ion is energetically unfavorable, the direct transfer of a hydrogen atom from the *N*-methylacridan radical cation to the benzophenone radical anion is not expected to be observed. Rather, a proton is transferred to yield the benzophenone ketyl radical/*N*-methylacridan radical pair in the triplet state. Transfer of the final electron follows only after intersystem crossing. Consequently, the mechanism for hydride transfer in the Bph–NMA system is not directly relevant to the transfer mechanism in the ground state. The Fl–NMA system, however, is relevant to the discussion of single state hydride transfer because the first excited state of fluorenone does not intersystem cross on the time scale of the initial electron transfer.[8] Hence, the resulting Fl–NMA radical ion pair is in the singlet state. Even though hydrogen atom transfer is energetically feasible with the singlet ion pair, proton transfer is observed.

We have thus established, as illustrated in Scheme I, that the transfer of a hydrogen atom following the initial transfer of an electron in the hydride reduction of the excited state of benzophenone by *N*-methylacridan occurs as a proton–electron sequence. The contact ion pair formed in the photochemical reduction of fluorenone is presumably the same ion pair formed if the ground-state reduction were to involve an initial electron transfer. Thus, if the ground-state reduction of an aromatic ketone were to proceed by an initial electron transfer, the subsequent hydrogen atom transfer would follow the proton–electron sequence.

Acknowledgment. This work is supported by a grant from the National Science Foundation, CHE-8117519.

Registry No. Benzophenone, 119-61-9; fluorenone, 486-25-9; *N*-methylacridan, 4217-54-3; hydride, 12184-88-2; benzophenone compounds with *N*-methylacridan, 82902-40-7; hydroxydiphenylmethyl radical, 4971-41-9; *N*-methylacridinyl radical, 76723-27-8; α-phenylbenzenemethanol anion, 82902-41-8; *N*-methylacridinium, 13367-81-2; benzhydrol, 91-01-0; fluorenol, 1689-64-1.

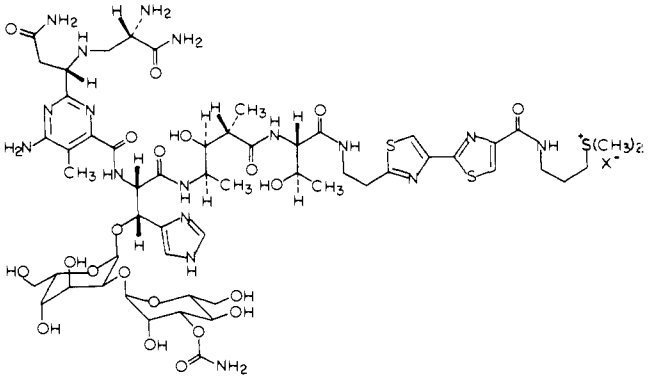
Total Synthesis of Bleomycin

Yoshiaki Aoyagi, Kiyoaki Katano, Hosbett Suguna, John Primeau, Li-Ho Chang, and Sidney M. Hecht*

Departments of Chemistry and Biology
University of Virginia, Charlottesville, Virginia 22901

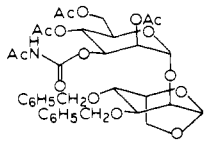
Received June 29, 1982

The bleomycins are a family of clinically useful antitumor antibiotics first isolated from *Streptomyces verticillus*.[1] Although the structure of bleomycin A_2 was first proposed 10 years ago[2] and later revised to that shown[3] (**1**), the complexity of the molecule

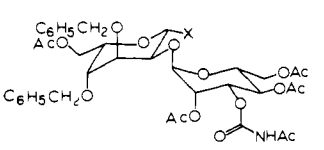


1

Chart I

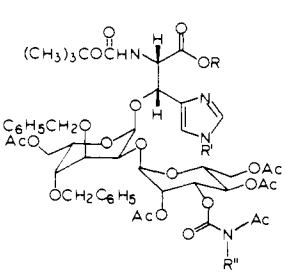


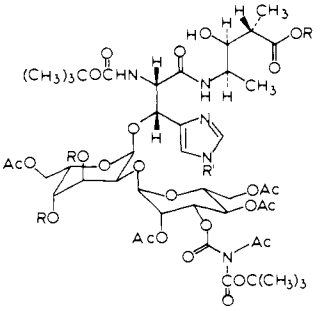
2



3, X = OAc

4, X = Cl





5, R = $CH_2C_6H_5$, R′, R″ = H

6, R = $CH_2C_6H_5$, R′, R″ = $COC(CH_3)_3$

7, R = H, R′, R″ = $COC(CH_3)_3$

8, R = $CH_2C_6H_5$, R′ = $COC(CH_3)_3$

9, R, R′ = H

and its noncrystalline nature have precluded verification of the assigned structure. Herein we report the total syntheses of bleomycin demethyl A_2 and bleomycin A_2 and a comparison of their properties with the respective natural products.[4]

