6, and 7) were carried out in our laboratory whereas that for 1 has already been reported. Good single crystals of thioketones were obtained upon recrystallizing the crude reaction products from suitable solvents. Full details of the X-ray crystal analyses of these compounds are published separately[6] and only the essential information needed for our discussion is provided here.

Reactive thioketones 3 and 7 were taken inside a Lindeman capillary and 5 and 6 were used as such for intensity data collection. Intensity data were collected on an Enraf-Nonius CAD-4 diffractometer using either a monochromated Cu K_α radiation (for 3, 5, and 7) or a monochromated Mo K_α radiation (for 6) in $\omega/2\theta$ scan mode. Two standard reflections were measured for every sixty reflections and no significant changes in the intensities of these reflections were observed.

All the structures were solved via the direct method program (MULTAN-80).[14] For thioketone 7, the first E map gave only the naphthalene ring and after Karle recycling all non-hydrogen atoms were identified. In the case of the other three thioketones, the first E map itself revealed the positions of all the non-hydrogen atoms. Hydrogen atoms were fixed from geometrical considerations and verified from difference map. Space group and cell constants of the four thioketones as well as those of 1 taken from the literature are provided in Table I.

Channel Cross Section Area.[15] For each thioketone (1, 3, 5, 6, and 7), the packing of the molecules viewing down the shortest crystal axis was drawn. It may be mentioned that the channel direction in all the cases was also the shortest crystal axis. The channel boundaries were delimitated by drawing circles centered on the atom positions with their corresponding van der Waal's radii. Since the sulfur atom is involved in the reaction, no circles were drawn around the thiocarbonyl sulfur atom. The cross sectional area is determined by integration. In the case of 4,4′-dimethoxythiobenzophenone (5) no channel was evident. The measured channel cross sectional areas for the other four thioketones are tabulated in Table I.

Powder Diffraction. X-ray powder photographs were taken only in the case of reactive thioketones 3 and 7. Thiobenzophenone 1 was too reactive to carry out any measurements. X-ray powder diffraction patterns were recorded using a Phillips powder diffractometer employing monochromated Cu K_α radiation. Powder patterns taken before irradiation and after complete oxidation of the samples were different and it could be concluded that the product ketone is formed as an aggregate of microcrystals.

Acknowledgment. University Grants Commission and Council of Scientific and Industrial Research, Government of India are thanked for financial support.

Registry No. 1, 1450-31-3; 2, 1141-08-8; 3, 1450-32-4; 4, 17435-08-4; 5, 958-80-5; 6, 1226-46-6; 7, 33083-79-3; 8, 40812-80-4; 9, 40812-81-5; 10, 58508-75-1; 11, 40812-79-1.

(14) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M. "Multan-80 System of Computer Programmes"; University of York: York, England, 1980.

(15) Perrier, P. R.; Byrn, S. R. *J. Org. Chem.* **1982**, *47*, 4671.

Total Synthesis of Two Furanomycin Stereoisomers

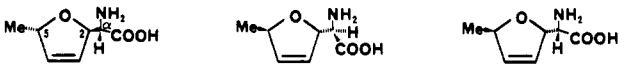
Shin-Yih Chen and Madeleine M. Joullié*

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Received November 2, 1983

D-Glucosamine hydrochloride (3), an inexpensive, commercially available reagent, has been transformed stereoselectively into two new stereoisomers of furanomycin, (αR,2S,5R)-furanomycin (**2a**) and its isomer with the opposite configuration at the amino acid functionality, (αS,2S,5R)-furanomycin (**2b**).

The antibiotic (+)-furanomycin or (+)-α-amino-2,5-dihydro-5-methylfuran-2-acetic acid (1) was isolated from

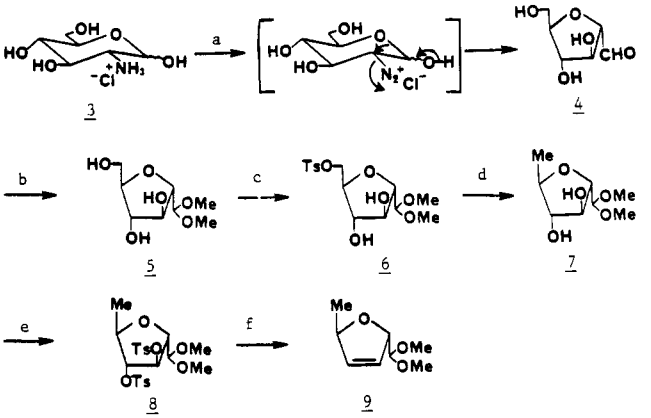


1 2a 2b

a culture filtrate of *Streptomyces* L-803 (ATCC 15795) by Katagiri and co-workers.[1] Compound 1 shows considerable activity against a number of Gram-negative bacteria and other microorganisms such as T_2, T_3 phage, and its activity is antagonized by L-isoleucine. The total synthesis of 1 from α-D-glucose showed its molecular configuration to be αS,2R,5S.[2] This assignment was confirmed by the X-ray crystal structure analysis of its *N*-acetyl derivative.[3]

