Notes

Functionalization at C-17 of an *Eburnea–Aspidosperma* Binary Alkaloid as a Model To Study Modified Vinblastine-Type Antitumor Alkaloids

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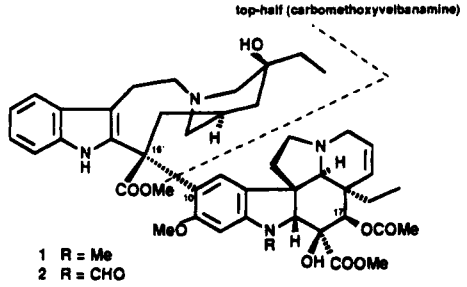
The antitumor binary alkaloids vinblastine (**1**), vincristine (**2**), and related compounds have attracted a great deal of attention from the synthetic point of view by virtue of their intriguing structural feeatures, potent pharmacological activity and limited natural availability from vegetable sources.[1]



The literature reports a number of approaches toward these molecules by means of the coupling of the catharanthine precursor of the carbomethoxyvelbanamine "top half" with the vindoline "bottom half", focusing on both the efficient creation of the C(10)–C(16′) bond and the correct stereochemistry at C-16′.[2]

Such syntheses have proved helpful not only in increasing the availability of the drugs but also in providing access to modified molecules that still manifest useful activity. However in spite of the continuous effort made in structure modification studies there is still insufficient data to lead to conclusions regarding structure–activity relationship; thus it may be importannt to find a synthetic route to modified vinblastine-type compounds.

In previous papers[3] the first highly enantioselective hemisynthesis of vindorosine (**3**) and vindoline (**4**) has been described starting from tabersonine (**5**) and the rare 11-methoxytabersonine (**6**) (Chart 1), the crucial step being the regio- and stereoselective hydroxylation of the vinylogous aminomethylene at C-17 performed by the unique reagent benzeneseleninic anhydride (BSA).

The 17-hydroxy derivatives **7** and **8** behaved as a vinylogous carbinolamine and under the catalysis of Lewis acids a great variety of nucleophiles could be introduced at C-17.[4] Remarkable is the formation of covalent adducts with aminopurines and aminopyrimidines.[5]

On the basis of these results we reasoned that the incorporation of a hydroxy function at C-17 position of the carbomethoxyvelbanamine/11-methoxytabersonine dimer **9** to form **10** could be viewed as a versatile point of entry into the preparation of new 17-substituted derivatives having vinblastine-type structures.

To test the feasibility of this delicate manipulation of an *Aspidosperma* moiety in a complex binary alkaloid molecule, we carried out a model study on the eburnamine/11-methoxytabersonine binary alkaloid **11**, accessible in 65% yield by acid-catalyzed condensation of the easily available (+)-eburnamine (**13**)[6] with 11-methoxytabersonine.

Here we describe the successful hydroxylation at C-17 of **11** to **12** and the obtainment of the 17β-substituted derivatives **14**, **15** and, **16** with imidazole, tri-*O*-acetylguanosine, and tri-*O*-acetyladenosine respectively. Furthermore, we were able to elaborate **12** into the eburnamine/vindoline dimer **20** which was found to be identical with the product of direct coupling of eburnamine to vindoline itself.

Oxidation of **11** with 1.1 equiv of benzeneseleninic anhydride occurred very smoothly in benzene at 35 °C for 12 h and gave the 17β-hydroxy derivative **12** in 81% yield. In the ^{1}H NMR spectrum, the signal of H-17 at δ 4.58 showed a long range coupling constant (J = 2 Hz) due to the α orientation that permits a W-space relationship with H-21. Two aromatic proton singlets were present at δ 6.87 and at δ 6.58 for H-9 and H-12 to confirm the regiochemistry of the coupling of the two halves. The configuration at C-16′ was suggested by analysis of the spin system and the coupling constants of H-16′β at δ 5.48, H-17′α and H-17′β [J(16′β,17′α) = 11.5 Hz; J(16′β,17′β) = 4.5 Hz].

A further support to C-16′ configuration was obtained by a NOE difference experiment. Saturation of H-16′ gave a substantial positive enhancement of a signal at δ

(1) For a comprehensive review of this area, see: Antitumor Bisindole Alkaloids from *Catharanthus roseus* (L.). *The Alkaloids*; Brossi, A., Ed.; Academic Press Inc.: San Diego, 1990; Vol. 37. For a general review of bisindole alkaloids, see: Cordell, G. A.; Saxton, J. E. Bisindole Alkaloids. *The Alkaloids*; Rodrigo, R. G., Ed.; Academic Press Inc.: San Diego, 1981; Vol. 20.