Disaccharide **2**[5] (Chart I) was converted to 2-*O*-[2,4,6-tri-*O*-acetyl-3-*O*-(*N*-acetylcarbamoyl)-α-D-mannopyranosyl]-3,4-di-*O*-benzyl-6-*O*-acetyl-L-gulopyranosyl acetate (**3**) in quantitative yield (3:1 Ac_2O–AcOH, containing 1% H_2SO_4, 1 h, 0 °C). Disaccharide **3** was isolated as a chromatographically homogeneous white foam, which was converted to the respective gulopyranosyl chloride (**4**) (HCl, CH_2Cl_2, 12 h). The chloride, isolated in quantitative yield as a white foam after extractive workup, was used directly in the next step. Condensation of **4** with L-*erythro*-N^{α},N^{im}-di-*tert*-butoxycarbonyl-β-hydroxyhistidine benzyl ester[6] (CF_3SO_3Ag, $(CH_3)_2NCON(CH_3)_2$, $ClCH_2CH_2Cl$) at 45 °C for 12 h provided **5** as a white foam in 20–25% yield after purification by flash chromatography. Verification of the structure of **5** was accomplished via high-field ^1H and ^{13}C NMR spectroscopy.[7,8] This included identification of the anomeric proton of gulose as a doublet at δ 5.16 ($J \approx 3.0$ Hz) coupled to the (C_2–H) resonance at δ 3.92 and the observation in the carbon spectrum that both anomeric carbons (at 96.9 and 97.8 ppm) had large $^1J_{CH}$ values (175.4 and 174 Hz, respectively). Treatment of **5** with di-*tert*-butylpyrocarbonate (pyridine, 1 h, 25 °C) effected reprotection of N^{im} and also resulted in addition of a BOC group to the carbamoyl moiety; the product (**6**) was isolated in 77% yield as a pale yellow foam after purification by flash chromatography. When compound **6** was hydrogenated over 5% palladium on charcoal in EtOAc (1 atm of H_2, 2 h, 45 °C), selective deben-

(1) (a) Umezawa, H. *Lloydia* **1977**, *40*, 67. (b) Umezawa, H. *Prog. Biochem. Pharmacol.* **1976**, *11*, 18.

(2) Takita, T.; Muraoka, Y.; Yoshioka, T.; Fujii, A.; Maeda, K.; Umezawa, H. *J. Antibiot. (Tokyo)* **1972**, *25*, 755.

(3) Takita, T.; Muraoka, Y.; Nakatani, T.; Fujii, A.; Umezawa, Y.; Naganawa, H. *J. Antibiot. (Tokyo)* **1978**, *31*, 801.

(4) Other workers have recently described what is presumably a relay synthesis of bleomycin A_2. See: 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.

(5) Pozsgay, V.; Ohgi, T.; Hecht, S. M. *J. Org. Chem.* **1981**, *46*, 3761.

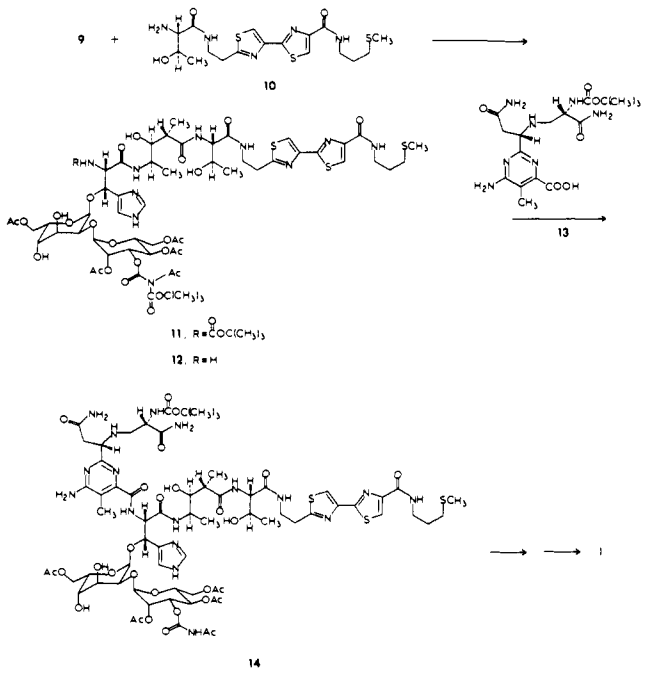
(6) Hecht, S. M.; Rupprecht, K. M.; Jacobs, P. M. *J. Am. Chem. Soc.* **1979**, *101*, 3982.

