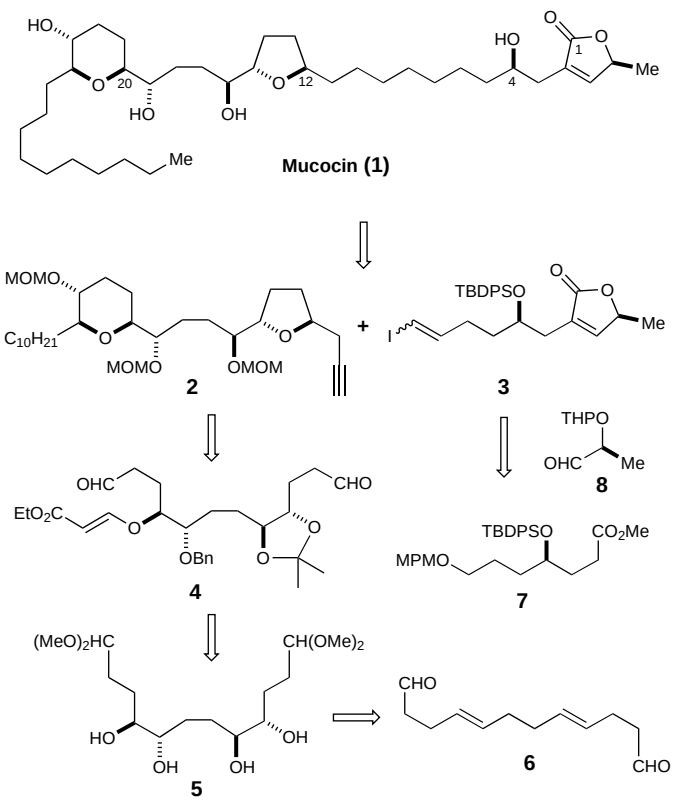
Stereoselective Total Synthesis of Mucocin, an Antitumor Agent**

Shunya Takahashi,* Akemi Kubota, and Tadashi Nakata*

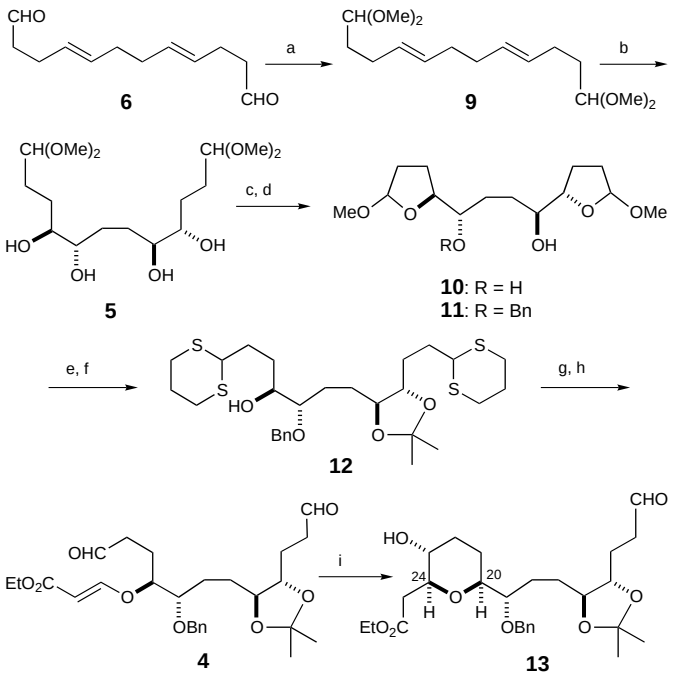
Mucocin (**1**) is a representative annonaceous acetogenin[1] having a tetrahydropyran (THP) and a tetrahydrofuran (THF) ring.[2] This novel type of acetogenin is known to show remarkable inhibitory activities against A-549 (lung cancer) and PACA-2 (pancreatic cancer) solid tumor lines with a potency of more than 10000 times that of adriamycin. The powerful antitumor activity and the unique structure of **1** have consequently stimulated synthetic efforts,[3] and quite recently three research groups (including ours) have succeeded in its total synthesis.[4] Recently, we developed a highly efficient method for the synthesis of tetrahydropyrans and oxepanes based on a SmI_2-induced[5] reductive cyclization of β-alkoxy acrylate containing a formyl group.[6] We thus planned the total synthesis of **1** to demonstrate the utility of the method and now describe here an efficient total synthesis of **1** based on the SmI_2-induced reductive cyclization as a key step.