(2) As leading references on this subject see: (a) Kutney, J. P.; Beck, J.; Bylsma, F.; Cook, J.; Cretney, W. J.; Fuji, K.; Imhof, R.; Treasurywala, A. M. *Helv. Chim. Acta* **1975**, *58*, 1690. (b) Langlois, N.; Gueritte, F.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1976**, *98*, 7017. (c) Vukovic, J.; Goodbody, A. E.; Kutney, J. P.; Misaw, M. *Tetrahedron* **1988**, *56*, 513. (d) Kuehne, M. E.; Matson, P. A.; Bornmann, W. G. *J. Org. Chem.* **1991**, *56*, 513. (e) Szantay, C., Jr.; Balazs, M.; Szantay, C. *Tetrahedron* **1991**, *41*, 1265. (f) Sundberg, R. J.; Gadamasetti, K. G.; Hunt, P. J. *Tetrahedron* **1992**, *48*, 277. (g) Magnus, P.; Mendoza, J. S.; Stamford, A.; Ladlow, M.; Willis, P. *J. Am. Chem. Soc.* **1992**, *114*, 10232.

(3) Danieli, B.; Lesma, G.; Palmisano, G.; Riva, R. *J. Chem. Soc., Chem. Commun.* **1984**, 909.

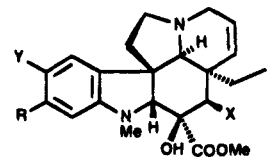
(4) Danieli, B.; Lesma, G.; Palmisano, G. In *Studies of Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1989; Vol. 4, pp 29–81.

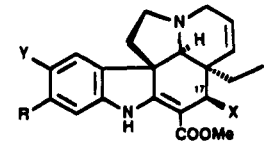
(5) Danieli, B.; Lesma, G.; Palmisano, G.; Passarella, D.; Pyuskyulev, B. *Nucleosides Nucleotides* **1991**, *10*, 1667.

(6) For the use of eburnamine in the synthesis of binary alkaloids, see: Lounasmaa, M.; Tolvanen, A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press Inc.: San Diego, 1992; Vol. 42, p 1.

0022-3263/94/1959-5810$04.50/0

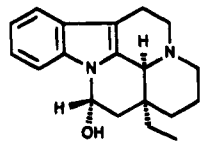
Chart 1



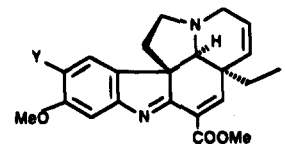


3 R = H X = OCOMe Y = H
4 R = OMe X = OCOMe Y = H
19 R = OMe X = OH Y = dihydroeburnamenine
20 R = OMe X = OCOMe Y = dihydroeburnamenine

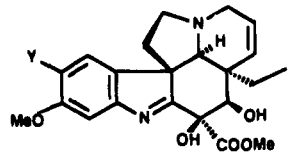
5 R = X = Y = H
6 R = OMe X = Y = H
7 R = Y = H X = OH
8 R = OMe X = OH Y = H
9 R = OMe X = H Y = carbomethoxyvelbanamine
10 R = OMe X = OH Y = carbomethoxyvelbanamine



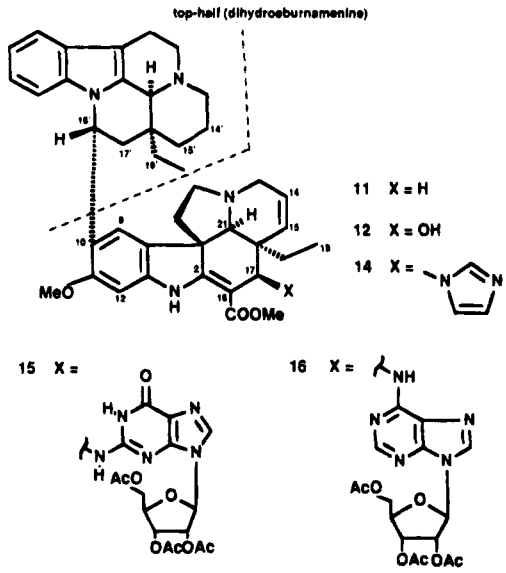
13



17 Y = dihydroeburnamenine



18 Y = dihydroeburnamenine



2.19 (dd; J_1 = 11.5 Hz, J_2 = 4.5 Hz)(H-17′α) and of a signal at δ 1.19 (td; J_1 = 14 Hz, J_2 = 4.5 Hz)(H-15′α).

In order to selectively modify the C-17 position, the compound **12** was reacted with nucleophiles (0.1 mmol/0.07 mmol of substrate) in the presence of TBDMSCl (0.15 mmol), *N,N*-diisopropylethylamine (DIPEA, 0.15 mmol).[5] In this way we synthesized three adducts using as nucleophiles imidazole, tri-*O*-acetylguanosine, and tri-*O*-acetyladenosine.

With imidazole the adduct **14** was isolated in 70% yield after 35 h. In ^{1}H NMR spectrum the H-17 proton was present at δ 5.01 as a broad singlet together with the signals at δ 6.88, 6.95, and 7.49 of the N-bounded imidazole protons, thus confirming the formation of the C—N bond. In the ^{13}C NMR spectrum C-17 appeared at 49.3 ppm.

