC (Figure 3). Under ambient room-light conditions, **NCAA** exists predominantly as the *trans* form (91%, Figure 3a). Irradiation with 360 nm light for 5 min in sodium cacodylate buffer (pH = 7.0, 10 mM) and NaCl (100 mM) resulted in the formation of the equilibrium mixture of 67% *cis* isomer (Figure 3b). The mixture was converted back



Scheme 3. Synthesis of **NCAA**.

into the original state (92% *trans* isomer, Figure 3c) without any by-products by irradiation at 430 nm for 5 min. Thermal *cis*-to-*trans* isomerization of **NCAA** was slow (<10% after 100 h incubation at 20 °C) and negligible under physiological conditions.

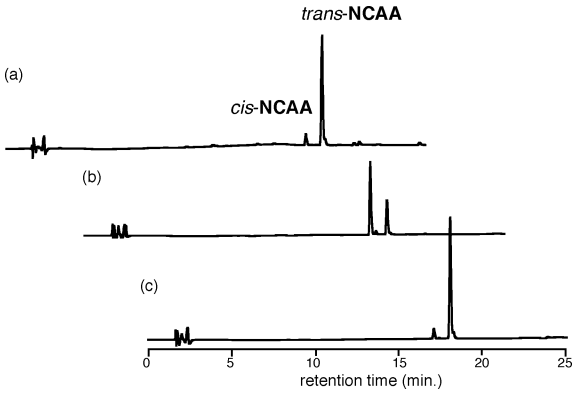


Figure 3. HPLC analysis of the photoisomerization of **NCAA**. The peak with the longer retention time is attributed to *trans*-**NCAA**. (a) Before irradiation, (b) after 360 nm irradiation for 5 min, (c) subsequent irradiation at 430 nm for 5 min.

Having established that **NCAA** undergoes reversible isomerization by UV and visible light, we next examined the interaction of **NCAA** with DNA. Figure 4a shows CD spectra of the DNA duplex 5′-(CTAA **CAG** AATG)-3′/5′-(CATT **CAG** TTAG)-3′, containing a target CAG/CAG binding sequence, in the presence of **NCAA**. With increasing concentrations of *cis*-**NCAA**, the induced CD bands derived from the ligand binding were observed at 320 and 430 nm (Figure 4a). At around 320 nm the CD bands are biphasic, suggesting an exciton coupling between naphthyridine and azaquinolone chromophores. In marked contrast, no induced CD band was observed in the presence of *trans*-**NCAA** (Figure 4a, inset). These results indicate that the *cis* isomer of **NCAA** made a significant contribution to binding with the CAG/CAG sequence, whereas the *trans* isomer did not. Similar CD spectra were observed with **NAA**, with its different linker structure.[12] The induced CD bands generated by *cis*-**NCAA** disappeared as a result of *cis*-to-*trans* isomerization after subsequent irradiation at 430 nm (Figure 4b). The binding of **NCAA** to the DNA duplex can be controlled reversibly and repeatedly through a combination of UV and visible-light irradiation.

The sequence selectivity of the **NCAA** binding was investigated by use of DNA duplexes 5′-(CTAA C**X**G AATG)-3′/5′-(CATT C**Y**G TTAG)-3′ containing single mismatch sites (**X**/**Y**). As would be expected from the base-recognition properties of the acylated aminonaphthyridine and azaquinolone, binding of *cis*-**NCAA** was also observed for the CAG/CGG sequence as well as the CAG/CAG sequence, but not for the other sequence.[12] The binding of **NCAA** to the DNA duplex occurs in a sequence-selective manner, which can be engineered by the combinations of base-recognition moieties.

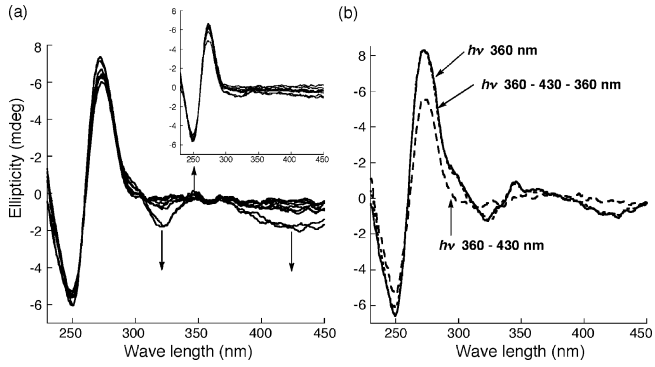


Figure 4. CD spectra of DNA (2.3 μM) containing a CAG/CAG sequence in the presence of **NCAA**. (a) CD spectra were measured during titration with photoirradiated (67% *cis*) **NCAA** (0, 1.1, 2.3, 4.5, 9.1, 13.6, 18.2, 36.3 45.4 μM). Inset: titration with **NCAA** without photoirradiation (91% *trans*). (b) Photoswitching of the **NCAA** binding. Solid line: CD spectra after 360 nm irradiation. Dashed line: subsequent 430 nm irradiation. Dotted line: subsequent 360 nm irradiation.

Conclusions

We have synthesized a new photoswitchable DNA-binding ligand containing two different base-recognition elements, **NCAA**, through the use of the bifunctional azobenzene derivative **1** as a key intermediate. **NCAA** recognized DNA duplex containing a CAG/CAG sequence, and the binding was reversibly regulatable by successive photoirradiation. The bifunctional azobenzene derivative **1** is a useful intermediate for the synthesis of photoswitchable MBLs containing various combinations of linkers and base-recognition elements. A set of photoswitchable ligands for various mismatch DNA sequences should be useful molecular tools for the regulation of DNA functions and the reversible assembly of DNA-based nanostructures.

