Synthesis of Tri- and Tetrapeptide S: The Extended C-Terminus of Bleomycin A_2

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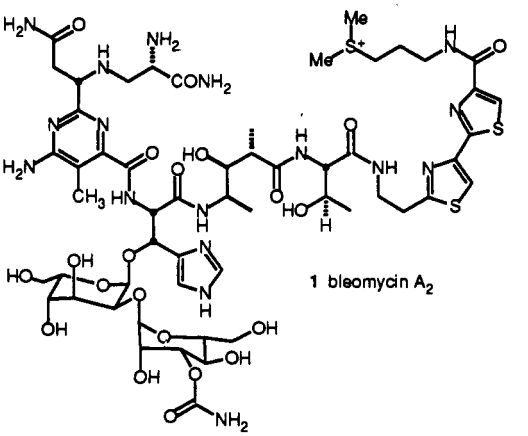
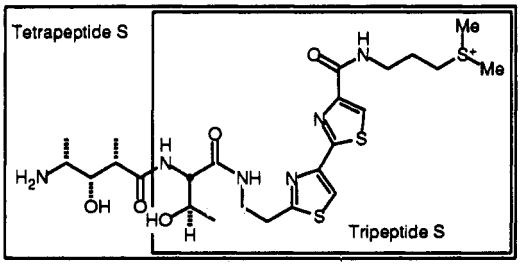
Summary: Concise diastereocontrolled syntheses of tri- and tetrapeptide S, key subunits of the antitumor antibiotic bleomycin A_2, are detailed.

Bleomycin A_2 (1), the major naturally-occurring constituent of the clinical antitumor drug blenoxane, is thought to derive its therapeutic effects from the ability to mediate the oxidative cleavage of double-stranded DNA by a process that is metal ion and oxygen dependent.[1] Consequently, bleomycin A_2, its naturally occurring congeners, its degradation products, and semisynthetic derivatives as well as synthetic analogs have been the subject of continued examination in efforts to define the fundamental functional roles of the individual subunits. The pyrimidoblamic acid subunit in conjunction with the adjacent erythro β-hydroxy-L-histidine provide the metal chelation coordination sites required for molecular oxygen activation and subsequent DNA cleavage and the potential contribution that this segment may make in polynucleotide recognition has been recently addressed.[2] The C-terminus tri- and tetrapeptide S subunits including the terminal sulfonium cation (electrostatic DNA binding affinity) and the bithiazole (DNA intercalation[3] and/or minor groove binding affinity and selectivity[4]) provide the majority of the bleomycin A_2 DNA binding affinity[5] and contribute to polynucleotide recognition[4] and cleavage selectivity. The position, number, and absolute stereochemistry of the substituents on the chain linking the bithiazole subunit with the metal chelation segment have been suggested to play important or subtle roles in the DNA binding selectivity or subsequent cleavage efficiency of the agents.[6] Representative of such subtle effects, Umezawa and coworkers have shown that the presence and absolute configuration of the C4 methyl substituent of the 4-amino-3-hydroxy-2,4-dimethylbutanoic acid subunit potentiates the biological potency (>10×) and DNA cleavage efficiency (>10×) and have suggested that such backbone substituents may effectively orient the metal chelation subunit in the minor groove.[6] Complementary to the efforts detailed by Umezawa and Hecht, herein we report concise, diastereocontrolled syntheses of **2** and optically active tri- and tetrapeptide S[7] amenable to the preparation of bleomycin A_2 structural analogs[1,8,9] in substantial quantities.