A shorter reaction time (5 h) was sufficient for the formation of the tri-*O*-acetylguanosine adduct **15**, isolated in 81% yield. A well-resolved spectrum could be obtained by operating in DMSO-d_6 at 100 °C. The H-17 appeared at δ 5.12 as a broad doublet of doublets coupled to H-21 at δ 2.57 ($J \cong 1$ Hz), and to NH-17 at δ 7.91 (J = 7.5 Hz), in agreement with the formation of a C—N bond between NH_2 of guanosine and C-17.

The tri-*O*-acetyladenosine adduct **16** was isolated in 79% yield after 12 h. The ^{1}H NMR spectrum could be run only at 45 °C and the H-17 signal appeared to overlap those of H-14 and H-3‴ in the range between δ 5.62 and δ 5.71. However substitution at C-17 with the primary nitrogen of adenosine was supported by the appearance of H-21 as a doublet at δ 2.58 ($J \cong$ Hz) and NH-17 at δ 8.55 as a doublet (J = 7.4 Hz). In ^{13}C NMR spectrum it is possible to distinguish a signal at δ 51.9 attributable to C-17, in accordance with the two preceding cases.

At 100 °C the ^{1}H NMR spectrum of **16** (and also that one of the imidazole adduct **14**) showed an unexpected fast and clean decomposition to the azadiene **17**. It had an unambiguous ^{1}H NMR spectrum with H-17 as a doublet at δ 7.09, maintaining a long-range coupling constant (J = 2 Hz) to H-21 through a W-space relationship. At the same time H-12 appeared shifted down field to δ 7.39. The same quantitative transformation into **17** was observed for the 17-OH compound **12**; however, conversion was slow (60 min) and could be monitored by ^{1}H-NMR.

We devised a further elaboration of **12** into the vindoline-containing dimer **20** through an electrophilic hydroxylation at C-16 to the indolenine **18** followed by reductive methylation to **19** and acetylation. For the C-16 oxygenation of **12** we opted to utilize the photooxygenation protocol.[7]

Bubbling oxygen into an irradiated 10^{-2} M solution of **12** (25 °C, 1 h) in methanol/water 6:1, containing Rose Bengal as sensitizer, sodium thiosulfate as reductant, and NaOH led to an almost complete conversion of **12** into a mixture of products, from which the 16-hydroxy indoline **18** could be isolated.

Because of its propensity to undergo decomposition, compound **18** was not characterized, but immediately converted into the stable *N*(1)-methyl-16-hydroxy-2,16-dihydro indoline **19** by reductive methylation. The ^{1}H NMR spectrum of **19** showed, in addition to H-9, H-12 (δ

(7) In principle, the allylic hydroxylation of the anilino acrylate moiety of *Aspidosperma* alkaloids could be performed using (a) peracids (Hugel, H.; Levy, G.; Le Men, J. *Acad. Sci., Ser. C.* **1972**, *274*, 1350), (b) ozone (Danieli, B.; Lesma, G.; Palmisano, G.; Gabetta, B. *J. Chem. Soc., Chem. Commun.* **1981**, 908), (c) dye-sensitized photooxygenation (Santamaria, J.; Herlem, D.; Khuong-Hou, F. *Tetrahedron* **1977**, *33*, 2389. Calabi, L.; Danieli, B.; Lesma, G.; Palmisano, G. *J. Chem. Soc., Perkin Trans 1* **1982**, 1371). The presence of basic nitrogens and sensitive indole nucleus in the eburnamine top-half dictated the use of the last mentioned protocol.

6.64 and δ 6.18) and H-16′ (δ 5.54), a singlet for H-2 at δ 3.68 and a broad singlet for H-17 at δ 3.98.

Noteworthy is the high field shift suffered by H_3-18 of the vindoline lower half from δ 0.40 to δ −0.10. This is caused by a shielding effect of the indole moiety of the eburnamine upper part and is a consequence of the sp^2–sp^3 rehybridization of C-2 and C-16, which causes the C-20 ethyl chain to point predominantly toward the negative anisotropic region of the aromatic system.[8]

Finally, acylation of **19** with acetic anhydride afforded **20** which was identical in all respects to the product obtained by the acid-catalyzed condensation of (+)-eburnamine (**13**) with vindoline (**4**).[8]

In conclusion, we have shown that the *Aspidosperma* lower half of the eburnamine/11-methoxytabersonine binary alkaloid can be successfully elaborated to form adducts at position 17 with the representative nucleophiles imidazole, tri-*O*-acetylguanosine, and tri-*O*-acetyladenosine.

These results encouraged us to perform an analogous reaction on the carbomethoxyvelbanamine/11-methoxytabersonine binary alkaloid **9** to afford modified dimers for biological evaluation. Synthesis of compound **9** is in progress.

Experimental Section[5]

The HR-FABMS spectra were obtained with a VGZAB IF-HF instrument. ^1H and ^{13}C NMR operating at 300 and 75.4 mHz, respectively, were used.