(7) Perlin, A. S. In "MTP International Review of Science, Carbohydrates, Organic Chemistry, Series Two"; Aspinall, G. O., Ed.; Butterworths: London, 1976; Vol. 7, pp 1–35.

(8) That the disaccharide was not attached to N^{im} of β-hydroxyhistidine (cf. ref 4) may also be judged by subsequent conversion of **5** to tri-*N*-BOC derivative **6** in good yield.

0002-7863/82/1504-5537$01.25/0

Scheme I



zylation of the ester was effected; free carboxylate **7** was isolated as a white foam in ~75–80% yield, $[\alpha]^{24}_D$ −9.3° (*c* 0.37, $CHCl_3$).

Condensation of **7** and benzyl (2*S*,3*S*,4*R*)-4-amino-3-hydroxy-2-methylvalerate[9] was carried out in CH_2Cl_2 (DCC, 1-hydroxybenzotriazole) at 25 °C for 3 h. The oily residue obtained after extractive workup was purified by flash chromatography, affording dipeptide analogue **8** as a white foam in 77% yield, $[\alpha]^{24}_D$ −12.2° (*c*, 2.3, C_2H_5OH), R_f 0.45 (silica gel TLC; 1:1 $CHCl_3$–EtOAc). Benzyl ester **8** was then dissolved in ethanol and hydrogenated over palladium black (1 atm of H_2, 55 °C) for 24 h, which effected removal of the benzyl groups and solvolysis of the N^{im}–BOC protecting group. The product (**9**)[10] was obtained in quantitative yield ($[\alpha]^{24}_D$ −0.3° (*c* 1.0, CH_3OH)) and in a good state of purity, as judged by silica gel TLC; it was used directly for condensation with "tripeptide S" derivative **10**[11] (DCC, 1-hydroxybenzotriazole) in DMF at 25° for 24 h (Scheme I). The pale yellow glass obtained after extractive workup of the reaction mixture was purified by chromatography on silica gel (elution with 5:1 $CHCl_3$–methanol). Compound **11** was obtained as a colorless glass in 61% yield. Removal of the BOC protecting groups (3:5 dimethyl sulfide–trifluoroacetic acid, 0 °C, 1 h) provided **12** in 59% yield as a colorless glass.

The final coupling of **12** (24 mg) with BOC–pyrimidoblamic acid (**13**)[12] (12 mg, 1.5 equiv) was effected via the agency of diphenylphosphoryl azide (DMF, 25 °C, 48 h). Following extractive workup (EtOAc–H_2O), deblocking of **14** was accomplished by successive treatments with 0.1 M NaOH (0 °C, 22 h) and 1:2 CH_3SCH_3–CF_3COOH (0 °C, 1 h). Chromatography on XAD-2 provided 21 mg of crude product, a portion of which provided pure bleomycin demethyl A_2 after chromatography on CM-Sephadex C-25. The purified sample, obtained as a colorless glass, was found to have chromatographic properties identical with authentic bleomycin demethyl A_2[13] on CM-Sephadex C-25 and silica TLC in several solvent systems. The synthetic and authentic samples also had identical 360-MHz ^1H NMR spectra. Bleomycin has recently been shown to effect epoxidation of *cis*-stilbene in the presence of Fe(III) and iodosobenzene;[14] the synthetic and authentic samples of bleomycin demethyl A_2 were both found to mediate this transformation. Moreover, the synthetic bleomycin demethyl A_2 solubilized radioactivity from [^3H]thymine-labeled *E. coli* DNA[15] to precisely the same extent as the authentic material. Conversion of synthetic bleomycin demethyl A_2 to bleomycin A_2 was carried out as described[16] and provided material identical with authentic bleomycin A_2 (**1**) in all respects. Bleomycin demethyl A_2 can be converted efficiently to bleomycinic acid[13] and therefore provides facile synthetic access to all of the naturally occurring bleomycins.

Acknowledgment. We thank Guy Ehrenfeld and Dr. Natesan Murugesan for carrying out the biochemical comparisons of synthetic and authentic bleomycins. Authentic bleomycin was obtained through the courtesy of Dr. William Bradner, Bristol Laboratories. This work was supported by PHS Research Grant CA27603, awarded by the National Cancer Institute, DHHS.

Supplementary Material Available: Listing of ^1H NMR spectral data for all new compounds prepared (1 page). Ordering information is given on any current masthead page.

(9) (a) Ohgi, T.; Hecht, S. M. *J. Org. Chem.* **1981**, *46*, 1232. (b) Narita, M.; Otsuka, M.; Kobayashi, S.; Ohno, M.; Umezawa, Y.; Morishima, H.; Saito, S.; Takita, T.; Umezawa, H. *Tetrahedron Lett.* **1982**, *23*, 525.

