of THF. The reaction mixture was stirred at 0 °C for 30 min and then cooled to −78 °C in an acetone/dry ice bath. To this was then added, very slowly over a 2-min period, via syringe a solution of 23.6 mg (0.1 mmol) of guaianolide **13** in 7.5 mL of anhydrous THF. The reaction was stirred at −78 °C for 45 min, and to it was added under a blanket of nitrogen 370 mg (2.0 mmol) of dimethylmethyleneammonium iodide (Eschenmoser's Reagent).[30] The reaction was stirred at −78 °C for 30 min, warmed to −30 °C for 4 h, and then quenched at −30 °C by addition of 10 mL of saturated sodium bicarbonate solution. The mixture was then warmed to room temperature over a 30 min period and stirred at room temperature several hours. This was then extracted 3 times with 5 mL of ether. The combined organic layers were dried, and chromatography on florisil with 9:1 petroleum ether/ether gives 25.9 mg (88%) of the (dimethylamino)methyl lactone as an oil: ^{1}H NMR (CCl_4) δ 4.86 (d, −C*H*−OC(=O), J = ~8 Hz), 3.0–0.8 (b m, skeletal H), 2.20 (s, NCH_3), 1.50 (s, C-4 CH_3), 0.95 (d's, C-10 CH_3); IR (CCl_4) 2940, 2770, 1775, 1465, 1425, 1385, 1335, 1315, 1270, 1170, 1050, 1015, 925, 895 cm^{-1}. High-resolution mass spectral analysis: calculated for $C_{17}H_{27}NO_3$, 293.1990; found: 293.1989.

To a solution of 25.0 mg of this tertiary amine in 2.0 mL of anhydrous THF was added 1.0 mL of methyl iodide. The solution was stirred at room temperature for 4 h and to it was added 5 mL of saturated sodium bicarbonate solution, and stirring was continued for another 3 h. This reaction mixture was then diluted with 10 mL of aqueous sodium chloride and 10 mL of ether. The organic layer was separated and the aqueous layer further extracted 3 times with 10 mL of ether. The combined ether layers were dried. Removal of solvent and recrystallization from 4:1 hexanes/ether give 9 mg (42.5%) of highly crystalline white solid **1**: mp 69.5–70.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.20 (d, 1 H, vinyl H, J = 3.5 Hz), 5.50 (d, 1 H, vinyl H, J = 3.5 Hz), 5.05 (d, 1 H, C-6 H, J = 8.6 Hz), 3.31 (m, 1 H, C-7 H), 2.30 (ABX m, 1 H, $C_{8\beta}$−H), 2.0–1.0 (b m, 9 H, skeletal H), 1.58 (s, 3 H, epoxide −CH_3), 0.94 (d, 3 H, C-10 CH_3, J = 6.0 Hz); IR (CCl_4) 2930, 1775 (α-methylene lactone), 1660, 1450, 1415, 1380, 1360, 1320, 1275, 1260, 1195, 1100, 1040, 1010, 940, 890 cm^{-1}.

High-resolution mass spectral analysis: calculated for $C_{15}H_{20}O_3$, 248.1412; found, 248.1413.

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Supplementary Material Available: Listings of observed and calculated structure factors as well as tables of anisotropic thermal parameters and fractional coordinates for the C and O and H atoms, listing of the structures and the $J_{10,14}$ coupling constants observed for the C-14 CH_3 doublets of four pairs of C-10 epimeric hydroazulenes, showing that in each case the 1,10 anti isomer has a higher $J_{10,14}$ coupling constant, and Figure 2, 300-MHz NMR spectrum of guaianolide **1** (20 pages). Ordering information is given on any current masthead page.

Total Synthesis of (+)-Furanomycin and Stereoisomers[1]

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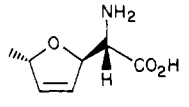
Contribution from the Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104. *Received June 13, 1980*

Abstract: The total synthesis of six stereoisomeric forms of α-amino-2,5-dihydro-5-methylfuranacetic acid is described. (+)-Furanomycin, the naturally occurring antibiotic of this series, was found to be identical with the isomer having the (αS,2R,5S) configuration, thereby requiring revision of the original (αR,2R,5R) assignment for this substance.

(+)-Furanomycin (**1**), an antibiotic α-amino acid containing a 2,5-dihydrofuran moiety, was first isolated by Katagiri and co-workers from the culture filtrate of *Streptomyces threomyceticus*. The structure of furanomycin was first assigned the (αR,2R,5R) configuration (**2**) based on a combination of spectroscopic and chemical degradation techniques.[3] This structural



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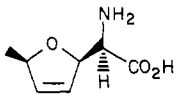

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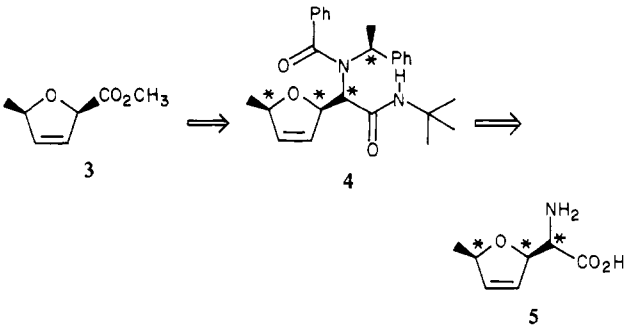
assignment rested largely on the coupling constants of the 2 and 5 protons ($J_{2,5}$). A large, long-range homoallylic coupling constant ($J_{2,5}$ = 5.7 Hz) was observed for **1** and from this information it was concluded that the 2 and 5 protons were cis to each other.[3] Additional support for this assignment was provided by the total synthesis of *dl*-furanomycin reported by Masamune and Ono.[4a] These authors used as their starting material a 5-methyl-2,5-dihydro-2-furoic acid[4b] which exhibited a coupling constant $J_{2,5}$ = 6 Hz and was therefore assigned the cis configuration, since elaboration of this substance produced an α-amino acid "identical in all respects" with the naturally occurring antibiotic. In contrast

Scheme I



3 4 5

(1) A preliminary account of this work was presented at the 178th National Meeting of the American Chemical Society, Washington, D.C., September 1979, ORG 124.

(2) (a) The synthetic studies of the cis stereoisomers of furanomycin were taken in part from the Ph.D. dissertation of J. Edward Semple, University of Pennsylvania, 1980; the synthetic investigations of the trans stereoisomers of furanomycin were taken in part from the Ph.D. dissertation of Pen C. Wang, University of Pennsylvania, 1980.

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

(4) (a) Masamune, T.; Ono, M. *Chem. Lett.* **1975**, 625. (b) Masamune, T.; Ono, M.; Matsue, H. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 491.