Preparation of Compound 11. A solution of 105 mg (0.287 mmol) of 11-methoxytabersonine (**6**) and 85 mg (0.287 mmol) of eburnamine (**13**) in 5 mL of 3% HCl/MeOH was heated to 60 °C for 48 h. Dilution with water, basification, and extraction with chloroform yielded a residue which was purified by flash chromatography (FC) (EtOAc/MeOH 7.5:2.5) to give **11** (123 mg, 65%): R_f ($CHCl_3$/EtOH 95:5) = 0.26 (CAS: pink); CD (MeOH) λ (Δε) 230 (+10.5), 330 (−4.7); ^1H NMR ($CDCl_3$, 50 °C) δ 0.43 (3 H, t, J = 7.5 Hz), 0.75 (1 H, dq, J = 14, 7 Hz), 0.83–1.01 (4 H, m), 1.18 (1 H, td, J = 14, 5.2 Hz), 1.30–1.45 (2 H, m), 1.50 (1 H, dq, J = 14, 7 Hz), 1.65–1.90 (3 H, m), 1.95–2.28 (3 H, m), 2.31–2.65 (7 H, m), 2.85–3.10 (3 H, m), 3.2–3.38 (3 H, m), 3.71 (3 H, s), 3.80 (3 H, bs), 4.02 (1 H, bs), 5.45 (1 H, dd, J = 4.5, 11 Hz), 5.51 (1 H, dd, J = 11 Hz), 5.60 (1 H, dd, J = 5, 11 Hz), 6.37 (1 H, bd, J = 8 Hz), 6.51 (1 H, s), 6.71 (1 H, t, J = 8 Hz), 6.89 (1 H, s), 6.91 (1 H, t, J = 8 Hz), 7.38 (1 H, d, J = 8 Hz), 9.05 (1 H, bs); ^{13}C NMR ($CDCl_3$) δ 8.0 (double), 17.5, 21.1, 25.0, 27.1, 29.5, 29.8, 35.6, 42.4, 43.2, 45.1, 45.2, 50.5, 50.8, 51.3, 51.5, 51.7, 55.3, 56.5, 60.3, 69.1, 93.7, 94.2, 105.3, 112.4, 118.1, 119.7, 121.0, 122.7, 125.3, 129.0, 131.2, 133.6, 134.5, 137.3, 133.6, 144.3, 157.1, 167.9, 169.5; FABMS m/z 645 (MH^+), 279; high-resolution MS, FAB ionization, calcd for $C_{41}H_{49}NO_3$ 645.3804; found 645.3815.

Preparation of Compound 12. A solution of 48 mg (0.075 mmol) of **11** in dry benzene (10 mL) was treated with 29 mg (0.083 mmol) of BSA and the mixture was heated at 35 °C for 12 h. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2, washed with 5% $NaHCO_3$, and purified by FC [5%-(1% NH_3–MeOH)/EtOAc–hexane 1:1] to give **12** (40 mg, 81%): R_f [5%(1%(NH_3–MeOH)/EtOAc–hexane 1:1] = 0.31 (CAS: yellow), CD (MeOH) λ (Δε) 235 (+11.5), 325 (−5.2); ^1H NMR ($CDCl_3$, 50 °C) δ 0.40 (3 H, t, J = 7.5 Hz), 0.78–0.97 (5 H, m), 1.19 (1 H, td, J = 14, 4.5 Hz), 1.33–1.46 (2 H, m), 1.51 (1 H, dq, J = 14, 7 Hz), 1.62–2.01 (3 H, m), 2.10–2.29 (2 H, m), 2.38–2.65 (5 H, m), 2.60 (1 H, d, J = 2 Hz), 2.90–3.12 (3 H, m), 3.31–3.42 (3 H, m), 3.78 (3 H, s), 3.85 (3 H, bs), 4.02 (1 H, bs), 4.58 (1 H, d, J = 2 Hz), 5.48 (1 H, bdd, J = 11.5, 4.5 Hz), 5.63 (1 H, bd, J = 11 Hz), 5.88 (1 H, dd, J = 11, 4.2 Hz), 6.33 (1 H, d, J = 8 Hz), 6.58 (1 H, s), 6.72 (1 H, t, J = 8 Hz), 6.87 (1 H, s), 6.95 (1 H, t, J = 8 Hz), 7.25 (1 H, s), 7.42 (1 H, d, J = 8 Hz), 9.15 (1 H, bs); ^{13}C NMR ($CDCl_3$) δ 8.0 (double), 17.7, 21.3, 25.1, 28.9, 29.5, 35.5, 37.1, 43.5, 45.2, 45.6, 51.2, 51.5, 51.7 (double), 51.9, 54.2, 56.6, 60.9, 68.2, 71.0, 95.2, 98.9, 105.6, 112.3, 118.1, 119.7, 120.1, 120.9, 123.4, 127.4, 129.2, 130.4, 131.7, 134.9, 137.3, 143.7, 157.2, 168.7, 169.3; FABMS m/z 661 (MH^+), 643; high-resolution MS, FAB ionization, calcd for $C_{41}H_{49}N_4O_4$ 661.3753, found 661.3761.