(10) Partial hydrolysis of one of the acetyl groups was noted in this intermediate. The mixture was transformed to **1** without separation.

(11) (a) Levin, M. D.; Subrahamanian, K., Katz, H.; Smith, M. B.; Burlett, D. J.; Hecht, S. M. *J. Am. Chem. Soc.* **1979**, *102*, 1452. (b) Aoyagi, Y.; Hecht, S. M., to be submitted for publication.

(12) (a) Umezawa, Y.; Morishima, H.; Saito, S.; Takita, T.; Umezawa, H.; Kobayashi, S.; Otsuka, M.; Narita, M.; Ohno, M. *J. Am. Chem. Soc.* **1980**, *102*, 6631. (b) Arai, H.; Hagmann, W. K.; Suguna, H.; Hecht, S. M. *Ibid.* **1980**, *102*, 6633.

(13) Obtained both by fractionation of blenoxane and by demethylation of bleomycin A_2. See: Tanaka, W.; Takita, T. *Heterocycles* **1979**, *13*, 469.

(14) Murugesan, N.; Ehrenfeld, G. M.; Hecht, S. M. *J. Biol. Chem.* **1982**, *257*, 8600.

(15) See, e.g.: Oppenheimer, N. J.; Rodriguez, L. O.; Hecht, S. M. *Biochemistry* **1980**, *19*, 4096.

(16) Roy, S. N.; Orr, G. A.; Brewer, C. F.; Horwitz, S. B. *Cancer Res.* **1981**, *41*, 4471.

Synthesis of β-Lactams by the Photolytic Reaction of Chromium Carbene Complexes with Imines

Michael A. McGuire and Louis S. Hegedus*

Department of Chemistry, Colorado State University
Fort Collins, Colorado 80523

Received July 6, 1982

Pentacarbonyl(methoxyalkyl- or -arylcarbene)chromium complexes are readily prepared by the reaction of chromium hexacarbonyl with alkyl- or aryllithium reagents, followed by alkylation with trimethyloxonium tetrafluoroborate.[1] Since the methoxy group can readily be replaced by nitrogen,[2] sulfur,[3] and carbon[4] nucleophiles, a wide range of differently substituted carbene complexes is readily available. Although the reactions of chromium carbene complexes have been extensively studied,[5] they have found only limited use in organic synthesis.[6] Recently chromium carbene complexes have been used in the synthesis of silyl-substituted vinylketenes,[7] cyclopropanes,[8] ketenimines,[9] indenones,[10] and naphthoquinones.[11]

(1) E. O. Fischer and R. Aumann, *Chem. Ber.*, **101**, 960, 963 (1968); **102**, 1495 (1969).

(2) E. O. Fischer and H.-J. Kollmeier, *Chem. Ber.*, **104**, 1339 (1971).

(3) E. O. Fischer, M. Leupold, C. G. Krieter, and J. Müller, *Chem. Ber.*, **105**, 150 (1972).

(4) C. P. Casey and T. J. Burkhardt, *J. Am. Chem. Soc.*, **95**, 5833 (1973).

(5) (a) E. O. Fischer, *Pure Appl. Chem.*, **24**, 407 (1970); (b) E. O. Fischer, *ibid.*, **30**, 353 (1972); (c) E. O. Fischer, *Angew. Chem.*, **86**, 651 (1974); (d) E. O. Fischer, *Adv. Organomet. Chem.*, **14**, 1 (1976).

(6) (a) C. P. Casey, in "Transition Metal Organometallics in Organic Synthesis", Vol. 1, H. Alper, Ed., Academic Press, New York, 1976, pp 189–233; (b) F. J. Brown, *Prog. Inorg. Chem.*, **27**, 1 (1980).

(7) K. H. Dötz and B. Fügen-Köster, *Chem. Ber.*, **113**, 1449 (1980).

(8) K. H. Dötz I. Pruskil, *Chem. Ber.*, **114**, 1980 (1981).

(9) G. G. Kreiter and R. Aumann, *Chem. Ber.*, **111**, 1223 (1978).

(10) K. H. Dötz and I. Pruskil, *Chem. Ber.*, **111**, 2059 (1978).

(11) (a) K. H. Dötz, R. Dietz, A. von Imhof, H. Lorentz, and G. Huttner, *Chem. Ber.*, **109**, 2033 (1976); (b) K. Dötz and R. Dietz, *ibid.*, **110**, 1555 (1977); (c) W. D. Wulff, P.-C. Tang, and J. S. McCallum, *J. Am. Chem. Soc.*, **103**, 7677 (1981).

0002-7863/82/1504-5538$01.25/0