(21 mmol) of $Na_2S \cdot 9H_2O$, 0.10 g of triethylamine (1 mmol), and 20 mL of reagent grade methanol which was stirred magnetically at room temperature.

The flask became warm during the addition, a white and yellow precipitate formed on the sides of the reaction vessel, and N_2 gas was evolved. The mixture was stirred for 18–24 h, and then 25 mL of 5% hydrochloric acid was added slowly. After the mixture was stirred for 3–12 h, during which time it became homogeneous and the white precipitate dissolved, 25 mL of diethyl ether was added and the mixture stirred for another 0.5 h.

The two layers were separated, and the aqueous layer was washed with two 25-mL portions of ether. The organic layers were combined and washed with two 25-mL portions of water and then with saturated sodium chloride solution.

The ether layer was dried with anhydrous magnesium sulfate and filtered, and the ether was removed under vacuum to give the crude ketone or aldehyde.

The products were further purified by distillation for liquids or crystallization for solids.

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Registry No. 1 (R = Ph; R′ = H), 16722-99-9; 1 (R = Ph; R′ = CH_3), 28022-21-1; 1 (R = Br; R′ = H), 34910-43-5; 1 (R = H; R = *t*-Bu), 40168-86-3; 1 (R, R′ = $-C_6H_4$-2-CH_2-), 16719-57-6; 1 (R = R′ = $(CH_2)_6$), 40934-24-5; 1 (R = C(O)Ph; R′ = Ph), 26087-01-4; **2** (R = Ph; R′ = H), 98-86-2; **2** (R = Ph; R′ = CH_3), 93-55-0; **2** (R = Bu; R′ = H), 591-78-6; **2** (R = H; R′ = *t*-Bu), 2987-16-8; **2** (R, R′ = $-C_6H_4$-2-CH_2-), 83-33-0; **2** (R = R′ = $(CH_2)_6$), 502-49-8; **2** (R = C(O)Ph; R′ = Ph), 23464-17-7.

Studies on Biologically Active Nucleosides and Nucleotides. 6. An Anodic Oxidation of 2′,3′-*O*-Isopropylideneuridine-5′-carboxylic Acid

Kazuhiko Kondo and Ichizo Inoue*

Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co., Ltd., 16-89 Kashima-3-chome, Yodogawa-ku, Osaka 532, Japan

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In recent years there has been a great deal of interest in the preparation of $C_{4'}$-substituted nucleosides. Much of this interest is a result of the isolation and structure identification of the nucleoside antibiotic nucleosidin, 4′-fluoro-5′-*O*-sulfamoyladenosine, which has a unique structure bearing a fluorine atom at $C_{4'}$ of the sugar moiety.[1] Synthetic methods developed for the introduction of various substituents at $C_{4'}$ thus far have included (a) prior construction of suitable carbohydrate derivatives followed by coupling with activated bases,[2] (b) the aldol coupling of nucleoside-5′-aldehydes,[3] and (c) the addition reaction to the exocyclic vinyl ether moiety of 4′,5′-unsaturated nucleosides.[4] Recently, a novel $C_{4'}$-alkylation has been developed by exploiting a "Claisen-type" rearrangement of an N-alkylated 4′,5′-enamine derivative of uridine.[5]

The reactions of suitably protected 4′,5′-unsaturated nucleosides with halogenating agents, e.g., *N*-bromosuccinimide,[4a,b] bromine,[4f] and iodine,[4d] in methanol have been shown to give 5′-halogeno-4′-methoxy nucleosides. In the addition reactions, when the opportunity exists for intramolecular participation by the C_2 carbonyl of the pyrimidine ring or N^3 of the adenine ring at $C_{4'}$, the formation of 2,4′-[4b,6] or N^3,4′-cyclo-5′-halogeno nucleosides[7] has been observed.

It has been well documented that the anodic oxidation of carboxylic acids substituted by the electron donating group in the α position generates carbonium ions which are stabilized by charge delocalization.[8] The resulting carbonium ions can undergo nucleophilic attack by alcoholic or carboxylic acid solvents to form ethers or esters, respectively.[8] We conceived that electrolysis of nucleoside-5′-carboxylic acid in these solvents might provide 4′-alkoxy, 4′-acyloxy, and 2(N^3),4′-cyclo nucleosides via intermediary 4′-carbonium ions. Such nucleosides, which lack the 4′-hydroxymethyl group, are of interest as intermediates for the derivatization at $C_{4'}$ and with respect to their possible biological activity. We report herein results on the anodic oxidation of 2′,3′-*O*-isopropylideneuridine-5′-carboxylic acid (**1**) in methanol and acetic acid. Very recently, while our study was in progress, the synthesis of aminocyclitol via anodic oxidation of uronic acid was reported.[9]