The first total synthesis of (±)-furanomycin was reported by Masamune and Ono.[4] The four stereoisomeric cis forms of 1 were synthesized by us[5] and by Parker and Robins,[6] and two of the trans forms, including 1, were also prepared in our laboratory.[5] We now wish to report the total synthesis of the other two trans forms. As a continuation of our studies using carbohydrates as "chiral templates", we have developed a stereocontrolled synthesis

Scheme I[a]



[a] a, N_2O_3 (g), H_2O; b, CH_3OH, $(CH_3O)_3CH$; c, *p*-TsCl, pyridine–chloroform (2:1); d, $LiAlH_4$, THF, Δ; e, *p*-TsCl, pyridine; f, NaI, Zn, DMF, Δ.

(1) Katagiri, K.; Tori, K.; Kimura, Y.; Yoshida, T.; Nagasaki, T.; Minato, H. *J. Med. Chem.* **1967**, *10*, 1149.

(2) Joullié, M. M.; Wang, P. C.; Semple, J. E. *J. Am. Chem. Soc.* **1980**, *102*, 887.

(3) Shiro, M.; Nakai, H.; Tori, K.; Nishikawa, J.; Yoshimura, Y.; Katagiri, K. *J. Chem. Soc., Chem. Commun.* **1980**, 375.

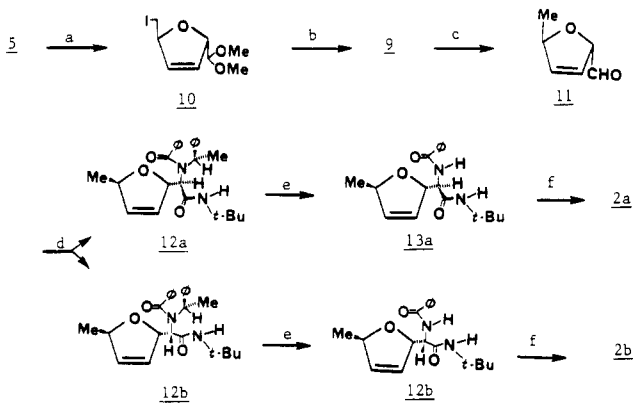
(4) Masamune, T.; Ono, M. *Chem. Lett.* **1975**, 625.

(5) Semple, J. E.; Wang, P. C.; Lysenko, Z.; Joullié, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 7505.

(6) (a) Robins, M. J.; Parker, J. M. R. *Can. J. Chem.* **1983**, *61*, 317. (b) Parker, J. M. R. Ph.D. Thesis, University of Alberta, 1980.

0022-3263/84/1949-1769$01.50/0

Scheme II[a]



[a] a, PPh_3, I_2, imidazole, benzene, Δ; b, $LiAlH_4$, Et_2O; c, *p*-TsOH·H_2O, THF, Δ, d, (i) *l*-(−)-α-methylbenzylamine, (ii) $PhCO_2H$, (iii) *t*-BuNC, CH_3OH; e, 95% HCO_2H; f, 6 N HCl, Δ.

to (αR,2S,5R)-furanomycin (**2a**) and its isomer (**2b**) with the opposite configuration at the amino acid functionality, (αS,2S,5R)-furanomycin, using inexpensive D-glucosamine hydrochloride (**3**) as a precursor.

Deamination of **3**, in aqueous solution, with dinitrogen trioxide[7a-d] afforded 2,5-anhydro-D-mannose (**4**) as shown in Scheme I. Aldehyde **4** was protected as its corresponding dimethyl acetal (**5**) using dry methanol and trimethyl orthoformate, in 70% overall yield from **3**. Selective tosylation of the primary hydroxyl group of **5** with *p*-toluenesulfonyl chloride in pyridine–chloroform (2:1) gave monotosylate **6** in 65% yield. Lithium aluminum hydride ($LiAlH_4$) reduction of **6** afforded diol **7** (80% yield) which was tosylated to yield **8** in 78% yield. Compound **8** was converted to 2,5-dihydrofuran **9** in 81% yield using Tipson's procedure.[8] Compound **9** is the enantiomer of the aldehyde dimethyl acetal used in the total synthesis of (+)-furanomycin.[2,5]