Our synthetic strategy directed toward **1** was based on a convergent process which involves a Pd-catalyzed cross-coupling reaction of the THP/THF segment **2** and a vinyl iodide **3** as illustrated in Scheme 1. The THP ring in the central core **2** could be constructed by the SmI_2-induced reductive cyclization, whereas the *trans*-THF ring should be synthesized by oxidative cyclization[7] of a homoallyl alcohol. This retrosynthetic approach can revert **2** back to the β-alkoxy acrylate **4** having two formyl groups, and then to a tetraol **5**. Therefore, dialdehyde **6** with the requisite carbon backbone was selected as the starting material. In this scenario, whether the C-12 formyl group in the reductive cyclization of **4** could be retained or not and the development of an efficient method for desymmetrization of C_2-symmetric **5** were problems to be solved. On the other hand, the γ-lactone **3** should be synthesized by aldol condensation of chiral ester **7** and aldehyde **8**.[8]

Synthesis began with acetalization of the dialdehyde **6**[4a] to afford the bis(dimethyl acetal) **9** in 99% yield (Scheme 2). The Sharpless asymmetric dihydroxylation[9] of **9** gave the C_2-symmetric tetraol **5**[10] in almost quantitative yield. To achieve efficient desymmetrization **5** was transformed into a bisTHF derivative **10** by treatment with CSA in methanol at −5 °C. Formation of THP derivatives was observed when the acetalization was conducted at RT. Benzylidenation of **10** followed by reduction with DIBAH gave a monobenzyl ether



Scheme 1. Structure of mucocin (**1**) and its retrosynthetic analysis.



Scheme 2. Synthesis of the THP derivative **13**: a) $HC(OMe)_3$ (6.0 equiv), CSA (0.02 equiv), MeOH, RT, 1 h, 99%; b) AD-mix α, $MeSO_2NH_2$, H_2O/*t*BuOH (1/1), 0 °C, 24 h; c) CSA (0.83 equiv), MeOH, −5 °C, 3 h, 89% (2 steps); d) BnBr (1.1 equiv), NaH (1.1 equiv), THF, −15 °C→RT, 16 h, 93%; e) 1,3-propanedithiol (6.0 equiv), $Zn(OTf)_2$ (1.5 equiv), $(CH_2Cl)_2$, 50 °C, 2 h; f) $Me_2C(OMe)_2$ (3.0 equiv), CSA (0.03 equiv), CH_2Cl_2, RT, 1 h, 86% (2 steps); g) ethyl propiolate (10 equiv), *N*-methylmorpholine (5.0 equiv), CH_2Cl_2, RT, 5 h; h) CH_3I (8.0 equiv), $NaHCO_3$ (12 equiv), $MeCN/H_2O$ (10/1), RT, 35 h, 73% (2 steps); i) SmI_2 (3.0 equiv), MeOH (4.4 equiv), THF, −5 °C, 15 min, 87%. CSA = 10-camphorsulfonic acid, Bn = benzyl, Tf = trifluoromethanesulfonyl.