The carboxylic acid **1** was prepared from uridine-5′-carboxylic acid in a good yield by a modification of the procedure previously described.[10] The electrolysis of **1** in methanol was carried out in the presence of a catalytic amount of sodium methoxide at 5–10 °C, using a graphite anode–graphite cathode in a nondivided cell. After 1.4 times a theoretical amount of current was passed, a mixture of products was separated into three major fractions by chromatography on silicic acid. The first fraction contained a roughly equal (NMR) mixture of 1-[2,3-*O*-isopropylidene-4(*R*)-methoxy-β-D-erythrofuranosyl]uracil (**4**) and 1-[2,3-*O*-isopropylidene-4(*S*)-methoxy-β-D-erythrofuranosyl]uracil (**5**) in a combined yield of 35%. The methoxy nucleoside could be resolved into its diastereoisomers by fractional crystallization, **4** and **5** being isolated in yields of 4 and 11%, respectively. The structures of **4** and **5** were confirmed by NMR spectroscopy. The spectra of both **4** and **5** showed the presence of a methoxyl group and the expected downfield shift of the $C_{4'}$ proton relative to that of **1**. In compound **4** the value of $J_{3',4'}$ was 4 Hz, while compound **5** had $J_{3',4'}$ = 0 Hz. These values are consistent with the assigned orientations (cis for **4** and trans for **5**) of $C_{3'}H$ and $C_{4'}H$.[11] In addition, the reported coupling data[12] for vicinal hydrogens in the

(1) (a) Morton, G. O.; Lancaster, J. E.; Van Lear, G. E.; Fulmor, W.; Meyer, W. E. *J. Am. Chem. Soc.* **1969**, *91*, 1535. (b) Hewitt, R. W.; Gumble, A. R.; Taylor, L. H.; Wallace, W. S. *Antibiot. Annu.* **1956–1957**, 722. (c) Tobie, E. J. *J. Parasitol.* **1957**, *43*, 291. (d) Stephan, L. E.; Gray, A. R. *Ibid.* **1960**, *46*, 509.

(2) (a) Leland, D. L.; Kotick, M. P. *Carbohydr. Res.* **1974**, C9. (b) Rosenthal, A.; Ratcliffe, M. *Ibid.* **1977**, *54*, 61.

(3) Youssefyeh. R.; Tegg, D.; Verheyden, J. P. H.; Jones, G. H.; Moffatt, J. G. *Tetrahedron Lett.* **1977**, 435.

(4) (a) Sasaki, T.; Minamoto, K.; Hattori, K. *J. Am. Chem. Soc.* **1973**, *95*, 1350. (b) Sasaki, T.; Minamoto, K.; Kuroyanagi, S.; Hattori, K. *Tetrahedron Lett.* **1973**, 2731. (c) Verheyden, J. P. H.; Jenkins, I. D.; Owen, G. R.; Dimitrijevich, S. D.; Richards, C. M.; Srivastava, P. C.; Le-Hong, N.; Moffatt, J. G. *Ann. N.Y. Acad. Sci.* **1975**, *255*, 151. (d) Verheyden, J. P. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1975**, *97*, 4386. (e) Cook, S. L.; Secrist III, J. A. *Carbohydr. Res.* **1976**, *52*, C3. (f) Jenkins, I. D.; Verheyden, J. P. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1976**, *98*, 3346. (g) Owen, G. R.; Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1976**, *41*, 3010.

(5) Secrist III, J. A.; Winter, W. J., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 2554.

(6) Sasaki, T.; Minamoto, K.; Asano, T.; Miyake, M. *J. Org. Chem.* **1975**, *40*, 106.

(7) McCarthy, J. R.; Robins, R. K.; Robins, M. J. *J. Am. Chem. Soc.* **1968**, *90*, 4993.

(8) See, e.g.: Ross, S. D.; Finkelstein, M.; Rudd, E. J. "Anodic Oxidation"; Academic Press: New York, 1975; Chapter 7.

(9) Kitagawa, T.; Yoshikawa, M.; Ohmori, H. "Abstracts of Papers", 98th Annual Meeting of the Pharmaceutical Society of Japan, Apr. 1978; Okayama; No. 5K11-4.

