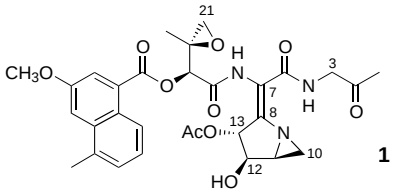
[9] C. Kloc, P. Simpkins, T. Siegrist, R. A. Laudise, *J. Cryst. Growth* **1997**, *182*, 416.
[10] D. Holmes, S.Kumaraswamy, A. J. Matzger, K. P. C. Vollhardt, *Chem. Eur. J.* **1999**, *5*, 3399.
[11] S. Berg, A. Markelz, G. A. Thomas, J. H. Schön, C. Kloc, P. B. Littlewood, B. Batlogg, *Phys. Rev. B*, in press.
[12] N. Karl, J. Marktanner, R. Stehle, W. Warta, *Synth. Met.* **1991**, *41 – 43*, 2473.
[13] W. Warta, N. Karl, *Phys. Rev. A* **1985**, *36*, 136.
[14] J. H. Schön, C. Kloc, E. Bucher, B. Batlogg, *Nature* **2000**, *403*, 408.
[15] J. H. Schön, S. Berg, C Kloc, B. Batlogg, *Science* **2000**, *287*, 1022.
[16] E. J. Gabe, Y. Le Page, J.-P. Charland, F. L. Lee, P. S. White, *J. Appl. Cryst.* **1989**, *22*, 384.
[17] R. C. Haddon, A. P. Ramirez, S. H. Glarum, *Adv. Mater.* **1994**, *6*, 316; M. P. Andrews, A. W. Cordes, D. C. Douglass, R. M. Fleming, S. H. Glarum, R. C. Haddon, P. Marsh, R. T. Oakley, T. T. M. Palstra, L. F. Schneemeyer, G. W. Trucks, R. Tycko, J. V. Waszczak, K. M. Young, N. M. Zimmerman, *J. Am. Chem. Soc.* **1991**, *113*, 3559.

Total Synthesis of Azinomycin A**

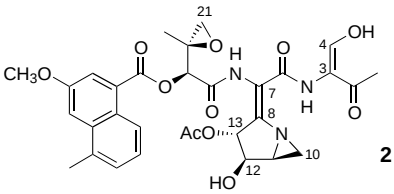
Robert S. Coleman,* Jing Li, and Antonio Navarro

The azinomycins A and B (**1** and **2**; Ac = acetyl) are a functionally complex family of antitumor agents isolated from fermentation broths of *Streptomyces griseofuscus*.[1] These natural products are of synthetic interest because of the unprecedented and densely functionalized aziridino[1,2-*a*]pyrrolidine ring system; additional attention has been focused on these agents because of their potential as lead compounds for the design of novel chemotherapeutic agents.[2] To date, and despite considerable effort from a number of laboratories,[3] the total synthesis of these challenging targets has not been achieved. Herein, we describe an asymmetric total synthesis of azinomycin A (**1**) that represents the first entry into this family of natural products.

The azinomycins exhibit cytotoxity against at sub-microgram per milliliter concentrations, but, more important, these agents show antitumor activity in mouse models that is comparable to that of mitomycin C.[4] Unfortunately, a detailed evaluation of the scope of the biological activity of the native agents has been prevented by the poor availability and significant instability of the agents, factors that have similarly impeded synthetic efforts.



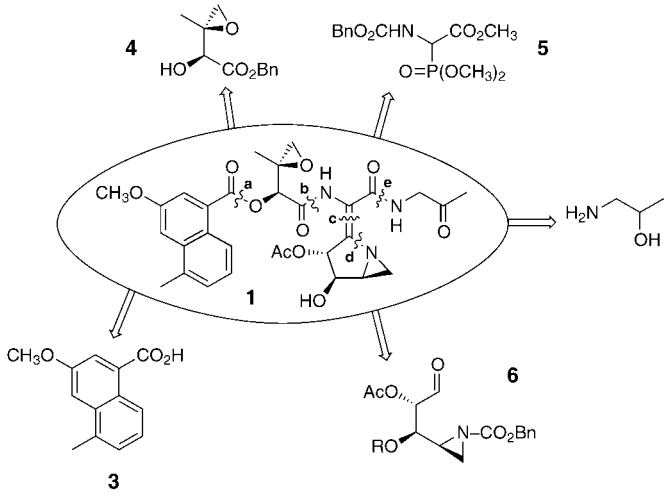
1



2

The azinomycins are one of a small set of molecules that interact with DNA in the major groove.[5] Azinomycin B (**2**) forms a covalent interstrand cross-link[6] between suitably disposed purine bases in the duplex sequence 5′-d(PuNPy)-3′, but the structural origin of the sequence selectivity and binding affinity are incompletely defined. We have recently described a computationally based model[7] that explains the experimentally observed cross-linking of azinomycin B (**2**).[8]

