The Journal of
Organic
Chemistry

VOLUME 57, NUMBER 6 MARCH 13, 1992

Communications

Synthesis of Desacetamido P-3A: 1,3,5-Triazine → Pyrimidine Heteroaromatic Azadiene Diels–Alder Reaction

Dale L. Boger* and Qun Dang

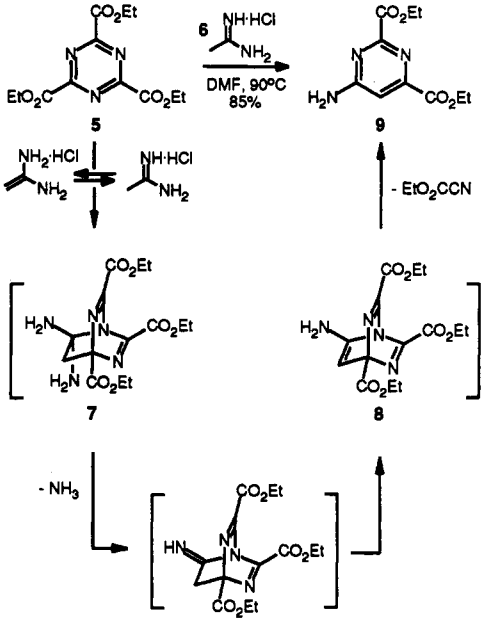
Department of Chemistry, The Scripps Research Institute, 10666 N. Torrey Pines Road, La Jolla, California 92037

Received November 8, 1991

Summary: A concise synthesis of desacetamido P-3A (2) is detailed which is based on an inverse electron demand [4 + 2] cycloaddition reaction of 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine with in situ generated 1,1-diaminoethene for the one-step preparation of an appropriately functionalized pyrimidine core.

P-3A (1),[1] a peptide-derived natural product isolated in the conduct of biosynthetic studies of the bleomycins and whose structure was unambiguously established in a single-crystal X-ray structure determination of its copper(II) complex, represents the simplest member of the class of agents related to the clinically important bleomycin antitumor antibiotics.[2] Its timely identification and the structural characterization of the copper(II) complex established the functionality responsible for metal chelation. Pertinent to the studies detailed herein, this provided the initial indication that the C2-acetamido side chain of P-3A and the related bleomycins may not be involved in the metal chelation. Herein, we detail the synthesis of desacetamido P-3A (2) based on the inverse electron demand

Scheme I



Diels–Alder reaction[3] of 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine (5)[4] in studies which establish the viability of a concise approach to the heterocyclic nucleus central to the structure of P-3A (1), pyrimidoblamic acid (3),[5] bleomycin

(1) Iitaka, Y.; Nakamura, H.; Nakatani, T.; Muraoka, Y.; Fujii, A.; Takita, T.; Umezawa, H. *J. Antibiot.* **1978**, *31*, 1070.

(2) Ohno, M.; Otsuka, M. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer-Verlag: New York, 1990; p 387. Hecht, S. M. *Acc. Chem. Res.* **1986**, *19*, 383. Stubbe, J.; Kozarich, J. W. *Chem. Rev.* **1987**, *87*, 1107. Sugiura, Y.; Takita, T.; Umezawa, H. *Metal Ions Biol. Syst.* **1985**, *19*, 81. Povirk, L. F. In *Molecular Aspects of Anti-Cancer Drug Action*; Neidle, S., Waring, M. J., Eds.; MacMillian: London, 1983. Hecht, S. M. In *Bleomycin: Chemical, Biochemical and Biological Aspects*; Hecht, S. M., Ed.; Springer-Verlag: New York, 1979. Umezawa, H. In *Anticancer Agents Based on Natural Product Models*; Cassady, J. M., Douros, J. D., Eds.; Academic Press: New York, 1980; p 148. Umezawa, H. In *Bleomycin: Current Status and New Developments*; Carter, S. K., Crooke, S. T., Umezawa, H., Eds.; Academic Press: New York, 1978. Umezawa, H. *Pure Appl. Chem.* **1971**, *28*, 665.