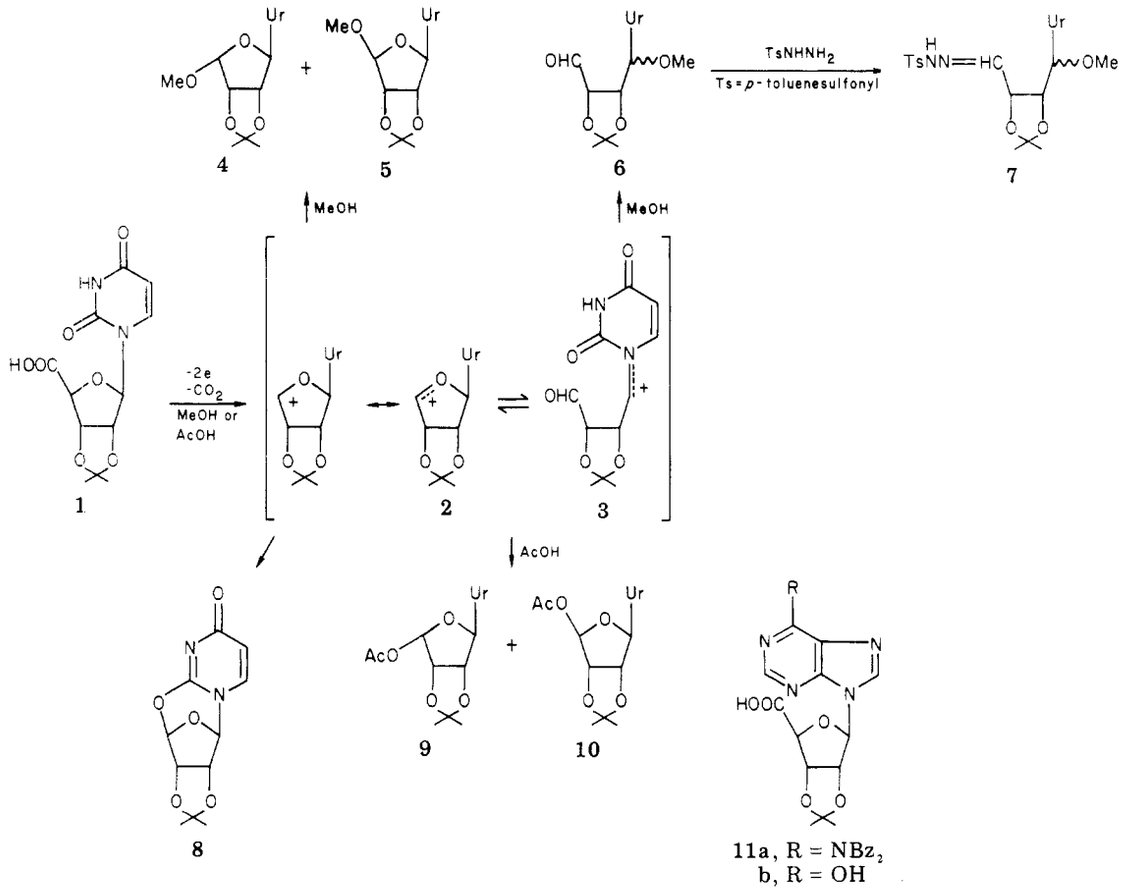
(10) Moss, G. P.; Reese, C. B.; Schofield, K.; Shapiro, R.; Todd, L. *J. Chem. Soc.* **1963**, 1149.

(11) (a) Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11. (b) Pitzer, K. S.; Donath, W. E. *J. Am. Chem. Soc.* **1959**, *81*, 3213.

(12) Imbach, J.-L. *Ann. N.Y. Acad. Sci.* **1975**, *255*, 177.

0022-3263/79/1944-4713$01.00/0

Scheme I



closely related α ($J_{1,2}$ = 4 Hz) and β (C_1H singlet) anomers of methyl 2,3-*O*-isopropylidene-D-ribofuranoside support these assignments.

The second fraction contained a roughly 2:1 mixture of diastereoisomeric 2(*S*),3(*R*)-dihydroxy-2,3-*O*-isopropylidene-4-methoxy-4-(uracil-1-yl)butyraldehydes (**6**) together with a small amount of impurity, as judged by NMR analysis. The spectrum in $CDCl_3$ showed the methoxyl (3.20 and 3.42 ppm) and formyl (9.65 and 9.72 ppm) groups as a pair of singlets. Attempts to isolate pure **6** by crystallization were unsuccessful. Therefore, **6** was transformed into its *p*-toluenesulfonylhydrazone (**7**) by treatment with *p*-toluenesulfonylhydrazine. By crystallization one diastereoisomer of **7** could be isolated in an overall yield of 11% from **1**. The NMR spectrum of this compound in Me_2SO-d_6 showed the absence of formyl proton and the presence of both the azomethine proton as a doublet ($J_{1,2}$ = 6.5 Hz) at 7.20 ppm and the methoxyl protons as a singlet at 3.10 ppm. No attempt was made to isolate the hydrazone of another isomer.