A more efficient route to **9** was developed using the Garegg–Samuelsson procedure.[9a,b] Treatment of **5** with triphenylphosphine, iodine, and imidazole, in refluxing benzene, converted the primary hydroxyl group into an iodide and the *trans*-diol into an olefin, thereby forming iodoalkene **10** in 67% yield (Scheme II). Reduction of **10** with $LiAlH_4$ afforded **9** in 80% yield. The sensitive aldehyde (**11**) obtained on acid hydrolysis of **9** with *p*-toluenesulfonic acid, in aqueous tetrahydrofuran (THF), was treated with (*S*)-(−)-α-methylbenzylamine, benzoic acid, and *tert*-butyl isocyanide sequentially to afford a "four-component condensation" (4CC) adduct,[10] separable by column chromatography into two diastereomers, **12a** and **12b**, in a 1:1 ratio, 55% overall yield. The 4CC adduct **12a** was debenzylated with 95% formic acid to afford **13a** in 96% yield. Hydrolysis of **13a** with 6 N hydrochloric acid at 100 °C (2 h) proceeded smoothly to give **2a**. The synthetic amino acid was isolated by treatment with a weakly basic ion-exchange resin (Amberlite IR-45), followed by column chromatography. Recrystallization of the crude product from water-acetone afforded **2a** in 45% yield. Under similar conditions, **13b** and **2b** were prepared in 83% and 50% yields, respectively. The configurations of the amino acid functionalities were determined from the ^1H NMR spectra of the 4CC adducts by inspection of the *tert*-butyl singlet resonances as reported by Ugi[11] and utilized by us to assign the configurations of the other furanomycin stereoisomers.[2]

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian EM-360A (60 MHz), a Bruker WM 250 (250 MHz), or an IBM WP 200 SY (200 MHz) Fourier transform spectrometer. Chemical shifts are in parts per million (δ) relative to tetramethylsilane. When deuterium oxide (D_2O) was used as the solvent, 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt hydrate (DSS) was used as the internal standard. Coupling constants (*J* values) are in Hertz (Hz). Infrared spectra (IR) were run on a Perkin-Elmer Model 281 A spectrometer. Mass spectra data were provided by the Mass Spectrometry Center at the Chemistry Department at the University of Pennsylvania. Optical rotations were recorded on a Perkin-Elmer Model 241 polarimeter at the sodium D line and ambient temperatures. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel F-254 plates (250 μ). Visualization was effected with ultraviolet light, ninhydrin (3% w/v) in 95% ethanol containing 2% acetic acid, and phosphomolybdic acid (PMA) reagent (7% w/v) in 95% ethanol.

2,5-Anhydro-D-mannose Dimethyl Acetal (5). 2,5-Anhydro-D-mannose (**4**) was prepared by a modification of the reported procedure.[7d] The crude product (**4**) obtained from D-glucosamine hydrochloride (43.1 g, 0.2 mol) was treated with 200 mL of dry methanol and 22 mL (0.20 mol) of trimethyl orthoformate. The stirred solution was refluxed overnight, cooled, and neutralized by passing it through a column filled with 200 mL of Amberlite IR-45 (OH^- form). After drying with $MgSO_4$, the solvent was removed to afford a brown syrup (40.9 g). A 10.0 g sample was purified by column chromatography with methanol–ethyl acetate (1:5) to give a colorless syrup (5.84 g, 70.1% from **3**): R_f 0.46 (methanol–ethyl acetate, 1:5, PMA); ^1H NMR (60 MHz, Me_2SO-d_6) δ 3.1–4.1 (m, 7 H), 3.32 (br s, 6 H), 4.37 (d, 1 H, *J* = 6.0), 4.5–4.8 (m, 1 H, D_2O exchangeable), 5.2 (br d, 1 H, D_2O exchangeable); IR (neat) 3300, 2900, 2800, 1720, 1650, 1450, 1370, 1250, 1200, 1070, 970, 865 cm^{-1}.

2,5-Anhydro-6-*O*-(*p*-tolylsulfonyl)-D-mannose Dimethyl Acetal (6). To a stirred solution of **5** (5.764 g, 27.71 mmol) in dry pyridine (20 mL) and chloroform (10 mL) at 5 °C was added *p*-toluenesulfonyl chloride (6.340 g, 33.25 mmol, 1.2 equiv) in small portions. Stirring was continued overnight at ambient temperature. Excess *p*-toluenesulfonyl chloride was decomposed with ice–water. The resulting solution was extracted with chloroform (200 mL). The chloroform layer was separated, treated successively with dilute acid, base, and water. The organic layer was dried ($MgSO_4$), and solvent removal afforded a brown syrup which was recrystallized from CH_2Cl_2-petroleum ether to give 6.561 g (65.4% yield) of a white solid: mp 93–94 °C; R_f 0.72 (ethyl acetate–methanol, 9.5:0.5, PMA, UV); ^1H NMR (60 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 3.39 (s, 3 H), 3.45 (s, 3 H), 3.90 (t, 1 H, *J* = 4.0), 4.0–4.25 (m, 7 H), 4.37 (d, 1 H, *J* = 4.5), 7.34 (d, 2 H, *J* = 9.0), 7.78 (d, 2 H, *J* = 9.0); IR (neat) 3360, 2900, 1645, 1600, 1445, 1400, 1360, 1310, 1290, 1195, 1190, 1080, 970, 920, 838, 820 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}O_8S$: C, 49.72; H, 6.12. Found: C, 49.80; H, 6.22.