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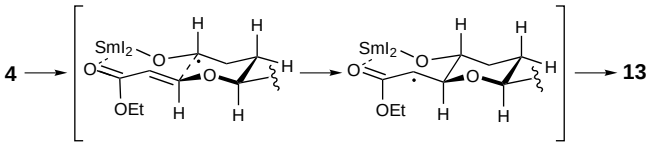
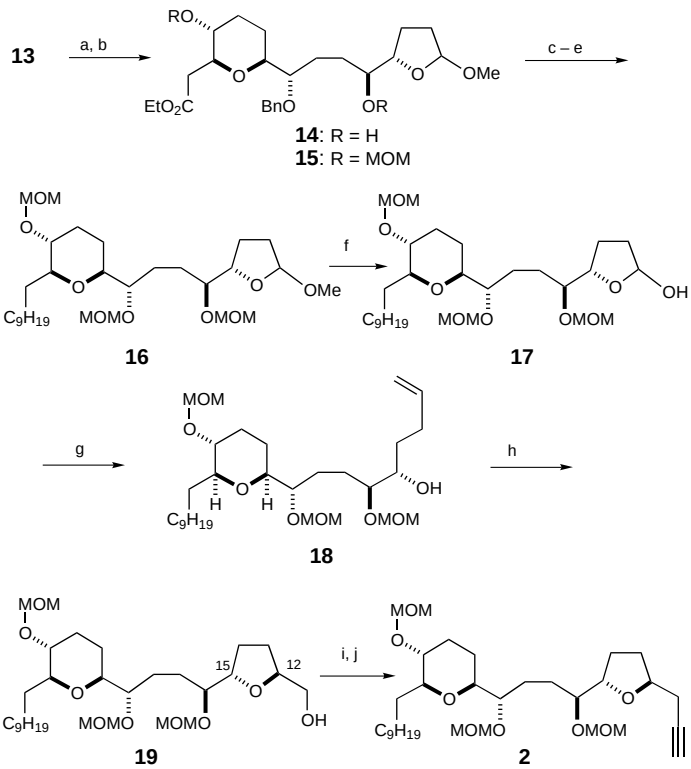
11 in 61% yield. After several attempts, a more efficient method for preparing **11** was found. Direct benzylation of **10** with BnBr (1.1 equiv) and NaH (1.1 equiv) in THF at −15°C afforded **11** in 93% yield. At this stage, exchange of the dimethylacetal into the corresponding dithioacetal was necessary for the latter step. Transacetalization[11] of **11** was achieved by using 6.0 equivalents of ethanedithiol in the presence of 1.5 equivalents of $Zn(OTf)_2$[12] in 1,2-dichloroethane at 50°C to give the desired bis(thioacetal) **12** in 86% yield after isopropylidenation. Hetero-Michael addition of **12** to ethyl propiolate followed by dethioacetalization (CH_3I, $NaHCO_3$, aq CH_3CN) afforded the key intermediate **4** in 73% yield. SmI_2-induced reductive cyclization of **4** was effected by treatment with 3.0 equivalents of SmI_2 in the presence of methanol (4.4 equiv) in THF at −5°C to give a 20,24-*syn*-23,24-*trans*-THP derivative **13**[13,14] in 87% yield. The stereochemistry of the THP ring system was established by NMR analysis: $J_{23,24} = 9.9$ Hz and an NOE effect was observed between H_{20} and H_{24}. The high stereoselectivity could be explained by the transition state involving a cyclic chelate as shown in Scheme 3. Very interestingly, the formyl group was retained during this reaction. However, a prolonged reaction time or the use of a large amount of SmI_2 caused destruction of this functional group and afforded higher polar substances such as reduction or pinacol-type coupling products.



Scheme 3. SmI_2-induced reductive cyclization of **4**.

As several attempts for the construction of the THF ring prior to completion of the C_{10} side chain gave unsatisfactory results, the formyl group was protected as an internal acetal with trimethyl orthoformate/CSA to give **14** in 93% yield (Scheme 4). To enable subsequent chain elongation, the two hydroxy groups were protected as methoxymethyl (MOM) ethers to afford **15** (91% yield). Installation of the C_{10} unit on **15** was conducted in three steps: 1) DIBAH reduction of the ester carbonyl group, 2) Wittig reaction ($Ph_3P^+C_8H_{17}Br^-$, *n*BuLi), and 3) hydrogenation. After methoxymethylation, exposure of the thus obtained **16** to mild acidic conditions led to selective hydrolysis of the methyl acetal to give **17**. The resulting hemiacetal **17** was subjected to olefination with $Ph_3P{=}CH_2$ to furnish **18** in 85% yield. The homoallyl alcohol **18** was oxidized with *t*BuO_2H in the presence of $[Co(modp)_2]$ in an oxygen atmosphere to give rise to 5-*exo* cyclization[7a] and afford alcohol **19** with a 12,15-*trans* THF ring system. The structure of **19** was established by comparison with an authentic sample, which had been previously synthesized by us.[4b,f] Transformation of **19** into the "left-half" segment **2**[15] proceeded in high overall yield (90%) as follows: 1) triflation of the primary hydroxy group, 2) a coupling reaction with lithium trimethylsilylacetylide, and 3) desilylation with potassium carbonate.