Experimental Section

General: Flash chromatography was performed with Wakogel (C-300). ^{1}H NMR and ^{13}C NMR spectra were recorded with JEOL LA-600 (600 MHz, 150 MHz) or JEOL LA-400 (400 MHz, 100 MHz) spectrometers with solvent resonances as the internal standards (^{1}H NMR, $CDCl_3$ at δ = 7.26 ppm and CD_3OD at δ = 3.31 ppm; ^{13}C NMR, $CDCl_3$ at δ = 77.2 ppm and CD_3OD at δ = 49.0 ppm) at room temperature unless otherwise noted. High-resolution ESI mass spectrometry analysis was performed with a JEOL JMS-T100LC AccuTOF mass spectrometer. Photoirradiation was carried out with an ASAHI SPECTRA LAX-102 instrument fitted with an appropriate band path filter.

***tert*-Butyl 2-[4-(1,3-Dioxolan-2-yl)phenyl]-1-[4-(methoxycarbonyl)-phenyl]hydrazinecarboxylate (7):** Compound **5** (1.17 g, 4.4 mmol), 2-(4-bromophenyl)-1,3-dioxolane (**6**; 884 mg, 3.9 mmol), palladium(II) acetate (0.20 mmol), tri-*tert*-butylphosphane (0.22 mmol), Cs_2CO_3 (1.9 g, 5.9 mmol), and toluene (30 mL) were placed under argon in an oven-dried flask. The mixture was stirred at room temperature for 20 min and was then heated at reflux and stirred for an additional 14 h. The resulting mixture was allowed to cool to room temperature and diluted with $CHCl_3$. After filtration, the organic phase was concentrated in vacuo. The residue was purified

by flash chromatography (AcOEt/hexane, 1:4) on silica gel to give **7** as a colorless oil (1.21 g, 75%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.98 (d, J = 8.8 Hz, 2 H, Ar-H), 7.70 (d, J = 8.8 Hz, 2 H, Ar-H), 7.35 (d, J = 8.5 Hz, 2 H, Ar-H), 6.76 (d, J = 8.6 Hz, 2 H, Ar-H), 6.46 (s, 1 H, C*H*), 5.72 (s, 1 H, N–H), 7.2–3.9 (4 H, OCH_2-CH_2O), 3.89 (s, 3 H, OCH_3), 1.37 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (600 MHz, $CDCl_3$): δ = 166.8, 153.4, 148.7, 146.8, 130.7, 130.5, 127.9, 125.6, 120.1, 116.5, 112.8, 103.8, 83.2, 65.3, 52.1, 28.1 ppm. HRMS (ESIMS, positive-ion mode, MeOH): calcd. for $C_{22}H_{26}N_2NaO_6$ [M + Na]$^+$ 437.1689; found 437.1691.

Methyl 4-{[4-(1,3-Dioxolan-2-yl)phenyl]diazenyl}benzoate (8): *N*-Bromosuccinimide (NBS; 789 mg, 4.5 mmol) was added to a solution of **7** (1.17 g, 2.82 mmol) in CH_2Cl_2 (16 mL). Immediately after the addition of NBS, the color of the mixture changed to orange. After the mixture had been stirred at ambient temperature for 2 h, it was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried with anhydrous $MgSO_4$ and filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel (AcOEt/hexane, 1:8) to give **8** as an orange solid (538.2 mg, 1.72 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, J = 8.5 Hz, 2 H, Ar-H), 7.97–7.94 (4 H, Ar-H), 7.65 (d, J = 8.1 Hz, 2 H, Ar-H), 5.90 (s, 1 H, 3-H), 4.18–4.06 (m, 4 H, OCH_2CH_2O), 3.96 (s, 3 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 155.1, 153.0 141.3, 131.9, 130.6, 127.3, 123.1, 122.7, 103.1, 65.4, 52.3 ppm. HRMS (ESIMS, positive-ion mode, MeOH): calcd. for $C_{17}H_{16}N_2O_4$ [M + H]$^+$ 313.1188; found 313.1183.

(4-{[4-(1,3-Dioxolan-2-yl)phenyl]diazenyl}phenyl)methanol (1): DIBAL-H (1 M in CH_2Cl_2, 480 μL, 0.48 mmol) was added dropwise at 5 °C to a solution of **8** (45 mg, 0.14 mmol) in THF (3 mL), and the mixture was stirred at 5 °C for 1 h. The resulting mixture was carefully poured into an aqueous solution of sodium potassium tartrate (1 M, 3 mL) and stirred for 30 min. The mixture was extracted with AcOEt, and the combined organic fractions were washed with brine and dried with $MgSO_4$, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel (AcOEt/hexane, 3:1) to afford **1** as an orange solid (39.1 mg, 96%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.93 (d, J = 6.2 Hz, 2 H, Ar-H), 7.92 (d, J = 5.9 Hz, 2 H, Ar-H), 7.63 (d, J = 8.4 Hz, 2 H, Ar-H), 7.05 (d, J = 8.5 Hz, 2 H, Ar-H), 5.89 (s, 1 H, C*H*), 4.78 (s, 2 H, CH_2), 4.2–4.0 (m, 4 H, OCH_2CH_2O), 1.87 (br, 1 H, O*H*) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 153.2, 152.2, 144.2, 140.7, 127.5, 127.4, 123.3, 123.0, 103.4, 65.5, 65.0 ppm. HRMS (ESIMS, positive-ion mode, MeOH): calcd. for $C_{16}H_{17}N_2O_3$ [M + H]$^+$ 285.1239; found 285.1236.