(3) Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*, Academic Press: San Diego, 1987. Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. Boger, D. L.; Patel, M. *Progr. Heterocycl. Chem.* **1989**, *1*, 30. Boger, D. L. *Tetrahedron* **1983**, *39*, 2869.

(4) Boger, D. L.; Dang, Q. *Tetrahedron* **1988**, *44*, 3379.

0022-3263/92/1957-1631$03.00/0

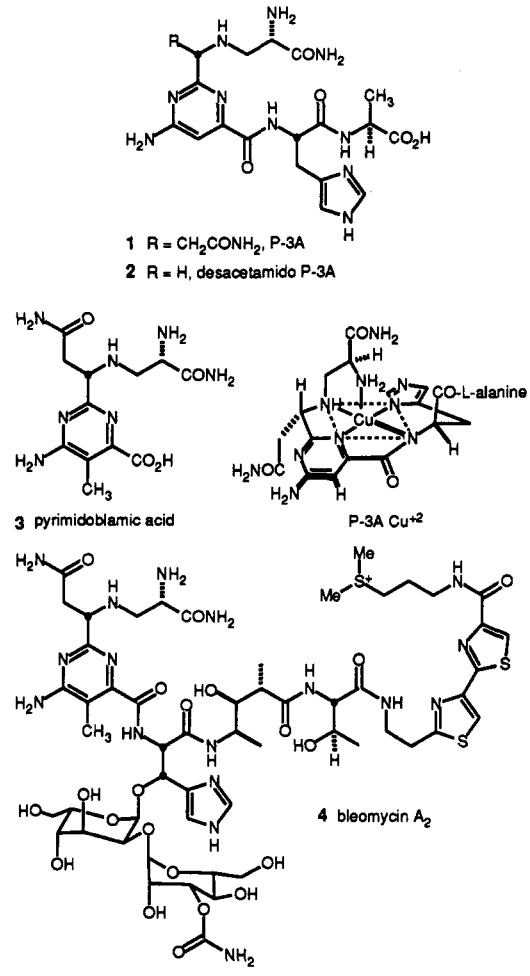
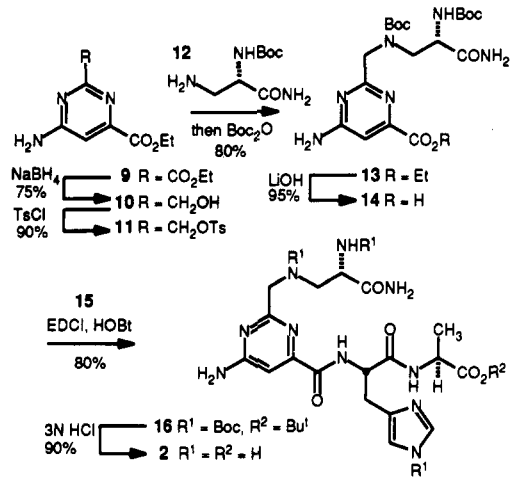


Figure 1.

A_2 (4)[6] and structurally related agents.[7] The pyrimidine nucleus constitutes the core of the iron(II) chelating subunit required for O_2 activation and the subsequent double-stranded DNA cleavage thought to be responsible for the therapeutic action of the agents.

Treatment of 5[4,8] with acetamidine hydrochloride (6) provided the pyrimidine 9 in a reaction that proceeds through reversible in situ tautomerization of 6 to 1,1-diaminoethene and its participation in an effective [4 + 2] cycloaddition reaction with 5 (Scheme I). The subsequent elimination of ammonia, tautomerization to 8, and retro-Diels–Alder loss of ethyl cyanoformate under the reaction conditions provided 9 directly in a reaction cascade for which the conversions proved sensitive to the reaction conditions. The thermal conditions (>80 °C) detailed facilitate amidine 6 tautomerization and are required for effecting the retro-Diels–Alder reaction of the initial [4 + 2] cycloadduct. Studies of the reaction of enamines with 5 in which the [4 + 2] cycloaddition reaction was found to occur at room temperature have demonstrated that the retro-Diels–Alder reaction of such adducts occur only slowly under thermal conditions (100–200 °C) and suffer from a problematic aromatization reaction.[4] Acid catalysis proved to promote both the retro-Diels–Alder reaction and the subsequent aromatization reaction, and useful conversions to pyrimidine products were observed at ca. 100 °C in the presence of acetic acid or *p*-TsOH. In the conversion of 5 and 6 to 9, the retro-Diels–Alder reaction of 8 and the tautomerization reaction of 7 requiring loss of ammonia are facilitated by the presence of an acid catalyst (HCl) derived from the use of the amidine hydrochloride.

