$BuC(O)SiMe_3$, n^{20}_D 1.4258 (77% yield); and n-$Bu_2C(OH)SiMe_3$ (2.7% yield).

An examination of the scope of this reaction (Table I) showed that such $RLi/CO/Me_3SiCl$ acyltrimethylsilane syntheses are very successful when R is a primary alkyl group, linear or with branching in the β position or further out along the chain. With *tert*-butyllithium a 50% yield of pivaloyltrimethylsilane was obtained. With secondary alkyllithium reagents the chemistry is not as clean. Thus, such a reaction in which *sec*-butyllithium was used (with an identical procedure) gave the expected acylsilane, $MeEtCHC(O)SiMe_3$, in only 30% yield. Also formed was the carbinol, $(MeEtCH)_2C(OH)SiMe_3$ (17% yield), and $MeEtCHC(O)CH(OH)CHEtMe$ (9% yield). The latter is the hydrolysis product of the O-silylated acyllithium "dimer", $MeEtCH(OSiMe_3)C{=}C(OSiMe_3)CHEtMe$. Similar byproducts were obtained in the i-$PrLi/CO/Me_3SiCl$ reaction, which produced $Me_2CHC(O)SiMe_3$ in 28% yield.

It is clear that the complications of the two-step procedure have not been avoided entirely by using the in situ procedure. However, for the synthesis of acyltrimethylsilanes containing primary alkyl groups and of pivaloyltrimethylsilane, the in situ procedures can be used to good advantage: the reactions are fairly clean and they give satisfactory yields of the desired $RC(O)SiMe_3$ product. The success of this procedure is a consequence of the known[12] low reactivity of trimethylchlorosilane toward many alkyllithium reagents. Thus trimethylchlorosilane may be used in large excess in these $RLi/CO/Me_3SiCl$ reactions. The alkyllithium reacts more rapidly with carbon monoxide (to form the acyllithium) than with Me_3SiCl, even in the presence of a large quantity of the chlorosilane, so that in favorable cases the $RSiMe_3$ byproduct yield is below 25%. At the same time, in the favorable cases, the reaction of RC(O)Li with trimethylchlorosilane is sufficiently rapid at the low temperatures used so that RC(O)Li "dimerization" does not offer serious competition to the formation of $RC(O)SiMe_3$. We emphasize that the practical limits of success are very narrow indeed. The reaction proceeds well when triethylchlorosilane is used in place of trimethylchlorosilane (an 84% yield of n-$BuC(O)SiEt_3$ when n-BuLi was used), but acylsilane yields fall to zero when the reactivity of the chlorosilane toward nucleophilic attack is increased as a result of more favorable steric (e.g., Me_2HSiCl) or electronic (e.g., $Me_2PhSiCl$) factors. A change from R = alkyl in RLi also can be unproductive. Thus, when phenyllithium was used, not $PhC(O)SiMe_3$ was formed, at least under the conditions that give good product yields when R = primary alkyl. Also, the experimental conditions that result in good $RC(O)SiMe_3$ product yields are crucial. A low reaction temperature must be used, and a controlled, slow (~0.5 mmol/min) rate of addition of the alkyllithium solution is essential.

The provenance of the $R_2C(OH)SiMe_3$ byproduct is not certain. It could derive from RLi addition to the C=O bond of the acylsilane (a known reaction[9a,13]) or from reaction of a $[R_2CO]Li_2$ intermediate (of the type suggested to obtain in the PhLi/CO reaction[8]) with trimethylchlorosilane. It is not yet clear why the $RLi/CO/Me_3SiCl$ reaction does not proceed as well with secondary alkyllithium reagents.

The reactions described in this communication are the first examples of the successful trapping of acyllithium reagents in high yield in which the products isolated are those formed initially, and a useful, one-step synthesis of primary acyltrimethylsilanes from readily accessible alkyllithiums, carbon monoxide, and trimethylchlorosilane is now in hand. Further examination of the scope of this new acyltrimethylsilane synthesis is in progress.

New compounds have been characterized by combustion analysis and by proton NMR and IR spectroscopy. Yields were determined by gas–liquid chromatography using the internal standard method.