We now report the asymmetric total synthesis of azinomycin A (**1**) that is based on a convergent and modular synthetic plan (Scheme 1). By the five disconnections at ester, amide,



Scheme 1. Modular and convergent synthetic strategy. Bn = benzyl.

olefin and C–N bonds, a – e, we arrive retrosynthetically at five simple fragments: 1) naphthoic acid **3**,[2q] 2) epoxyalcohol **4**,[9] 3) glycine phosphonate **5**,[10] 4) aziridine carbaldehyde **6**,[11, 12] and 5) 1-amino-2-propanol. The ordering of steps a – e was not predetermined, although we had established the necessity of introducing the reactive azabicyclic system (bond d) as the penultimate step. The most relevant variable was the timing of the C7 – C8 dehydroamino acid olefination of aldehyde **6** (bond c) with respect to amide bond formations b and e. In other words, would the dehydroamino acid be introduced before or after elaboration of the amide/ester backbone?

[*] Prof. Dr. R. S. Coleman, Dr. J. Li, Dr. A. Navarro
Department of Chemistry
The Ohio State University
100 West 18th Avenue, Columbus, OH 43210-1185 (USA)
Fax: (+1) 614-292-4647
E-mail: coleman@chemistry.ohio-state.edu

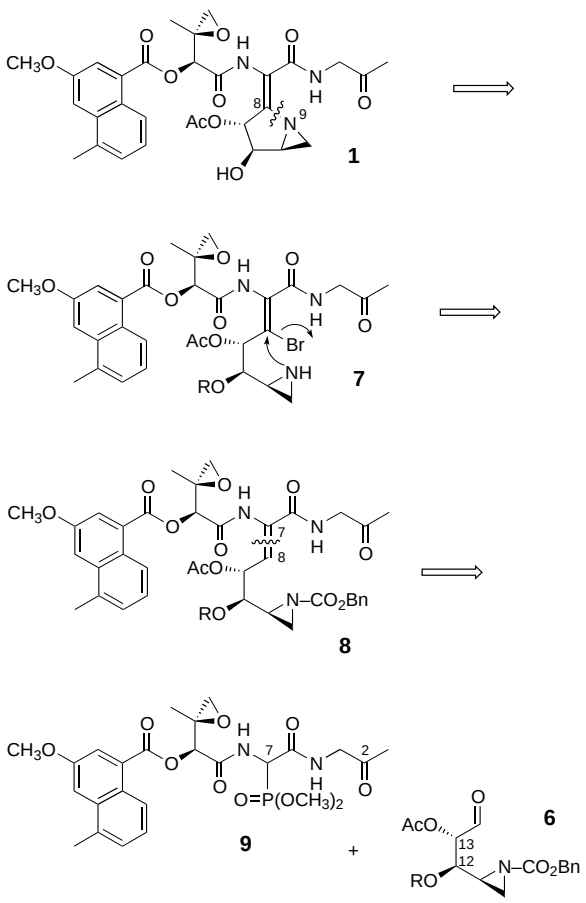
[**] This work was supported by a grant from the National Cancer Institute (NIH CA-65875). A.N. was the recipient of a fellowship from the Spanish Ministerio de Educacion (EX0052672518). R.S.C. was an Alfred P. Sloan Foundation Research Fellow (1995 – 1998).

  1433-7851/01/4009-1736 $ 17.50+.50/0

Olefination of aldehydes such as **6** with glycine-based phosphonates is problematic due to the proximal C13 acetyl group.[13] However, having the acetate installed prior to olefination avoided problematic protecting group manipulations on advanced dehydroamino acid systems.[13b] We viewed the strategy of bringing the "top half" of the molecule into the olefination reaction intact (bond c) as more advantageous than the complementary strategy of building the C7–C8 dehydroamino acid double bond before incorporating the left (bond b) and right portions (bond e), since this strategy minimized transformations on systems bearing the reactive aziridine ring. In the end, **1** was synthesized by formation of bonds a and e first, followed by bonds b, c, and finally d (Scheme 1).