Scheme II



Selective reduction of the electrophilic C2-ethoxycarbonyl group provided 10 and was most effectively conducted with sodium borohydride at low temperature (−30 to −20 °C, Scheme II). Although the reduction proceeded in a satisfactory manner in ethanol, the reaction proved much faster (1–3 vs 6 days), cleaner (75–88% vs 68–78%), and more selective (6–7:1 vs 2–4:1 C2-CH_2OH/C4-CH_2OH) when conducted in 2-propanol (3 days) or 1:2 *t*-BuOH–THF (7:1 C2-CH_2OH/C4-CH_2OH, 87%, 24 h) presumably due to the enhanced stability of the reagent to the reaction conditions.[9] Conversion of 10 to the corresponding tosylate 11 (95%) followed by clean displacement with amine 12[10] and subsequent protection of the secondary amine provided 13 (80%, two steps). Ethyl ester hydrolysis (91%) and EDCI-promoted coupling

(5) Structure determination: (a) Yoshioka, T.; Muraoka, Y.; Takita, T.; Maeda, K.; Umezawa, H. *J. Antibiot.* **1972**, *25*, 625. Synthesis: (b) Umezawa, Y.; Morishima, H.; Saito, S.; Takita, T.; Umerzawa, H.; Kobayashi, S.; Otsuka, M.; Narita, M.; Ohno, M. *J. Am. Chem. Soc.* **1980**, *102*, 6630. (c) Otsuka, M.; Narita, M.; Yoshida, M.; Kobayashi, S.; Ohno, M.; Umezawa, Y.; Morishima, H.; Saito, S.; Takita, T.; Umezawa, H. *Chem. Pharm. Bull.* **1985**, *33*, 520. (d) Arai, H.; Hagmann, W. K.; Suguna, H.; Hecht, S. M. *J. Am. Chem.* Soc. **1980**, *102*, 6631. (e) Aoyagi, Y.; Chorghade, M. S.; Padmapriya, A. A.; Suguna, H.; Hecht, S. M. *J. Org. Chem.* **1990**, *55*, 6291.

(6) Synthesis: 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. 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. 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. Aoyagi, Y.; Katano, K.; Suguna, H.; Primeau, J.; Chang, L.-H.; Hecht, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 5537. Saito, S.; Umezawa, Y.; Yoshioka, T.; Takita, T.; Umezawa, H.; Muraoka, Y. *J. Antibiot.* **1983**, *36*, 92.

(7) Kittaka, A.; Sugano, Y.; Otsuka, M.; Ohno, M. *Tetrahedron* **1988**, *44*, 2811, 2821. Suga, A.; Sugiyama, T.; Sugano, Y.; Kittaka, A.; Otsuka, M.; Ohno, M.; Sugiura, Y.; Maeda, K. *Synlett.* **1989**, *70*. Shipley, J. B.; Hecht, S. M. *Chem. Res. Toxicol.* **1988**, *1*, 25. Carter, B. J.; Reddy, K. S.; Hecht, S. M. *Tetrahedron* **1991**, *47*, 2463 and references cited therein.

(8) Ott, E. *Chem. Ber.* **1919**, *52*, 656. Grundmann, C.; Weisse, G.; Seide, S. *Liebigs Ann. Chem.* **1952**, *577*, 77.

(9) 2D ^1H–^1H NOESY NMR of the isomeric alcohols and the corresponding tosylates derived from the major and minor reduction products unambiguously confirmed the isomer assignments through observation of a diagnostic $-CH_2OR$/C5-H NOE crosspeak for the minor isomer.