2,5-Anhydro-6-deoxy-D-mannose Dimethyl Acetal (7). To a stirred solution of **6** (2.262 g, 6.236 mmol) in dry THF (30 mL) was added $LiAlH_4$ (0.72 g, 18.72 mmol, 3.0 equiv) in portions. The mixture was refluxed overnight, cooled, and excess $LiAlH_4$ destroyed. The solvent was removed under reduced pressure and the residue diluted with water. The aqueous solution was extracted continuously with ether (100 mL) for 2 h. The ether solution was dried ($MgSO_4$) and concentrated and the residue was purified by column chromatography (ethyl acetate–methanol, 9.5:0.5) to afford 0.975 g (80.2% yield) of a colorless oil: R_f 0.42

(7) (a) Ledderhose, G. *Z. Physiol. Chem.* **1880**, *4*, 139. (b) Bera, B. C.; Foster, A. B.; Stacey, M. *J. Chem. Soc.* **1956**, 4531. (c) Angibeaud, P.; Defaye, J.; Franconie, H. *Carbohydr. Res.* **1980**, *78*, 195. (d) Angibeaud, P.; Bosso, C.; Defaye, J.; Horton, D. *J. Chem. Soc. Perkin Trans 1* **1979**, 1583.

(8) Tipson, R. S.; Cohen, A. *Carbohydr. Res.* **1965**, *1*, 338.

(9) (a) Garegg, P. J.; Samuelsson, B. *Synthesis* **1979**, 469. (b) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1979**, 978.

(10) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 61.

(11) Marquarding, D.; Hoffmann, P.; Heitzer, H.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 1969.

(ethyl acetate–methanol, 9.5:0.5, PMA); ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.31 (d, 3 H, J = 6.0), 3.42 (s, 3 H), 3.46 (s, 3 H), 3.50–4.70 (m, 7 H); IR ($CHCl_3$) 3430, 3380, 2950, 2890, 1445, 1370, 1290, 1235, 1190, 1070, 972, 910, 885, 860 cm^{-1}.

Anal. Calcd for $C_8H_{16}O_5$: C, 49.97; H, 8.39. Found: C, 49.86; H, 8.24.

2,5-Anhydro-6-deoxy-3,4-bis-*O*-(*p*-tolylsulfonyl)-D-mannose Dimethyl Acetal (8). A stirred solution of **7** (1.020 g, 5.309 mmol) in 5 mL of anhydrous pyridine at 0 °C was treated with *p*-toluenesulfonyl chloride (2.430 g, 12.74 mmol, 2.4 equiv). Stirring was continued at 0 °C for 4 days, after which time it was treated with 10 mL of ice water and diluted with 200 mL of ether. The ether solution was treated successively with dilute acid, dilute base, and water. The organic layer was dried ($MgSO_4$) and solvent removal was followed by column chromatography with ether–petroleum ether (2:1) to give 2.070 g (78% yield) of a white solid: mp 95–97 °C; R_f 0.22 (ether–petroleum ether, 1:1). Recrystallization from the same solvent system afforded white crystals: mp 96–97.2 °C; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.19 (d, 3 H, J = 6.0), 2.42 (s, 6 H), 3.22 (s, 3 H), 3.28 (s, 3 H), 4.15 (dq, 1 H, J = 2.0), 4.27 (d, 1 H, J = 6.3), 4.28 (dd, 1 H, J = 2), 4.73 (m, 1 H), 4.95 (m, 1 H), 7.34 (d, 2 H, J = 7.8), 7.38 (d, 2 H, J = 8.0), 7.78 (d, 2 H), 7.82 (d, 2 H); IR (KBr) 2850, 1590, 1480, 1440, 1390, 1365, 1355, 1285, 1190, 1180, 1150, 1095, 1075, 1050, 1035, 1010, 995, 965, 880, 865, 818, 785 cm^{-1}.

(2*S*,5*R*)-(−)-2,5-Dihydro-5-methyl-2-furaldehyde Dimethyl Acetal (9). A mixture of ditosylate **8** (1.007 g, 2.00 mmol), sodium iodide (0.900 g, 6.00 mmol), and zinc dust (1.307 g, 20.0 mmol) in anhydrous DMF (8 mL) was heated at 140 °C for 4 h with stirring. The reaction mixture was cooled, diluted with 200 mL of ether–petroleum ether (2:1), and filtered. The ether layer was separated, washed with water, saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated. Flash column chromatography with ether–petroleum ether (1:1) gave 0.255 g (80.7% yield) of a colorless oil: bp 93–95 °C (42 mmHg); R_f 0.68 (ether–petroleum ether, 1:1, PMA); $[\alpha]^{27}_D$ −246.0 (c 1.56, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.27 (d, 3 H, J = 6.3), 3.44 (s, 3 H), 3.45 (s, 3 H), 4.18 (d, 1 H, J = 5.9), 4.86 (m, 1 H, J = 5.9, 1.8, 1.8), 5.00 (m, 1 H, J = 1.5, 1.8), 5.80 (o, 1 H, J = 6.3), 5.92 (o, 1 H); IR ($CHCl_3$) 2945, 1670, 1520, 1420, 1375, 1345, 1310, 1280, 1225, 1190, 1135, 1095, 1070, 990, 970 cm^{-1}; HRMS (CI) calcd for $C_8H_{13}O_3$ (M^+ − 1), 157.0865; found, 157.0867.