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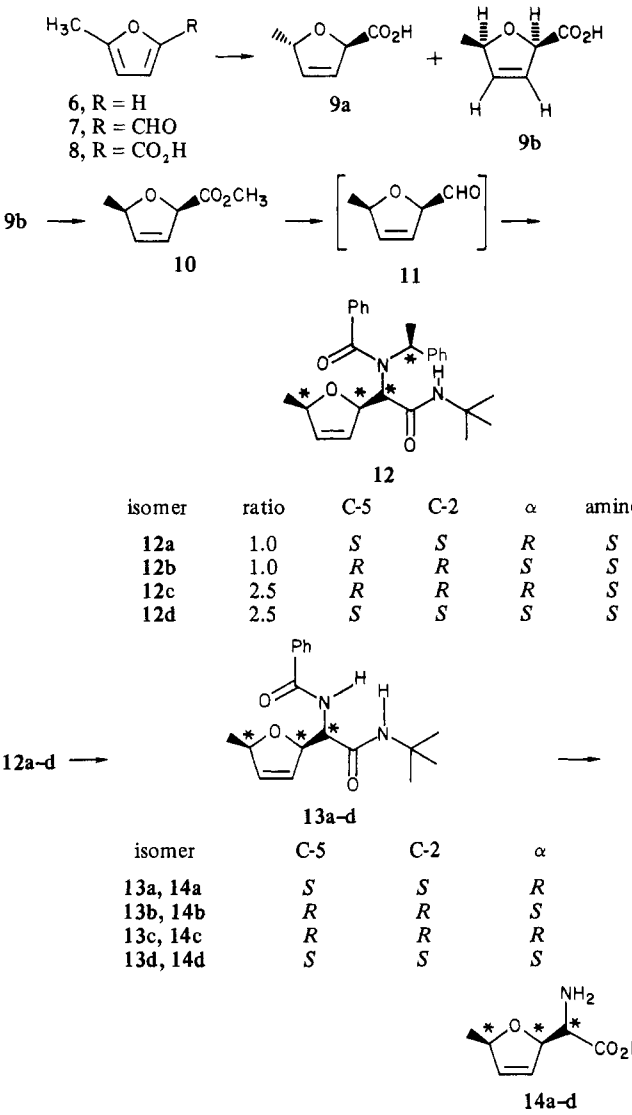
with these reports, Moffatt and co-workers[5] had unequivocally synthesized some related *cis*-2,5-dihydrofurans which exhibited coupling constants $J_{2,5}$ = 3 Hz. In order to establish the correct structure of **1** we investigated synthetic approaches which would provide both cis and trans forms of **1** from readily available precursors. Our efficient unequivocal total synthesis of ($\alpha S,2R,5S$)-furanomycin[6] (**1**) conclusively demonstrated that the natural antibiotic did not possess structure **2** as originally assigned.[3] This finding was further supported by the synthesis of the four stereoisomeric cis forms of **2** by our group and by Robins' group at the University of Alberta.[7a,b] The physical and spectroscopic properties of these isomers were totally different from those of the naturally occurring product.[8]

Results and Discussion

Our earlier interest in the Ugi "four-component condensation" reaction[9a-d] (4CC) for the asymmetric synthesis of α-amino acids, coupled with our studies of the Birch reduction of 2-furoic acids,[9b,10] suggested a potential entry into the cis series of furanomycins via cis ester **3**. Elaboration of this material into the 4CC adduct **4**, followed by sequential deblocking steps, should afford four optically active stereoisomeric forms (**5**) of the *cis*-furanomycins. This route (Scheme I) is synthetically facile and produces four diastereomeric cis adducts (**4**) which are readily separable via conventional chromatographic techniques.

The Vilsmeier formylation of 2-methylfuran (**6**), using a mixture of *N,N*-dimethylformamide and phosphorus oxychloride (0–25 °C), gave 5-methyl-2-furfural (**7**) in quantitative yield (Scheme II). Oxidation of aldehyde **7** with an aqueous alkaline suspension of silver oxide at 25 °C gave 5-methyl-2-furoic acid (**8**) in 92% yield. Rapid addition of acid **8** to a solution of 2.6 equiv of lithium in liquid ammonia at −78 °C afforded a 1:1 mixture of *cis*- and *trans*-5-methyl-2,5-dihydro-2-furoic acids (**9a,b**). Fractional distillation of the acids in vacuo on a spinning band column afforded trans acid **9a** heavily contaminated with isomeric tetrahydrofuran carboxylic acids. Attempted purification of **9a** by distillation or chromatographic methods failed. The cis acid **9b** was obtained in pure form as a colorless liquid, bp 60 °C (0.13 mm), which crystallized on standing at 0 °C (mp 71.0–73.0 °C). The 220-MHz ^{1}H NMR spectrum of **9b** in deuterium oxide displayed a methyl group doublet at δ 1.28 ($J_{6,5}$ = 6.4 Hz) and multiplets at δ 5.06 and 5.26, for which $J_{2,5}$ = 3.4 Hz. This coupling constant value is of the same order of magnitude as the values determined by Moffatt and co-workers[5] ($J_{2,5} \simeq$ 3 Hz) for related *cis*-2,5-dihydrofuran systems, and is considerably different from the value ($J_{2,5}$ = 6 Hz) reported by Masamune and Ono for the cis acid (**9b**).[4b] Treatment of the cis acid with diazomethane in ether at 0 °C produced the *cis*-methyl ester **10** in 81% yield. Reaction of **10** in toluene solution at −78 °C with 1 equiv of diisobutylaluminum hydride afforded, after hydrolysis, the highly labile *cis*-5-methyl-2,5-dihydro-2-furfural (**11**) which was not isolated but was treated successively with 2 equiv of (*S*)-(−)-α-methylbenzylamine, 2 equiv of benzoic acid, and 1 equiv of *tert*-butyl isocyanide to afford a mixture of stereoisomeric products (**12**). Separation of the crude reaction product by column chromatography produced four stereoisomers (**12a–d**), in a ratio of 1.0:1.0:2.5:2.5, respectively. The overall yield for this facile

Scheme II



isomer	ratio	C-5	C-2	α	amine
12a	1.0	*S*	*S*	*R*	*S*
12b	1.0	*R*	*R*	*S*	*S*
12c	2.5	*R*	*R*	*R*	*S*
12d	2.5	*S*	*S*	*S*	*S*

isomer	C-5	C-2	α
13a, 14a	*S*	*S*	*R*
13b, 14b	*R*	*R*	*S*
13c, 14c	*R*	*R*	*R*
13d, 14d	*S*	*S*	*S*

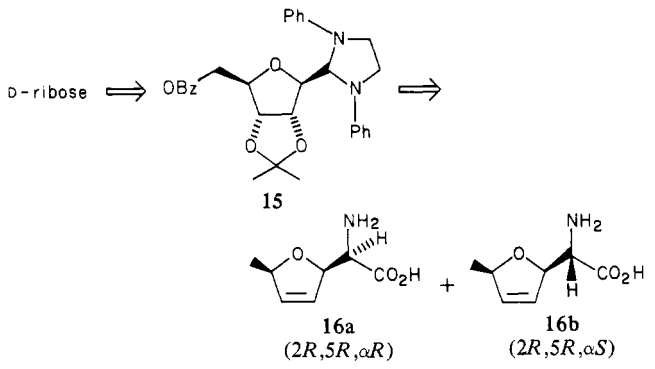
reduction and condensation process was 70%. The assignment of the configuration of these diastereomers was based on their chromatographic properties, the ^{1}H NMR chemical shift of their *tert*-butyl groups,[11] and direct comparison of the physical and spectroscopic properties of the derived α-amino acids (**14a–d**) with those of the α-amino acids recently synthesized by Robins and Parker.[7a,b] Each of the stereoisomers **12a–d** were individually treated with concentrated formic acid at 50–60 °C to afford debenzylated adducts **13a–d** in 74–91% yields. The debenzylation reaction of **12a** and **12b** gave 16–18.5% epimerized products. These diastereomers were readily separated by chromatography. The resultant pure enantiomers (**13a** and **13b**) had identical melting points, infrared spectra, and nuclear magnetic resonance spectra. Final proof of their enantiomeric relationship was obtained by comparison of their optical rotations, i.e., **13a** exhibited $[\alpha]^{25}_D$ −61.1° (*c* 1, EtOH), and **13b** showed $[\alpha]^{25}_D$ +62.4 (*c* 1, EtOH). Analogously, debenzylation of **12c** and **12d** gave enantiomers **13c** and **13d**, respectively. As expected, the physical properties of these compounds were identical while **13c** exhibited an optical rotation $[\alpha]^{25}_D$ −4.9° (*c* 1, EtOH) and **13d** exhibited $[\alpha]^{25}_D$ +5.2° (*c* 1, EtOH). Finally, each of the debenzylated adducts (**13a–d**) was individually converted into the corresponding α-amino acids (**14a–d**) by hydrolysis in refluxing 6 N hydrochloric acid. The α-amino acids were isolated by elution through a weakly basic ion-exchange resin (Amberlite IRA-4B) followed by column

(5) Jain, T. C.; Jenkins, I.; Russell, A. F.; Verdeyden, J. P. H.; Moffatt, J. *J. Org. Chem.* **1974**, *39*, 30.
(6) Joullié, M. M.; Wang, P. C.; Semple, J. E. *J. Am. Chem. Soc.* **1980**, *102*, 887.
(7) (a) Private communication from Professor M. J. Robins; (b) Ph.D. Dissertation of J. M. R. Parker, University of Alberta, 1980.
(8) A recent communication from Dr. Katagiri has informed us of X-ray diffraction studies on furanomycin *N*-acetate, which revealed that the natural antibiotic does possess the ($\alpha S,2R,5S$) configuration (**1**), thereby supporting our findings; *J. Chem. Soc., Chem. Commun.* **1980**, 375.
(9) (a) Divanfard, H. R.; Lysenko, Z.; Wang, P. C.; Joullié, M. M. *Synth. Comm.* **1978**, *8*, 269. (b) H. R. Divanfard, Ph.D. Dissertation, University of Pennsylvania, 1977. (c) Z. Lysenko, Ph.D. Dissertation, University of Pennsylvania, 1980. (d) Divanfard, H. R.; Lysenko, Z; Semple, J. E.; Wang, P.C.; Joullié, M. M.; Blount, J. F. unpublished work.
(10) Divanfard, H. R.; Joullié, M. M. *Org. Prep. Proced. Int.* **1978**, *10*, 94.
(11) Marquarding, D.; Hoffmann, P.; Heitzer, H.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 1969.