General Procedure for the Reaction of 17-OH Adduct with Nucleophiles. To a solution of the 17-hydroxy adduct **12** (0.07 mmol) in dry CH_2Cl_2 (5 mL) under a nitrogen atmosphere, the appropriate nucleophile (0.1 mmol) was added. The mixture was cooled (0 °C), and DIPEA (0.15 mmol) followed by TBDMSCl (0.15 mmol) in CH_2Cl_2 (1 mL) was added dropwise. Stirring was continued (5–35 h) until the reaction reached room temperature. The reaction mixture was neutralized and the solvent removed *in vacuo*. The residue was purified as specified in each case.

Imidazole Adduct 14: Reaction time, 35 h; purification, FC ($CHCl_3$/MeOH 19:1) to give 35 mg (70%) of **14**. R_f ($CHCl_3$/MeOH 19:1) = 0.31 (CAS: yellow); ^1H NMR ($CDCl_3$, 45 °C) δ 0.41 (3 H, m), 0.85–0.95 (1 H, m), 0.89 (3 H, t, J = 7 Hz), 1.00–1.25 (2 H, m), 1.33–1.90 (6 H, m), 2.10–2.30 (2 H, m), 2.31–2.88 (5 H, m), 2.60 (1 H, bs), 2.88–3.10 (3 H, m), 3.30–3.40 (3 H, m), 3.68 (3 H, s), 3.90 (3 H, bs), 4.04 (1 H, bs), 5.01 (1 H, bs), 5.39 (1 H, d, J = 10.7 Hz), 5.51 (1 H, dd, J = 4.5, 10.7 Hz), 5.59 (1 H, dd, J = 5.5, 10.7 Hz), 6.32 (1 H, d, J = 7 Hz), 6.61 (1 H, s), 6.73 (1 H, t, J = 7 Hz), 6.79 (1 H, s), 6.88 (1 H, bs), 6.95 (1 H, bs), 6.96 (1 H, t, J = 7 Hz), 7.42 (1 H, d, J = 7 Hz), 7.49 (1 H, s), 9.40 (1 H, bs); ^{13}C NMR ($CDCl_3$) δ 8.16, 8.75, 17.7, 21.1, 24.8, 29.5, 30.9, 35.6 (double), 43.6, 45.2 (double), 49.3, 50.8, 51.6 (4 C), 52.1, 54.7, 56.6, 60.3, 66.2, 92.5, 95.1, 105.5, 112.4, 118.2, 119.7, 121.1, 122.0, 123.8, 126.5, 127.5, 129.2, 129.3, 129.5, 130.1, 134.9, 137.3, 143.3, 157.2, 168.8, 172.2; FABMS m/z 711 (MH^+), 643; high-resolution MS, FAB ionization, calcde for $C_{44}H_{51}N_6O_4$ 711.4022, found 711.4030.

Tri-*O*-acetylguanosine Adduct 15: Reaction time, 5 h; purification, FC ($CHCl_3$/MeOH 95:5) to give 61 mg (81%) of **15**. R_f ($CHCl_3$/MeOH 95:5) = 0.45 (CAS: pink); ^1H NMR (DMSO-d_6, 100 °C) δ 0.40 (3 H, t, J = 7.1 Hz), 0.88 (3 H, t, J = 7.5 Hz), 0.85–0.94 (1 H, tq, J = 14, 7.1 Hz), 1.01 (1 H, tq, J = 14, 7.1 Hz), 1.11 (1 H, td, J = 13, 4 Hz), 1.33–1.45 (2 H, m), 1.51 (1 H, dq, J = 14, 7 Hz), 1.60–2.60 (10 H, m), 2.02 (3 H, s), 2.06 (3 H, s), 2.09 (3 H, s), 2.57 (1 H, bs), 2.85–3.05 (3 H, m), 3.15–3.28 (2 H, m), 3.45 (1 H, dd, J = 14.5, 5.5 Hz), 3.75 (3 H, s), 3.83 (3 H, s), 4.01 (1 H, bs), 4.25–4.43 (3 H, m), 5.12 (1 H, bd, J = 7.5 Hz), 5.43 (1 H, dd, J = 12, 5 Hz), 5.46 (1 H, d, J = 12 Hz), 5.55 (1 H, t, J = 5.5 Hz), 5.78 (1 H, dd, J = 11, 5.5 Hz), 5.88 (1 H, t, J = 5.5 Hz), 6.03 (1 H, d, J = 5.5 Hz), 6.32 (1 H, d, J = 8 Hz), 6.68 (1 H, t, J = 8 Hz), 6.86 (1H, t, J = 8 Hz), 6.98 (1 H, s), 6.99 (1 H, s), 7.32 (1 H, d, J = 8 Hz), 7.75 (1 H, s), 7.91 (1 H, d, J = 7.5 Hz), 8.53 (1 H, s), 10.8 (1 H, bs); ^{13}C NMR ($CDCl_3$) δ 8.2 (double), 17.9, 21.0, 21.2, 21.4, 25.3, 29.4, 29.6, 35.7, 43.6, 45.0, 45.3, 45.6, 50.6, 51.3, 51.8, 51.9, 52.3, 53.7, 55.0, 56.8, 60.3, 64.1, 68.1, 71.2, 73.8, 80.4, 87.9, 95.4, 105.7, 112.4, 118.3, 119.8, 120.5, 121.0, 124.1, 129.2, 129.5, 130.0, 130.7, 135.1, 136.3, 137.3, 143.1, 152.3, 153.1, 157.3, 168.7, 169.7, 169.8, 171.0; FABMS m/z 1052 (MH^+), 644; high-resolution MS, FAB ionization, calcd for $C_{57}H_{66}N_9O_{11}$ 1052.4881, found 1052.4894.