1 bleomycin A_2



An appropriately protected derivative of the erythro β-hydroxy-L-histidine subunit that links the tetrapeptide S and pyrimidoblamic acid subunits was prepared as detailed in Scheme I. The derivative **2** was prepared from

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(8) Bleomycin A_2 total synthesis: (a) Takita, T.; Umezawa, Y.; Saito, S.; Morishima, H.; Naganawa, H.; Umezawa, H.; Tsuchiya, T.; Miyake, T.; Kageyama, S.; Umezawa, S.; Muraoka, Y.; Suzuki, M.; Otsuka, M.; Narita, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1982**, *23*, 521. (b) Aoyagi, Y.; Katano, K.; Suguna, H.; Primeau, J.; Chang, L.-H.; Hecht, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 5537. Deglycobleomycin A_2 total synthesis: (c) Takita, T.; Umezawa, Y.; Saito, S.; Morishima, H.; Umezawa, H.; Muraoka, Y.; Suzuki, M.; Otsuka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1981**, *22*, 671. (d) Saito, S.; Umezawa, Y.; Morishima, H.; Takita, T.; Umezawa, H.; Narita, M.; Otsuka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1982**, *23*, 529. (e) Aoyagi, Y.; Suguna, H.; Murugesan, N.; Ehrenfeld, G. M.; Chang, L.-H.; Ohgi, T.; Shekhani, M. S.; Kirkup, M. P.; Hecht, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 5237. (f) Saito, S.; Umezawa, Y.; Yoshioka, T.; Takita, T.; Umezawa, H.; Muraoka, Y. *J. Antibiot.* **1983**, *36*, 92.

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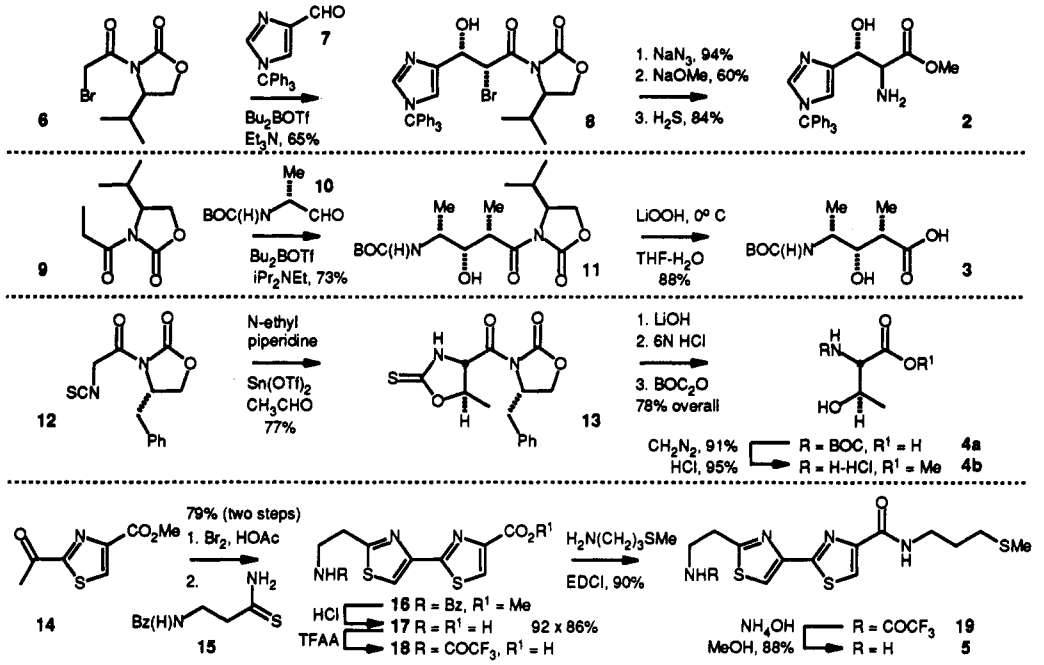
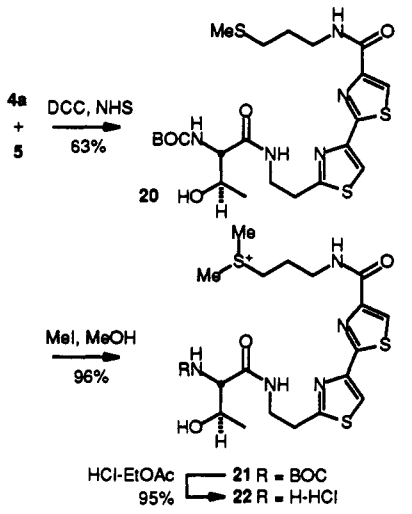
Scheme I