(12) Bey, A. E.; Weyenberg, D. R. *J. Org. Chem.* **1966**, *31*, 2036. For a more recent example see: Seyferth, D.; Wursthorn, K. R. *J. Organomet. Chem.* **1979**, *182*, 455.

(13) (a) Kuwajima, I.; Atsumi, K.; Tanaka, T.; Inoue, T. *Chem. Lett.* **1979**, 1239. (b) Reich, H. J.; Olson, R. E.; Clark, M. C. *J. Am. Chem. Soc.* **1980**, *102*, 1423. (c) Reich, H. J.; Rusek, J. J.; Olson, R. E. *Ibid.* **1979**, *101*, 2225.

Acknowledgment. We are grateful to the U.S. Air Force Office of Scientific Research (NC)-AFSC for generous support of this work and to Rhône Poulenc Co. for the award of a fellowship to R.M.W.

Note Added in Proof. We have found recently that trimethylchlorosilane does not need to be present in large excess in order to obtain satisfactory yields of an acyltrimethylsilane. For example, a reaction in which 2 mL (15.8 mmol) of Me_3SiCl and 7.0 mmol of n-BuLi were used gave a 65% yield (GLC) of n-$BuC(O)SiMe_3$. A reaction in which 11 mL (88 mmol) of Me_3SiCl and 7.0 mmol of n-BuLi were used gave a 67% yield of this product. Thus this acylsilane synthesis may be applied to reactions in which trialkylchlorosilanes other than the readily available and cheap Me_3SiCl are used.

Registry No. n-$C_4H_9C(O)SiMe_3$, 82903-02-4; n-$C_5H_{11}C(O)SiMe_3$, 63578-18-7; n-$C_6H_{13}C(O)SiMe_3$, 82903-03-5; $(CH_3)_2CHCH_2C(O)SiMe_3$, 63578-20-1; $(CH_3)_2CHCH_2CH_2C(O)SiMe_3$, 71821-71-1; $(CH_3)_3CC(O)SiMe_3$, 13411-49-9; $(CH_3)_2CHC(O)SiMe_3$, 56583-93-8; $C_2H_5CH(CH_3)C(O)SiMe_3$, 82903-04-6; n-C_4H_9Li, 109-72-8; n-$C_5H_{11}Li$, 3525-31-3; n-$C_6H_{13}Li$, 21369-64-2; $(CH_3)_2CHCH_2Li$, 920-36-5; $(CH_3)_2CHCH_2CH_2Li$, 7488-31-5; $(CH_3)_3CLi$, 594-19-4; $(CH_3)_2CHLi$, 1888-75-1; $C_2H_5CH(CH_3)Li$, 598-30-1; CO, 630-08-0; Me_3SiCl, 75-77-4.

Picosecond Dynamics of Hydride Transfer

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The mechanisms of carbonyl reduction by hydride-donating reagents has been extensively investigated.[1] The net transfer of a hydride may be conceived as proceeding through one of three mechanisms: direct hydride transfer or stepwise via an initial one-electron transfer followed by either a hydrogen atom transfer or a proton–electron transfer process. For the reducing reagents nicotinamide[2] and the metal hydrides,[3] there is supporting evidence for the initial transfer of an electron during the reduction of aromatic carbonyls. However, for these reactions there is no direct evidence pertaining to the pathway of subsequent hydrogen atom transfer, as in most instances the initial electron transfer is rate limiting, and thus subsequent transformations are relatively fast and the intermediates difficult to detect. If the rate of the initial electron transfer could be enhanced so that it were no longer rate limiting, these subsequent intermediates might then be detectable. A method for accelerating charge transfer is the photoexcitation of the oxidant, resulting in a lowering of its reduction potential by the energy of its excited state,[4] a method recently employed in our study of the photochemical reduction of benzophenone by aromatic amines.[5] In this communication we examined the phootoinduced hydride reduction of benzophenone (Bph) and fluorenone (Fl) by N-methylacridan (NMA)[6] in order to deter-

(1) For example see: Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449. Brown, H. C.; Krishnamurthy, S. *Ibid.* **1979**, *35*, 567. Sigman, D. S.; Hajdu, J.; Creighton, D. J. In "Bioorganic Chemistry"; van Tamelen, E. E., Ed.; Academic Press: New York, 1978; Vol. 4, Chapter 14. Bruice, T. C. In "Progress in Bioorganic Chemistry"; Kaiser, E. T., Kezdy, F. J. Ed.; Wiley: New York, 1976. Martens, F. M.; Verhoeven, J. W.; Gase, R. A.; Pandit, U. K.; DeBoer, Th. J. *Tetrahedron* **1978**, *34*, 443.