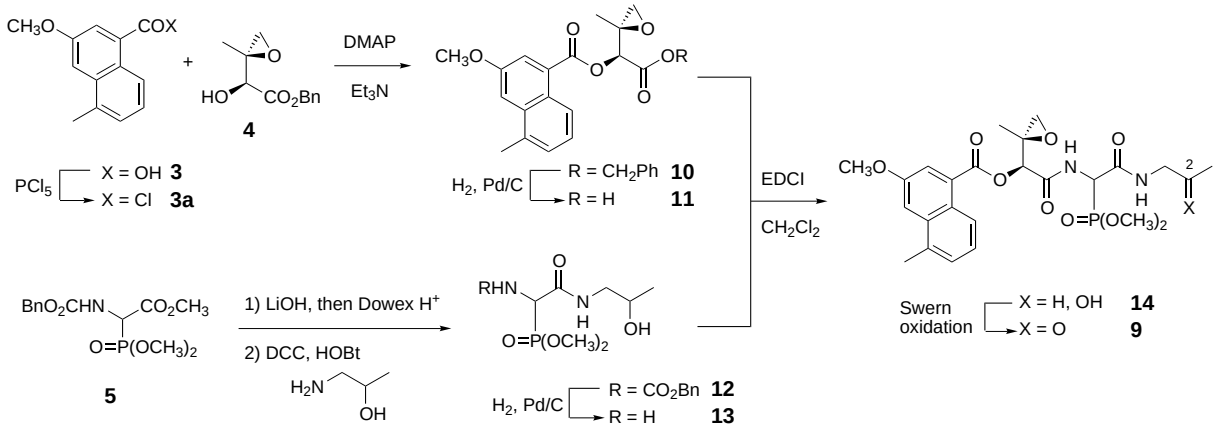
The most important step requiring stereochemical control is the intramolecular addition–elimination reaction sequence of **7** to form the azabicyclic ring system of **1** (Scheme 2). Stereocontrol in the bromination of **8** is critical to constructing the *E*-olefin of **1**, because the addition–elimination reaction sequence of **7** is stereospecific.[13] The C7–C8 double bond of **8** was formed by an olefination reaction[14] between aldehyde **6**[11] and the phosphonate "top piece" **9**. This synthetic strategy is direct, but it relies on a complex, high-risk olefination reaction between **6** and **9** as the convergent step.

Phosphonate **9** was constructed in a convergent fashion by a series of ester and amide bond formations (Scheme 3). Naphthoic acid **3** (X = OH), most effectively prepared according to Shibuya and co-workers,[2q] was activated as the acid chloride **3a** (X = Cl; PCl_5, Et_2O, reflux, 2 h) and coupled under standard conditions (DMAP, Et_3N, CH_2Cl_2, 0 °C, 4 h) with enantiomerically pure epoxyalcohol **4**, prepared by Sharpless kinetic resolution,[9] to afford **10** (88%). Hydrogenolysis of the benzyl ester of **10** (1 atm H_2, 10% Pd/C, MeOH, 2 h, 25 °C) afforded unstable epoxyacid **11** (>99%), which was coupled directly with the aminophosphonate **13**. This, in turn, was prepared from glycine phosphonate **5** by saponification (LiOH, THF/MeOH/H_2O, 25 °C, 30 min) to afford the crude acid in quantitative yield after acidification with Dowex H^+. The acid was coupled with (±)-1-amino-2-propanol using dicyclohexylcarbodiimide (HOBt, CH_2Cl_2, 0–25 °C, 24 h) to afford **12** (86%). Hydrogenolysis of the benzyl carbamate of **12** (1 atm H_2, 10% Pd/C, MeOH, 25 °C, 2 h) afforded amine **13** (>99%). Coupling of acid **11** and amine **13** using ethyl(3-dimethylaminopropyl)carbodiimide (HOBt, CH_2Cl_2, 0–25 °C, 9 h) afforded the fully elaborated "top half" phosphonate **14** in good yield (79%).