Table I. ^{1}H NMR of 4CC Adducts

α-amino acid center	chiral inducing amine	*tert*-butyl resonance (δ)
S	*S*	1.14
R	*R*	1.14
R	*S*	1.39
S	*R*	1.39

Scheme III



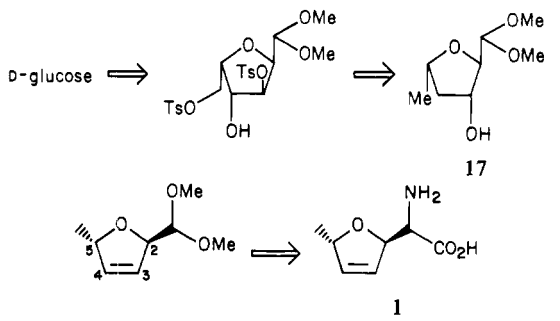
chromatography on silica gel. Recrystallization of the resultant solids from aqueous acetone afforded α-amino acids **14a–d** in 53–63% yields. Isomers **14a,c,d** were isolated in pure form. Unfortunately, isomer **14b** was shown by ^{1}H NMR to contain ca. 33% of an unknown diastereomeric α-amino acid which formed during the hydrolysis step and could not be separated from the desired product **14b** by either crystallization or chromatographic procedures. α-Amino acid **14a** exhibited $[\alpha]^{25}_D$ +6.9 (*c* 1, 1 N HCl). α-Amino acids **14c** and **14d** had identical physical and spectroscopic properties with **14c** having $[\alpha]^{25}_D$ +47.4° (*c* 1, 1 N HCl) and **14d** having $[\alpha]^{25}_D$ −57.6° (*c* 1, 1 N HCl), thus confirming their enantiomeric relationship.

Stereochemistry of the Cis Series

The configurations of the α-amino acid centers were determined from the ^{1}H NMR spectra of the "four-component condensation" adducts **12a–d** by simple inspection of the *tert*-butyl singlet resonances. Ugi and co-workers[11] demonstrated that the use of α-methylbenzylamine as the chiral inducing agent causes the singlet resonance of the *tert*-butyl groups in the resultant 4CC adducts to appear around δ 1.14 or 1.39. Thus, adducts which exhibit a resonance for this group at δ 1.14 have either (*S*,*S*) or (*R*,*R*) configurations, while adducts which display this resonance at δ 1.39 have either the (*S*,*R*) or (*R*,*S*) configuration. As the configuration of the amine is known, it is easy to determine the configuration of the newly created α-amino acid center. In our work (Table I), the chiral inducing amine had the (*S*) configuration, and therefore the configuration of the α-amino acid centers in adducts **12b** and **12d** also had an (*S*) configuration, since the *tert*-butyl resonances for these products were observed at δ 1.12 and 1.13, respectively. Similarly, as the *tert*-butyl resonances of adducts **12a** and **12c** were observed at δ 1.34 for both isomers, the configurations at the α-amino acid centers were assigned as *R*. The validity of these assignments was further supported by X-ray crystallographic studies in the norfuranomycin series,[9c,d] the results of which were in agreement with the configurational assignments at the α-amino acid centers made according to Ugi's findings.

Although we could not obtain single crystals from the cis adducts **12a–d** for X-ray diffraction studies, we were able to compare two of our α-amino acids with those prepared by Robins and Parker[7a,b] (**16a** and **16b**) from D-ribose derivative **15** (Scheme III). Since **15** is known to have the (2*R*,5*R*) absolute configuration, the derived α-amino acids **16a** and **16b** should be related to two of our products. Direct comparison of our samples with those of Robins and Parker showed that the physical and spectroscopic properties of **16a** were indeed identical with those of α-amino acid **14c**. Similarly, **16b** was shown to be enantiomeric with α-amino acid **14a**. The only difference in the physical properties of **14a** and **16b** was the sign of their optical rotation. From these considerations, the configurations of adducts **12a–d** and **13a–d** have been assigned as previously described and follow from their physical and spectroscopic relationships.

Scheme IV



The physical and spectroscopic properties of cis amino acids **14a–d** and **16a** and **16b** were different from those of the naturally occurring isomer; therefore, we proceeded to investigate the synthesis of the *trans*-furanomycins from appropriate carbohydrate precursors.

Our strategy for the stereospecific synthesis of **1** from α-D-glucose was based on the construction of a chiral 2,5-dihydrofuran and subsequent introduction of an optically active amino acid functionality, thereby establishing three asymmetric centers. Our previous investigations leading to the synthesis of D-epiallomuscarine[12a] and D-isoepiallomuscarine[12b] demonstrated the use of carbohydrates as precursors for optically pure tetrahydrofurans.

In the sequence outlined in Scheme IV, alcohol **17** was chosen as a precursor for the preparation of **1**. Introduction of the double bond between C-3 and C-4, followed by construction of the amino acid functionality, would afford the final target.