8[10,11] through adaptation of the approach detailed by Ohno and co-workers with modifications in which the competitive retro aldol reaction was suppressed during the azide displacement reaction (5 equiv of NaN_3, DMF, 45 °C, 1.5 h, 94%) and which provide an appropriately protected derivative suitable for direct coupling with the pyrimidoblamic acid subunit without further functionalization (1.1 equiv of $NaOCH_3$, CH_3OH, 0 °C, 5 min, 60%; H_2S, H_2O–CH_3OH, 25 °C, 48 h, 84%).[12]

(2*S*,3*S*,4*R*)-*N*-(*tert*-Butoxycarbonyl)-4-amino-3-hydroxy-2-methylpentanoic acid (**3**)[13] was prepared through diastereoselective syn aldol addition of the boron (*Z*)-enolate derived from **9**[14] (1.1 equiv of Bu_2BOTf, 1.2 equiv of iPr_2NEt, CH_2Cl_2, 0 °C, 45 min) with *N*-(*tert*-butoxycarbonyl)-D-alaninal (**10**)[15] to provide **11** (73%, –78 to 25 °C, 24 h), Scheme I. Hydrolysis of the chiral auxiliary provided subunit **3** in excellent yield (88%, 2 equiv of LiOH, 6 equiv of H_2O_2, THF–H_2O (3:1), 0 °C, 3 h). Similarly, the L-threonine subunit **4** was prepared through diastereoselective syn aldol addition of the stannous (*Z*)-enolate derived from **12** (1.2 equiv of *N*-ethylpiperidine, 0.9 equiv of $Sn(OTf)_2$, THF, –78 °C, 1.5 h) with acetaldehyde to provide **13** (77%, 1.5 h, –78 °C) following the procedure detailed by Evans and co-workers.[16] Exhaustive deprotection of **13** (1.1 equiv of LiOH, THF–H_2O, 0 °C, 30 min; 0.5 N aqueous HCl, reflux, 14 h) followed by BOC protection of the amine (1.1 equiv of BOC_2O, 1 N aqueous $NaHCO_3$–THF (3:2), 25 °C, 20 h, 78% overall) provided *N*-(*tert*-butoxycarbonyl)-L-threonine (**4a**)[16] suitably protected for carboxylate coupling. Subsequent methyl ester formation (91%, CH_2N_2, Et_2O, 0 °C, 30 min) and *N*-BOC deprotection (95%, 3 N HCl–EtOAc, 25 °C, 1 h) provided L-threonine methyl ester (**4b**)[16] suitable for coupling at the amine terminus.

Scheme II



Coupling of **4a** with the free base of bithiazole **5**[8e,17] prepared through minor modification of the approach of

(10) For **2**: mp 95–97 °C, $[\alpha]^{25}_D$ + 37.3 (*c* 0.095, $CHCl_3$). Erythro β-hydroxy-L-histidine: (a) Owa, T.; Otsuka, M.; Ohno, M. *Chem. Lett.* **1988**, 1873. (b) Hecht, S. M.; Rupprecht, K. M.; Jacobs, P. M. *J. Am. Chem. Soc.* **1979**, *101*, 3982. (c) Owa, T.; Otsuka, M.; Ohno, M. *Chem. Lett.* **1988**, 83. (d) Saito, S.; Umezawa, Y.; Yoshioka, T.; Takita, T.; Umezawa, H.; Muraoka, Y. *J. Antibiot.* **1983**, *36*, 92.

(11) For the preparation of **7**, see: Kelley, J. L.; Miller, C. A.; McLean, E. W. *J. Med. Chem.* **1977**, *20*, 721.

(12) Alternative methods for azide reduction including Ph_3P, THF–H_2O; Bu_3SnH; Na_2S–$9H_2O$, Et_3N; and $NiCl_2$–$6H_2O$, $NaBH_4$ proved less successful.