The third fraction contained 2,4′-didehydro-1-(2′,3′-*O*-isopropylidene-β-D-erythrofuranosyl)uracil (**8**) which was isolated in crystalline form in 20% yield. Confirmation of the structural assignment of **8** was obtained from its ultraviolet (UV) and NMR data. The UV spectrum of **8** was very similar to those of 2,4′-didehydro-1-(α-L-lyxosyl)uracil derivatives[6] and showed maxima at 231 and 248 (shoulder) nm. The NMR spectrum in Me_2SO-d_6 showed the $C_{4'}$ proton as a singlet at 6.20 ppm which overlapped the $C_{1'}$ proton. The downfield position of $C_{4'}H$ strongly supports the 2,4′-cyclo structure. As anticipated, the cyclo nucleoside **8** was susceptible to nucleophilic attack on the $C_{4'}$ position. Thus, compound **8** was converted into a mixture of 4(*R*)-methoxy and 4(*S*)-methoxy nucleosides (**4** and **5**) in a ratio of 1:2 (NMR) by refluxing with methanol; no ring-opening product **6** was detected in the reaction.

The use of platinum anode gave roughly comparable results as that of the graphite anode except for the relative proportion of **4** and **5**. Examination of the reaction mixture by high-pressure liquid chromatography indicated that at the graphite anode the ratio of **4** to **5** was roughly 1:1, whereas at the platinum anode it was roughly 1:2. For the moment, we see no explanation for the stereoselectivity shown in the methanolysis and the electrolysis at the platinum anode.

The mechanism of the anodic oxidation of **1** in methanol most likely involves initial formation of the carbonium ion which would be stabilized as an oxonium ion **2** (Scheme I). Subsequent attack by methanol to this species would then give rise to the methoxy nucleoside **4** or **5**, while participation by the C_2 carbonyl of the uracil ring would form the cyclo nucleoside **8**. The oxonium ion **2** could be equilibrated to a ring-opening intermediate **3**, which would react with methanol to give the aldehyde **6**. The possibility of the formation of the methoxy nucleosides **4** and **5** via the cyclonucleoside **8** can be excluded because compound **8** was stable under the electrolysis conditions.

The anodic oxidation of **1** in acetic acid was carried out under the conditions similar to those used in the electrolysis in methanol. Unexpectedly, the reaction accompanied severe discoloration and led to a complex mixture of products. By a combination of column chromatography on silicic acid and fractional crystallization, 1-[4(*S*)-acetoxy-2,3-*O*-isopropylidene-β-D-erythrofuranosyl]uracil (**9**) and 1-[4(*R*)-acetoxy-2,3-*O*-isopropylidene-β-D-erythrofuranosyl]uracil (**10**) were isolated in yields of 7 and 4%, respectively. The NMR spectra of these compounds showed the presence of an acetoxy function, and the $C_{4'}$ proton was deshielded by roughly 1.8 ppm relative to that

in **1**. As in the case of 4′-methoxy nucleosides **4** and **5**, the assignment of configuration at $C_{4'}$ was made on the basis of the coupling constant ($J_{3',4'}$ = 4 Hz for **9** and 0 Hz for **10**) observed for the $C_{4'}$ proton. Unlike the electrolysis in methanol, only a trace amount of the cycle nucleoside **8** could be detected in the reaction mixture by TLC analysis.

The formation of the acetoxy nucleosides **9** and **10** would be explained by attack of acetic acid on the $C_{4'}$ of the oxonium ion intermediate **2**. In acidic media, the cyclo nucleoside **8** formed could be equilibrated to the oxonium ion **2** by protonation at N^3 and would undergo acetolysis to give the acetoxy nucleosides **9** and **10** during the electrolysis. This mechanism is consistent with the observation that treatment of the cyclo nucleoside **8** with acetic acid at ambient temperature for 2 h gave a roughly equal (NMR) mixture of the acetoxy nucleosides **9** and **10**. An alternate explanation for the formation of **9** and **10** involves an S_N2 type of displacement at $C_{4'}$ of the initially formed cyclo nucleoside **8** by acetate anion giving the 4(*S*)-acetoxy isomer **9**. Subsequent epimerization of **9** would give the observed products **9** and **10**. This possibility, however, can be excluded because no epimerization of compound **9** was observed (TLC) under the electrolysis conditions. While the electrolysis of **1** and the solvolysis of **8** could proceed via the common oxonium ion intermediate **2**, from the above it is clear that there is a distinct difference in the distribution of products. This may be due to an unsolvated or less solvated cation character[13] of **2** generated by the anodic decarboxylation.