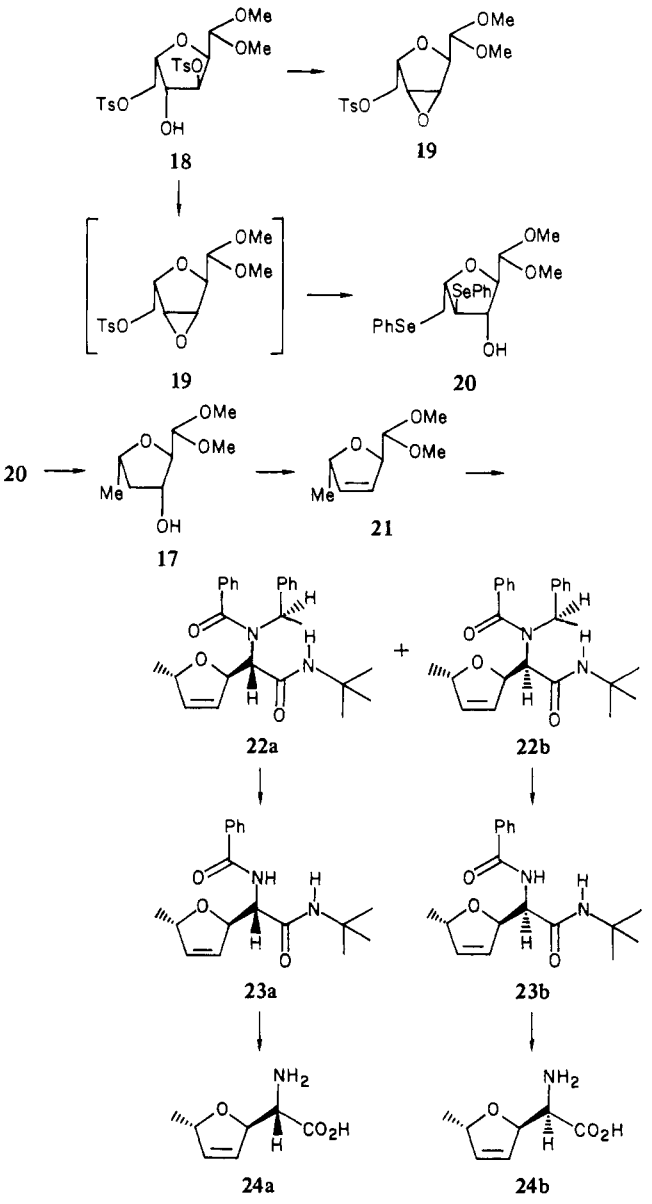
Furanose **18**, obtainable in 64% overall yield from D-glucose,[13] was treated with an excess of sodium phenylselenide to afford diselenide **20** in 85% yield (Scheme V). The formation of **20** was believed to proceed through the intermediacy of epoxide **19**, formed by backside attack of the hydroxyl group at C-4 onto the neighboring tosylate moiety. Subsequent ring opening induced by nucleophilic attack of sodium phenylselenide from the less sterically hindered side of the epoxide group leads to **20**. Further support for this assumption was obtained from the reaction of **18** with sodium hydride, which gave epoxide **19** in 90% yield. Treatment of **19** with sodium phenylselenide afforded **20** in 92% yield. The intermediacy of an epoxide was also observed in the reaction of **18** with sodium acetate.[13b] The direction of epoxide ring opening appears to be governed by a combination of steric and polar effects associated with the group adjacent to the epoxide ring. In the absence of polar effects, the direction of cleavage of the epoxide seems to be dependent on steric effects.[14] Reductive removal of the phenylseleno groups with W-4 Raney nickel produced alcohol **17** in 96% yield.[12b] Tosylation of **17** followed by base-catalyzed elimination with sodium methoxide in refluxing methanol afforded 2,5-dihydrofuran **21** in 72% yield (25% overall yield from D-glucose). The sensitive aldehyde obtained by acid hydrolysis of **21** was treated with 2 equiv of (*R*)-(+)-α-methylbenzylamine, 1 equiv of benzoic acid, and 1 equiv of *tert*-butyl isocyanide to afford diastereomeric adducts **22a** and **22b** (1:1) that were separable by column chromatography. The overall yield for this facile hydrolysis and condensation was 63% based on the 2,5-dihydrofuran precursor **21**. Since the aldehyde precursor is chiral and would be expected to retain its configuration at C-2 and C-5 during asymmetric induction at the aldehyde carbon and since the absolute configuration of the inductive amine center is

(12) (a) Wang, P. C.; Lysenko, Z.; Joullié, M. M. *Tetrahedron Lett.* **1978**, 1657. (b) Wang, P. C.; Lysenko, Z.; Joullié, M. M. *Heterocycles* **1978**, *9*, 753.

(13) (a) Ogawa, T.; Matsui, M.; Ohrui, H.; Kuzuhara, H.; Emoto, S. *Agric. Biol. Chem.* **1972**, *36*, 1449. (b) *Ibid.* **1972**, 1655.

(14) Williams, N. R. *Adv. Carbohydr. Chem.* **1970**, *25*, 155.

Scheme V



fixed, the 4CC should only produce two diastereomers. The absolute configurations of the α-amino acid centers were assigned on the basis of the chemical shifts of the *tert*-butyl groups in compounds **22a** and **22b** as previously described.[11] Debenzylation of **22a** with 95% formic acid afforded **23a** in 85% yield. Hydrolysis of **23a** with 6 N hydrochloric acid proceeded smoothly to give (αS,2*R*,5*S*)-furanomycin (**24a**) which was found to be identical with the natural (+)-furanomycin (**1**). A detailed comparison of the physical properties and spectral data of our product with those of the naturally occurring furanomycin is included in the Experimental Section. Amino acid derivative **22b** was converted into (αR,2*R*,5*S*)-furanomycin (**24b**) by using the same series of reactions.

As a result of our synthetic study, the structure of naturally occurring furanomycin is revised to (+)-α(*S*)-amino-2,5-dihydro-5(*S*)-methylfuran-2(*R*)-acetic acid instead of (+)-α(*R*)-amino-2,5-dihydro-5(R)-methylfuran-2(*R*)-acetic acid as originally assigned by Katagiri.[3]

Experimental Section

General. ^{1}H NMR spectra were obtained on Varian A-60 (60 MHz), Varian EM-360A (60 MHz), Varian HR-220 (220 MHz), Bruker WP-250 (250 MHz), or Bruker WH-360 (360 MHz) NMR spectrometers. ^{13}C NMR spectra were recorded on a JEOL-JNM-PS 100-NMR spectrometer operating at 25 MHz. High-resolution mass spectra were obtained on an Hitachi Perkin-Elmer RMH-2 high-resolution double-focusing electron-impact spectrometer interfaced with a Kratos DS-50-S data system. Infrared spectra were recorded on a Perkin-Elmer 137 infrared spectrophotometer as a thin film (neat) on sodium chloride plates or in potassium bromide disks (KBr). Optical rotations were determined on a Perkin-Elmer Model 241 polarimeter.

Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Elemental microanalyses were performed at Robertson Laboratory, Florham Park, NJ. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel plates (250 μm) with fluorescent indicator, supplied by E. Merck. Visualization was effected with ultraviolet light, 7% w/v ethanolic 12-molybdophosphoric acid, or ninhydrin (1% w/v in 1-propanol). Column chromatography utilized Merck SG-60 (70–230 mesh) silica gel, and medium pressure liquid chromatography employed columns filled with Merck SG-60 (230–400 mesh) silica gel. Tetrahydrofuran and ether were predried over sodium ribbon and distilled from sodium metal under a nitrogen atmosphere, using benzophenone ketyl as indicator. *N*,*N*-Dimethylformamide, methanol, and toluene were distilled from calcium hydride.

5-Methyl-2-furaldehyde (7). A 2-L flask was charged with *N*,*N*-dimethylformamide (77.4 mL, 73.1 g, 1.0 mol) and 1,2-dichloroethane (200 mL). The solution was stirred and cooled to 0 °C whereupon phosphorus oxychloride (81.4 mL, 136.0 g, 0.90 mol) was added through a dropping funnel while keeping the temperature below 25 °C. To the resultant mixture was gradually added 2-methylfuran **6** (66.1 mL, 54.7 g, 0.67 mol) at such a rate as to maintain the temperature below 25 °C. The mixture was stirred at 0 °C for 1 h and then allowed to stir at 26 °C overnight. A saturated sodium carbonate solution (400 mL) was then added slowly to hydrolyze and neutralize the mixture. The solution was extracted with 3 × 250 mL of ether. The organic layers were extracted with water and saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Removal of solvent under reduced pressure gave a dark liquid which was distilled in vacuo to afford 73.0 g (99.6% yield) of colorless product **7**: bp 44–45 °C (0.30 mm) (lit.[15] bp 64 °C (7 mm)); IR (neat) 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3 H), 6.23 (m, 1 H), 7.18 (d, 1 H), 9.44 (s, 1 H).

5-Methyl-2-furoic Acid (8). Into a 2-L two-necked round-bottomed flask fitted with a mechanical stirrer and dropping funnel were placed a solution of sodium hydroxide (133.6 g, 3.34 mol) in 800 mL of water and a solution of silver nitrate (340.8 g, 2.01 mol) in 800 mL of water. The mixture was stirred and cooled to 0 °C, whereupon 5-methyl-2-furaldehyde **7** (74.8 mL, 82.8 g, 0.75 mol) was added dropwise. The ice bath was removed and the mixture was stirred at 25 °C for 2.5 days. The silver precipitate was removed by filtration and washed with hot water. The combined filtrates were cooled to 5 °C, acidified to pH 1 with 250 mL of concentrated hydrochloric acid, and extracted with 5 × 400 mL of ethyl acetate. The combined organic extracts were then washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Removal of solvent afforded the crude product which was purified by recrystallization from 250 mL of water to give 84.2 g of **8**. The filtrate was concentrated, treated with decolorizing charcoal, and cooled to 0 °C to afford an additional 3.15 g of product. The total yield of **8** was 87.35 g (92.1%): near colorless needles; mp 108.5–110 °C (lit.[16] mp 108–109 °C); IR (KBr) 2900, 1675 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3 H), 6.15 (m, 1 H), 7.22 (d, 1 H), 11.42 (s, 1 H).