(2*S*,5*S*)-(−)-2,5-Dihydro-5-(iodomethyl)-2-furaldehyde Dimethyl Acetal (10). A solution of **5** (2.005 g, 9.605 mmol), triphenylphosphine (10.080 g, 38.44 mmol), and imidazole (2.617 g, 38.44 mmol) were refluxed in benzene (100 mL) with stirring. Iodine (9.757 g, 38.44 mmol) was added in small portions. The reaction was completed in 3 h and the benzene layer was decanted into a stirred solution of saturated aqueous $NaHCO_3$ (100 mL). The residue left in the reaction flask was extracted with 4 × 25 mL of ether. The organic phase was washed with dilute sodium thiosulfate (40 mL), dilute $NaHCO_3$, water, and dried (Na_2SO_4). The product was contaminated with triphenylphosphine oxide and purified by column chromatography on silica gel (ether–petroleum ether, 1:1) to afford a colorless oil (1.817 g, 6.396 mmol, 66.6%): R_f 0.60 (ether–petroleum ether, 1:1, PMA); $[\alpha]^{27}_D$ −182.8 (c 4.04, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.24 (dd, 1 H, J = 10.0, 6.6), 3.32 (dd, 1 H, J = 3.7), 3.45 (s, 3 H), 3.46 (s, 3 H), 4.21 (d, 1 H, J = 5.5), 4.93 (m, 2 H), 5.98 (d, 1 H, J = 6.4), 6.02 (d, 1 H); IR (neat) 2850, 2780, 1680, 1580, 1510, 1450, 1435, 1385, 1375, 1345, 1275, 1195, 1135, 1110, 1085, 1025, 975, 965, 945 cm^{-1}.

$LiAlH_4$ Reduction of 10 to 9. $LiAlH_4$ (0.233 g, 6.142 mmol) was added in small portions to a stirred solution of **10** (1.745 g, 6.142 mmol) in 40 mL of dry ether. The reaction was stirred overnight at ambient temperature. Excess hydride was decomposed by careful addition of 0.5 mL of water. The ether layer was decanted and the residue was extracted with 4 × 20 mL portions of ether. The combined organic phases were washed with saturated NaCl solution, dried ($MgSO_4$), and concentrated in vacuo. Flash column chromatography of the residue with ether–petroleum ether (1:1) afforded **9** as a colorless oil (0.775 g, 79.8% yield) which was identical with the previously prepared compound.

(α*R*,2*S*,5*R*)-*N*-*tert*-Butyl-2,5-dihydro-5-methyl-α-(*N*-(*S*)-(α-methylbenzyl)benzamido)-2-furanacetamide (12a) and Its (α*S*,2*S*,5*R*)-Isomer (12b). A stirred solution of **9** (0.505 g, 3.192 mmol) in 30 mL of THF and 0.5 mL of water was treated with *p*-toluenesulfonic acid monohydrate (0.609 g, 3.20 mmol). The reaction mixture was refluxed for 3 h, cooled to 0 °C, and diluted with 30 mL of methanol followed by the sequential addition of (*S*)-(−)-α-methylbenzylamine (0.82 mL, 6.40 mmol), benzoic acid (0.391 g, 3.20 mmol), and *tert*-butyl isocyanide (0.291 g, 3.50 mmol). The reaction mixture was stirred vigorously and allowed to come to ambient temperature. Stirring was continued overnight. After removal of the solvent, the residue was dissolved in ether and washed with water, dilute aqueous NaOH, dilute HCl, and finally with a saturated NaCl solution. The ether solution was dried ($MgSO_4$) and the solvent removed under reduced pressure. Column chromatography of the oily residue (ether–petroleum ether, 1:1) gave two diastereomers. The less polar isomer was obtained as a white, amorphous solid (0.382 g, 0.908 mmol) which was recrystallized from ether–petroleum ether (1:1) to afford colorless prisms: mp 124.5–125.5 °C, $[\alpha]^{23}_D$ −264.4 (c 0.5, $CHCl_3$); R_f 0.60 (ether–petroleum ether, 1:1, PMA, UV); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.09 (d, 3 H, J = 6.3), 1.38 (s, 9 H), 1.56 (d, 3 H, J = 6.6), 3.34 (d, 1 H, J = 8.5), 3.95 (br s, 1 H), 5.06–5.20 (q, 1 H), 5.55–5.85 (dd, 2 H), 5.86 (br s, 1 H), 7.20–7.60 (m, 10 H), 8.12 (br s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) ppm 17.9, 21.4, 28.7, 51.0, 59.0, 68.3, 80.9, 82.3, 126.1, 127.3, 127.7, 128.2, 128.3, 128.9, 129.6, 133.0, 137.4, 137.8; IR ($CHCl_3$) 3200, 2900, 2800, 1720, 1675, 1650, 1610, 1545, 1445, 1360, 1325, 1260, 1220, 1090, 1060 cm^{-1}.