Scheme 2. Retrosynthetic analysis of the azabicyclic system.

At this point, we dealt with the issue of the C2 oxidation state by synthesizing ketone **9** by Swern oxidation of alcohol **14** (DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C, 83%). The

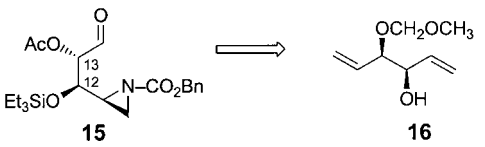


Scheme 3. Synthesis of the intact phosphonate "top piece". DMAP = 4-dimethylaminopyridine, DCC = dicyclohexylcarbodiimide, HOBt = 1-hydroxy-1*H*-benzotriazole, EDCI = ethyl(3-dimethylaminopropyl)carbodiimide.

  1433-7851/01/4009-1737 $ 17.50+.50/0

avoidance of synthetic manipulations subsequent to dehydroamino acid introduction outweighed potential problems with a competing, intramolecular olefination.

The other partner in the Wadsworth–Horner–Emmons olefination reaction was aldehyde **15** (Scheme 4), which was prepared in a high yielding sequence of reactions from



Scheme 4. Origin of the azabicyclic precursor aldehyde.

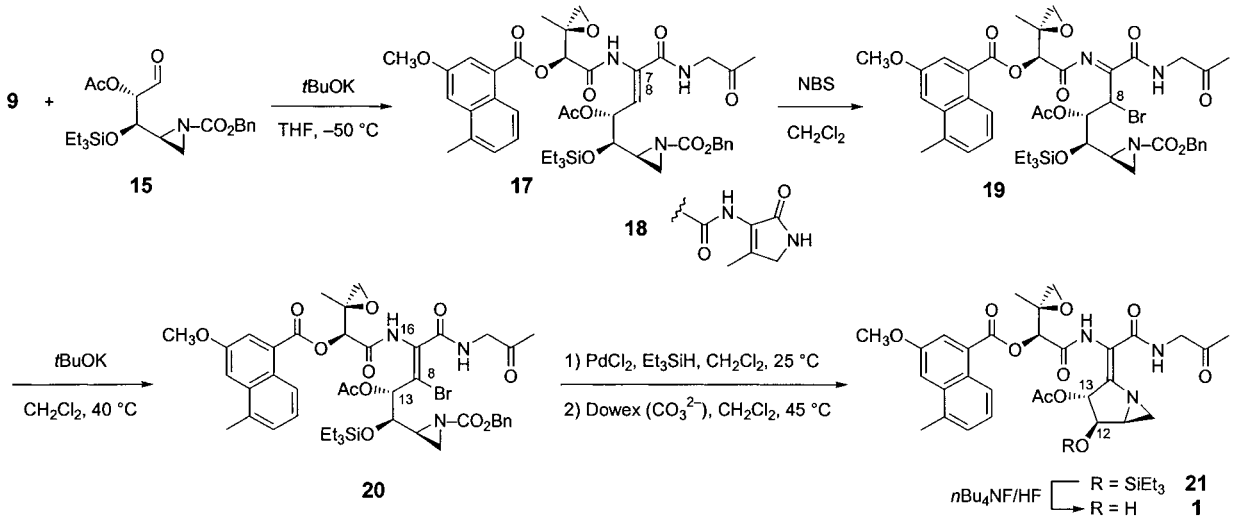
unsymmetrically protected 1,5-hexadiene-3,4-diol **16**, available using Brown's diisopinylcampheylborane reagent,[15] as described previously.[11a,c] For the present work, we used a triethylsilyl ether for protection of the C12 hydroxy group of **15** (azinomycin numbering) rather than the previously described *para*-methoxybenzyl ether; the C13 acetyl group was carried through the synthesis intact.

Wadsworth–Horner–Emmons olefination of aldehyde **15** with the phosphonate **9** bearing the C2 carbonyl group (Scheme 5) proceeded smoothly using potassium *tert*-butoxide at low temperature (THF, $-50\,^{\circ}C$, 18 h). The (*Z*)-dehydroamino acid **17** could be isolated as the major product of the reaction with the minor *E* isomer in a modest yield (40%), which thereby completed formation of the entire azinomycin skeleton. The low yield for this transformation was more than offset by the sheer simplicity of the approach to this advanced intermediate, particularly with regard to the successful avoidance of protecting group manipulations and oxidations subsequent to olefination, which have proven to be the downfall of other approaches to **1** and **2**. To our satisfaction, intramolecular olefination of the phosphonate anion onto the C2 ketone of **9** to afford **18** proved to be a minor reaction pathway ($\leq 5\%$).