Reverse Birch Reduction of 5-Methyl-2-furoic Acid (8). Preparation of *cis*- and *trans*-5-Methyl-2,5-dihydro-2-furoic Acids (9a and 9b). A 2-L three-necked flask was equipped with a mechanical stirrer fitted with a glass blade, a gas inlet tube, a stopper, and a dry ice condenser connected to an anhydrous potassium carbonate drying tube and oil bubbler. The flask was flame dried under a stream of nitrogen and then cooled to −78 °C with a dry ice–acetone bath. Dry ammonia (1500 mL) was condensed in the flask and finely cut lithium wire (8.17 g, 2.6 equiv, 1.18 g-atom) was added in small portions. 5-Methyl-2-furoic acid (**8**) (57.1 g, 0.453 mol) was introduced in one portion. After 4 min, the reaction mixture was quenched by addition of solid ammonium chloride (69.3 g, 1.3 mol) and the ammonia was then allowed to evaporate overnight. The residue was dissolved in 150 mL of water and acidified with hydrogen chloride gas to pH 1 with cooling. The solution was extracted with 3 × 200 mL of ether and the combined organic layers were dried over anhydrous magnesium sulfate. Removal of solvent gave an oil which was distilled in vacuo to afford 40.33 g (69.5% yield) of pale yellow isomeric acids (**9a,9b**): bp 68–71 °C (0.68 mm) (lit.[4a] bp 99–101 °C (4 mm)); R_f 0.31, 0.38 (ether–petroleum ether 2:1 with 3% formic acid); IR (neat) 3000, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 + 1.39 (2 d, 3 H, $J \simeq 7$ Hz, $J \simeq 6.8$ Hz), 5.15 (m, 2 H), 5.93 (m, 2 H), 8.90 (s, 1 H).

(15) Taylor, D. A. H. *J. Chem. Soc.* **1959**, 2767.
(16) Runde, M. M.; Scott, E. W.; Johnson, J. R. *J. Am. Chem. Soc.* **1930**, *52*, 1284.

Separation of *cis*- and *trans*-5-Methyl-2,5-dihydro-2-furoic Acids by Distillation under Reduced Pressure. The dihydrofuroic acid mixture was fractionally distilled in vacuo by using a Nester-Faust NF-190 spinning band column (6 × 450 mm, 23 theoretical plates) to give the trans isomer heavily contaminated with 5-methyltetrahydrofuran-2-carboxylic acids. The cis isomer **9b** was obtained as a pure colorless liquid, bp 60 °C (0.13 mm), which slowly crystallized on standing at 0 °C; mp 71.0–73.0 °C; R_f 0.38 (ether–petroleum ether 2:1 with 3% formic acid); IR (melt) 2900, 1735 cm^{-1}; ^{1}H NMR (D_2O, 200 MHz) δ 1.28 (d, 3 H, $J_{6,5}$ = 6.4 Hz, CH_3), 5.06 (m, 1 H, $J_{5,3} \simeq$ 1.5 Hz, $J_{5,4} \simeq$ 2.0 Hz, $J_{5,2} \simeq$ 3.4 Hz, $J_{5,6}$ = 6.4 Hz, 5-H), 5.26 (m, 1 H, $J_{2,3}$ = 2.6 Hz, $J_{2,4}$ = 1.8 Hz, $J_{2,5}$ = 3.4 Hz, 2-H), 5.90 (t plus t, 1 H, $J_{4,3}$ = 6.2 Hz, $J_{4,5} \simeq J_{4,2} \simeq$ 2.0 Hz, 4-H), 6.06 (dd plus dd, 1 H, $J_{3,5}$ = 1.5 Hz, $J_{3,4}$ = 6.2 Hz, $J_{3,2}$ = 2.6 Hz, 3-H); ^{13}C NMR ($CDCl_3$) δ 22.0, 84.0, 84.4, 124.1, 133.9, 175.0. Anal. Calcd for $C_6H_8O_3$: C, 56.25; H, 6.29. Found: C, 56.19; H, 6.36.

Methyl *cis*-5-Methyl-2,5-dihydro-2-furoate (10). To a magnetically stirred solution of diazomethane (ca. 0.089 mol) in 300 mL of dry ether at 0 °C was added a solution of *cis*-5-methyl-2,5-dihydro-2-furoic acid (**9b**) (8.83 g, 0.069 mol) in 20 mL of dry ether over a period of 10 min. Thirty minutes after the completion of the addition, the excess diazomethane was removed by passing a stream of dry nitrogen through the solution, and the ether was removed under reduced pressure. Distillation of the residue in vacuo afforded 7.92 g (81% yield) of product **10** as a colorless liquid: bp 38–39 °C (0.3 mm); R_f 0.55 (petroleum ether–ether 2:1); IR (neat) 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.36 (d, 3 H, J = 6.4 Hz), 3.73 (s, 3 H), 4.99 (m, 1 H), 5.23 (m, 1 H), 5.87 (m, 2 H). Anal. Calcd for $C_7H_{10}O_3$: C, 59.15; H, 7.09. Found: C, 58.86; H, 7.18.

Reduction of Ester 10 and Four-Component Condensation. A 250-mL round-bottomed flask equipped with a magnetic stirring bar was charged with 25 mL of dry toluene and methyl *cis*-5-methyl-2,5-dihydro-2-furoate (**10**) (7.108 g, 0.050 mol). The flask was purged with dry nitrogen and then stoppered with a serum cap and fitted with a positive pressure nitrogen-filled balloon. After the flask was cooled to −78 °C in a dry ice–acetone bath, diisobutylaluminum hydride (28.4 mL of 1.76 M in hexane, Aldrich, 0.050 mol) was added dropwise, via a syringe, over a period of 30 min. The mixture was stirred at −78 °C for 3 h and then treated with 100 mL of 10% aqueous methanol. After 5 min, (*S*)-(−)-α-methylbenzylamine (6.45 mL, 6.06 g, 0.050 mol) was added. The resulting mixture was stirred at −78 °C for 1 h and then warmed to −30 °C and an additional portion of (*S*)-(−)-α-methylbenzylamine (6.45 mL, 6.06 g, 0.050 mol) was added. After 20 min at −30 °C, benzoic acid (12.2 g, 0.10 mol) and *tert*-butyl isocyanide[17] (4.16 g, 0.050 mol) were added. The reaction mixture was stirred at −30 to −10 °C for 1.5 h, at 0 °C for 1.5 h, and at 25 °C for 17 h. The solvents were removed in vacuo and the residue was dissolved in 500 mL of methylene chloride. This solution was washed with 2 × 100 mL of 2.0 N hydrochloric acid, 2 × 100 mL of 2.0 N sodium hydroxide, 2 × 100 mL of water, and 2 × 100 mL of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and then evaporated to afford 16.0 g of crude product as a viscous brown oil.

The diastereomeric products were separated by medium-pressure liquid chromatography by using petroleum ether–ether (3:2) as eluent. Three fractions were collected; the first and third fractions were shown by NMR to be pure diastereomers, while the second fraction was shown to be a mixture of two diastereomers. The second fraction was resolved by column chromatography on silica gel by using petroleum ether–ether (3:2) containing 2% formic acid by volume. The overall yield for the combined reduction and 4CC was 70%.