Anal. Calcd for $C_{26}H_{32}N_2O_3$: C, 74.26; H, 7.67; N, 6.66. Found: C, 74.02; H, 7.73; N, 6.60.

The more polar isomer was obtained as a colorless syrup (0.359 g, 0.854 mmol): $[\alpha]^{23}_D$ −129 (c 0.38, $CHCl_3$); R_f 0.28 (ether–petroleum ether, 1:1, PMA, UV); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.12 (s, 9 H), 1.29 (d, 3 H, J = 6.3), 1.52 (d, 3 H, J = 7.0), 3.60 (d, 1 H, J = 5.5), 5.08–5.15 (m, 2 H), 5.92 (br s, 3 H), 6.13 (br s, 1 H), 7.27 (m, 5 H), 7.48 (m, 5 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) ppm 18.4, 21.7, 28.6, 50.7, 57.6, 63.4, 81.9, 85.4, 126.1, 126.3, 128.0, 128.5, 128.7, 128.8, 129.5, 132.6, 137.4, 139.1, 167.2; IR ($CHCl_3$) 3300, 3200, 2940, 2850, 1680, 1640, 1600, 1530, 1510, 1490, 1450, 1410, 1385, 1360, 1310, 1270, 1240, 1210, 1170, 1080, 1065, 1025 cm^{-1}. The overall yield for this one-pot hydrolysis and 4CC was 55.2%.

(α*R*,2*S*,5*R*)-α-Benzamido-*N*-*tert*-butyl-2,5-dihydro-5-methyl-2-furanacetamide (13a). Compound **12a** (0.152 g, 0.382 mmol) was stirred at ambient temperature with 10 mL of 95% formic acid for 2 h and then stirred for another 2 h at 60 °C. The dark brown solution was mixed with 100 mL of chloroform and washed with water until the washings became neutral. The chloroform layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed with ether–petroleum ether (2:1) to afford the debenzylated product as a white solid (0.110 g, 0.348 mmol, 96.1% yield). Recrystallization from CH_2Cl_2–petroleum ether (1:1) afforded a white, fibrous product: mp 110–112.5 °C; R_f 0.28 (ether–petroleum ether, 2:1, PMA, UV); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.27 (d, 3 H, J = 6.3), 1.34 (s, 9 H), 4.74 (dd, 1 H, J = 4.0, 6.6), 5.03 (m, 1 H), 5.39 (m, 1 H), 5.82 (m, 1 H, J = 6.3), 5.91 (m, 1 H), 6.25 (br s, 1 H), 7.30 (d, 1 H, J = 4.8), 7.40–7.55 (m, 3 H), 7.80–7.90 (m, 2 H); IR ($CHCl_3$) 3300, 2950, 2820, 1670, 1655, 1595, 1575, 1505, 1480, 1450, 1360, 1230, 1085 cm^{-1}.

(α*S*,2*S*,5*R*)-α-Benzamido-*N*-*tert*-butyl-2,5-dihydro-5-methyl-2-furanacetamide (13b). A procedure similar to that described for making **13a** was used to debenzylate **12b** (0.145 g, 0.345 mmol). The desired product (**13b**) was isolated by column chromatography (ether–petroleum ether, 3:1) as a white solid (0.090 g, 0.284 mmol, 82.5% yield). Recrystallization from CH_2Cl_2–petroleum ether (1:1) afforded a white, fibrous solid: mp 130–131 °C; R_f 0.25 (ether–petroleum ether, 2:1, PMA, UV); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.25 (d, 3 H, J = 6.3), 1.36 (s, 9 H), 4.73 (dd, 1 H, J = 5.70, 7.90), 5.04 (m, 1 H), 5.13 (m, 1 H), 5.91 (m, 1 H, J = 6.3, 1.5), 5.97 (m, 1 H), 6.51 (br s, 1 H), 7.16 (d, 1 H), 7.40–7.55 (m, 3 H), 7.80–7.88 (m, 2 H); IR ($CHCl_3$) 3320, 3280, 2940, 2820, 1670, 1655, 1600, 1575, 1505, 1480, 1450, 1360, 1340, 1230, 1100, 1085, 1060 cm^{-1}.