Introduction of the vinyl bromide necessary for pyrrolidine formation proved to be problematic, despite the extensive previous work on simple model systems.[16] The initial bromination of **17** (Scheme 5) proceeded smoothly using *N*-bromosuccinimide in the presence of a silica gel catalyst (CH_2Cl_2, $25\,^{\circ}C$, 30 min) to afford the isolable α-bromoimine **19** (75%). Unfortunately, previously defined conditions to effect tautomerization to the vinyl bromide (*E*)-**20** (that is, 2,2,6,6-tetramethylpiperidine, $25\,^{\circ}C$, 18 h), or the use of other amine bases (for example, DABCO, DMAP, Et_3N), gave the undesired isomer (*Z*)-**20** as the sole vinyl bromide product, and was often accompanied by products resulting from hydrolysis of the imine C=N bond (DABCO = 1,4-diazabicyclo[2.2.2]octane). Alkoxide bases (*t*BuOK, CH_2Cl_2, $40\,^{\circ}C$, 18 h) proved more effective at providing the correct vinyl bromide (*E*)-**20**,[17] but it was always formed as a separable mixture with the undesired (*Z*)-vinyl bromide. The configuration about the stereogenic double bond of (*E*)-**20** was assigned by correlation with spectral data of related systems,[18] and by the observation of a reciprocal nuclear Overhauser enhancement between C13-H and N16-H (C13-H $\rightarrow$N16-H: 7.1%; N16-H $\rightarrow$C13-H: 8.7%).

Selective removal of the aziridine *N*-benzyl carbamate of **20** (Scheme 5) using a palladium-catalyzed, silane-mediated process (Et_3SiH, $PdCl_2$, Et_3N, CH_2Cl_2, $25\,^{\circ}C$, 50 min)[19] afforded the corresponding free aziridine (50% yield of isolated product), without complication from reduction of other functional groups in the molecule (that is, the vinyl bromide and olefin).[20] Cyclization was effected upon warming in the presence of Dowex anion exchange resin (CO_3^{2-} form, CH_2Cl_2, $45\,^{\circ}C$, 18 h) to afford 12-*O*-triethylsilyl azinomycin A (**21**), stereospecifically and as a single stereoisomer (64%).[21] Final removal of the C12 hydroxy protecting group with nBu$_4$NF/HF/pyridine[22] (THF, $25\,^{\circ}C$, 50 min, 95%) afforded unstable azinomycin A (**1**),[23] identical with an authentic sample by ^{1}H NMR and thin layer chromatography (silica gel; EtOAc, 5% MeOH/$CHCl_3$, and acetone), and thereby completed the total synthesis of an natural product that has proven to be among the most elusive of synthetic targets.

As we anticipated from previous studies[24] and from observations made during isolation of the azinomycins from



Scheme 5. Olefination, bromination, pyrrolidine introduction, and completion of the total synthesis of azinomycin A. NBS = *N*-bromosuccinimide.

  1433-7851/01/4009-1738 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **2001**, *40*, No. 9

their natural source,[25] the synthetic material proved unstable. This instability is largely, if not exclusively, a result of the C12-hydroxy group of **1**, since the penultimate intermediate 12-*O*-triethylsilyl azinomycin A (**21**) possessed a greater degree of stability towards isolation. Not surprisingly, one of the major pathways of reactivity of **1** is ring opening of the aziridine by nucleophilic attack at C10. The instability of the natural products has prevented their study as chemotherapeutic agents, and overcoming this will require further work to understand both the mechanism by which the instability is manifested and to construct structurally and functionally related agents for more detailed biological evaluation.