Extension of the anodic oxidation to purine nucleosides was not successful. Thus, electralysis of N^6,N^6-dibenzoyl-2′,3′-*O*-isopropylideneadenosine-5′-carboxylic acid (**11a**) or 2′,3′-*O*-isopropylideneinosine-5′-carboxylic acid (**11b**)[14] in methanol under the conditions similar to those above led to a very complex mixture of products and has not been explored further.

Experimental Section

Melting points are uncorrected. Proton magnetic resonance (NMR) spectra were determined at 60 MHz with a Hitachi Perkin-Elmer R20A spectrometer and at 100 MHz with a JEOL PS-100 spectrometer. Spectra are recorded in parts per million downfield of an internal standard of tetramethylsilane. Ultraviolet (UV) spectra were recorded on a Hitachi EPS-3T spectrometer. High-pressure liquid chromatography (high-pressure LC) was done using a Waters 244 instrument. The parameters: column (μBondapak, NH_2) size, 0.4 × 30 cm; solvent, 1:1:8 MeOH–$CHCl_3$–*n*-C_6H_{14}; flow rate, 1.5 mL/min, building up a back pressure of about 500 psi; elution is monitored with a UV detector (254 nm). Thin-layer chromatography (TLC) was performed on Merck pre-coated TLC plates (silica gel 60 F-254). Column chromatography was done using Merck silica gel 60 (0.05–0.20 mm particle size). The electrolyses were carried out by use of a Hokuto Potentio-Galvanostat HA 104 (1A-55V) attached to a Hokuto HA-108A Coulomb meter.

2′,3′-*O*-Isopropylideneuridine-5′-carboxylic Acid (1). A suspension of uridine-5′-carboxylic acid[10] (2.5 g, 9.7 mmol), 2,2-dimethoxyethane (6.5 g, 63 mmol), and dried (by azeotropic distillation with benzene) Daiaion SK-1B (H^+ form, 12.5 g) in dry acetone (600 mL) was stirred at room temperature for 2.5 h. The mixture was filtered, and the filtrate was evaporated to dryness in vacuo. The residue was crystallized from acetone–Et_2O, giving 2.2 g (76%) of **1**: mp 185–186 °C (lit.[10] mp 187–188 °C); NMR (Me_2SO-d_6, 60 MHz) δ 1.30 and 1.46 (s, 3, CMe_2), 4.55 (s, 1, C_4′H), 5.19 (s, 2, C_2′H and C_3′H), 5.60 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.74 (s, 1, C_1′H), 7.74 (d, 1, C_6H), 11.28 (br s, 1, NH), 12.65 (br s, 1, CO_2H).

Electrolysis of 1 in Methanol. A graphite anode (5.5 × 8 cm) was placed ~2 mm apart from a graphite cathode in an ordinary beaker. A solution of **1** (6 g, 20.1 mmol) in MeOH (300 mL) was put in the electrolysis cell. After addition of 1 N NaOMe (0.4 mL), the solution was electrolyzed at a constant current of 500 mA at 5 °C. The amount of current passed was 55 mFaradays. The electrolyzed solution was evaporated to dryness in vacuo below 30 °C, and a solution of the residue in $CHCl_3$ was applied to a 3.8 × 63 cm column of silicic acid. Elution with $CHCl_3$–MeOH (97:3) gave 2.0 g (35%) of a mixture of 1-[2,3-*O*-isopropylidene-4(*R*)-methoxy-β-D-erythrofuranosyl]uracil (**4**) and 1-[2,3-*O*-isopropylidene-4(*S*)-methoxy-β-D-erythrofuranosyl]uracil (**5**) (**4**/**5** roughly 1:1 by NMR) as a syrup in the first fraction. Crystallization of the syrup from H_2O (10 mL) gave 0.65 g (11%) of **5**: mp 195–197 °C; UV λ_{max} (MeOH) 260 nm (ε 9200); NMR (Me_2SO-d_6, 100 MHz) δ 1.30 and 1.44 (s, 3, CMe_2), 3.22 (s, 3, OMe), 4.77 (d, 1, $J_{2',3'}$ = 6 Hz, C_3′H), 5.09 (d, 1, C_2′H), 5.10 (s, 1, C_4′H), 5.64 (dd, 1, $J_{5,6}$ = 8 Hz, $J_{5,NH}$ = 2 Hz, C_5H), 6.07 (s, 1, C_1′H), 7.40 (d, 1, C_6H), 11.20 (br s, 1, NH).

Anal. Calcd for $C_{12}H_{16}N_2O_6$ (248.28): C, 50.70; H, 5.67; N, 9.86. Found: C, 50.68; H, 5.89; N, 9.68.