(α*R*,2*S*,5*R*)-Furanomycin (2a). A solution of **13a** (0.100 g, 0.316 mmol) in 10 mL of 6 N aqueous HCl was heated at 100 °C for 2 h, cooled to ambient temperature, diluted with an equal volume of water, and extracted with 5 mL of CH_2Cl_2. The aqueous solution was neutralized by passing through a weakly basic ion-

exchange resin (Amberlite IR-45). Concentration of the eluent afforded a residue which was further purified by column chromatography (15% aqueous propanol). The fractions containing the desired amino acid were combined and concentrated to dryness in vacuo to afford a white solid which was recrystallized from water–acetone to give colorless plates (0.022 g, 0.143 mmol, 45.2% yield): mp 221–223 °C dec; R_f 0.40 (*n*-PrOH–H_2O, 7:3, ninhydrin); ^{1}H NMR (250 MHz, D_2O) δ 1.25 (d, 3 H, J = 6.4), 3.85 (d, 1 H, J = 2.6), 5.10 (m, 1 H), 5.43 (m, 1 H), 5.84 (ddd, 1 H, J = 1.7, 2.0, 6.2), 6.17 (ddd, 1 H, J = 2.0, 1.7); IR (KBr) 3430, 3130, 2970, 2925, 2875, 2560, 1630, 1555, 1520, 1400, 1385, 1350, 1105, 1085, 1050 cm^{-1}; HRMS (CI) calcd for $C_7H_{12}O_3N$ (M^+ + 1), 158.0817; found, 158.0819.

(αS,2S,5R)-Furanomycin (2b). A procedure similar to that used to hydrolyze **13a** was used to hydrolyze **13b** (0.085 g, 0.269 mmol). The amino acid was isolated as a white solid which was recrystallized from water–acetone to afford colorless plates (0.021 g, 0.134 mmol, 49.7% yield): mp 222–223 °C dec; R_f 0.43 (*n*-PrOH–H_2O, 7:3, ninhydrin); ^{1}H NMR (250 MHz, D_2O) δ 1.26 (d, 3 H, J = 6.5), 3.99 (d, 1 H, J = 4.0), 5.12 (m, 1 H), 5.43 (m, 1 H), 5.67 (ddd, 1 H, J = 1.7, 1.9), 6.19 (ddd, 1 H, J = 1.7, 6.3, 1.5); IR (KBr) 3430, 3070, 2970, 2880, 2740, 2640, 1610, 1585, 1510, 1410, 1340, 1310, 1085, 1060 cm^{-1}; HRMS (CI) calcd for $C_7H_{12}O_3N$ (M^+ + 1), 158.0817; found, 158.0824.

Acknowledgment. We gratefully acknowledge the generous support of this investigation by the Dow Chemical Company Foundation.

Synthesis of Epoxytrichothecenes: Verrucarin J and Verrucarin J Isomers[1]

William R. Roush*[2] and Timothy A. Blizzard[3]

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received October 26, 1983

A five-step synthesis of verrucarin J (**1**) from verrucarol (**2**) is described. Esterification of (*E*)-**21** and **2** with DCC in the presence of catalytic DMAP was highly regioselective but afforded a 3–4:1 mixture of (*E*)-**23** and the corresponding *Z* olefin isomer. Two routes from (*E*)-**23** to seco acid **13** are described, the most efficient of which involves the coupling of (*E*)-**24** ("verrol") with muconate ester **28**. Macrolactonization of seco acid **13** via mixed anhydride **31** afforded 55–60% of **1** together with 25–30% of *E,E,E* isomer **32**. Although attempts to suppress the formation of **32** were unsuccessful, treatment of **32** with I_2 in C_6H_6 effected clean isomerization to a 2:1 mixture of **1** and *E,Z,E* isomer **33**. The overall yield of verrucarin J from verrucarol, after a recycle of **32**, was 27–30%. Also described are syntheses of (*Z,E,Z*)-verrucarin (**40**) and *Z,E,E* isomer **41**. Verrucarins **1** and **40** are nearly equipotent in the in vitro L1210 mouse leukemia assay, but the (*E,E*)-muconate isomers **32** and **41** are less active by an order of magnitude. These data may reflect the solvolytic reactivity of **32** and **41**, since these compounds rapidly transesterify in EtOH. Seco acid **13** was essentially inactive in the L1210 assay.

The trichoverroids, verrucarins, and roridins are important groups of epoxytrichothecene mycotoxins produced by various *Myrothecium* species.[4] The macrocyclic verrucarin and roridins, in particular, have attracted considerable attention as a consequence of their potent cytotoxic properties.[5] Thus, for example, in the past three years syntheses of verrucarin A were reported by Still[6] and Tamm,[7] trichoverrin B and verrucarin J by the Fraser-Reid/Jarvis collaborative effort,[8] and roridin E and baccharin B5 by Still.[9] Syntheses of verrucarin J,[1] trichoverrol B,[10] and verrucarin B[11] have been completed in our laboratory. In addition to these, syntheses of verrucarol,[12] anguidine,[13] and calonectrin,[14] which possess the terpene skeleton of the simple trichothecene mycotoxins, have also been reported.[15]

(1) A preliminary account of a portion of this work has been published: Roush, W. R.; Blizzard, T. A. *J. Org. Chem.* **1983**, *48*, 758.