Received: February 5, 2001 [Z16558]

[1] a) K. Nagaoka, M. Matsumoto, J. Oono, K. Yokoi, S. Ishizeki, T. Nakashima, *J. Antibiot.* **1986**, *39*, 1527; b) K. Yokoi, K. Nagaoka, T. Nakashima, *Chem. Pharm. Bull.* **1986**, *34*, 4554. Azinomycin B (**2**) is apparently identical to carzinophilin A, an antitumor agent isolated in 1954 from *Streptomyces sahachiroi*: T. Hata, F. Koga, Y. Sano, K. Kanamori, A. Matsumae, R. Sugawara, T. Hoshi, T. Shimi, S. Ito, S. Tomizawa, *J. Antibiot. Ser. A* **1954**, *7*, 107.

[2] a) J. A. Hartley, A. Hazrati, L. R. Kelland, R. Khanim, M. Shipman, F. Suzenet, L. F. Walker, *Angew. Chem.* **2000**, *112*, 3609; *Angew. Chem. Int. Ed.* **2000**, *39*, 3467; b) J. A. Hartley, A. Hazrati, T. J. Hodgkinson, L. R. Kelland, R. Khanim, M. Shipman, F. Suzenet, *Chem. Commun.* **2000**, 2325; c) T. J. Hodgkinson, L. R. Kelland, M. Shipman, F. Suzenet, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 239.

[3] a) H. J. Bryant, C. Y. Dardonville, T. J. Hodgkinson, M. Shipman, A. M. Z. Slawin, *Synlett* **1996**, 973; b) H. J. Bryant, C. Y. Dardonville, T. J. Hodgkinson, M. B. Hursthouse, K. M. A. Malik, M. Shipman, *J. Chem. Soc. Perkin Trans. 1* **1998**, 1249; c) R. W. Armstrong, J. E. Tellew, E. J. Moran, *Tetrahedron Lett.* **1996**, *37*, 447; d) E. J. Moran, J. E. Tellew, Z. Zhao, R. W. Armstrong, *J. Org. Chem.* **1993**, *58*, 7848; e) R. W. Armstrong, E. J. Moran, *J. Am. Chem. Soc.* **1992**, *114*, 371; f) A. P. Combs, R. W. Armstrong, *Tetrahedron Lett.* **1992**, *33*, 6419; g) R. W. Armstrong, J. E. Tellew, E. J. Moran, *J. Org. Chem.* **1992**, *57*, 2208; h) E. J. Moran, R. W. Armstrong, *Tetrahedron Lett.* **1991**, *32*, 3807; i) P. England, K. H. Chun, E. J. Moran, R. W. Armstrong, *Tetrahedron Lett.* **1990**, *31*, 2669; j) M. Hashimoto, S. Terashima, *Heterocycles* **1998**, *47*, 59; k) M. Hashimoto, S. Terashima, *Tetrahedron Lett.* **1994**, *35*, 9409; l) M. Hashimoto, S. Terashima, *Chem. Lett.* **1994**, *6*, 1001; m) M. Hashimoto, M. Matsumoto, K. Yamada, S. Terashima, *Tetrahedron Lett.* **1994**, *35*, 2207; n) M. Hashimoto, K. Yamada, S. Terashima, *Chem. Lett.* **1992**, *6*, 975; o) Y. Konda, T. Machida, T. Sasaki, K. Takeda, H. Takayanagi, Y. Harigaya, *Chem. Pharm. Bull.* **1994**, *42*, 285; p) K. Ando, T. Yamada, M. Shibuya, *Heterocycles* **1989**, *29*, 2209; q) K. Shishido, T. Omodani, M. Shibuya, *J. Chem. Soc. Perkin Trans. 1* **1992**, 2053; r) M. Shibuya, H. Terauchi, *Tetrahedron Lett.* **1987**, *28*, 2619; s) M. Shibuya, *Tetrahedron Lett.* **1983**, *24*, 1175.

[4] S. Ishizeki, M. Ohtsuka, K. Irinoda, K.-i. Kukita, K. Nagaoka, T. Nakashima, *J. Antibiot.* **1987**, *40*, 60. In vitro cytotoxicity: $IC_{50} = 0.07\ \mu g\,mL^{-1}$ (**1**) and $0.11\ \mu g\,mL^{-1}$ (**2**) against L5178Y cells. In vivo antitumor activity: 193% ILS at $16\ \mu g\,kg^{-1}$ **2** (3/7 survivors) against P388 leukemia; 161% ILS at $32\ \mu g\,kg^{-1}$ **2** (5/8 survivors) against Erlich carcinoma. In the same system, mitomycin C exhibited a 204% ILS at $1\ mg\,kg^{-1}$ against P388 leukemia.