4-{[4-(1,3-Dioxolan-2-yl)phenyl]diazenyl}benzaldehyde (9): Dess–Martin periodinane (70 mg, 0.17 mmol) was added to a stirred solution of **1** (47 mg, 0.17 mmol) in CH_2Cl_2 (5 mL). The solution was stirred at room temperature for 1 h. The organic layer was washed with water and dried with $MgSO_4$. After removal of the solvent, the mixture was purified by flash chromatography on silica gel (AcOEt/hexane, 3:1) to give **9** as an orange solid (46 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.11 (s, 1 H, C*H*O), 8.05 (s, 4 H, Ar-H), 7.98 (d, J = 8.3 Hz, 2 H, Ar-H), 7.66 (d, J = 8.5 Hz, 2 H, Ar-H), 5.91 (s, 1 H, C*H*), 4.2–4.0 (m, 4 H, OCH_2CH_2O) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 191.8, 155.9, 153.1, 141.8, 137.6, 130.8, 127.5, 123.5, 123.4, 103.2, 103.2, 65.6 ppm. HRMS (ESIMS, positive-ion mode, MeOH): calcd. for $C_{16}H_{15}N_2O_3$ [M + H]$^+$ 283.1083; found 283.1084.

7-Methyl-1,8-naphthyridin-2(1*H*)-one 8-Oxide (11): *m*CPBA (70%, 7.5 g, 14.8 mmol) in $CHCl_3$ (30 mL) was slowly added to a stirred solution of **10** (4.0 g, 25.0 mmol) in $CHCl_3$ (30 mL), and the resulting mixture was heated at reflux for 18 h. The mixture was directly dried with $MgSO_4$, and the solution was concentrated in vacuo. The crude mixture was purified by flash chromatography on silica gel ($CHCl_3$/MeOH, from 150:1 to 40:1) to afford **11** as a pale yellow solid (4.2 g, 95%). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.99 (d, J = 9.7 Hz, 1 H, Ar-H), 7.77 (d, J = 8.4 Hz, 1 H, Ar-H), 7.34 (d, J = 8.4 Hz, 1 H, Ar-H), 6.73 (d, J = 9.7 Hz, 1 H, Ar-H), 2.66 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 164.1, 151.1, 143.3, 140.6, 128.6, 124.6, 120.4, 116.7, 17.9 ppm. HRMS (ESIMS, positive-ion mode, MeOH): calcd for $C_9H_8N_2NaO_2$ [M + Na]$^+$ 199.0484; found 199.0483.

7-(Hydroxymethyl)-1,8-naphthyridin-2(1*H*)-one (12): Trifluoroacetic anhydride (2 mL) was carefully added at 0 °C to a solution of **11** (62 mg, 0.35 mmol) in $CHCl_3$ (1 mL), and the mixture was heated at reflux for 15 min. The resulting solution was concentrated in vacuo. The residue was dissolved in MeOH (3 mL). K_2CO_3 (155 mg, 1.12 mmol) was then added to the mixture, which was stirred at 55 °C for 1 h. The resulting mixture was directly concentrated in vacuo. The residue was purified by flash chromatography on silica gel ($CHCl_3$/MeOH, from 100:1 to 20:1) to afford **12** (60.8 mg, 98%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ = 8.08 (d, J = 8.1 Hz, 1 H, Ar-H), 7.94 (d, J = 9.5 Hz, 1 H, Ar-H), 7.41 (d, J = 8.0 Hz, 1 H, Ar-H), 6.62 (d, J = 9.5 Hz, 1 H, Ar-H), 4.74 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 166.1, 165.0, 150.1, 141.3, 138.3, 122.6, 116.8, 115.0, 65.8 ppm. HRMS (ESIMS, positive-ion mode, MeOH): calcd. for $C_9H_8N_2NaO_2$ [M + Na]$^+$ 199.0484; found 199.0480.

7-(Chloromethyl)-1,8-naphthyridin-2(1*H*)-one (13): A mixture of **12** (23 mg, 0.13 mmol) and $SOCl_2$ (500 μL) was stirred at 0 °C for several minutes and then heated at reflux for 2 h. After cooling to room temperature, the mixture was concentrated in vacuo. The residue was diluted with $CHCl_3$, washed with saturated aqueous $NaHCO_3$ solution, and dried with anhydrous $MgSO_4$. After filtration, the organic phase was concentrated to dryness. The residue was purified by flash chromatography on silica gel (AcOEt/hexane, 3:1) to afford **13** (24 mg, 94%) as pale yellow needles. ^{1}H NMR (600 MHz, CD_3OD): δ = 8.12 (d, J = 8.0 Hz, 1 H, Ar-H), 7.97 (d, J = 9.5 Hz, 1 H, Ar-H), 7.44 (d, J = 7.7 Hz, 1 H, Ar-H), 6.67 (d, J = 9.5 Hz, 1 H, Ar-H), 4.74 (s, 2 H, CH_2) ppm. ^{13}C NMR (151 MHz, CD_3OD): δ = 166.0, 160.0, 150.3, 140.9, 138.8, 123.6, 119.3, 115.7, 47.1 ppm. HRMS (ESIMS, positive-ion mode, MeOH): calcd. for $C_9H_7ClN_2NaO$ [M + Na]$^+$ 217.0145; found 217.0147.