(10) (a) Prepared from L-serine by the following reactions: (i) MeOH, $SOCl_2$; (ii) Boc_2O, K_2CO_3, THF–H_2O, 22 °C, 10 h, 90% for two steps; (iii) HN_3, DEAD, Ph_3P, THF, −70 to 22 °C, 8 h, 88%,[10b] (iv) NH_3, MeOH, −20 to 20 °C, 7 h, 85%; (v) H_2, 10% Pd–C, MeOH, 22 °C, 5 h, 95%. (b) For the preparation and use of N^{α}-Boc-L-β-aminoalanine methyl ester, see: Otsuka, M.; Kittaka, A.; Iimori, T.; Yamashita, H.; Kobayashi, S.; Ohno, M. *Chem. Pharm. Bull.* **1985**, *33*, 509. For alternative preparations of 12, see ref 5b,d.

of the carboxylic acid 14 with N^{im}-Boc-L-His-L-Ala-OBu^t (15)[11] provided desacetamido P-3A in its fully protected form 16 (80%).[12] Acid-catalyzed deprotection provided 2 [90%, $[\alpha]^{22}_D$ −13.3 (c 0.15, CH_3OH), $[\alpha]^{22}_D$ −18.0 (c 0.15, 0.1 N HCl)].

(11) Prepared from N^{α}-CBZ-L-histidine (17) and L-alanine *tert*-butyl ester hydrochloride (18) by the following reactions: (i) 17, Boc_2O, aq NaOH (86%); (ii) 18, EDCI, HOBt, DMF (51%); (iii) H_2, 10% Pd–C, CH_3OH (90%). The attempts to use the corresponding methyl ester of 15 resulted in significant amounts of intramolecular lactam formation with diketopiperazine formation.

(12) EDCI = [3-(dimethylamino)propyl)]ethylcarbodiimide, HOBt = 1-hydroxybenzotriazole.

The examination of the properties of 2 as well as the extension of this work to the synthesis of P-3A, pyrimidoblamic acid, and the bleomycins are in progress and will be reported in due course.

Acknowledgment. We gratefully acknowledge the financial support of the National Institute of Health (CA41986 and 42056).

Supplementary Material Available: Full experimental details and characterization of 9–13, 15–16, and 2 (11 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.

Spontaneous Free-Radical Formation in Reactions of *m*-Chloroperbenzoic Acid with *C*-Phenyl-*N*-*tert*-butylnitrone (PBN) and 3- or 4-Substituted PBN's

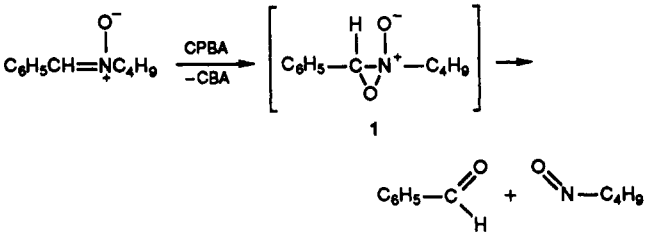
Edward G. Janzen,*,† Chiou-Rong Lin, and Randall D. Hinton

National Biomedical Center for Spin Trapping and Free Radicals,‡ Molecular Toxicology Research Program, Oklahoma Medical Research Foundation, 825 N.E. 13th Street, Oklahoma City, Oklahoma 73104

Received October 14, 1991

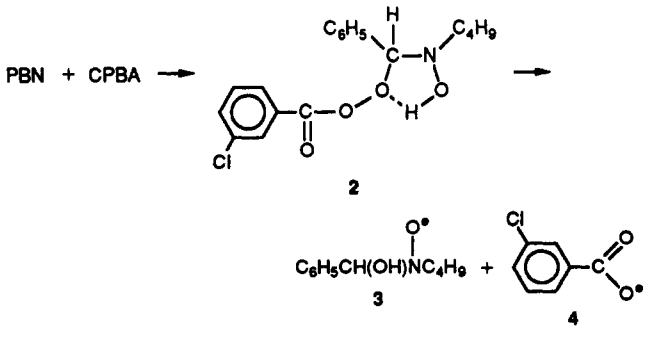
Summary: A molecular reaction between *m*-chloroperbenzoic acid and *C*-phenyl-*N*-*tert*-butylnitrone (PBN) produces significant amounts of aminoxyl radicals assigned to the *m*-chlorobenzoyloxyl adduct of PBN and benzoyl-*tert*-butylaminoxyl.