(α*R*,2*S*,5*S*)-*N*-*tert*-Butyl-2,5-dihydro-5-methyl-α-[*N*-[(*S*)-α-methylbenzyl]benzamido]-2-furanacetamide (12a): 2.04 g; colorless solid; recrystallized from petroleum ether; mp 113.5–115.5 °C; $[\alpha]^{25}_D$ −220.1° (*c* 1, EtOH); R_f 0.55 (petroleum ether–ether 1:1); IR (KBr) 3480, 3220, 3010, 1665, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 3 H, $J \simeq$ 6.6 Hz), 1.34 (s, 9 H), 1.58 (d, 3 H, J = 7 Hz), 3.54 (d, 1 H, $J \simeq$ 8.2 Hz), 4.76 (br m, 1 H), 5.09 (q, 1 H, J = 7 Hz), 5.77 (m, 3 H), 7.40 (m, 10 H), 7.88 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.2, 22.0, 28.7, 51.0, 59.0, 69.4, 82.4, 83.2, 126.0, 126.3, 127.3, 127.5, 127.7, 128.0, 128.1, 128.4, 128.7, 129.5, 129.7, 132.7, 137.3, 139.1, 169.9, 174.0. Anal. Calcd for $C_{26}H_{32}N_2O_3$: C, 74.26; H, 7.67; N, 6.66. Found: C, 73.99; H, 7.75; N, 6.47.

(α*S*,2*R*,5*R*)-*N*-*tert*-Butyl-2,5-dihydro-5-methyl-α-[*N*-[(*S*)-α-methylbenzyl]benzamido]-2-furanacetamide (12b): 2.1 g; colorless solid; recrystallized from petroleum ether; mp 139.5–141.0 °C; $[\alpha]^{25}_D$ +60.4° (*c* 1, EtOH); R_f 0.38 (petroleum ether–ether 1:1); IR (KBr) 3200, 3000, 1675, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 9 H), 1.38 (d, 3 H, $J \simeq$ 6.4 Hz), 1.63 (d, 3 H, J = 7 Hz), 3.49 (d, 1 H, $J \simeq$ 9.0 Hz), 4.96 (m, 1 H), 5.11 (q, 1 H, J = 7 Hz), 5.75 (m, 1 H), 5.87 (m, 2 H), 7.22 (s, 5 H), 7.47 (m, 5 H). Anal. Calcd for $C_{26}H_{32}N_2O_3$: C, 74.26; H, 7.67; N, 6.66. Found: C, 74.31; H, 7.80; N, 6.39.

(α*R*,2*R*,5*R*)-*N*-*tert*-Butyl-2,5-dihydro-5-methyl-α-[*N*-[(*S*)-α-methylbenzyl]benzamido]-2-furanacetamide (12c): oil; 5.27 g; R_f 0.63 (ether–petroleum ether, 2:1); IR (neat) 3290, 3000, 1680, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 3 H, $J \simeq$ 6.5 Hz), 1.35 (s, 9 H), 1.53 (d, 3 H, J = 7 Hz), 3.34 (d, 1 H, $J \simeq$ 7.6 Hz), 4.75 (m, 1 H), 5.09 (q, 1 H, J = 7 Hz), 5.22 (m, 2 H), 5.67 (dd, 1 H, $J \simeq$ 7.6 Hz), 7.10 (br s, 1 H), 7.20 (s, 5 H), 7.48 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 16.6, 23.0, 29.0, 51.0, 57.9, 65.5, 83.0, 85.4, 126.2, 127.0, 128.0, 128.4, 128.7, 129.1, 131.2, 137.7, 140.2, 168.4, 172.3.

(α*S*,2*S*,5*S*)-*N*-*tert*-Butyl-2,5-dihydro-5-methyl-α-[*N*-[(*S*)-α-methylbenzyl]benzamido]-2-furanacetamide (12d): oil; 5.26 g; R_f 0.53 (ether–petroleum ether, 2:1); IR (neat) 3300, 3210, 3000, 1675, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.13 (s, 9 H), 1.37 (d, 3 H, $J \simeq$ 6.5 Hz), 1.55 (d, 3 H, J = 7 Hz), 3.56 (d, 1 H, $J \simeq$ 7.0 Hz), 4.95 (br m, 1 H), 5.11 (q, 1 H, J = 7 Hz), 5.72 (br m, 1 H), 5.90 (m, 2 H), 6.38 (br s, 1 H), 7.24 (s, 5 H), 7.46 (m, 5 H).

2,5-Anhydro-4,6-diselenophenyl-L-mannose Dimethyl Acetal (20). Diphenyldiselenide (3.2 g, 0.01 mol) was dissolved in 50 mL of dry DMF and then treated with sodium borohydride (1.0 g, 0.026 mol), added slowly over a period of 20 min. After 2 h at ambient temperature (or until the disappearance of the yellow color), ditosylate **18** (4.0 g, 0.0078 mol) in 15 mL of dry DMF was added dropwise to the reaction mixture while maintaining the temperature at 80 °C. After completion of the reaction, as monitored by TLC (ether–petroleum ether, 1:1, R_f 0.37), the mixture was diluted with 200 mL of ether. The organic phase was washed with water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and evaporated to give the crude product which was purified by column chromatography (ether–petroleum ether, 1:2) to afford diselenide **20** (3.3 g, 85% yield) as a yellow syrup: IR (neat) 3400, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$, 220 MHz) δ 2.72 (br s, 1 H), 3.02 (dd, 1 H), 3.33 (s, 3 H), 3.37 (s, 3 H), 3.35–3.60 (m, 2 H), 3.88 (dd, 1 H), 4.09–4.20 (m, 2 H), 4.26 (d, 1 H), 7.18 (m, 6 H), 7.48 (m, 4 H). MS Calcd for $C_{20}H_{24}O_2Se_2$: 488.0005. Found: 488.0005.

2,5:3,4-Dianhydro-L-talose Dimethyl Acetal *p*-Toluenesulfonate (19). 2,5-Anhydro-3,6-di-*O*-tosyl-L-idose dimethyl acetal (**18**) (1.55 g, 3 mmol), in 20 mL of dry DMF, was treated with 160 mg of sodium hydride (3.1 mmol as a 50% dispersion in mineral oil). After 2 h at ambient temperature, the stirred mixture was diluted with 150 mL of ether and then 5 mL of water was added. The organic phase was washed with water, dried with magnesium sulfate, and concentrated to afford the crude epoxide as a brown syrup. After column chromatography (ether–petroleum ether, 1:1), 930 mg of epoxide **19** was isolated (90% yield): IR (neat) 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$, 220 MHz) δ 2.46 (s, 3 H), 3.44 (s, 3 H), 3.47 (s, 3 H), 3.80 (q, 2 H), 4.05–4.11 (m, 3 H), 4.20–4.30 (m, 2 H), 7.35 (d, 2 H), 7.80 (d, 2 H). Anal. Calcd for $C_{15}H_{20}O_7S$: C, 52.31; H, 5.86. Found: C, 52.06; H, 5.89.

Reaction of 19 with Sodium Phenylselenide. Diphenyl diselenide (3.2 g, 0.01 mol) was dissolved in 50 mL of dry DMF and treated with sodium borohydride (1.0 g, 0.026 mol), added slowly over a period of 20 min. After 2 h at ambient temperature (or until the disappearance of the yellow color of the solution), epoxide **19** (2.6 g, 0.0078 mol) in 15 mL of dry DMF was added to the reaction mixture while the temperature was maintained at 80 °C. After completion of the reaction as monitored by TLC (ether–petroleum ether, 1:1, R_f 0.37), the mixture was diluted with 200 mL of ether. The organic phase was washed with water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and evaporated in vacuo to give the crude product which was purified by column chromatography (ether–petroleum ether, 1:2). The product **20** (3.4 g, 92% yield) was identical with that previously obtained from the reaction of ditosylate **18** with sodium phenylselenide.

2,5-Anhydro-4,6-dideoxy-L-*lyxo*-hexose Dimethyl Acetal (17). To a warm (50 °C) solution of sodium hydroxide (36 g) in 150 mL of water was cautiously added Raney Ni powder[18] (Ni-Al; 50/50). The suspension was stirred for 50 min and then cooled to ambient temperature and washed successively with water until neutral, dry ethanol, and finally tetrahydrofuran. To the resultant stirred suspension was added **20** (1.5 g, 3.14 mmol) in 10 mL of tetrahydrofuran. After 2 h at ambient temperature, the mixture was filtered through Celite and dried over anhydrous magnesium sulfate. Removal of solvent gave a syrup which was chromatographed on silica, using ether as eluent, to afford 0.533 g (96% yield) of alcohol **17**: IR (neat) 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$, 220 MHz) δ 1.31 (d, 3 H), 1.61 (m, 1 H), 2.33 (m, 1 H), 2.76 (br s, 1 H), 3.43 (s, 3 H), 3.45 (s, 3 H), 3.84 (t, 1 H), 4.18 (m, 1 H), 4.30 (d, 1 H), 4.35 (m, 1 H). Anal. Calcd for $C_8H_{16}O_4$: C, 54.52; H, 9.15. Found: C, 54.88; H, 8.83.