7-(Iodomethyl)-1,8-naphthyridin-2(1*H*)-one (14): NaI (2.3 g, 15.4 mmol) was added to a stirred solution of **13** (1.0 g, 5.1 mmol) in dry acetone (33 mL), and the resulting mixture was heated at reflux under argon for 2 h. The solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$. The organic layer was washed with water and dried with $MgSO_4$. After filtration, the organic phase was concentrated to dryness in vacuo to afford **14** (1.35 g, 92%) as a brown solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.02 (d, J = 8.0 Hz, 1 H, Ar-H), 7.93 (d, J = 9.5 Hz, 1 H, Ar-H), 7.37 (d, J = 7.8 Hz, 1 H, Ar-H), 6.63 (d, J = 9.3 Hz, 1 H, Ar-H), 4.61 (s, 2 H, CH_2) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 163.3, 160.2, 149.0, 138.6, 137.2, 123.6, 118.4, 114.1, 5.19 ppm. HRMS (ESIMS, positive-ion mode, MeOH): calcd. for $C_9H_8IN_2O$ [M + Na]$^+$ 308.9501; found 308.9493.

3-Amino-*N*-[(7-oxo-7,8-dihydro-1,8-naphthyridin-2-yl)methyl]propanamide (3): Compound **14** (0.58 g, 2.4 mmol) was dissolved in liquid ammonia (20 mL) at –78 °C, and the solution was stirred for 3 h. The liquid ammonia was evaporated by removing the cooling bath, and the reaction mixture was allowed to warm to room tem-

perature to afford **15** quantitatively as a pale yellow solid. Compound **16** (785 mg, 2.21 mmol) and diisopropyl(ethyl)amine (DIPEA, 850 μL, 4.9 mmol) were added to a stirred solution of **15** (300 mg, 1.70 mmol) in DMF (15 mL). The resulting mixture was stirred at 40 °C for 19 h. The solvent was evaporated in vacuo, and the residue was diluted with $CHCl_3$. The organic layer was washed with saturated aqueous $NaHCO_3$, and the mixture was dried with $MgSO_4$. After removal of the solvent under reduced pressure, the resulting crude products were purified by flash chromatography on silica gel ($CHCl_3$/MeOH, 50:1) to afford Boc-protected **3** as a white solid (449 mg, 76%, 2 steps). ^{1}H NMR (600 MHz, CD_3OD): δ = 8.03 (d, J = 7.9 Hz, 1 H, Ar-H), 7.93 (d, J = 9.5 Hz, 1 H, Ar-H), 7.23 (d, J = 7.9 Hz, 1 H, Ar-H), 6.62 (d, J = 9.5 Hz, 1 H, Ar-H), 4.54 (s, 2 H, CH_2), 3.35 (t, J = 6.5 Hz, 2 H, tBocNHCH_2), 2.48 (t, J = 6.6 Hz, 2 H, COCH_2), 1.41 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 174.2, 166.1, 161.7, 158.4, 150.3, 141.2, 138.4, 122.8, 117.8, 115.0, 80.2, 45.7, 38.0, 37.3, 28.8 ppm. HRMS (ESIMS, positive-ion mode, MeOH): calcd. for $C_{17}H_{22}N_4NaO_4$ [M + Na]$^+$ 369.1539; found 369.1539. Hydrogen chloride in AcOEt (4 N, 2 mL) was added to a solution of Boc-protected **3** (30.6 mg, 88.4 mmol) in $CHCl_3$ (2 mL), and the mixture was stirred for 1 h. The reaction mixture was concentrated to afford **3**. ^{1}H NMR (600 MHz, D_2O): δ = 7.83 (d, J = 8.0 Hz, 1 H, Ar-H), 7.83 (d, J = 9.5 Hz, 1 H, Ar-H), 7.21 (d, J = 8.1 Hz, 1 H, Ar-H), 6.54 (d, J = 9.5 Hz, 1 H, Ar-H), 4.51 (s, 2 H, CH_2), 3.27 (t, J = 6.2 Hz, 2 H, NH_2CH_2), 2.78 (t, J = 6.6 Hz, 2 H, COCH_2) ppm. ^{13}C NMR (150 MHz, D_2O): δ = 173.3, 166.1, 159.9, 148.2, 141.7, 139.2, 121.3, 118.0, 115.0, 44.9, 36.3, 32.5 ppm. HRMS (ESIMS, positive-ion mode, MeOH): calcd. for $C_{12}H_{15}N_4O_2$ [M + H]$^+$ 247.1195; found 247.1199.