Tri-*O*-acetyladenosine Adduct 16: Reaction time, 12 h; purification, FC (EtOAc/EtOH 7:3) to give 58 mg (79%) of **16**. R_f (EtOAc/EtOH 7:3) = 0.40 (CAS: yellow); $[\alpha]^{20}_D$ = +56.9 (c = 0.65, $CHCl_3$); CD (MeOH) λ (Δε) 233 (+14.8), 283.4 (−8.0), 308 (+8.7); ^1H NMR ($CDCl_3$, 40 °C) δ 0.45 (3 H, t, J = 7 Hz), 0.91 (3 H, t, J = 7.1 Hz), 0.91–1.18 (2 H, m), 1.21 (1 H, dd, J = 14, 4 Hz), 1.33–1.49 (2 H, m), 1.53 (1 H, dq, J = 14, 7 Hz), 1.62–2.71 (7 H, m), 1.83 (1 H, dd, J = 11, 3.5 Hz), 2.04 (3 H, s), 2.09 (3 H, s), 2.11 (3 H, s), 2.20 (1 H, dd, J = 14, 7 Hz), 2.52 (1 H, td, J = 11.5, 3), 2.65 (1 H, bs), 2.89–3.11 (3 H, m), 3.22–3.51 (3 H, m), 3.78 (3 H, s), 3.87 (3 H, s), 4.09 (1 H, bs), 4.30–4.47 (3 H, m), 5.40–5.65 (4 H, m), 5.68 (1 H, t, J = 5.5 Hz), 5.93 (1 H, *t*, J = 5.5), 6.10 (1 H, d, J = 5.5 Hz), 6.36 (1 H, d, J = 7.5 Hz), 6.58 (1 H, s), 6.75 (1 H, t, J = 7.5 Hz), 6.89 (1 H, bs), 6.95 (1 H, t, J = 7.5 Hz), 7.41 (1 H, d, J = 7.5 Hz), 7.72 (1 H, bs), 8.31 (1 H, bs), 8.75 (1 H, bd, J = 7.5 Hz), 9.19 (1 H, bs); ^1H NMR (DMSO-d_6, 45 °C) δ 0.50 (3 H, t, J = 7 Hz), 0.91 (3 H, t, J = 7.1 Hz), 0.93 (1 H, dq, J = 14, 7 Hz), 1.09 (1 H, dq, J = 14, 7 Hz), 1.17 (1 H, td, J = 14, 4 Hz), 1.35–1.50 (2 H, m), 1.58 (1 H, dq, J = 14, 7.1

(8) The dimer **20** was recently obtained by Szantay, Jr. *et al.*, who made an extensive study of the NMR spectra in relation to conformation analysis. (a) Szantay, C., Jr.; Demeter, A.; Honty, K.; Kolonits, P.; Szantay, C. *Magn. Reson. Chem.* **1993**, *31*, 773. (b) Honty, K.; Szantay, C., Jr.; Kolonits, P.; Demeter, A.; Szantay, C. *Tetrahedron* **1993**, *49*, 10421.