[5] K. S. Gates in *Comprehensive Natural Products Chemistry*, *Vol. 7* (Eds.: D. Barton, K. Nakanishi, O. Meth-Cohn), Pergamon, **1999**, pp. 491–552.

[6] For a review on DNA cross-linking agents, see: S. R. Rajski, R. M. Williams, *Chem. Rev.* **1998**, *98*, 2723.

[7] a) S. Alcaro, R. S. Coleman, *J. Med. Chem.* **2000**, *43*, 2783; b) S. Alcaro, R. S. Coleman, *J. Org. Chem.* **1998**, *63*, 4620.

[8] a) H. Zang, K. S. Gates, *Biochemistry* **2000**, *39*, 14968; b) T. Fujiwara, I. Saito, H. Sugiyama, *Tetrahedron Lett.* **1999**, *40*, 315; c) R. W. Armstrong, M. E. Salvati, M. Nguyen, *J. Am. Chem. Soc.* **1992**, *114*, 3144; d) J. W. Lown, K. C. Majumdar, *Can. J. Biochem.* **1977**, *55*, 630.

[9] a) R. S. Coleman, C. R. Sarko, J. P. Gittinger, *Tetrahedron Lett.* **1997**, *38*, 5917; b) R. S. Coleman, J. D. McKinley, *Tetrahedron Lett.* **1998**, *39*, 3433.

[10] a) U. Schmidt, A. Lieberknecht, J. Wild, *Synthesis* **1984**, 53; b) U. Zoller, D. Ben-Ishai, *Tetrahedron* **1975**, *31*, 863.

[11] a) R. S. Coleman, J.-S. Kong, T. E. Richardson, *J. Am. Chem. Soc.* **1999**, *121*, 9088; b) R. S. Coleman, T. E. Richardson, A. J. Carpenter, *J. Org. Chem.* **1998**, *63*, 5738; c) R. S. Coleman, J.-S. Kong, *J. Am. Chem. Soc.* **1998**, *120*, 3538.

[12] R. S. Coleman, A. J. Carpenter, *J. Org. Chem.* **1992**, *57*, 5813.

[13] a) R. S. Coleman, *Synlett* **1998**, 1031; b) R. S. Coleman, A. J. Carpenter, *Tetrahedron* **1997**, *53*, 16313.

[14] A. Lieberknecht, J. Schmidt, J. J. Stezowski, *Tetrahedron Lett.* **1991**, *32*, 2113.

[15] H. C. Brown, P. K. Jadhav, K. S. Bhat, *J. Am. Chem. Soc.* **1988**, *110*, 1535.

[16] R. S. Coleman, A. J. Carpenter, *J. Org. Chem.* **1993**, *58*, 4452. For the topic of "working models that do not work", see chapter 2 in: M. A. Sierra, M. C. de la Torre, *Angew. Chem.* **2000**, *112*, 1628–1650; *Angew. Chem. Int. Ed.* **2000**, *39*, 1538–1559.

[17] Compound (*E*)-**20** was characterized: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.53$ (br s, 1H), 8.66 (dd, $J = 7.1$, 2.8 Hz, 1H), 8.06 (d, $J = 2.6$ Hz, 1H), 7.65 (t, $J = 4.8$ Hz, 1H), 7.46 (d, $J = 2.4$ Hz, 1H), 7.37–7.31 (m, 7H), 5.38 (s, 1H), 5.36 (d, $J = 8.1$ Hz, 1H), 5.05 (AB system, $J = 12.2$ Hz, $\Delta\nu = 82.3$ Hz, 2H), 4.43 (dd, $J = 8.1$, 4.3 Hz, 1H), 4.25 (d, $J = 4.9$ Hz, 2H), 3.95 (s, 3H), 3.02 (d, $J = 4.6$ Hz, 1H), 2.87–2.84 (m, 1H), 2.69 (d, $J = 3.9$ Hz, 1H), 2.67 (s, 3H), 2.44 (d, $J = 3.6$ Hz, 1H), 2.26 (d, $J = 4.0$ Hz, 1H), 2.25 (s, 3H), 2.08 (s, 3H), 1.57 (s, 3H), 0.95 (t, $J = 8.0$ Hz, 9H), 0.63 (q, $J = 8.0$ Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 202.9$, 171.3, 165.5, 165.3, 163.7 (2C), 155.9, 135.9, 135.5, 134.2, 132.9, 128.4 (2C), 128.3 (2C), 128.2, 127.9, 127.6, 127.1, 125.0, 124.0, 122.5, 112.9, 108.3, 75.7, 74.9, 69.8, 68.8, 55.9, 55.4, 52.1, 50.2, 37.6, 29.7, 27.6, 20.6, 20.1, 17.9, 6.71 (3C), 4.85 (3C); IR (neat) $\tilde{\nu}_{max}$ 2919, 2860, 1727, 1684, 1508, 1458, 1214, 1082 cm^{-1}; HR-MS (ESI), *m*/*z* 946.2562 (calcd for $C_{44}H_{54}N_3O_{12}SiBr + Na$: 946.2558).