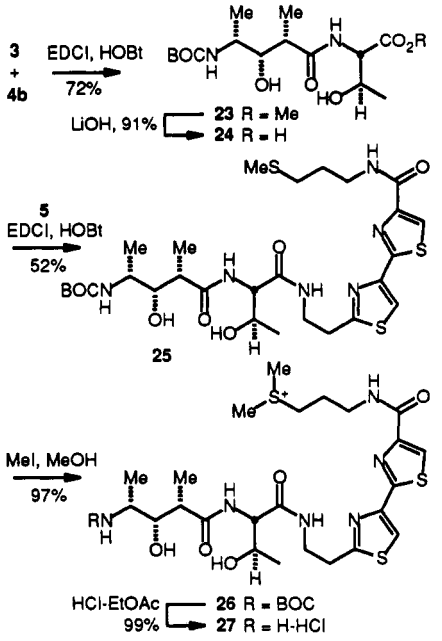
(13) For **3**: $[\alpha]^{25}_D$ + 8.4 (*c* 1.0, CH_3OH); (2*S*,3*S*,4*R*)-4-amino-3-hydroxy-2-methylpentanoic acid: DiPardo, R. M.; Bock, M. G. *Tetrahedron Lett.* **1983**, *24*, 4805. Narita, M.; Otsuka, M.; Kobayashi, S.; Ohno, M.; Umezawa, Y.; Morishima, H.; Saito, S.; Takita, T.; Umezawa, H. *Tetrahedron Lett.* **1982**, *23*, 525. Ohgi, T.; Hecht, S. M. *J. Org. Chem.* **1981**, *46*, 1232. Levin, M. D.; Subrahamanian, K.; Katz, H.; Smith, M. B.; Burlett, D. J.; Hecht, S. M. *J. Am. Chem. Soc.* **1980**, *102*, 1452. Yoshioka, T.; Hara, T.; Takita, T.; Umezawa, H. *J. Antibiot.* **1974**, *27*, 356.

(14) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.

(15) (a) Prepared from *N*-BOC-D-alanine through the following sequence: (1) 1.0 equiv of MeN(OMe)H–HCl, 1.05 equiv of EDCI, 1.0 equiv of HOBt, 4 equiv of $NaHCO_3$, DMF, 25 °C, 15 h, 83%; (2) 5.0 equiv of $LiAlH_4$,[15b] THF, 0 °C, 1 h, 76%. For **10**: mp 85–86 °C, $[\alpha]^{20}_D$ –43.6 (*c* 1.05, $CHCl_3$) (lit.[15c] mp 88 °C, $[\alpha]^{20}_D$ –43.2 (*c* 1.05, $CHCl_3$)). (b) Fehrentz, J. A.; Castro, B. *Synthesis* **1983**, 676. (c) Narita, M.; Otsuka, M.; Kobayashi, S.; Ohno, M.; Umezawa, Y.; Morishima, H.; Saito, S.; Takita, T.; Umezawa, H. *Tetrahedron Lett.* **1982**, *23*, 525.

(16) For **4a**: $[\alpha]^{25}_D$ –2.49 (*c* 0.06, CH_3OH) (lit.[16b] $[\alpha]^{25}_D$ –2.52 (*c* 0.98, CH_3OH)). For **4b**: $[\alpha]^{23}_D$ –15.2 (*c* 0.17, 5 N aqueous HCl) (lit. $[\alpha]^{20}_D$ –14.5 (*c* 0.5, 5 N aqueous HCl), Fluka). (a) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757. (b) Hofmann, K.; Schmiechen, R.; Wells, R. D.; Wolman, Y.; Yanaihara, N. *J. Am. Chem. Soc.* **1965**, *87*, 611.