3-{[(2-Nitrophenyl)sulfonyl]amino}propyl (7-Methyl-1,8-naphthyridin-2-yl)carbamate (2): Triethylamine (34 mL, 0.25 mmol) and 2-nitrobenzene-1-sulfonyl chloride (46 mg, 0.21 mmol) were added at 0 °C to a stirred solution of 3-aminopropyl *N*-(7-methyl-1,8-naphthyridin-2-yl)carbamate[6] (50 mg, 0.19 mmol) in CH_2Cl_2 (2 mL), and the mixture was stirred for 3.5 h. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried with anhydrous $MgSO_4$. After filtration, the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel ($CHCl_3$/MeOH, 50:1) to give **2** as a pale yellow powder (78 mg, 92%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.22 (d, J = 8.8 Hz, 1 H, Ar-H), 8.16 (m, 1 H, Ar-H), 8.13 (d, J = 8.8 Hz, 1 H, Ar-H), 8.01 (d, J = 8.3 Hz, 1 H, Ar-H), 7.86 (m, 1 H, Ar-H), 7.8–7.6 (2 H, Ar-H), 7.67 (br, 1 H, NH), 7.28 (d, J = 8.3 Hz, 1 H, Ar-H), 5.78 (t, J = 6.2 Hz, 1 H, Ar-H), 4.31 (t, J = 5.9 Hz, 2 H, OCH_2), 3.27 (q, J = 6.6 Hz, 2 H, CH_2NH), 2.76 (s, 3 H, CH_3), 1.98 (quint, J = 6.2 Hz, 2 H, CH_2CH_2CH_2), 1.24 (s, 1 H, NH) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 163.5, 154.8, 153.2, 153.2, 148.2, 139.3, 136.6, 133.8, 133.8, 133.0, 131.1, 125.6, 121.7, 118.2, 112.7, 62.6, 40.6, 29.5, 25.8 ppm. HRMS (ESIMS, positive-ion mode, MeOH): calcd. for $C_{19}H_{19}N_5NaO_6S$ [M + Na]$^+$ 468.0954; found 468.0954.

3-{(4-{[4-(1,3-Dioxolan-2-yl)phenyl]diazenyl}benzyl)[(2-nitrophenyl)-sulfonyl]amino}propyl (7-Methyl-1,8-naphthyridin-2-yl)carbamate (18): Compound **1** (105 mg, 0.37 mmol) and PPh_3 (123 mg, 0.47 mmol) in THF/CH_2Cl_2 (1:1, 4 mL), together with diethyl azodicarboxylate (DEAD) in toluene (40% solution, 229 mL, 0.47 mmol), were added at 0 °C under argon to a stirred solution of **2** (137 mg, 0.31 mmol), and the mixture was stirred at room temperature for 10 h. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried with anhydrous $MgSO_4$. After filtration, the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (AcOEt/hexane, 3:1) to give **18** (200 mg, 91%). NMR analysis showed that **18** consists of 92% of the *trans* isomer and of 8% of the *cis* isomer. NMR signals of the *cis* isomer are denoted by "*cis*". ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, J = 8.6 Hz, 1 H, Ar-H), 8.04–7.90 (2 H, Ar-H), 7.86 (d, J = 8.3 Hz, 1 H, Ar-H), 7.82–7.78 (4 H, Ar-H, NH), 7.65–7.58 (4 H, Ar-H), 7.54 (d, J = 8.6 Hz, 2 H, Ar-H), 7.41 (d, J = 8.3 Hz, 2 H, Ar-H), 7.32 (d, J = 8.3 Hz, *cis*), 7.16 (d, J = 8.3 Hz, 1 H, Ar-H), 6.77 (d, J = 8.5 Hz, *cis*), 6.74 (d, J = 8.0 Hz, *cis*), 5.82 (s, 1 H, CH), 5.66 (s, *cis*), 4.57 (s, 2 H, ArCH_2), 4.42 (s, *cis*), 4.1–3.9 (6 H, OCH_2 + OCH_2CH_2O), 3.37 (t, J = 7.6 Hz, 2 H, CH_2NH), 3.29 (t, J = 7.3 Hz, *cis*), 2.39 (s, 3 H, CH_3), 1.80 (quint, J = 6.8 Hz, 2 H, CH_2CH_2CH_2), 1.67 (quint, J = 6.8 Hz, *cis*) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 163.0, 154.4, 152.8, 152.7, 152.4, 152.0, 147.8, 140.6, 138.8, 138.4, 136.2, 133.7, 132.8, 131.7, 130.8, 128.8, 128.5, 127.0, 126.9, 124.2, 123.2, 122.7, 121.2, 120.7, 120.1, 117.8, 112.3, 103.0, 102.7, 65.2, 62.5, 51.3, 44.3, 27.1, 25.4 ppm. HRMS (ESIMS, positive-ion mode, MeOH): calcd. for $C_{35}H_{34}N_7O_8S$ [M + H]$^+$ 712.2190; found 712.2192.

3-[(4-{[4-(1,3-Dioxolan-2-yl)phenyl]diazenyl}benzyl)amino]propyl (7-Methyl-1,8-naphthyridin-2-yl)carbamate (19): 2-Mercaptoethanol (33 mL, 0.48 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 72 mL, 0.48 mmol) were added to a stirred solution of **18** (200 mg, 0.28 mmol) in acetonitrile (4 mL). The resulting solution was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel ($CHCl_3$/MeOH, 50:1) to give **19** as a pale yellow powder (141 mg, 96%). NMR analysis showed that **19** consists of 92% of the *trans* isomer and of 8% of the *cis* isomer. NMR signals of the *cis* isomer are denoted by "*cis*". ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, J = 8.8 Hz, 1 H, Ar-H), 8.07 (d, J = 8.8 Hz, 1 H, Ar-H), 7.93 (d, J = 8.3 Hz, 1 H, Ar-H), 7.9–7.8 (4 H, Ar-H + NH), 7.59 (d, J = 8.3 Hz, 2 H, Ar-H), 7.47 (d, J = 8.3 Hz, 2 H, Ar-H), 7.2 (d, J = 8.3 Hz, 1 H, Ar-H), 6.83 (d, J = 8.6 Hz, *cis*), 6.79 (d, J = 8.3 Hz, *cis*), 5.87 (s, 1 H, CH), 5.70 (s, *cis*), 4.32 (t, J = 6.3 Hz, 2 H, OCH_2), 4.2–4.0 (4 H, OCH_2CH_2O), 3.89 (s, 2 H, ArCH_2), 3.73 (s, *cis*), 2.79 (t, J = 6.6 Hz, 2 H, CH_2NH), 2.71 (s, 3 H, 1-H), 1.92 (quint, J = 6.8 Hz, 2 H, CH_2CH_2CH_2), 1.22 (s, 1 H, NH) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 163.2, 154.7, 153.5, 153.3, 153.2, 151.8, 140.5, 139.1, 136.5, 128.9, 127.3, 123.1, 122.9, 121.4, 120.9, 120.4, 118.0, 112.7, 103.3, 103.3, 65.5, 64.0, 53.6, 45.7, 29.2, 25.7, 25.7 ppm. HRMS (ESIMS, positive-ion mode, MeOH): calcd. for $C_{29}H_{31}N_6O_4$ [M + H]$^+$ 527.2407; found 527.2408.