Scheme 4. Synthesis of the THP/THF segment **2**: a) $HC(OMe)_3$ (2.0 equiv), CSA (0.2 equiv), MeOH, 0°C, 30 h, 93%; b) MOMBr (4.0 equiv), *i*Pr_2NEt (8.0 equiv), $(CH_2Cl)_2$, 0°C, 0.5 h; →40°C, 7.5 h, 91%; c) DIBAH (1.0 equiv), CH_2Cl_2, −78°C, 1 h and then $C_8H_{17}PPh_3Br$ (2.7 equiv), *n*BuLi (2.5 equiv), THF, −15°C, 1 h, 91%; d) 10% Pd/C, H_2 (1 bar), MeOH, RT, 24 h; e) MOMBr (4.0 equiv), *i*Pr_2NEt (8.0 equiv), $(CH_2Cl)_2$, 0°C, 0.5 h; →60°C, 1 h, 95% (2 steps); f) AcOH/H_2O (4/1), RT, 2 h; →40°C, 1 h, 77%; g) CH_3PPh_3I (6.0 equiv), NaHMDS (5.0 equiv), THF, −15°C, 1 h; →RT, 1 h, 85%; h) $[Co(modp)_2]$ (0.04 equiv), O_2, *t*BuO_2H (2.0 equiv), 4Å-MS, *i*PrOH, 50°C, 5 h, 78%; i) Tf_2O (1.1 equiv), 2,6-lutidine (2.3 equiv), CH_2Cl_2, −78°C, 30 min; j) TMSC≡C−Li (8.0 equiv), HMPA (15 equiv), THF, −78°C, 40 min, and then K_2CO_3 (1.1 equiv) MeOH, RT, 17 h, 90% (2 steps). MOM = methoxymethyl, DIBAH = diisobutylaluminium hydride, NaHMDS = sodium hexamethyldisilazide, $[Co(modp)_2]$ = bis(1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentanedionato)cobalt(II), Tf_2O = trifluoromethanesulfonic anhydride, HMPA = hexamethylphosphoric triamide, TMS = trimthylsilyl.

Synthesis of terminal butenolide unit **3** began with asymmetric allylation[16] of **20** to give **21** (> 98% *ee*) in 76% yield (Scheme 5). After silylation of **21**, hydroboration followed by Jones oxidation and methylation gave methyl ester **7** in 58% yield. Aldol reaction of the lithium enolate prepared from **7** with the chiral aldehyde **8**[8a] gave a mixture of coupled products, which was, without purification, submitted sequentially to lactonization, mesylation, and β-elimination reaction, giving butenolide **22** in 67% overall yield. After deprotection of the MPM group, the resulting alcohol was oxidized to an aldehyde, which was then transformed into the corresponding vinyl iodide **3** according to the method of Takai et al.[17]

The complete carbon skeleton of **1** was assembled by joining **2** and **3** under Hoye's conditions[18] to give **23** in 84% yield (Scheme 6). Finally, regioselective reduction of **23** using Wilkinson's catalyst gave **24** in which all the protecting groups were removed to afford mucocin (**1**). The spectral data of **1** were indistinguishable from those of the natural product.