(17) *tert*-Butyl isocyanide was prepared by a modification of the procedure of Ugi et al. ("Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, p 300). Diphenyl ether was used instead of petroleum ether.

(18) Prepared according to: Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, p 729.

(2*R*,5*S*)-2,5-Dihydro-5-methyl-2-furaldehyde Dimethyl Acetal (21). A solution of 2.5-anhydro-4,6-dideoxy-L-*lyxo*-hexose dimethyl acetal (**17**) (300 mg, 1.8 mmol) in 20 mL of dry pyridine was cooled to 0 °C and treated with *p*-toluenesulfonyl chloride (350 mg, 1.8 mmol). The mixture was stored at 0 °C for 3 days, whereupon it was treated with 10 mL of ice water and diluted with ether. The organic phase was extracted with 10% hydrochloric acid, dried over anhydrous magnesium sulfate, and evaporated in vacuo to afford 550 mg (98% yield) of the tosylate as a yellow oil. This product was used directly without further purification.

The tosylate (495 mg, 1.5 mmol) was dissolved in 10 mL of methanol and added to a solution of sodium methoxide (108 mg, 2.00 mmol) in 30 mL of dry methanol. The solution was refluxed for 18 h and then concentrated in vacuo. The residue was diluted with 50 mL of water and extracted with methylene chloride. The combined organic extracts were dried over anhydrous magnesium sulfate and evaporated to give a brown oil which was purified by column chromatography (ether–petroleum ether, 1:2) to afford 2,5-dihydrofuran **21** (170 mg, 72% yield) as a colorless oil: R_f 0.60 (ether–petroleum ether, 1:1); IR (neat) 2880, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 220 MHz) δ 1.25 (d, 3 H, $J_{6,5}$ = 6.3 Hz, Me), 3.38 (s, 6 H, OMe), 4.10 (d, 1 H, $J_{1,2}$ = 6.2 Hz, OCHO), 4.58–5.15 (m, 2 H, $J_{2,1}$ = 6.2 Hz, $J_{2,3}$ = $J_{2,4}$ = 1.8 Hz, $J_{2,5}$ = 5.9 Hz, $J_{5,6}$ = 6.3 Hz, $J_{5,4}$ = 1.8 Hz, $J_{5,3}$ = 1.5 Hz, 2-H + 5-H), 5.68–5.92 (m, 2 H, $J_{3,2}$ = 1.8 Hz, $J_{3,4}$ = 6.3 Hz, $J_{3,5}$ = 1.5 Hz, $J_{4,5}$ = 1.8 Hz, $J_{4,2}$ = 1.8 Hz, HC=CH). Anal. Calcd for $C_8H_{14}O_3$: C, 60.73; H, 8.92. Found: C, 61.02; H, 8.77.

Hydrolysis of Acetal 21 and Four-Component Condensation. A magnetically stirred solution of 2,5-dihydrofuran acetal (**21**) (253 mg, 1.6 mmol) and *p*-toluenesulfonic acid (600 mg, 3.2 mmol) in 15 mL of tetrahydrofuran and 1 mL of water was refluxed for 3 h, diluted with 15 mL of methanol, and cooled to 0 °C. To this mixture was added (*R*)-(+)-α-methylbenzylamine (0.41 mL, 3.2 mmol), benzoic acid (192 mg, 1.6 mmol), and *tert*-butyl isocyanide[17] (150 mg, 1.7 mmol) in portions over 1-min intervals. The resultant solution was stirred at ambient temperature for 12 h and then diluted with ether. The organic phase was washed with 3 × 20 mL of 0.2 N sodium hydroxide, 3 × 20 mL of 0.1 N hydrochloric acid, 1 × 30 mL of water, and 1 × 20 mL of saturated sodium chloride, dried over anhydrous magnesium sulfate, and evaporated to give an oil which was chromatographed on silica (ether–petroleum ether, 1:1). The overall yield for the hydrolysis and 4CC was 63%.

(α*S*,2*R*,5*S*)-*N*-*tert*-Butyl-2,5-dihydro-5-methyl-α-[*N*-[(*R*)-α-methylbenzyl]benzamido]-2-furanacetamide (22a): 261 mg; colorless solid; recrystallized from ether–petroleum ether (1:1); mp 126 °C; $[\alpha]^{25}_D$ +253° (*c* 1, EtOH); R_f 0.60 (ether–petroleum ether, 1:1); IR (KBr) 3200, 3000, 2910, 1675, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (d, 3 H), 1.37 (s, 9 H), 1.58 (d, 3 H), 3.39 (m, 1 H), 4.85–5.38 (m, 2 H), 5.50–5.95 (m, 3 H), 7.59 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 17.9, 21.3, 28.7, 51.0, 59.0, 68.1, 81.0, 82.3, 126.0, 127.2, 127.6, 128.1, 128.8, 129.5, 130.0, 133.0, 137.3, 138.9, 170.0, 173.7. Anal. Calcd for $C_{26}H_{32}N_2O_3$: C, 74.26; H, 7.67; N, 6.66. Found: C, 74.57; H, 8.01; N, 6.59.

(α*R*,2*R*,5*S*)-*N*-*tert*-Butyl-2,5-dihydro-5-methyl-α-[*N*-[(*R*)-α-methylbenzyl]benzamido]-2-furanacetamide (22b): oil; 265 mg; $[\alpha]^{25}_D$ +82° (*c* 1, EtOH); R_f 0.28 (ether–petroleum ether, 1:1); IR (neat) 3300, 3000, 2900, 1680, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (s, 9 H), 1.24 (d, 3 H), 1.51 (d, 3 H), 3.63 (d, 1 H), 4.86–5.31 (m, 2 H), 5.73–6.12 (m, 3 H), 6.22 (br s, 1 H), 7.20 (s, 5 H), 7.46 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 18.4, 21.6, 28.6, 50.6, 57.6, 63.5, 81.9, 85.4, 126.1, 128.0, 128.6, 128.8, 129.5, 130.0, 132.6, 137.3, 139.1, 167.3, 172.1. Anal. Calcd for $C_{26}H_{32}N_2O_3$: C, 74.26; H, 7.67; N, 6.66. Found: C, 74.06; H, 7.90; N, 6.60.

General Procedure for Debenzylation of the Four-Component Condensation Adducts. The 4CC adduct, in 95% formic acid (10 mL/mmol), was stirred at ambient temperature for 2 h and then heated to 50–60 °C for 1–2 h (TLC monitoring). Upon completion of the reaction, the mixture was diluted with 10 volumes of methylene chloride, extracted with water until the washings were neutral (pH paper), and dried over anhydrous magnesium sulfate. Removal of the solvent and purification of the residue by medium-pressure liquid chromatography, using ether–petroleum ether (1:1) as eluent, afforded the debenzylation product which was then recrystallized from methylene chloride–petroleum ether mixtures.

13a: mp 106.0–107.0 °C; $[\alpha]^{25}_D$ −61.1° (*c* 1, EtOH); R_f 0.67 (ether); IR (KBr) 3240, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (partially masked d, 3 H), 1.32 (s, 9 H), 4.65–5.50 (m, 3 H), 5.83 (m, 2 H), 6.28 (br s, 1 H), 7.25 (br s, 1 H), 7.63 (m, 5 H). Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.52; H, 7.68; N, 8.70.

13b: mp 105.5–107.0 °C; $[\alpha]^{25}_D$ +62.4° (*c* 1, EtOH); TLC, IR, and ^1H NMR identical with those of **13a**. Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.62; H, 7.89; N, 8.61.