3-[(*tert*-Butoxycarbonyl)(4-{[4-(1,3-dioxolan-2-yl)phenyl]diazenyl}-benzyl)amino]propyl (7-Methyl-1,8-naphthyridin-2-yl)carbamate (20): Compound **19** (141 mg, 0.27 mmol) and di-*tert*-butyl dicarbonate (118 mg, 0.54 mmol) were dissolved in $CHCl_3$ (5 mL), and the mixture was stirred at room temperature for 1.5 h. The resulting mixture was concentrated in vacuo. The residue was purified by flash chromatography on silica gel ($CHCl_3$/MeOH, 50:1) to give **20** as an orange powder (172 mg, 100%). NMR analysis showed that **20** consists of 89% of the *trans* isomer and of 11% of the *cis* isomer. NMR signals of the *cis* isomer are denoted by "*cis*". ^{1}H NMR (600 MHz, $CDCl_3$, 45 °C): δ = 8.21 (d, J = 8.8 Hz, 1 H, Ar-H), 8.11 (d, J = 8.8 Hz, *cis*), 8.06 (d, J = 8.8 Hz, 1 H, Ar-H), 7.98 (d, J = 8.0 Hz, *cis*), 7.95 (d, J = 8.0 Hz, 1 H, Ar-H), 7.89–7.85 (4 H, Ar-H + NH), 7.66 (br., 1 H, Ar-H), 7.60 (d, J = 8.4 Hz, 2 H, Ar-H), 7.38 (br. d, J = 6.6 Hz, 2 H, Ar-H), 7.36 (d, J = 8.5 Hz, *cis*), 7.24 (d, J = 8.4 Hz, 1 H, Ar-H), 7.11 (br. d, J = 6.6 Hz, *cis*), 6.85–6.80 (*cis*), 5.88 (s, 1 H, CH), 5.71 (s, *cis*), 4.53 (br., 2 H, CH_2), 4.37 (br., *cis*), 4.22 (br., 2 H, CH_2), 4.16–3.95 (4 H, OCH_2CH_2O), 3.36 (br., 2 H, CH_2NH), 2.75 (s, 3 H, CH_3), 1.95 (br., 2 H,

$CH_2CH_2CH_2$), 1.49 [br., 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 163.3, 156.0, 155.7, 154.4, 154.1, 153.5, 153.2, 153.1, 152.3, 152.0, 146.8, 141.9, 141.7, 140.6, 139.2, 137.0, 128.6, 128.1, 127.9, 127.4, 127.3, 123.3, 123.0, 121.5, 121.1, 120.5, 118.1, 112.8, 103.4, 103.3, 103.2, 85.3, 80.3, 65.5, 63.6, 51.1, 50.2, 44.3, 43.9, 28.5, 27.9, 27.5, 25.5, 1.3, 1.1 ppm. HRMS (ESIMS, positive-ion mode, MeOH): calcd. for $C_{34}H_{39}N_6O_6$ $[M + H]^+$ 627.2931; found 627.2923.

3-[(*tert*-Butoxycarbonyl){4-[(4-formylphenyl)diazenyl]benzyl}-amino]propyl (7-Methyl-1,8-naphthyridin-2-yl)carbamate (21): Compound **20** (171 mg, 0.27 mmol) and *p*-toluenesulfonic acid (PTSA, 77 mg, 0.41 mmol) were dissolved in water/THF (1:25, 5 mL). The mixture was stirred at 50 °C for 1 h. The mixture was extracted with $CHCl_3$ and dried with anhydrous $MgSO_4$. After filtration, the organic layer was concentrated in vacuo. The residue was purified by flash chromatography on silica gel ($CHCl_3$/MeOH, 50:1) to give an orange powder (147 mg, 94%). NMR analysis showed that **21** consists of 92% of the *trans* isomer and of 8% of the *cis* isomer. NMR signals of the *cis* isomer are denoted by "*cis*". ^1H NMR (600 MHz, $CDCl_3$, 45 °C): δ = 10.10 (s, 1 H), 9.92 (s, *cis*), 8.22 (d, *J* = 8.5 Hz, 1 H), 8.08 (d, *J* = 8.8 Hz, 1 H), 8.05–7.98 (4 H), 7.69 (d, *J* = 8.0 Hz, 1 H), 7.92 (d, *J* = 8.1 Hz, 2 H), 7.78 (d, *J* = 7.3 Hz, *cis*), 7.60 (br., 1 H), 7.42 (br., 2 H), 7.25 (d, *J* = 11.7 Hz, 1 H), 7.12 (br., *cis*), 6.94 (d, *J* = 8.0 Hz, *cis*), 6.83 (d, *J* = 7.7 Hz, *cis*), 4.55 (br., 2 H, CH_2), 4.23 (br., 2 H, CH_2), 3.35 (br., 2 H, CH_2NH), 2.75 (s, 3 H, CH_3), 1.96 (br., 2 H, $CH_2CH_2CH_2$), 1.50 [br., 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 163.4, 156.0, 154.8, 153.3, 153.1, 152.0, 142.9, 142.7, 139.1, 137.5, 136.5, 130.8, 128.6, 128.0, 123.7, 123.4, 121.5, 120.4, 118.1, 112.6, 80.4, 63.7, 63.6, 51.1, 50.3, 44.3, 44.0, 29.8, 28.5, 27.6, 27.5, 25.7 ppm. HRMS (ESIMS, positive-ion mode, MeOH): calcd. for $C_{32}H_{34}N_6NaO_5$ $[M + Na]^+$ 605.2488; found 605.2480.