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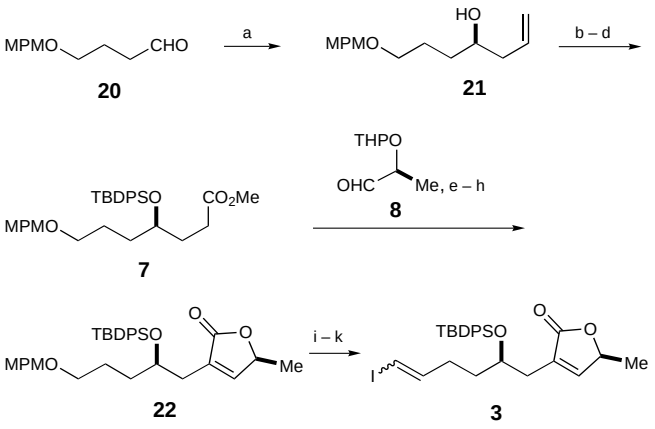
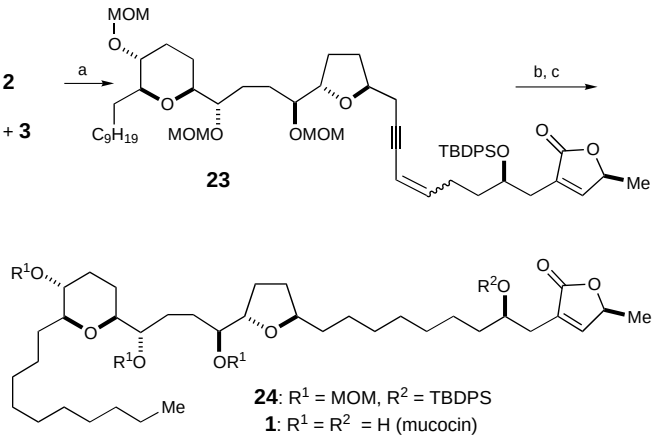


Scheme 5. Synthesis of the lactone **3**: a) (*S*)-binol (0.2 equiv), $Ti(OiPr)_4$, (0.2 equiv), allyltributyltin (1.1 equiv), −78 °C, 1 h; →−25 °C, 5 d, 76 %; b) TBDPSCl (1.1 equiv), imidazole (2.5 equiv), DMF, RT, 6 h; c) BH_3·THF (1.5 equiv), THF, 0 °C→RT, 24 h and then NaOH, 30 % H_2O_2, 0 °C→RT, 1 h; d) Jones reagent, acetone, 0 °C, 30 min and then CH_2N_2, diethyl ether, 0 °C, 30 min, 58 % (3 steps); e) LDA (1.6 equiv), **8** (2.0 equiv), THF, −78 °C, 1 h; f) CSA (1.1 equiv), MeOH/H_2O (9/1), RT, 4 h; g) MsCl (3.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, −10 °C, 1.5 h; h) DBU (2.0 equiv), CH_2Cl_2, −10 °C, 30 min, 67 % (4 steps); i) DDQ (2.0 equiv), CH_2Cl_2/phosphate buffer (pH 7.4, 10/1), 0 °C, 2 h; j) $(COCl)_2$ (3.0 equiv), DMSO (6.0 equiv), CH_2Cl_2, −78 °C, 30 min, and then Et_3N (12 equiv), −78 °C→RT, 2 h; k) $CrCl_2$ (6.8 equiv), CHI_3 (2.3 equiv), THF, 0 °C→RT, 4 h, 83 % (3 steps). binol = bi-2-naphthol, TBDPS = *tert*-butyldiphenylsilyl, LDA = lithium diisopropylamide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, Ms = methanesulfonyl, DMSO = dimethylsulfoxide.



Scheme 6. Total synthesis of mucocin (**1**): a) $[PdCl_2(Ph_3P)_2]$ (0.1 equiv), CuI (0.3 equiv), Et_3N, 0 °C→RT, 1 h, 84 %; b) $(Ph_3P)_3RhCl$, H_2, C_6H_6/EtOH (1/1), RT, 48 h, 85 %; c) 10 % HCl/MeOH, CH_2Cl_2, 0 °C→RT, 95 %.

In summary, we have succeeded in an efficient synthesis of **1** through desymmetrization of **5**, an SmI_2-induced radical cyclization reaction of **4**, and oxidative cyclization of **18** as the key steps. This procedure would also be useful for the preparation of a variety of analogues of **1**.

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[10] The enantiopurity (> 97 % *ee*) was determined by the ^1H NMR analyses of the corresponding MTPA esters of **12**. Furthermore, the optical purity could be improved by recrystallization of **5** from hexane/ethyl acetate to give an optically pure **5**, m.p. 82–82.5 °C (*n*-hexane/ethyl acetate), $[\alpha]_D^{26} = -27.9°$ ($c = 0.84$, $CHCl_3$).