The mother liquor from the crystallization was evaporated to dryness, and the residue was crystallized from 2-PrOH. This material was recrystallized from MeOH to yield 0.25 g (4%) of **4**: mp 225–228 °C; UV λ_{max} (MeOH) 260 nm (ε 9300); NMR (Me_2SO-d_6, 100 MHz) 1.28 and 1.43 (s, 3, CMe_2), 3.39 (s, 3, OMe), 4.88 (dd, 1, $J_{2',3'}$ = 6 Hz, $J_{3',4'}$ = 4 Hz, C_3′H), 4.98 (d, 1, C_2′H), 5.18 (d, 1, C_4′H), 5.60 (dd, 1, $J_{5,6}$ = 8 Hz, $J_{5,NH}$ = 2 Hz, C_5H), 5.73 (s, 1, C_1′H), 7.65 (d, 1, C_6H), 11.42 (br s, 1, NH).

Anal. Calcd for $C_{12}H_{16}N_2O_6$ (248.28): C, 50.70; H, 5.67; N, 9.86. Found: C, 50.57; H, 5.82; N, 9.81.

Evaporation of the second fraction gave 1.3 g of 2(*S*),3(*R*)-dihydroxy-2,3-*O*-isopropylidene-4-methoxy-4-(uracil-1-yl)-butyraldehyde (**6**) as a froth that could not be crystallized: NMR ($CDCl_3$, 60 MHz) δ 3.20 and 3.42 (s, total 3, OMe), 9.65 and 9.72 (s, total 1, CHO). This material was shown by NMR to be a roughly 2:1 mixture of diastereoisomers and contaminated with a small amount of impurity. For characterization, the crude product was converted into its *p*-toluenesulfonylhydrazone (**7**) as follows.

A solution of crude **6** (1.2 g) and *p*-toluenesulfonylhydrazine (0.79 g, 4.2 mmol) in AcOEt (2.5 mL) was stored at room temperature for 19 h. The resulting crystals were collected by filtration and washed with AcOEt, giving 1.0 g (11%) of **7** with mp 140–142 °C dec. An analytical sample from AcOEt had mp 142–143 °C dec. This substance was shown by NMR to be a single diastereoisomer: UV λ_{max} (MeOH) 235 nm (ε 12900), 260 (sh, 9000); NMR (Me_2SO-d_6, 60 MHz) δ 1.27 and 1.43 (s, 3, CMe_2), 2.40 (s, 3, Ar**Me**), 3.10 (s, 3, OMe), 4.40 (dd, 1, $J_{3,4}$ = 2 Hz, $J_{2,3}$ = 6.5 Hz, C_3H), 4.66 (t, 1, $J_{1,2}$ = 6 Hz, C_2H), 5.20 (d, 1, C_4H), 5.64 (dd, 1, $J_{5,N^3\text{-H}}$ = 2 Hz, $J_{5,6}$ = 8 Hz, C_5H), 7.20 (d, 1, CH=N), 7.3–7.9 (m, 5, ArH, C_6H), 11.34 (d, 1, N^3-H), 11.53 (s, 1, NNH).

Anal. Calcd for $C_{19}H_{24}N_4O_7S{\cdot}H_2O$ (470.52): C, 48.50; H, 5.57; N, 11.91. Found: C, 48.76; H, 5.62; N, 12.03.

The third fraction gave 1.0 g (20%) of 2,4′-didehydro-1-(2′,3′-*O*-isopropylidene-β-D-erythrofuranosyl)uracil (**8**) with mp 275–276 °C dec. An analytical sample from EtOH had: mp 276–277 °C dec; UV λ_{max} (MeOH) 231 nm (ε 12800), 248 (sh, 8000); NMR (Me_2SO-d_6, 60 MHz) δ 1.30 and 1.42 (s, 3, CMe_2), 5.08 (s, 2, C_2′H, C_3′H), 5.87 (d, 1, $J_{5,6}$ = 7.5 Hz, C_5H), 6.18 (s, 1, C_1′H or C_4′H), 6.20 (s, 1, C_1′H or C_4′H), 7.64 (d, 1, C_6H).

Anal. Calcd for $C_{11}H_{12}N_2O_5$ (252.14): C, 52.38; H, 4.80; N, 11.11. Found: C, 52.40; H, 5.02; N, 11.03.