m-Chloroperbenzoic (CPBA) acid is commonly used as a reagent for producing epoxides from olefins.[1] *m*-Chlorobenzoic acid (CBA) is the only other product formed. In an analogous reaction with *C*-phenyl-*N*-*tert*-butylnitrone (PBN), the compounds benzaldehyde and 2-methyl-2-nitrosopropane might be produced since the oxazirane *N*-oxide 1 is not expected to be stable:



1

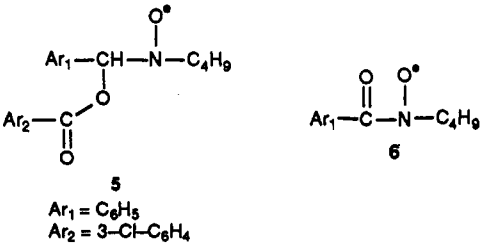
However, if a precursor molecular addition product is formed having the structure of the hydroxylamine of the peroxyl adduct 2 this addition product might be expected to produce aminoxyl radicals spontaneously by an internal redox reaction:



2

3 4

The products would be the hydroxyl adduct of PBN 3 and the *m*-chlorobenzoyloxyl radical 4. The latter should be readily trapped by PBN[2] to give the spin adduct 5.

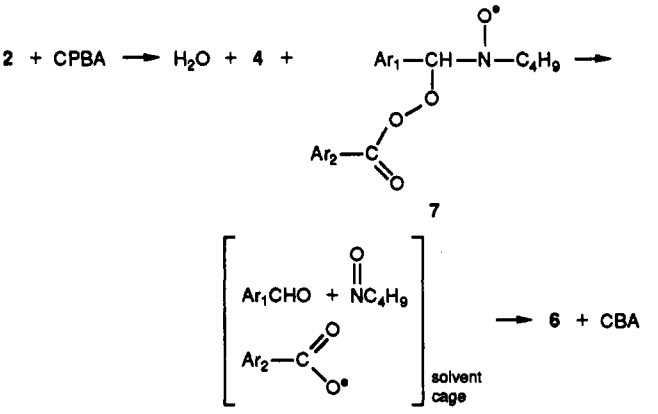


5

$Ar_1 = C_6H_5$
$Ar_2 = 3\text{-}Cl\text{-}C_6H_4$

6

Another mechanism involving oxidation of 2 before internal disproportionation is possible:



7

solvent cage

If the reaction within the solvent cage is very efficient then approximately equal amounts of 5 and 6 might be expected. Decomposition of peroxyl adducts is known to produce acyl aminoxyls 6 and oxyl adducts of PBN 5.[3] The benzoyloxyl adduct of 2-methyl-2-nitrosopropane (MNP) is not known. In general, oxyl adducts of MNP are not persistent aminoxyls at room temperature.

† Alternate Address: Departments of Clinical Studies and Biomedical Sciences, Ontario Veterinary College, University of Guelph, Guelph, Ontario, N1G2W1 Canada.

‡ Support by NIH Grant No. RR05517, awarded by The National Center for Research Resources.

(1) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley and Sons: New York, 1967; p 135–137.
(2) Janzen, E. G.; Evans, C. A.; Nishi, Y. *J. Am. Chem. Soc.* **1972**, *94*, 8236–8238.
(3) Janzen, E. G.; Krygsman, P. H.; Lindsay, D. A.; Haire, D. L. *J. Am. Chem. Soc.* **1990**, *112*, 8279–8284.

0022-3263/92/1957-1633$03.00/0