Acknowledgment. Support of this research by Grant No. CA 11045 from the National Cancer Institue of the Public Health Service is gratefully acknowledged. We thank Dr. Masaru Moriyama for carrying out the experiment on the hydrolysis of **2**.

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(5) Phosphoranes **3** and **4** were prepared independently by photoreaction of **1** with EtOOEt and *i*-PrOOPr-*i* and purified by column chromatography (T. Kawashima, unpublished results). This study will be reported separately.

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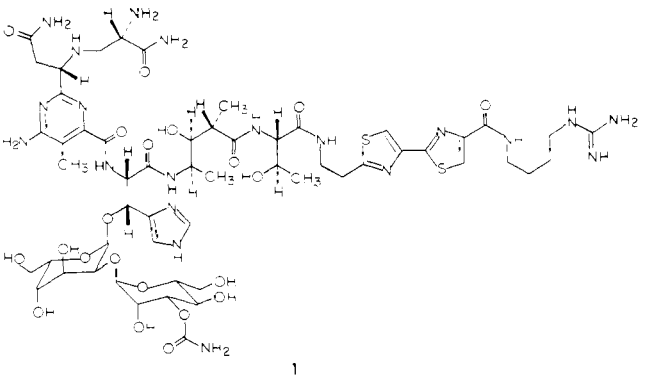
Synthesis of L-*erythro*-β-Hydroxyhistidine from D-Glucosamine

Sir:

Bleomycin is the generic name for a family of structurally related antitumor antibiotics elaborated by *Streptomyces verticillus;* the compounds are of current interest because of their clinically useful activity against squamous cell carcinomas and malignant lymphomas, including Hodgkin's disease.[1] As part of an effort to effect the total synthesis of bleomycin B_2 (**1**),[2] we have investigated methods suitable for the preparation of L-*erythro*-β-hydroxyhistidine,[3] a novel amino acid constituent of the glycopeptide-derived antibiotic.

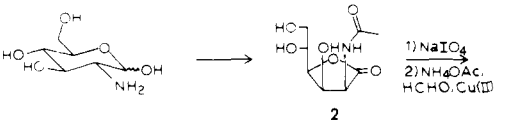
β-Hydroxyhistidine has been prepared previously by Takita et al.,[4] who obtained it in unspecified yield as a 2.5:1 mixture of the racemic erythro and threo species by treatment of imidazole-4-carboxaldehyde[5] with copper glycinate in sodium carbonate solution.[6] We found that substitution of *N*-pyruvylideneglycinatoaquocopper(II) dihydrate resulted in better (70–80%) yields of DL-*erythro*-β-hydroxyhistidine,[7] which could be resolved via the agency of D-amino acid oxidase. The



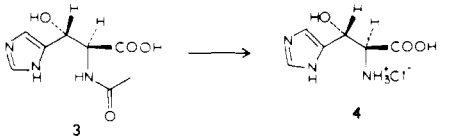
1

product had $[\alpha]^{25}_D$ +35° (*c* 1.34, H_2O), lit.[4] $[\alpha]^{28}_D$ +40° (*c* 1, H_2O). Although this improved procedure provided a workable route to L-*erythro*-β-hydroxyhistidine, a more efficient, stereospecific synthesis was sought.

2-Acetamido-2-deoxy-D-mannono-1,4-lactone (**2**) is a masked amino acid readily accessible from D-glucosamine.[9] Although lactones of this type undergo facile solvolysis,[11] it was possible to effect selective oxidative cleavage of the C-5–C-6 bond with aqueous $NaIO_4$ (1.0 equiv, 4 °C, 50 min) to afford the desired C-5 aldehyde, convertible directly to **3** after

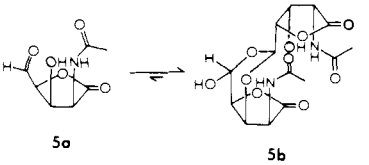


2



3 4

removal of $NaIO_3$ or isolable in quantitative yield as a white solid, mp 148–150 °C dec. In analogy with the work of Schaffer and Isbell[12a] and Inch[12b] on the structure of the species resulting from oxidation of 1,2-*O*-isopropylidene-α-D-glucofuranose, this solid was assigned structure **5b.** Consistent with its formulation as a (reversibly formed) hemiacetal dimer, the mass spectrum of **5** included a fragment ion at *m/e*



5a 5b

338 ($M^+ - 2H_2O$); the IR spectrum (KBr) had only a weak absorption at 2930 cm^{-1} corresponding to an aldehyde group, and the NMR (Me_2SO-d_6, Me_4Si) had a correspondingly small signal at δ 9.52 (10% of the integration that would have been expected for **5a**), as well as two sets of doublets of unequal intensity centered at δ 8.17 and 8.26 (NH, J = 9 Hz).[10] As anticipated, though, **5** could also be converted (65% yield) to the respective 2,4-dinitrophenylhydrazone, which was characterized fully.[13]