(2) (a) Creighton, D. J.; Hajdu, J.; Mooser, G.; Sigman, D. S. *J. Am. Chem. Soc.* **1973**, *95*, 6855. (b) Creighton, D. J.; Hajdu.; Sigman, D. S. *Ibid.* **1976**, *98*, 4619. (c) Hajdu, J.; Sigman, D. S. *Ibid.* **1976**, *98*, 6060.

(3) Ashby, E. C.; Boone, J. R. *J. Am. Chem. Soc.* **1976**, *98*, 5524.

(4) Rehm, D.; Weller, A. *Isr. J. Chem.* **1970**, *8*, 259.

(5) Simon, J. D.; Peters, K. S. *J. Am. Chem. Soc.* **1981**, *103*, 6403.

(6) N-methylacridan (NMA) was prepared by the method of Saito et al. (Saito, G.; Colter, A. K.; Sharom, F. J. *Can. J. Chem.* **1977**, *55*, 2741). To demonstrate the photochemical reduction of benzophenone (Bph) by NMA, we photolyzed a benzene solution of 0.001 M Bph + 0.1 M NMA + 0.1 M methanol at wavelengths between 350 and 380 nm. The reaction, which produced 1 equiv of N-methylacridinium ion (ϵ 26 000 L^{-1} M^{-1} s^{-1}) was monitored at 350 nm. Benzhydrol is produced. Identical results were obtained for the photolysis of 0.001 M Fl + 0.1 M NMA + 0.1 M methanol.

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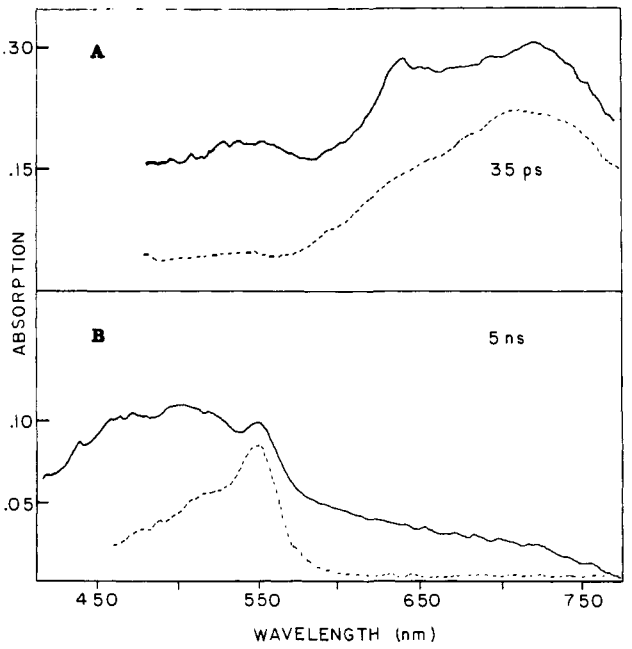


Figure 1. (A) Transient absorption spectrum observed 35 ps following 355-nm photolysis of Bph–NMA. Absorbance at 720 nm is 0.30 OD. The dashed line is the benzophenone radical anion absorption spectrum. (b) Transient absorption spectrum observed 5 ns following 355-nm photolysis af Bph–NMA. Absorbance at 545 nm is 0.10 OD. The dashed line is the benzophenone ketyl radical absorption spectrum.