Scheme III



Sakai and co-workers provided **20**[18] which proved to be a convenient, stable storage intermediate (63%, 1.5 equiv of DCC, 1.2 equiv of NHS; 2.0 equiv of $NaHCO_3$, DME, 25 °C, 24 h), Scheme II. S-Methylation of **20** (96%, 50 equiv of CH_3I, CH_3OH, 25 °C, 72 h) provided the *N*-BOC derivative of tripeptide S (**21**),[18] and subsequent acid-catalyzed deprotection afforded tripeptide S[18] (**22**, 95%, 3 N HCl–EtOAc, 25 °C, 1.5 h) identical in all respects to authentic material. Although a linear synthesis of tetrapeptide S based on the coupling of tripeptide S and **3** has been detailed in the independent efforts of Umezawa and Hecht,[8] an alternative and more convergent preparation was employed for the work detailed herein. Coupling of **3** with **4b** (71%, 1.05 equiv of EDCI, 1.0 equiv of HOBt, 4 equiv of $NaHCO_3$, DMF, 25 °C, 24 h) followed by hydrolysis of the methyl ester **23** (91%, 4 equiv of LiOH, THF–CH_3OH–H_2O (3:1:1), 25 °C, 3 h) provided **24**, Scheme III. Coupling of **24** with **5** (52%, 1.05 equiv of EDCI, 1.0 equiv of HOBt, 4 equiv of $NaHCO_3$, DMF, 25 °C, 72 h) afforded **25**[19] which has proven to be a stable storage intermediate in our synthetic efforts. Subsequent S-methylation (97%, 50 equiv of CH_3I, CH_3OH, 25 °C, 80 h) provided the *N*-BOC derivative of tetrapeptide S (**26**)[19] and acid-catalyzed deprotection of **26** (99%, 3 N HCl–EtOAc, 25 °C, 1.5 h) provided tetrapeptide S (**27**).[19] Because of the sensitivity of **21–22** and **26–27** to prolonged storage, they are prepared from **20** and **25** immediately prior to use.

The incorporation of tetrapeptide S (**27**) and subunit **2** in the synthesis of deglyco desacetamidobleomycin A_2 is detailed in the accompanying paper,[20] and the approach detailed herein has been employed in the preparation of structural analogs of **22** and **27**. The incorporation of **22**, **27**, and such agents into structural analogs of bleomycin A_2 will be reported in due course.

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (CA42056). We wish to thank Dr. Mona Patel for the initial preparation of **20**, Professor M. Ohno and M. Otsuka for a generous supply of authentic, comparison tripeptide S, and Professor S. M. Hecht for copies of the ^1H NMR spectra of tripeptide S and **25**.

Supplementary Material Available: Full experimental details and characterization for **2–5**, **8**, **11**, **13**, and **20–27** (13 pages). This material is contained in many 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.

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(18) For **20**: mp 105–106 °C (EtOAc–hexane); $[\alpha]^{23}_D$ −19.2 (*c* 0.66, CH_3OH) [lit.[8c] mp 106–107 °C (EtOAc–iPr_2O), $[\alpha]^{24}_D$ −20 (*c* 1, CH_3OH)]; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.12 (s, 1 H), 7.85 (s, 1 H), 7.65 (br t, 1 H), 7.25 (br t, 1 H), 5.60 (d, 1 H, *J* = 8 Hz), 4.40 (m, 1 H), 4.15 (m, 1 H), 3.75 (m, 2 H), 3.59 (q, 2 H, *J* = 7 Hz), 3.30 (t, 2 H, *J* = 6 Hz), 2.61 (t, 2 H, *J* = 7 Hz), 2.13 (s, 3 H), 1.98 (p, 2 H, *J* = 7 Hz), 1.40 (s, 9 H), 1.17 (d, 3 H, *J* = 8 Hz). For **21**: $[\alpha]^{23}_D$ −17.4 (*c* 0.095, CH_3OH); ^1H NMR (CD_3OD, 400 MHz) δ 8.20 (s, 1 H), 8.17 (s, 1 H), 4.20 (m, 1 H), 3.92 (m, 1 H), 3.75 (m, 1 H), 3.61 (t, 3 H, *J* = 6.5 Hz), 3.41 (t, 2 H, *J* = 7.5 Hz), 3.28 (t, 2 H, *J* = 6.5 Hz), 2.96 (s, 6 H), 2.16 (p, 2 H, *J* = 7.0 Hz), 1.42 (s, 9 H), 1.14 (d, 3 H, *J* = 6.5 Hz). For **22**: $[\alpha]^{23}_D$ −16.5 (*c* 0.04, 0.1 N HCl) [lit.[8c] $[\alpha]^{23}_D$ −15 (*c* 0.75, 0.1 N HCl), authentic sample[8c] $[\alpha]^{23}_D$ −16.2 (*c* 0.04, 0.1 N HCl)]; ^1H NMR (CD_3OD, 400 MHz) δ 8.27 (s, 1 H), 8.26 (s, 1 H), 4.05 (m, 1 H), 3.82 (m, 1 H), 3.72 (m, 1 H), 3.66 (m, 3 H), 3.49 (t, 2 H, *J* = 7 Hz), 3.38 (m, 2 H), 3.00 (s, 6 H), 2.18 (p, 2 H, *J* = 7 Hz), 1.25 (d, 3 H, *J* = 6.5 Hz).