Electrolysis of 1 in Acetic Acid. A graphite anode (4 × 8 cm) was placed ~2 mm apart from a graphite cathode in a beaker. A solution of **1** (2.0 g, 6.7 mmol) in AcOH–tetrahydrofuran (3:1, 120 mL) was put in the electrolysis cell. After the addition of triethylamine (0.16 mL), the solution was electrolyzed at a constant current of 600 mA at 15 °C. The reaction was discontinued when 67 mFaradays passed. The electrolyzed solution was evaporated to dryness in vacuo below 40 °C, and the residue was coevaporated several times with benzene. The final residue was chromatographed on a 2.3 × 70 cm column of silicic acid, using AcOEt–benzene (1:1). Evaporation of the first fraction followed by crystallization of the residue from AcOEt–Et_2O gave 0.15 g (7%) of 1-[4(*S*)-acetoxy-2,3-*O*-isopropylidene-β-D-erythrofuranosyl]uracil (**9**): mp 138–139 °C; λ_{max} (MeOH) 258 nm (ε 10600); NMR ($CDCl_3$, 60 MHz) δ 1.40 and 1.58 (s, 3, CMe_2), 2.15 (s, 3, OAc),

(13) See, e.g.: (a) Skell, P. S.; Reichenbacher, P. H. *J. Am. Chem. Soc.* **1968**, *90*, 2309. (b) Reference 8, pp 169–173.

(14) Schmidt, R. R.; Schloz, U.; Schwille, D. *Chem. Ber.* **1968**, *101*, 590.

5.05 (d, 1, $J_{2',3'}$ = 6 Hz, C_2·H), 5.23 (dd, 1, $J_{3',4'}$ = 4 Hz, C_3·H), 5.58 (s, 1, C_1·H), 5.73 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.37 (d, 1, C_4·H), 7.18 (d, 1, C_6H), 9.83 (br s, 1, NH).

Anal. Calcd for $C_{13}H_{16}N_2O_7$ (312.29): C, 50.00; H, 5.17; N, 8.97. Found: C, 50.00; H, 5.30; N, 8.73.

Evaporation of the second fraction left a syrup that was crystallized from AcOEt–benzene, giving 0.09 g (4%) of 1-[4-(*R*)-acetoxy-2,3-*O*-isopropylidene-β-D-erythrofuranosyl]uracil (**10**): mp 137–138 °C; λ_{max} (MeOH) 258 nm (ε 10 700); NMR ($CDCl_3$, 60 MHz) 1.35 and 1.53 (s, 3, CMe_2), 2.07 (s, 3, OAc), 4.84 (d, 1, $J_{2',3'}$ = 6 Hz, C_2·H), 5.13 (d, 1, C_3·H), 5.72 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.92 (s, 1, C_1·H), 6.29 (s, 1, C_4·H), 7.27 (d, 1, C_6H), 9.25 (br s, 1, NH).

Anal. Calcd for $C_{13}H_{16}N_2O_7$ (312.29): C, 50.00; H, 5.17; N, 8.97. Found: C, 49.87; H, 5.23; N, 8.93.

Methanolysis of 8. A solution of **8** (50 mg) in MeOH (2 mL) was heated under reflux for 6 h. Evaporation of the solvent in vacuo gave a crystalline solid which was shown by NMR to consist of **4** and **5** in a ratio of 1:2.

Acetolysis of 8. A solution of **8** (300 mg) in AcOH (2 mL) was stored at room temperature for 2 h. The solvent was removed in vacuo, and the residue was coevaporated several times with AcOEt, giving a syrup which was shown by NMR to consist of **9** and **10** in a ratio of 1:1.

N^6,N^6-Dibenzoyl-2′,3′-*O*-isopropylideneadenosine-5′-carboxylic acid (**11a**) was prepared from 2′,3′-*O*-isopropylideneadenosine-5′-carboxylic acid[15] by condensation with benzyl alcohol, using *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, followed by N^6,N^6-dibenzoylation with benzoyl chloride in pyridine and catalytic hydrogenation of the benzyl group in the presence of Pearlman catalyst[16] in AcOEt. The crude product was purified by crystallization from 1,2-dimethoxyethane to give the acid **11a** as the solvate: mp 119–120 °C dec; λ_{max} (MeOH) 251 nm (ε 39 400) 278 (sh, 31 100); NMR ($CDCl_3$, 60 MHz) δ 1.38 and 1.59 (s, 3, CMe_2), 3.39 (s, 6, MeO's), 3.54 (s, 4, OCH_2CH_2O), 4.75 (s, 1, C_4·H), 5.37 (s, 2, C_2·H, C_3·H), 6.29 (s, 1, C_1·H), 7.2–8.0 (m, 10, ArH), 8.48 (s, 1, C_2H or C_8H), 8.52 (s, 1, C_2H or C_8H), 10.25 (br s, 1, CO_2H).

Anal. Calcd for $C_{27}H_{23}N_5O_7 \cdot C_4H_{10}O_2$ (619.64): C, 60.09; H, 5.37; N, 11.30. Found: C, 60.01; H, 5.54; N, 11.27. The overall yield was 53%.