({3-[4-({4-[(3-Oxo-3-{[(7-oxo-7,8-dihydro-1,8-naphthyridin-2-yl)-methyl]amino}propyl)amino]methyl}phenyl)diazenyl]benzyl}amino)-propyl (7-Methyl-1,8-naphthyridin-2-yl)carbamate (NCAA): Compounds **21** (147 mg, 0.25 mmol) and **3** (77 mg, 0.31 mmol) were dissolved in $CHCl_3$/methanol (2:1, 15 mL), and the pH of the mixture was adjusted to 5–6 by addition of acetic acid. The mixture was stirred at room temperature for 30 min. Sodium cyanoborohydride (19.5 mg, 0.31 mmol) in MeOH (1 mL) was then added to the stirred solution. The mixture was stirred at room temperature for 10 h. The resulting mixture was washed with saturated aqueous $NaHCO_3$ and brine, and dried with $MgSO_4$. After concentration, the mixture was purified by flash chromatography on silica gel ($CHCl_3$/MeOH, 50:1) to give **22** (114 mg, 56%). Hydrogen chloride in ethyl acetate (4 M, 5 mL) was added to a solution of **22** (114 mg, 141 mmol) in $CHCl_3$ (5 mL), and the mixture was stirred for 1 h. The reaction mixture was concentrated to afford **NCAA** as a hydrochloride salt (101.6 mg). For NMR analysis **NCAA** was neutralized with saturated aqueous $NaHCO_3$. The solution was extracted several times with $CHCl_3$, and the combined organic layers were dried with anhydrous $MgSO_4$. After filtration, the solvent was removed under reduced pressure. NMR spectra of this residue were measured without further purification. ^1H NMR (600 MHz, $CDCl_3$): δ = 10.84 (br., 1 H, NH), 8.54 (br., *J* = 5.8 Hz, 1 H, NH), 8.24 (d, *J* = 8.8 Hz, 1 H, Ar-H), 8.09 (d, *J* = 8.8 Hz, 1 H, Ar-H), 7.96 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.82 (d, *J* = 8.4 Hz, 2 H, Ar-H), 7.78 (d, *J* = 8.1 Hz, 1 H, Ar-H), 7.74 (d, *J* = 8.4 Hz, 2 H, Ar-H), 7.62 (d, *J* = 9.5 Hz, 1 H, Ar-H), 7.46 (d, *J* = 8.1 Hz, 2 H, Ar-H), 7.37 (d, *J* = 8.4 Hz, 2 H, Ar-H), 7.23 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.21 (d, *J* = 7.7 Hz, 1 H, Ar-H), 6.60 (d, *J* = 9.5 Hz, 1 H, Ar-H), 4.64 (d, *J* = 5.9 Hz, 2 H, $ArCH_2$), 4.33 (t, *J* = 6.2 Hz, 2 H, OCH_2), 3.89 (s, 2 H, $ArCH_2$), 3.86 (s, 2 H, $ArCH_2$), 2.97 (t, *J* = 6.2 Hz, 2 H, CH_2NH), 2.79 (t, *J* = 7.0 Hz, 2 H, CH_2NH), 2.72 (s, 3 H, CH_3), 2.51 (t, *J* = 6.2 Hz, 2 H, CH_2CO), 1.94 (quint, *J* = 6.6 Hz, 2 H, $CH_2CH_2CH_2$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.8, 164.0, 163.3, 160.3, 154.8, 153.6, 153.4, 151.8, 151.8, 149.3, 143.5, 143.0, 139.1, 139.1, 137.3, 136.5, 128.9, 128.9, 123.1, 123.0, 122.9, 121.5, 118.1, 117.9, 113.8, 112.8, 64.1, 53.7, 53.3, 45.8, 45.1, 44.7, 35.9, 29.4, 25.7 ppm. HRMS (ESIMS, positive-ion mode, MeOH): calcd. for $C_{39}H_{40}N_{10}NaO_4$ $[M + Na]^+$ 735.3132; found 735.3138.

Measurements of UV/Vis Spectra: NCAA (30 μM) was dissolved in a sodium cacodylate buffer (10 mM, pH = 7.0) containing NaCl (100 mM). UV/Vis absorption spectra were recorded with a Beckman Coulter DU® 800 spectrometer in a 1 cm pathlength cell at ambient temperature before and after photoirradiation at 360 nm for the indicated time period.