Conceptually, the conversion **5** → **3** involves simple solvolysis of the 1,4-lactone and construction of an imidazole utilizing C-4 and C-5 of the carbohydrate. In practice, however, these transformations proved somewhat more difficult to effect, since both are ordinarily carried out in the presence of strong bases and imidazole formation proceeds only at elevated temperature in the presence of Cu(II);[14] unfortunately both **3** and **5** decompose readily under these conditions. To maximize the production of **3**, and minimize its subsequent de-

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struction, **5** was dissolved in 6.8 M NH_4OAc, which was found to be capable of effecting solvolysis of the 1,4-lactone at 25 °C, and then heated (110 °C; 3 h) with 1.0 equiv of $Cu(OAc)_2$ and excess HCHO. These conditions were found to be optimal for the desired transformation. Workup (desalting on Biorex-70, crystallization from CH_3OH–EtOAc) gave N^{α}-acetyl-L-*erythro*-β-hydroxyhistidine as a pale green solid (Cu(II) complex of **3**) routinely in about 25% yield, $[\alpha]^{25}_D$ +28° (*c* 0.28, H_2O). As 2-acetamido-2-deoxy-D-mannono-1,4-lactones are known[10,11a] to epimerize readily at C-2 and to eliminate water in the presence of amines, and since an authentic sample of **3** decomposed slowly under the reaction conditions, careful characterization of the product was deemed necessary. After removal of Cu(II) (H_2S; Dowex 50-X8 (H^+ form)), the product was shown to be identical with authentic N^{α}-acetyl-DL-*erythro*-β-hydroxyhistidine as judged by paper chromatography in several solvent systems and NMR ((D_2O, external Me_4Si) δ 2.00 (s, 3), 4.66 (d, 1, J = 6 Hz), 5.28 (d, 1, J = 6 Hz), 7.41 (s, 1), and 8.66 (s, 1)), but not with an authentic sample of the N-acetylated threo isomer. Comparison with authentic samples after deacetylation in quantitative yield (1 M HCl, 3 h, 100 °C) demonstrated that the product had the erythro configuration; $[\alpha]^{25}_D$ +36° (*c* 0.96, H_2O).

Mechanistically, the formation of **4** must parallel the formation of other imidazoles from the respective α-hydroxyaldehydes and ketones. This could involve the well-precedented[15,16] Cu(II) oxidation of the α-hydroxyaldehyde derived from **5** to a dicarbonyl species, the latter of which could form the respective diimine. Condensation of the diimine with formaldehyde would then afford **3**. Alternatively, after solvolysis of **5** in aqueous NH_4OAc, the derived hydroxyaldehyde could react with 2 equiv of NH_3 to form a vicinal enediamine. Oxidation of this species before or after condensation with HCHO could also lead to the formation of **3**.[14,16] As Cu(II) binds tightly to **3**, it is also possible that the metal facilitates the transformation in a nonoxidative fashion. One may note, however, that formation of **3** using stoichiometric $Cu(OAc)_2$ in the absence of O_2, such that no Cu(II) was present at the end of the reaction, had essentially no effect on the yield of **3**.

Since the epimers of **4** were less easily accessible from imidazole-4-carboxaldehyde, it was also of interest to attempt their preparation in analogy with the transformations **2** → **3** → **4**. 2-Acetamido-2-deoxy-D-glucono-1,4-lactone was prepared as described[11b] and utilized for this purpose; its conversion to D-*threo*-β-hydroxyhistidine[17] was achieved in yields comparable to those obtained for **4**. On the basis of these experiments, it is suggested that 2-acetamido-2-deoxy-1,4-lactones may be of more general utility as convenient starting materials for the synthetic elaboration of amino acids having chirality at positions in addition to C^{α}.

Acknowledgment. This investigation was supported in part by Contract No. NO1-CM-43712 and Research Grant No. CA-22614 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare.

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(5) Accessible in ~45% overall yield via nitric acid oxidation of 4-hydroxymethylimidazole, the latter of which is commercially available as the picrate. See (a) J. R. Totter and W. J. Darby, "Organic Syntheses", Collect. Vol. III, Wiley, New York, 1955, p 460; (b) F. L. Pyman, *J. Chem. Soc.*, **109**, 186 (1916).

(6) Our efforts at optimization of this reaction afforded the four possible isomers of β-hydroxyhistidine in total yields up to ~20%. The ratio of diastereomers, which could be separated chromatographically with some difficulty (the erythro and threo isomers had R_f values of 0.35 and 0.22, respectively, on Whatman No. 1 paper, development with 80:20:4 methanol–H_2O–pyridine), was about the same as that noted previously.[4]

(7) In a typical experiment, imidazole-4-carboxaldehyde (7.5 g, 78 mmol) and *N*-pyruvylideneglycinatoaquocopper(II) dihydrate (19.5 g, 75 mmol) were stirred in 300 mL of H_2O for 4 h. The solution was acidified (HOAc, pH 4.5), treated with H_2S, and filtered.[8] After precipitation of the product from the neutralized filtrate with aqueous $HgCl_2$, the solid was dissolved in 1 M HCl and treated with H_2S; concentration of the filtrate (decolorization) gave DL-*erythro*-β-hydroxyhistidine hydrochloride (12.6 g, 81%) as a solid, contaminated with (<10%) DL-*threo*-β-hydroxyhistidine hydrochloride. Crystallization from H_2O–C_2H_5OH–*i*-C_3H_7OH gave **4** as colorless needles (11.0 g, 70%): mp 228 °C dec; NMR (D_2O, ext Me_4Si) δ 4.64 (d, 1, J = 3 Hz), 5.67 (d, 1, J = 3 Hz), 7.56 (s, 1), and 8.33 (s, 1).