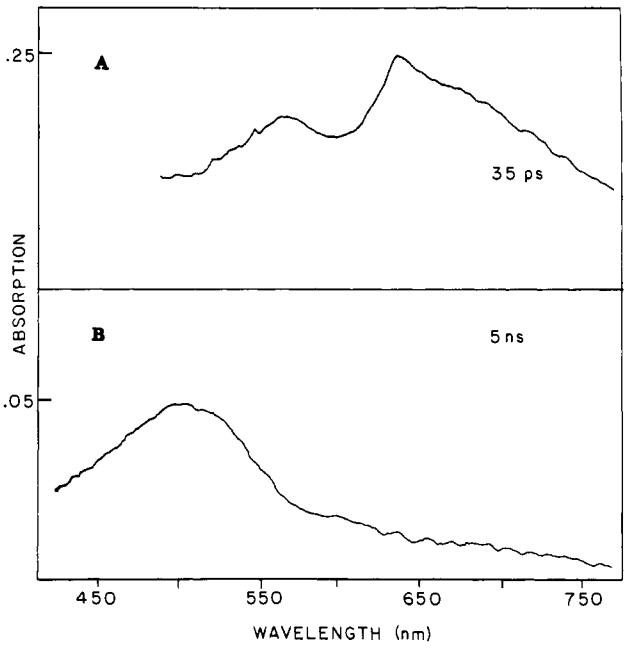


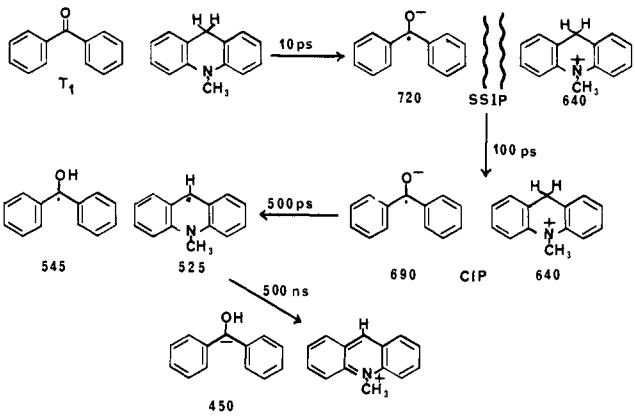
Figure 2. (a) Transient absorption spectrum observed 35 ps following 355-nm photolysis of Fl–NMA. Absorbance at 650 nm is 0.25 OD. (B) Transient absorption spectrum observed 5 ns following 355-nm photolysis of Fl–NMA. Absorbance at 525 nm is 0.05 OD.

mine the pathway of hydrogen atom transfer following an initial electron transfer. The hydrogen atom transfer occurs by a proton–electron sequence.

The experimental procedure for obtaining absorption spectra of photolysis intermediates with a time resolution of 25 ps has been previously described.[7] The energy of excitation at 355 nm was 0.5 mJ for a sample of optical density of 2.0 in a 2-mm flowing cell. Two chemical systems were investigated: 0.1 M Bph + 1 M NMA in benzene (Bph–NMA) and 0.1 Fl + 1 M NMA in benzene (Fl–NMA). Excitation of Bph–NMA at 355 nm results in the formation of the triplet state of benzophenone (λ_{max} 525 nm) within 10 ps. The benzophenone triplet is quenched in less than 25 ps with the concomitant formation of a transient spectrum characterized by two maxima, at 640 and 720 nm (Figure 1a). Similar behavior is observed for Fl–NMA except that only one transient with λ_{max} 640 nm is observed (Figure 2a). The absorption at 720 nm is known to be due to the radical anion of benzophenone.[5] Hence, the absorption at 640 nm is due to the radical cation of *N*-methylacridan. This assignment is confirmed by the Fl–NMA system, Figure 2A, in which the fluorenone radical anion is known to absorb only at wavelengths shorter than 600 nm.[8]

Subsequent to the formation of the benzophenone radical anion, the maximum of its absorption spectrum shifts from 720 to 690 nm with a half-life of 100 ± 50 ps. This shift has been previously observed and is the result of contact ion-pair formation from the solvent separated form.[5] Upon contact ion-pair formation, the transients with λ_{max} 640 and 690 nm decay with a half-life of 500 ± 100 ps to form the intermediates shown in Figure 1B. This spectrum is a composite of the benzophenone ketyl radical, λ_{max} 545 nm[5], and the *N*-methylacridinium radical, λ_{max} 525 nm, resulting from proton transfer within the contact ion pair. The assignment of the absorption at 525 nm to the *N*-methylacridinium radical is supported by the observation that the radical cation of *N*-methylacridan in the Fl–NMA system decays in 250 ± 75 ps

Scheme I



to form an intermediate with λ_{max} 525 nm (Figure 2B).[9]

For completion of the transfer of a hydride, a second electron must be transferred from the *N*-methylacridinium radical to the ketyl radical to form a hydroxydiphenylmethyl carbanion and *N*-methylacridinium ion. The absorption spectrum of the hydroxydiphenylmethyl carbanion is expected to have λ_{max} at approximately 450 nm.[10] When the transient absorption spectrum of Bph–NMA is monotored at 10 μs, the radical pair is no longer observed. A new transient with λ_{max} 448 nm is observed and is assigned to the hydroxydiphenylmethyl carbanion.