Hz), 1.65–2.70 (7 H, m), 1.90 (1 H, dd, J = 14, 11.5 Hz), 2.02 (3 H, s), 2.05 (3 H, s), 2.13 (3 H, s), 2.34 (1 H, dq, J = 14, 7.1 Hz), 2.40 (1 H, td, J = 11.5, 3 Hz), 2.58 (1 H, bs), 2.85–3.08 (3 H, m), 3.23 (1 H, dd, J = 8.0, 6.1 Hz), 3.25–3.34 (1 H, m), 3.41 (1 H, dd, J = 15.5, 5 Hz), 3.75 (3 H, s), 3.85 (3 H, s), 4.09 (1 H, bs), 4.26–4.48 (3 H, m), 5.44 (1 H, dd, J = 11.5, 4.5 Hz), 5.48 (1 H, bd, J = 10 Hz), 5.62–5.71 (2 H, m), 5.68 (1 H, t, J = 5.5 Hz), 6.05 (1 H, t, J = 5.5 Hz), 6.17 (1 H, d, J = 5.5 Hz), 6.38 (1 H, d, J = 7.5 Hz), 6.71 (1 H, t, J = 7.5 Hz), 6.89 (1 H, t, J = 7.5 Hz), 6.99 (2 H, s), 7.36 (1 H, d, J = 7.5 Hz), 8.15 (2 H, s), 8.55 (1 H, d, J = 7.4 Hz), 9.49 (1 H, bs); ^{13}C NMR ($CDCl_3$, 40 °C) δ 8.2, 8.6, 17.8, 21.03 (double), 21.2, 21.3, 25.0, 29.4, 29.6, 35.7, 43.6, 45.2, 45.4, 46.2, 51.1, 51.7, 51.8, 51.9 (double), 52.0, 54.5, 56.8, 60.5, 63.9, 67.8, 71.5, 73.8, 80.8, 86.8, 95.2, 97.5, 105.6, 112.5, 118.3, 119.1, 119.9 (double), 121.3, 123.3, 127.9, 129.2, 130.7, 131.0, 137.4, 138.0, 140.2, 144.0, 149.1, 151.6, 155.6, 157.0, 169.2, 170.1, 170.2, 170.9, 171.2; FABMS m/z 1036 (MH^+), 643; high-resolution MS, FAB ionization, calcd for $C_{57}H_{66}N_9O_{10}$ 1036.4932, found 1036.4944.

Azadiene 17: ^{1}H NMR (DMSO-d_6, 100 °C) δ 0.49 (3 H, t, J = 7.5 Hz), 0.78 (1 H, dq, J = 14, 7 Hz), 0.91 (3 H, t, J = 8.1 Hz), 1.00 (1 H, dq, J = 14, 7 Hz), 1.16 (1 H, td, J = 14, 4 Hz), 1.35–1.43 (2 H, m), 1.50–1.79 (3 H, m), 1.89 (1 H, dd, J = 14, 11.5 Hz), 2.04–2.16 (2 H, m), 2.29 (1 H, dd, J = 14, 4.5 Hz), 2.30–2.45 (1 H, m), 2.48–2.68 (3 H, m), 2.58 (1 H, bs), 2.82–3.07 (3 H, m), 3.21–3.38 (3 H, m), 3.83 (3 H, s), 3.93 (3 H, s), 4.04 (1 H, bs), 5.54 (1 H, dd, J = 11.5, 4.5 Hz), 5.72 (1 H, bd, J = 11 Hz), 5.86 (1 H, dd, J = 11, 4.1 Hz), 6.33 (1 H, d, J = 8 Hz), 6.69 (1 H, t, J = 8 Hz), 6.91 (1 H, t, J = 8 Hz), 7.09 (1 H, d, J = 2 Hz), 7.17 (1 H, s), 7.38 (1 H, d, J = 8 Hz), 7.39 (1 H, s); ^{13}C NMR (DMSO-d_6, 45 °C) δ 7.38 (double), 16.8, 20.4, 24.3, 28.3, 30.1, 34.5, 35.8, 44.28 (double), 44.3, 49.9, 50.3, 50.4, 51.7, 52.1, 56.4, 58.8, 62.5, 65.9, 105.0, 105.2, 111.1, 117.6, 118.8, 119.8 (double), 122.0, 125.8, 127.5, 128.5, 129.8, 134.5, 136.0, 137.2, 154.6 (double), 156.9, 163.9, 180.1; high-resolution MS, FAB ionization, calcd for $C_{41}H_{47}N_4O_3$ 643.3664, found 643.3671.