(8) After filtration of Cu_2S, **4** could be obtained directly (albeit in lower yield) by adjusting the solution to pH 6.3–6.4 and permitting the free base to precipitate. Purification was then completed by recrystallization from water (personal communication from Dr. W. A. Szabo, Aldrich Chemical Co.).

(9) D-Glucosamine was oxidized to D-glucosaminic acid (69% yield) with yellow HgO (M. L. Wolfrom and M. J. Cron, *J. Am. Chem. Soc.*, **74**, 1715 (1952)) and then converted to 2-amino-2-deoxy-D-manno-1,4-lactone (77%) as described (P. A. Levene, *J. Biol. Chem.*, **36**, 73 (1918)). Acetylation (Ac_2O; Dowex 1-X4 (HCO_3^- form); vigorous stirring) gave **4** as colorless crystals in 81% yield. The same compound could also be obtained in a single step[10] by Br_2 oxidation of commercially available, albeit expensive, *N*-acetyl-D-mannosamine.

(10) N. Pravdic and H. G. Fletcher, Jr., *Carbohyd. Res.*, **19**, 339 (1971).

(11) See, e.g., (a) E. Zissis, H. W. Diehl, H. G. Fletcher, Jr., and N. Pravdic, *Carbohyd. Res.*, **28**, 327 (1973); (b) N. Pravdic, E. Zissis, M. Pokorny, and H. G. Fletcher, Jr., *ibid.*, **32**, 115 (1974).

(12) (a) R. Schaffer and H. S. Isbell, *J. Am. Chem. Soc.*, **79**, 3864 (1957); (b) T. D. Inch, *Carbohyd. Res.*, **5**, 53 (1967).

(13) In addition, compound **5** (mass spectrum *m/e* 338, 169, 141, and 99) could be oxidized at C-5 with 1.1 equiv of *m*-chloroperbenzoic acid, giving a colorless, crystalline product whose mass spectrum (*m/e* 141, 99, and 44) reflected facile loss of CO_2.

(14) H. Bredereck, R. Gompper, H. G. v. Schuh, and G. Thelig, in "Newer Methods of Preparative Organic Chemistry", Vol. 3, W. Foerst, Ed., Academic Press, New York, 1964, pp 245 ff.

(15) See, e.g., (a) M. Henze, *Hoppe-Seyler's Z. Physiol. Chem.*, **198**, 82 (1931); (b) M. Henze, *ibid.*, **200**, 232 (1931); (c) J. K. Hamilton and F. Smith, *J. Am. Chem. Soc.*, **74**, 5162 (1952).

(16) W. G. Nigh, in "Oxidation in Organic Chemistry", Part B, W. S. Trahanovsky, Ed., Academic Press, New York, 1973, pp 35 ff.

(17) D-*threo*-β-Hydroxyhistidine hydrochloride was obtained as a pale yellow solid (NMR (D_2O, ext Me_4Si) δ 4.60 (1 H, d, J = 4 Hz), 5.73 (1 H, d, J = 4 Hz), 7.70 (1 H, d, J = 1 Hz), and 8.87 (1 H, d, J = 1); $[\alpha]^{25}_D$ +15° (*c* 1.2, H_2O)) by acid hydrolysis of the initially formed N^{α}-acetyl-D-*threo*-β-hydroxyhistidine (NMR (D_2O, ext Me_4Si) δ 2.03 (3 H, s), 4.62 (1 H, d, J = 3.5 Hz), 5.48 (1 H, d, J = 3.5 Hz), 7.37 (1 H, s), and 8.47 (1 H, s); $[\alpha]^{25}_D$ −17° (*c* 1.25, H_2O)). Limited (<10%) conversion to the erythro species was observed during the synthesis of the threo isomer, presumably reflecting the greater thermodynamic stability of the former; the specific rotations given above for (N^{α}-acetyl)-D-*threo*-β-hydroxyhistidine are not corrected for the epimeric impurities.

(18) National Cancer Institute Career Development Awardee, 1975–1980; Alfred P. Sloan Research Fellow, 1975–1979; John Simon Guggenheim Fellow, 1977–1978.

(19) National Science Foundation Predoctoral Fellow, 1975–1978.

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A Facile Synthesis of Substituted *N*-Hydroxy-2-azetidinones. A Biogenetic Type β-Lactam Synthesis

Sir:

Synthesis of 2-azetidinones **1**, the basic structural unit of the β-lactam antibiotics, remains the object of considerable interest, especially because of the recent discovery of unusual, naturally occurring β-lactams.[1] β-Lactam ring synthesis has been approached from nearly every conceivable way.[2-4] For-

0002-7863/79/1501-3983$01.00/0