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Registry No. 1, 71774-76-0; 4, 71774-77-1; 5, 71806-80-9; 6 isomer A, 71774-78-2; 6 isomer B, 71806-81-0; 7, 71774-79-3; 8, 71774-80-6; 9, 71774-81-7; 10, 71806-82-1; 11a, 71774-83-9; uridine-5′-carboxylic acid, 3415-07-4; 2,2-dimethoxyethane, 534-15-6; *p*-toluenesulfonylhydrazine, 1576-35-8; 2′,3′-*O*-isopropylideneadenosine-5′-carboxylic acid, 3415-09-6.

(15) Harmon, R. E.; Zenarosa, C. V.; Gupta, S. K. *Chem. Ind.* **1969**, 1141.

(16) Hiskey, R. G.; Northrop, R. C. *J. Am. Chem. Soc.* **1961**, *83*, 4798.

Simple Synthetic Route to Lasiodiplodin

Samuel Danishefsky* and Sarah Jane Etheredge

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

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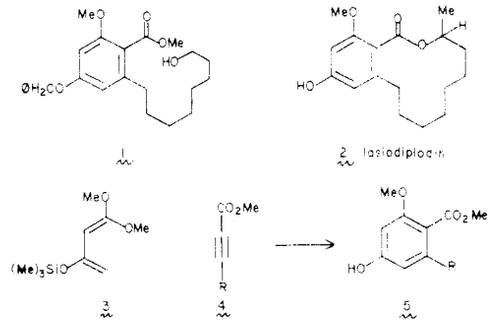
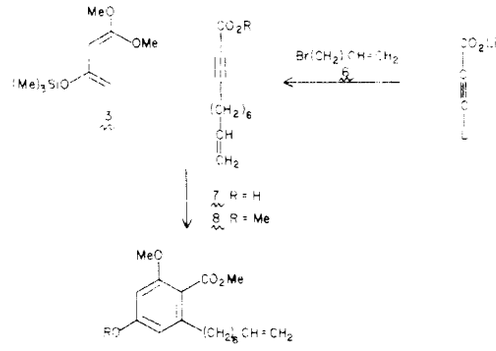
Recently Gerlach and Thalmann described the total synthesis of the plant growth inhibitor lasiodiplodin (**2**).[1,2] Gerlach's synthesis passed through the tetrasubstituted aromatic system **1**. The yields in going from **1** to **2** were excellent.

In examining the structure of lasiodiplodin and its precursor, **1**, we took note of the presence of a monomethylated resorcinol derivative wherein the methoxy group is ortho to a carbonyl function. Recently, we described a rather direct construction of such a ring system.[3] Our approach is summarized in the formalism **3** + **4** → **5**.



We had only investigated this reaction in the two cases where R was hydrogen or carbomethoxyl. It was thus of interest to explore the feasibility of a direct synthesis of a tetrasubstituted benzenoid product such as **5**, where R would be alkyl. We describe our findings with respect to applying this methodology to a synthesis of lasiodiplodin. Specifically, we focused on a synthesis of compound **1**.

The required dienophile, **7**, was easily obtained by drawing upon the chemistry of Carlson.[4] Thus, alkylation of the dianion of propiolic acid with the commercially available 1-bromo-7-octene (**6**) followed by suitable workup



afforded a 68% yield of crude acid **7**. This was converted (potassium carbonate, methyl iodide, dimethyl formamide) into **8**, which was readily purified by distillation. The yield of pure **8** over the two steps was 55%.

Compound **8** was heated with **3** in xylene at ca. 140 °C for 18 h. Workup in the usual way afforded crude **9**. To merge most conveniently with the Gerlach's synthesis, we benzylated **9**. The overall yield of the resultant **10** over the two steps was 35%. Hydroboration–oxidation of **10** afforded an 80% yield of **1**. Its structure followed from its spectral properties and from the correspondence of these properties with those described by Gerlach.[1]

The yield of the Diels–Alder step was thus, not surprisingly, lower than those encountered in the two model cases described above. Nonetheless, it is seen that this methodology provides rapid access to tetrasubstituted

(1) H. Gerlach and A. Thalmann, *Helv. Chim. Acta*, **60**, 2866 (1977).

(2) A recent study in this series was provided by T. Takahashi, K. Kasuga, and J. Tsuji, *Tetrahedron Lett.*, 4917 (1978). Though the route is commendably brief, in its published form it does not provide differentiation among the aromatic oxygen functions.

(3) S. Danishefsky, R. K. Singh, and R. B. Gammill, *J. Org. Chem.*, **43**, 379 (1978).

(4) R. M. Carlson, A. R. Oyler, and J. C. Peterson, *J. Org. Chem.*, **40**, 1610 (1975).

0022-3263/79/1944-4716$01.00/0