[18] In a variety of model systems related to **20** and **1**, the C13-H consistently resonates upfield in the (*E*)-isomer, whereas the N16-H resonates downfield in this isomer: see ref. [13b].

[19] L. Birkofer, E. Bierwirth, A. Ritter, *Chem. Ber.* **1961**, *94*, 821. See also: M. Sakaitani, Y. Ohfune, *J. Org. Chem.* **1990**, *55*, 870.

[20] R. S. Coleman, J. A. Shah, *Synthesis* **1999**, 1399.

[21] Compound (*E*)-**21** was characterized: ^{1}H NMR (500 MHz, CD_2Cl_2): $\delta = 9.48$ (t, $J = 4.4$ Hz, 1H), 8.58 (d, $J = 7.8$ Hz, 1H), 7.99 (br s, 1H), 7.96 (d, $J = 2.6$ Hz, 1H), 7.53 (d, $J = 2.5$ Hz, 1H), 7.40–7.35 (m, 2H), 5.51 (d, $J = 2.6$ Hz, 1H), 5.30 (s, 1H), 4.71 (dd, $J = 5.1$, 2.8 Hz, 1H), 4.21 (ABX, $J = 19.7$, 5.0 Hz, $\Delta\nu = 27.6$ Hz, 2H), 4.00 (s, 3H), 3.28 (dd, $J = 5.3$, 4.0 Hz, 1H), 3.00 (d, $J = 4.5$ Hz, 1H), 2.73 (d, $J = 4.6$ Hz, 1H), 2.70 (s, 3H), 2.59 (d, $J = 5.3$ Hz, 1H), 2.29 (d, $J = 4.0$ Hz, 1H), 2.16 (s, 3H), 2.06 (s, 3H), 1.54 (s, 3H), 0.94 (t, $J = 8.0$ Hz, 9H), 0.62 (q, $J = 8.0$ Hz, 6H); ^{13}C NMR (150 MHz, CD_2Cl_2): $\delta = 203.2$, 169.9, 165.7, 165.4, 163.3, 156.4, 153.9, 134.7, 133.8, 128.8, 128.0, 127.1, 125.3, 124.1, 122.2, 119.4, 108.7, 84.7, 76.4, 75.7, 56.0, 52.8, 50.9, 48.3, 37.9, 30.1, 27.4, 20.8, 20.2, 18.1, 6.71 (3C), 4.84 (3C); IR (neat) $\tilde{\nu}_{max}$ 2917, 2849, 1725, 1660, 1643, 1619, 1461, 1232 cm^{-1}; HR-MS (ESI), *m*/*z* 732.2927 (calcd for $C_{36}H_{47}N_3O_{10}Si + Na$: 732.2928).

[22] B. L. Gaffney, R. A. Jones, *Tetrahedron Lett.* **1982**, *23*, 2257.

[23] Compound **1** was characterized: HR-MS (ESI), *m*/*z* 618.1979, 596.2205 (calcd for $C_{30}H_{33}N_3O_{10} + Na$: 618.2064; calcd for $C_{30}H_{33}N_3O_{10} + H$: 596.2244).

[24] Model systems for the azabicyclic system of the natural products also exhibited instability when the C12-hydroxy protecting group was removed. In simple systems, deprotection of a trimethylsilyl ether was run in situ in an NMR tube because the product could not be isolated. For details, see ref. [11].

[25] R. J. Perez, unpublished observations from this lab.

  1433-7851/01/4009-1739 $ 17.50+.50/0