(2) Roger and Georges Firmenich Career Development Associate Professor of Natural Products Chemistry; Fellow of the Alfred P. Sloan Foundation, 1982–1984.

(3) National Science Foundation Predoctoral Fellow 1979–1982; Fellow of the Whitaker Health Sciences Fund, 1982–1984.

(4) (a) Jarvis, B. B.; Vrudhula, V. M.; Midiwo, J. O.; Mazzola, E. P. *J. Org. Chem.* **1983**, *48*, 2576. (b) Jarvis, B. B.; Stahly, G. P.; Pavanasasivam, G.; Midiwo, J. O.; De Silva, T.; Holmlund, C. E., Mazzola, E. P.; Geoghegan, R. F., Jr. *Ibid.* **1982**, *47*, 1117. (c) Härri, E.; Loeffler, W.; Sigg, H. P.; Stähelin, H.; Stoll, C.; Tamm, C.; Wiesinger, D. *Helv. Chim. Acta* **1962**, *45*, 839. (d) Böhner, B.; Fetz, E.; Härri, E.; Sigg, H. P.; Stoll, C.; Tamm, C. *Ibid.* **1965**, *48*, 1079.

(5) (a) Jarvis, B. B.; Eppley, R. M.; Mazzola, E. P. In "Developments in Food Science—Trichothecenes: Chemical, Biological and Toxicological Aspects"; Ueno, Y., Ed.; Kodansha: Tokyo, 1983; Vol 4, p 20. (b) Jarvis, B. B.; Mazzola, E. P. *Acc. Chem. Res.* **1982**, *15*, 388. (c) Doyle, T. W.; Bradner, W. T. In "Anticancer Agents Based on Natural Product Models"; Cassidy, J. M., Douros, J., Eds.; Academic Press: New York, 1980; Chapter 2. (d) Tamm, C. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 63. (e) Bamburg, J. R.; Strong, F. M. In "Microbial Toxins"; Kadis, S., Ciegler, A., Ajl, S. J., Eds.; Academic Press: New York, 1971; Vol 7, p 207.

(6) Still, W. C.; Ohmizu, H. *J. Org. Chem.* **1981**, *46*, 5242.

(7) (a) Mohr, P.; Tori, M.; Grossen, P.; Herold, P.; Tamm, C. *Helv. Chim. Acta* **1982**, *65*, 1412. (b) Herold, P.; Mohr, P.; Tamm, C. *Ibid.* **1983**, *66*, 744.

(8) Esmond, R.; Fraser-Reid, B.; Jarvis, B. B. *J. Org. Chem.* **1982**, *47*, 3358.

(9) Still, W. C.; Gennari, C.; Noguez, J. A.; Pearson, D. A. *J. Am. Chem. Soc.* **1984**, *106*, 260. We thank Professor Still for providing a copy of this manuscript prior to publication.

(10) Roush, W. R.; Spada, A. P. *Tetrahedron Lett.* **1983**, *24*, 3693.

(11) Roush, W. R.; Blizzard, T. A., manuscript in preparation.

(12) (a) Schlessinger, R. H.; Nugent, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 1116. (b) Trost, B. M.; McDougal, P. G. *Ibid.* **1982**, *104*, 6110. (c) Roush, W. R.; D'Ambra, T. E. *Ibid.* **1983**, *105*, 1058.

(13) Brooks, D. W.; Grothaus, P. G.; Mazdiyasni, H. *J. Am. Chem. Soc.* **1983**, *105*, 4472.

(14) Kraus, G. A.; Roth, B.; Frazier, K.; Shimagaki, M. *J. Am. Chem. Soc.* **1982**, *104*, 1114.

(15) For leading references to other studies on the synthesis of the macrocyclic epoxytrichothecenes, see: (a) Ong, C. W. *Heterocycles* **1982**, *19*, 1685. (b) Yamamoto, Y.; Maeda, N.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1983**, 774. (c) Trost, B. M.; McDougal, P. G. *Tetrahedron Lett.* **1982**, *23*, 5497. (d) Tomioka, K.; Sato, F.; Koga, K. *Heterocycles* **1982**, *17*, 311. (e) White, J. D.; Carter, J. P.; Kezar, H. S., III *J. Org. Chem.* **1982**, *47*, 929. (f) Roush, W. R.; Blizzard, T. A.; Basha, F. Z. *Tetrahedron Lett.* **1982**, *23*, 2331. (g) Roush, W. R.; Spada, A. P. *Ibid.* **1982**, *23*, 3773. (h) Tulshian, D. B.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1981**, *103*, 474.

0022-3263/84/1949-1772$01.50/0