Preparation of Compound 19. Photoirradiation of a solution of 40 mg of **12** (0.060 mmol) in methanol/water 6:1 (6 mL) containing Rose Bengal (2.10^{-5} M) in the presence of sodium thiosulfate (20 mg, 0.127 mmol) and 2 N NaOH (20 μL), with an OSRAM Concentra 350-W wire lamp (35°) at 20 °C (water cooling) with oxygen gas bubbled through the solution, gave, after FC [5%(1% NH_3–MeOH)/EtOAc–EtOH 7.5:2.5] 35 mg (86%) of **18**. The compound was immediately dissolved in 3 mL of CH_3CN. To the stirred solution (acetate buffer, pH 4.2) were added 20 mL (0.25 mmol) of 37% aqueous formaldehyde and 10 mg (0.16 mmol) of $NaCNBH_3$ at room temperature. After 10 min HCl (dilute) was added, the reaction mixture was poured into water, basified (NH_4OH), extracted with CH_2Cl_2, and submitted to FC (CH_2Cl_2/EtOH 49:1) to give **19** (25 mg, 62%): R_f ($CHCl_3$/EtOAc/NH_3 90:10:0.1) = 0.15 (CAS: pink). $[\alpha]^{20}_D$ = +13.1 (c = 3.8, $CHCl_3$) (lit.[8b] $[\alpha]^{20}_D$ = +24.2, c = 1, $CHCl_3$); CD (MeOH) λ ($\Delta\epsilon$) 208 (−18.2), 221 (+6.5), 257 (+10.1); ^{1}H NMR ($CDCl_3$, 50 °C) δ −0.10 (3 H, t, J = 7 Hz), 0.68 (1 H, dq, J = 14, 7 Hz), 0.89 (3 H, t, J = 7.5 Hz), 1.03–1.29 (2 H, m), 1.30–1.92 (6 H, m), 1.99–2.30 (3 H, m), 2.35–2.57 (5 H, m), 2.58–2.77 (2 H, m), 2.79 (3 H, m), 2.89–3.10 (1 H, m), 3.21–3.45 (4 H, m), 3.68 (1 H, s), 3.83 (3 H, s), 3.90 (3 H, bs), 3.98 (1 H, bs), 4.09 (1 H, s), 5.54 (1 H, dd, J = 4.5, 11.25 Hz), 5.62 (1 H, bd, J = 10.5 Hz), 5.70 (1 H, dd, J = 10.5, 4.5 Hz), 6.18 (1 H, s), 6.62 (1 H, d, J = 7.5 Hz), 6.64 (1 H, s), 6.83 (1 H, t, J = 7.5 Hz), 6.97 (1 H, t, J = 7.5 Hz), 7.40 (1 H, d, J = 7.5 Hz), 9.05 (1 H, bs); ^{13}C NMR ($CDCl_3$) δ 7.3, 8.2, 17.7, 21.0, 24.7, 29.6, 33.3, 35.8, 39.4, 43.0, 43.7, 45.3, 45.6, 48.7, 51.0, 51.4, 51.7, 52.9, 53.9, 56.6, 60.5, 67.8, 74.5, 81.7, 83.6, 93.5, 105.1, 112.5, 118.4, 120.0, 121.4, 121.9, 122.2, 124.2, 125.8, 129.0, 131.1, 133.8, 137.4, 153.5, 158.1, 174.1; FABMS m/z 693 (MH^+); high-resolution MS, FAB ionization, calcd for $C_{42}H_{53}N_4O_5$ 693.4024, found 643.4031.

Preparation of Compound 20. **19** (26 mg, 0.038 mmol) was dissolved in Ac_2O (3 mL) in the presence of anhydrous NaOAc (20 mg). After 24 h at room temperature the mixture was poured into 5% $NaHCO_3$ solution, basified (NH_4OH), extracted with CH_2Cl_2, and purified by FC (CH_2Cl_2/EtOH 98:2) to give **20** (25 mg, 89%): R_f (CH_2Cl_2/EtOAc/NH_3 90:10:0.1) = 0.26 (CAS: pink); $[\alpha]^{20}_D$ = +87.2 (c = 2, $CHCl_3$) (lit.[8b] $[\alpha]^{20}_D$ = +94.3, c = 1, $CHCl_3$); CD (MeOH) λ ($\Delta\epsilon$) 211 (−24.4), 221 (+7.7), 254 (+11.5); ^{1}H NMR ($CDCl_3$, 50 °C) δ −0.35 (3 H, t, J = 7 Hz), 0.88 1 H, dq, J = 14, 7 Hz), 0.81–0.99 (1 H, m), 1.12 (1 H, td, J = 14, 4.5 Hz), 1.19–1.88 (7 H, m), 2.03 (3 H, s), 2.05–2.31 (3 H, m), 2.35–2.52 (3 H, m), 2.46 (1 H, bs), 2.52–2.64 (1 H, m), 2.68 (1 H, bd, J = 15 Hz), 2.73 (3 H, s), 2.93–3.09 (1 H, m), 3.25–3.39 (4 H, m), 3.70 (1 H, s), 3.78 (3 H, s), 3.91 (3 H, bs), 4.06 (1 H, s), 5.15 (1 H, d, J = 10.5 Hz), 5.53 (1 H, dd, J = 4.5, 11.5 Hz), 5.70 (1 H, dd, J = 10.5, 4.5 Hz), 6.18 (1 H, s), 6.67 (1 H, s), 6.68 (1 H, d, J = 7.5 Hz), 6.84 (1 H, t, J = 7.5 Hz), 6.95 (1 H, t, J = 7.5 Hz), 7.38 (1 H, d, J = 7.5 Hz), 9.32 (1 H, bs); ^{13}C NMR ($CDCl_3$) δ 7.2, 8.0, 17.7, 21.0, 21.5, 24.8, 29.5, 31.4, 35.7, 38.7, 43.4, 43.7, 45.1 (double), 48.4, 51.2, 51.4, 51.7, 52.5, 53.8, 56.5, 60.3, 66.5, 76.8, 80.4, 83.9, 93.7, 104.9, 112.3, 118.0, 119.7, 121.5 (double), 122.3, 124.1, 125.6, 128.9, 131.2, 133.9, 137.3, 153.3, 158.0, 170.9, 172.3; FABMS m/z 735 (MH^+); high-resolution MS, FAB ionization, calcd for $C_{44}H_{55}N_4O_6$ 735.4121, found 735.4131.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of compounds (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.