[11] The thioacetalization of **11** with ethanedithiol and other Lewis acids such as BF_3·Et_2O and $TiCl_4$ furnished the corresponding bis(thioacetal) in a low yield because of the unstability of the benzyl ether moiety under the conditions employed.

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[13] Data for **13**: $[\alpha]_D^{26} = -41.1°$ ($c = 1.09$ in $CHCl_3$); ^1H NMR (400 MHz, C_6D_6): $\delta = 9.33$ (t, $J = 1.5$ Hz, 1H), 7.40–7.07 (m, 5H), 4.55 (dd, $J = 11.7$, 11.7 Hz, 2H), 4.00 (m, 2H), 3.70 (ddd, $J = 8.8$, 8.8, 4.3 Hz, 1H), 3.49, (m, 2H), 3.44 (ddd, $J = 8.3$, 5.4, 2.5 Hz, 1H), 3.36 (m, 1H), 3.10 (ddd, $J = 9.8$, 8.8, 4.3 Hz, 1H), 2.94 (dd, $J = 15.1$, 3.4 Hz, 1H), 2.53 (dd, $J = 15.1$, 8.8 Hz, 1H), 2.20–2.02 (m, 2H), 1.85–1.37 (m, 2H), 1.70–1.59 (m, 8H), 1.35 (s, 3H), 1.34 (s, 3H), 0.95 ppm (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 200.4$, 171.9, 139.8, 128.5, 128.2, 128.0, 127.9, 127.8, 108.2, 80.9, 80.7, 80.3, 79.7, 73.1, 72.8, 70.0, 60.4, 40.5, 38.6, 33.1, 29.0, 27.6, 27.4, 27.2, 26.4, 25.3, 14.2 ppm; IR (neat): $\tilde{\nu} = 3447$, 2984, 2936, 2868, 1732, 1456, 1379, 1371, 1348, 1302, 1248, 1221, 1180, 1159, 1092, 1029, 950, 921, 887, 748, 700, 683 cm^{-1}; HRMS calcd for $C_{27}H_{40}O_8Na$ $[M+Na]^+$: m/z 515.2621, found: 515.2621.

[14] The numbering of mucocin was adopted.

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[15] Data for **2**: $[\alpha]_D^{26} = -61.4°$ ($c = 1.04$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.81–4.59$ (m, 6H), 4.10, (m, 2H), 3.47 (m, 2H), 3.39 (s, 3H), 3.38 (s, 3H), 3.36 (s, 3H), 3.33 (m, 1H), 3.21 (m, 1H), 3.10 (m, 1H), 2.47 (ddd, $J = 4.9, 2.9, 1.7$ Hz, 1H), 2.35 (ddd, $J = 7.3, 2.4, 1.7$ Hz, 1H), 2.24–1.22 (m, 12H), 1.25 (br s, 18H), 0.88 ppm (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 96.9, 96.8, 95.3, 81.6, 81.0, 80.9, 79.7, 79.5, 79.1, 77.1, 75.8, 69.6, 55.7, 55.5, 32.1, 31.9, 31.3, 30.1, 29.7, 29.6, 29.3, 28.2, 26.9, 26.6, 26.3, 25.5, 25.3, 22.7, 14.1$ ppm; IR (neat): $\tilde{\nu} =$ 3312, 3273, 2926, 2855, 2823, 1465, 1457, 1396, 1375, 1363, 1340, 1293, 1214, 1150, 1103, 1075, 1036, 918 cm^{-1}; HRMS calcd for $C_{32}H_{58}O_8Na$ $[M+Na]^+$: m/z 593.4029, found: m/z 593.4037.