HPLC Analysis: A solution (total volume 100 μL) containing **NCAA** (40 μM) in sodium cacodylate buffer (10 mM, pH = 7.0) and aqueous NaCl (100 mM) was exposed to 360 and 430 nm light for 5 min. After the photoirradiation, the sample solution was analyzed by reversed-phase HPLC on a Cosmosil packed column (Nacalai tesque, 4.6 × 150 mm) fitted with a photodiode array detector (Jasco, MD-2010); elution was carreid out with a solvent mixture of 0.1% trifluoroacetic acid/water and 0.1% trifluoroacetic acid/acetonitrile (5–30% for 25 min) at a flow rate of 1.0 mL min^{-1}. The *cis*/*trans* ratios were determined by the HPLC peak areas determined at the isosbestic point (277 nm).

Circular Dichroism (CD) Measurements: CD experiments were performed with a J-725 CD spectrometer (Jasco). CD spectra of DNA [2.3 μM, 5′-d(CTAA **CAG** AA TG)-3′/5′-d(CATT **CAG** TTAG)-3′] in sodium cacodylate buffer (10 mM, pH = 7.0), NaCl (100 mM) and Tween 20 (0.1%) were measured in the presence of different concentration of **NCAA** at 25 °C. For the titration with *cis*-**NCAA**, pre-photoirradiated **NCAA** (360 nm irradiation for 5 min, 67% of *cis* isomer) was used instead of the dark equilibrated **NCAA** (91% of *trans* isomer).

Supporting Information (see footnote on the first page of this article): CD spectra with different DNAs and synthetic details of **NAA**.

Acknowledgments

This work was supported by a Grant in Aid for Scientific Research (S) from the Japan Society for the Promotion of Science (18105006) to K. N.

[1] a) P. B. Dervan, *Bioorg. Med. Chem.* **2001**, *9*, 2215–2231; b) T. Bando, H. Sugiyama, *Acc. Chem. Res.* **2006**, *39*, 935–944; c) W. C. Tse, D. L. Boger, *Chem. Biol.* **2004**, *11*, 1607–1617.

[2] a) B. A. Jackson, J. K. Barton, *J. Am. Chem. Soc.* **1997**, *119*, 12986–12987; b) S. Neidle, G. Parkinson, *Nat. Rev. Drug Discovery* **2002**, *1*, 383–393; c) E. M. Rezler, D. J. Bearss, L. H. Hurley, *Annu. Rev. Pharmacol. Toxicol.* **2003**, *43*, 359–379.

[3] K. Nakatani, S. Sando, I. Saito, *J. Am. Chem. Soc.* **2000**, *122*, 2172–2177.

[4] a) K. Nakatani, S. Sando, I. Saito, *Nat. Biotechnol.* **2001**, *19*, 51–55; b) S. Hagihara, H. Kumasawa, Y. Goto, G. Hayashi, A. Kobori, I. Saito, K. Nakatani, *Nucleic Acids Res.* **2004**, *32*, 278–286; c) A. Kobori, H. Horie, H. Suda, I. Saito, K. Nakatani, *J. Am. Chem. Soc.* **2004**, *126*, 557–562.

[5] a) K. Nakatani, S. Hagihara, Y. Goto, A. Kobori, M. Hagihara, G. Hayashi, M. Kyo, M. Nomura, M. Mishima, C. Kojima, *Nat. Chem. Biol.* **2005**, *1*, 39–43; b) T. Peng, K. Nakatani, *Angew. Chem. Int. Ed.* **2005**, *44*, 7280–7283; c) T. Peng, H. He, M. Hagihara, K. Nakatani, *ChemBioChem* **2008**, *9*, 1893–1897.

[6] C. Dohno, S. Uno, K. Nakatani, *J. Am. Chem. Soc.* **2007**, *129*, 11898–11899.
[7] J. Andersson, S. Li, P. Lincoln, J. Andréasson, *J. Am. Chem. Soc.* **2008**, *130*, 11836–11837.
[8] a) T. Fukuyama, C.-K. Jow, M. Cheung, *Tetrahedron Lett.* **1995**, *36*, 6373–6374; b) T. Kan, T. Fukuyama, *Chem. Commun.* **2004**, 353–359.
[9] a) Z. Wang, R. T. Skerlj, G. J. Bridger, *Tetrahedron Lett.* **1999**, *40*, 3543–3546; b) Y.-K. Lim, K.-S. Lee, C.-G. Cho, *Org. Lett.* **2003**, *5*, 979–982.
[10] K. Nakatani, H. He, S. Uno, T. Yamamoto, C. Dohno, *Current Protocols in Nucleic Acid Chemistry*, John Wiley & Sons, New York, **2008**, unit 8.6, 1.
[11] a) V. J. Traynelis, R. F. Martello, *J. Am. Chem. Soc.* **1958**, *80*, 6590–6593; b) W. Korytnyk, N. A. Srivastava, P. G. G. Potti, B. Paul, *J. Med. Chem.* **1973**, *16*, 1096–1101; c) M. van den Heuvel, T. A. van den Berg, R. M. Kellogg, C. T. Choma, B. L. Feringa, *J. Org. Chem.* **2004**, *69*, 250–262.
[12] See Supporting Information.

Received: March 25, 2009
Published Online: July 2, 2009