When analyzing the mechanism for the photochemical reduction of carbonyl, the spin state of the system must be considered. Photoexcitation of benzophenone results in the formation of the triplet state in less than 10 ps.[5] Triplet benzophenone reacts with ground-state single *N*-methylacridan to produce an overall triplet radical ion pair. The nature of the next step is determined by the energetics of the resulting *N*-methylacridan radical cation species: because the production of triplet state *N*-methylacridinium

(7) The interrogation times of ref 5 have been extended to 5, 10, 50, and 250 ns by the use of fiber optics. The 10 μs data were obtained by a PAR 1211 gated OMA 11 Vidicon (PAR-1215-1216-1205 I) used in conjunction with a tungsten–halogen lamp.

(8) Peters, K. S.; Freilich, S. C.; Shaefer, C. G. *J. Am. Chem. Soc.* **1980**, *102*, 5701.

(9) The 9-hydroxyfluorenyl radical, λ_{max} 500 nm (Davidson, R. S.; Santhanan, M., *J. Chem. Soc., Perkin Trans. 2* **1972**, 2355), is weakly absorbing and not detectable with our apparatus.

(10) Buncel, E., Menon, B. C.; Colpa, J. P. *Can. J. Chem.* **1979**, *57*, 999. The solvent-separated ion pair of diphenylmethyl lithium has λ_{max} 450 nm. Substitution of a hydroxyl group for a hydrogen should cause only a minor perturbation on the absorption spectrum.

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

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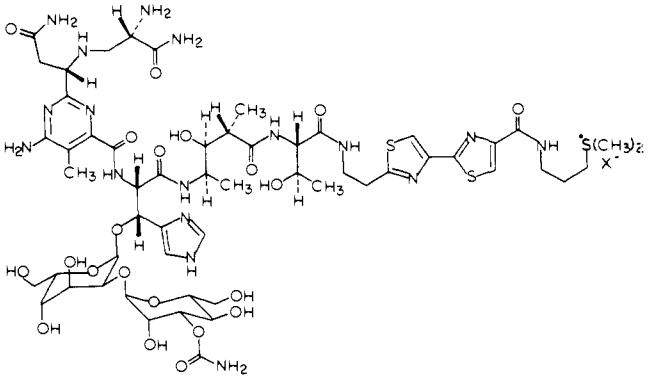
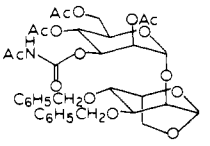
The bleomycins are a family of clinically useful antitumor antibiotics first isolated from *Streptomyces verticillus*.[1] Although the structure of bleomycin A_2 was first proposed 10 years ago[2] and later revised to that shown[3] (**1**), the complexity of the molecule



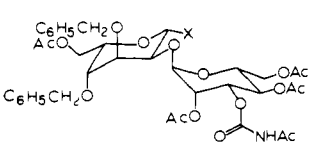
1

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]

Chart I

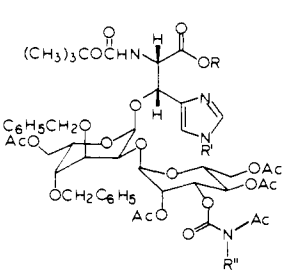


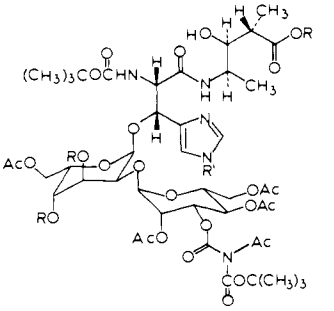
2



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

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.

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