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Structure of a Drug-Induced DNA T-Bulge: Implications for DNA Frameshift Mutations**

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The biological function of nucleic acids is recognized to embrace a wide variety of structural topologies whose stability, conformation, and dynamics may be strongly influenced by the interaction of drug molecules. Single-base bulges, arising from slippage of DNA strands, particularly in homopolymeric tracts of DNA, can result in mutation "hotspots" due to DNA strand misalignment during replication.[1] Addition or deletion mutations at these sites can arise according to whether the extra base stacks within the DNA helix or is displaced into solution. Unpaired pyrimidines have been shown to adopt either an intrahelical or extrahelical conformation depending on flanking sequence, while purines preferentially stack within the helix.[2] The interaction of drug molecules at bulge sites has been of considerable interest since binding close to these sites has the potential to stabilize and increase the lifetime of the bulge state and its susceptibility to frameshift mutations. It has already been demonstrated that ethidium bromide and 9-aminoacridine have increased affinity for sites on duplex DNA carrying an extrahelical cytosine,[3] while neocarzinostatin induces highly efficient site-specific strand cleavage at bulge sites in folded single-stranded DNA.[4] In other cases, chemical modification (base alkylation) of DNA and RNA by drugs appears to occur primarily near bulge sites because of better binding site access,[5] while selective drug binding to RNA bulges has been shown to inhibit protein–RNA recognition.[6] In general, detailed structural information is lacking, although a number of low-resolution NMR studies of bulge recognition by simple DNA intercalators have been described.[3]

The anthracycline antibiotic nogalamycin (Figure 1) has a high sequence specificity for 5′-CG or 5′-TG sites with its bound orientation dictated by the requirement for a guanine (G) base on the 3′-side of the intercalation site.[7] Nogalamycin

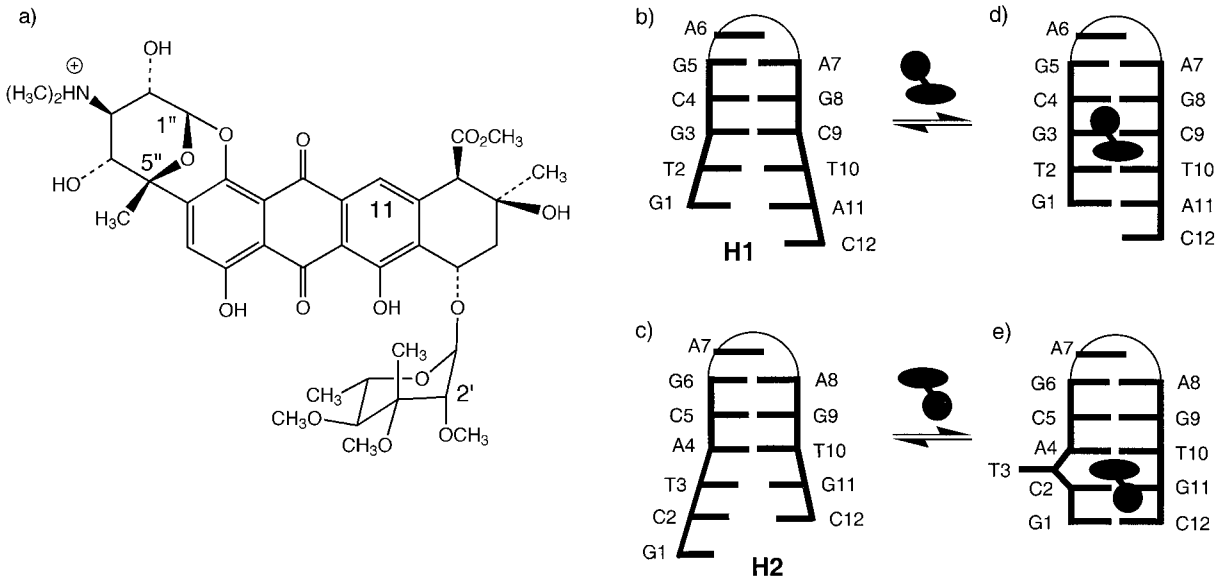

Figure 1. a) Structure of nogalamycin, and oligonucleotide sequences **H1** (b) and **H2** (c) in their proposed folded conformation with frayed ends. Conformations and base-pair alignment adopted in the bound stated with nogalamycin intercalated at the 5′-TpG step ((d) and (e)).

threads its aglycon chromophore through the DNA helix and positions bulky sugar residues in both grooves simultaneously. Interactions in the major groove involving the two hydroxy groups on the bicycloaminoglucose sugar appear to account for the drugs orientational specificity through hydrogen bonding to guanine. Thus, binding to the 5′-TG site results in a unique binding orientation dictated by the G base. With

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