13c: mp 122.5–123.5 °C; $[\alpha]^{25}_D$ −4.9° (*c* 1, EtOH); R_f 0.58 (ethyl acetate–hexane, 1:1); IR (KBr) 3230, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (partially masked d, 3 H), 1.32 (s, 9 H), 4.60–5.20 (m, 3 H), 5.90 (br s, 2 H), 6.68 (br s, 1 H), 7.23 (br s, 1 H), 7.60 (m, 5 H). Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.13; H, 7.61; N, 8.62.

13d: mp 119–121 °C; $[\alpha]^{25}_D$ +5.2° (*c* 1, EtOH); TLC, IR, and ^1H NMR identical with those of **13c**; ^{13}C NMR ($CDCl_3$) δ 22.4, 28.8, 51.6, 57.6, 82.8, 86.8, 127.0, 127.2, 128.5, 131.6, 133.2, 134.3, 167.3, 168.6. Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.16; H, 7.69; N, 8.83.

23a: mp 116–117 °C; R_f 0.13 (ether–petroleum ether 1:1); IR (KBr) 3150, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, 3 H), 1.30 (s, 9 H), 4.75 (q, 1 H), 5.08 (m, 1 H), 5.40 (m, 1 H), 5.86 (m, 2 H), 6.25 (br s, 1 H), 7.60 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 21.8, 28.8, 51.5, 56.3, 83.3, 85.4, 125.8, 127.2, 128.6, 131.7, 133.6, 134.1, 167.1, 167.9. Anal. Calcd for $C_{18}H_{24}N_2O_3 \cdot {}^1/_2H_2O$: C, 66.62; H, 7.77. Found: C, 66.83; H, 7.78.

23b: mp 127–129 °C; R_f 0.25 (ether–petroleum ether 2:1); IR (KBr) 3200, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (d, 3 H), 1.35 (s, 9 H), 4.74–5.35 (m, 3 H), 5.95 (m, 2 H), 6.82 (br s, 1 H), 7.31 (br s, 1 H), 7.65 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 21.8, 28.8, 51.5, 56.8, 82.8, 86.7, 126.7, 127.3, 128.4, 131.6, 133.8, 134.4, 167.3, 168.6.

General Procedure for the Synthesis of α-Amino Acids. The debenzylation product (316.4 mg, 1.00 mmol) in 15 mL of 6 N hydrochloric acid was stirred *vigorously* at reflux for 1.5–2.0 h (TLC monitoring). The solution was then diluted with 40 mL of water, washed with methylene chloride, and evaporated in vacuo (water bath 50–60 °C). To remove excess hydrochloric acid, the residue was dissolved four times in 25-mL portions of methanol–water (1:1), each portion being separately evaporated to dryness in vacuo. The crude amino acid hydrochloride was applied to a weakly basic ion-exchange column (Amberlite IRA-4B, 1 × 12 cm) and slowly eluted with 100 mL of water. Removal of the water in vacuo gave the crude α-amino acid which was applied to a silica gel column (2 × 15 cm) and eluted with acetone–water (6:1). Fractions enriched in α-amino acid were combined and evaporated in vacuo. Final purification was effected by column chromatography (silica gel, 2 × 15 cm), using 1-propanol–water (9:1) as the eluent. Small fractions were collected and those enriched in α-amino acid were combined and evaporated. Recrystallization of the crude product from an acetone–water mixture gave the colorless α-amino acid.

14a: mp 187–189 °C dec; $[\alpha]^{25}_D$ +6.9° (*c* 1, 1 N HCl); R_f 0.41 (1-propanol–water 7:3); IR (KBr) 3330, 2900, 2550, 1625 cm^{-1}; ^1H NMR (D_2O, 360 MHz) δ 1.32 (d, 3 H, *J* = 6.7 Hz, Me), 3.88 (d, 1 H, *J* = 3.7 Hz, α-H), 5.00 (m, 1 H, 5-H), 5.31 (m, 1 H, 2-H), 5.87 (d, 1 H, =CH), 6.15 (m, 1 H, =CH). Anal. Calcd for $C_7H_{11}NO_3$: C, 53.50; H, 7.05; N, 8.91. Found: C, 53.51; H, 7.30; N, 8.63.

14b: mp 189–191 °C dec; R_f 0.41 (1-propanol–water 7:3); IR (KBr) 3320, 2970, 2550, 1635 cm^{-1}; ^1H NMR (D_2O, 360 MHz) δ 1.27 + 1.33 (2 d, ca. 2:1, 3 H, *J* = 6.1 Hz, *J* = 6.1 Hz Me), 3.86 + 3.88 (2d, 1 H, *J* = 3.1 Hz, *J* = 2.3 Hz, α-H), 5.00 + 5.02 (2 m, 1 H, 5-H), 5.31 (m, 1 H, 2-H), 5.87 + 5.88 (2 m, 1 H, =CH), 6.15 + 6.18 (2 m, 1 H, =CH). Anal. Calcd for $C_7H_{11}NO_3$: C, 53.50; H, 7.05; N, 8.91. Found: C, 53.41; H, 7.21; N, 8.71.

14c: mp 204–205 °C dec; $[\alpha]^{25}_D$ +47.4° (*c* 1, 1 N HCl); R_f 0.41 (1-propanol–water 7:3); IR (KBr) 3270, 3010, 2890, 2600, 1620 cm^{-1}; ^1H NMR (D_2O, 360 MHz) δ 1.31 (d, 3 H, *J* = 6.7 Hz, Me), 4.01 (d, 1 H, *J* = 3.7 Hz, α-H) 5.03 (m, 1 H, 5-H), 5.32 (br m, 1 H, 2-H), 5.71 (d, 1 H, =CH), 6.13 (d, 1 H, =CH). Anal. Calcd for $C_7H_{11}NO_3$: C, 53.50; H, 7.05; N, 8.91. Found: C, 53.29; H, 7.27; N, 8.91.

14d: mp 202–203 °C dec; $[\alpha]^{25}_D$ −57.6° (*c* 1, 1 N HCl); TLC, IR, and ^1H NMR identical with those of **14c**. Anal. Calcd for $C_7H_{11}NO_3$: C, 53.50; H, 7.05; N, 8.91. Found: C, 53.24; H, 7.12; N, 8.69.

24a: mp 222.5–224.5 °C dec; $[\alpha]^{25}_D$ +140° (*c* 1, H_2O), $[\alpha]^{25}_D$ +160° (*c* 1, 1 N HCl); R_f 0.41 (1-propanol–water 7:3); IR (KBr) 3300, 3050, 2800, 2510, 1635 cm^{-1}; ^1H NMR (D_2O, 360 MHz) δ 1.26 (d, 3 H, *J* = 6.7 Hz, Me), 3.86 (d, 1 H, *J* = 3.1 Hz, α-H), 5.12 (t, 1 H, 5-H), 5.45 (br m, 1 H, 2-H), 5.86 (d, 1 H, =CH), 6.19 (d, 1 H, =CH).

24b: mp 224.5–225.5 °C dec; $[\alpha]^{25}_D$ +251° (*c* 1, 1 N HCl); R_f 0.43 (1-propanol–water 7:3); IR (KBr) 3320, 2820, 2700, 2580, 1580 cm^{-1}; ^1H NMR (D_2O, 360 MHz) δ 1.28 (d, 3 H, *J* = 6.1 Hz,Me), 4.02 (d, 1 H, *J* = 4.3 Hz, α-H), 5.14 (t, 1 H, 5-H), 5.44 (br m, 1 H, 2-H), 5.69 (d, 1 H, =CH), 6.19 (d, 1 H, =CH). Anal. Calcd for $C_7H_{11}NO_3$: C, 53.50; H, 7.05; N, 8.91. Found: C, 53.41; H, 7.07; N, 8.70.

Natural furanomycin (1): mp 220–223 °C dec; $[\alpha]^{25}_D$ +136.1° (*c* 1, H_2O), $[\alpha]^{25}_D$ +164° (*c* 1, 1 N HCl); TLC, IR, and ^1H NMR identical with those of **24a**.

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