(19) For **25**: $[\alpha]^{23}_D$ +14.4 (*c* 0.075, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 8.12 (s, 1 H), 7.85 (s, 1 H), 7.65 (br t, 1 H), 7.45 (br t, 1 H), 7.02 (br d, 1 H), 4.90 (br d, 1 H), 4.35 (br d, 1 H), 4.30–4.10 (m, 2 H), 3.70 (m, 2 H), 3.65–3.50 (m, 5 H), 3.25 (t, 2 H, *J* = 6.5 Hz), 2.60 (t, 2 H, *J* = 7.0 Hz), 2.59 (br s, 1 H), 2.12 (s, 3 H), 1.95 (p, 2 H, *J* = 7.0 Hz), 1.43 (s, 9 H), 1.22 (d, 3 H, *J* = 7.0 Hz), 1.11 (d, 6 H, *J* = 6.0 Hz). For **26**: $[\alpha]^{25}_D$ +22.2 (*c* 0.055, CH_3OH); ^1H NMR (CD_3OD, 400 MHz) δ 8.26 (s, 1 H), 8.20 (s, 1 H), 4.38 (d, 1 H, *J* = 4.5 Hz), 4.15 (m, 1 H), 3.70 (m, 3 H), 3.62 (br t, 3 H), 3.45 (t, 2 H, *J* = 7.5 Hz), 3.34 (m, 2 H), 2.99 (s, 6 H), 2.62 (m, 1 H), 2.16 (p, 2 H, *J* = 7.0 Hz), 1.46 (s, 9 H), 1.24 (d, 3 H, *J* = 7.0 Hz), 1.18 (d, 3 H, *J* = 6.5 Hz), 1.17 (d, 3 H, *J* = 6.5 Hz). For **27**: [lit.[8d] $[\alpha]^{20}_{365}$ −52 (*c* 0.5, 0.1 N HCl)]; ^1H NMR (CD_3OD, 400 MHz) δ 8.27 (s, 1 H), 8.25 (s, 1 H), 4.26 (d, 1 H, *J* = 4.5 Hz), 4.12 (m, 1 H), 3.80 (m, 3 H), 3.66 (br t, 3 H), 3.44 (t, 2 H, *J* = 7.5 Hz), 3.34 (m, 2 H), 3.00 (s, 6 H), 2.65 (m, 1 H), 2.20 (p, 2 H, *J* = 7.0 Hz), 1.34 (d, 3 H, *J* = 6.0 Hz), 1.33 (d, 3 H, *J* = 6.0 Hz), 1.19 (d, 3 H, *J* = 6.5 Hz).

(20) Boger, D. L.; Menezes, R. F.; Dang, Q. Following paper in this issue.

Synthesis of Desacetamidopyrimidoblamic Acid and Deglyco Desacetamidobleomycin A_2

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Summary: A concise synthesis of desacetamidopyrimidoblamic acid (**3**) is detailed based on the inverse electron demand [4 + 2] cycloaddition reaction of 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine (**5**) with 1-bis(benzylamino)-1-propyne or in situ generated 1,1-diaminopropene for the one-step preparation of an appropriately functionalized pyrimidine nucleus. The incorporation of **3** into synthetic deglyco desacetamidobleomycin A_2 (**4**) and the preliminary comparison of the functional cleavage of duplex DNA by Fe(II)-**4** are described. Fe(II)-**4** proved to be 0.3–0.2× as effective as Fe(II)-deglycobleomycin A_2 in its efficiency of cleavage of supercoiled φX174 RFI DNA.

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