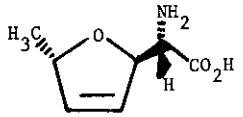
FURANOMYCIN ANALOGS: OPTICALLY ACTIVE NORFURANOMYCINS

Hosein R. Divanfard, Zenon Lysenko, J. Edward Semple, Pen-Chung Wang, and Madeleine M. Joullié*, Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104

John F. Blount, Hoffmann-La Roche Inc., Nutley, NJ 07110

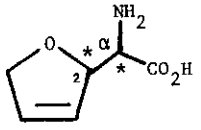
Abstract - *The total synthesis of the four stereoisomeric forms of norfurnanomycin is described. The absolute stereochemistry of these novel amino acids was established by X-ray crystallography.*

Furanomycin (1) is an antibiotic obtained from the culture broth of Streptomyces threomyceticus.[1] The structure of 1 was first assigned the (αR,2R,5R) configuration based on a combination of spectroscopic and chemical degradation techniques. The total synthesis of 1, however, required revision of the original assignment to the (αS,2R,5S) configuration.[2]



1

The biological activity of 1 led us to prepare some analogs. Norfuranomycin, an analog without the 5-methyl group (2) was chosen for this purpose. Norfuranomycin possesses two asymmetric centers and therefore can exist in four optically active forms (2a-d).

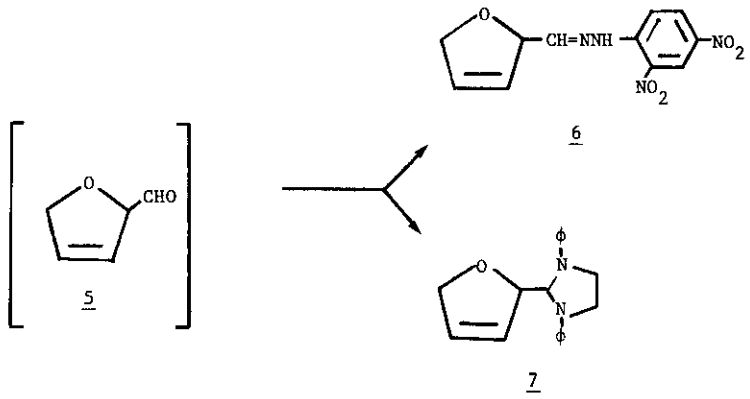


2

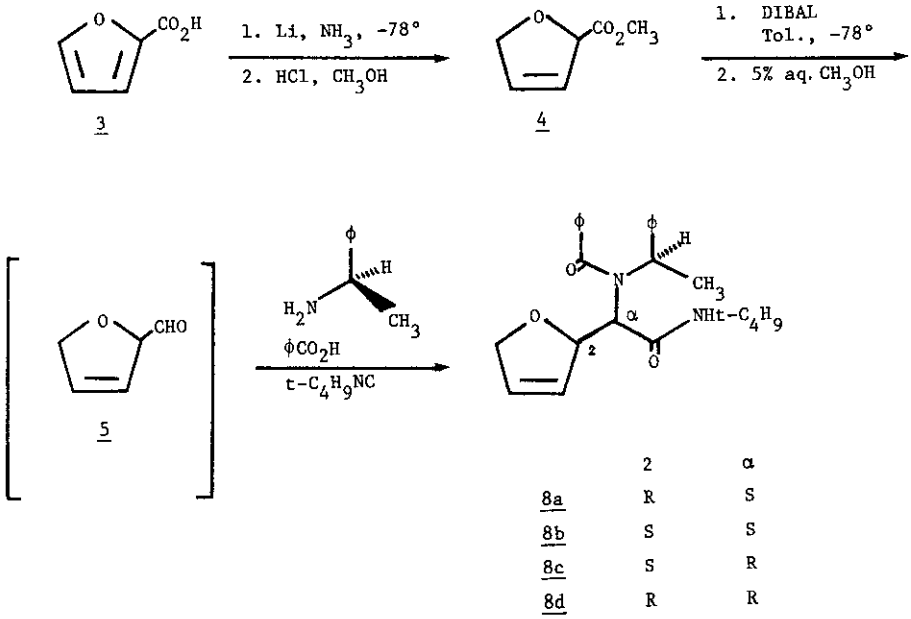
	2	α
2a	R	S
2b	S	S
2c	S	R
2d	R	R

The key element in the synthesis of compounds such as 1 and 2 is the functionalized 2,5-dihydrofuran moiety. Furoic acid (3) was reduced under Birch conditions to afford 2,5-dihydrofuroic acid which was then converted to the corresponding methyl ester (4) in 85% overall yield.[3] Compound 4 was treated under nitrogen with one equivalent of diisobutylaluminum hydride (DIBAL), in anhydrous

toluene, at -78°C to give aldehyde (5) which was trapped with both 2,4-dinitrophenylhydrazine and 1,2-dianilinoethane affording crystalline 6 and 7, respectively.



The sensitivity of the aldehyde required that the amino acid functionality be introduced under mild conditions such as those implicit in the Ugi four-component condensation (4CC).[4] Thus, quenching of the DIBAL reduction product (5) with 5% aqueous methanol at -78°C followed by the addition of d-(+)-α-methylbenzylamine, benzoic acid and tert-butylisonitrile in a 2:2:1 ratio at 0°C, afforded four diastereomeric amino acid derivatives (8a-d) which could be separated chromatographically (Scheme 1).



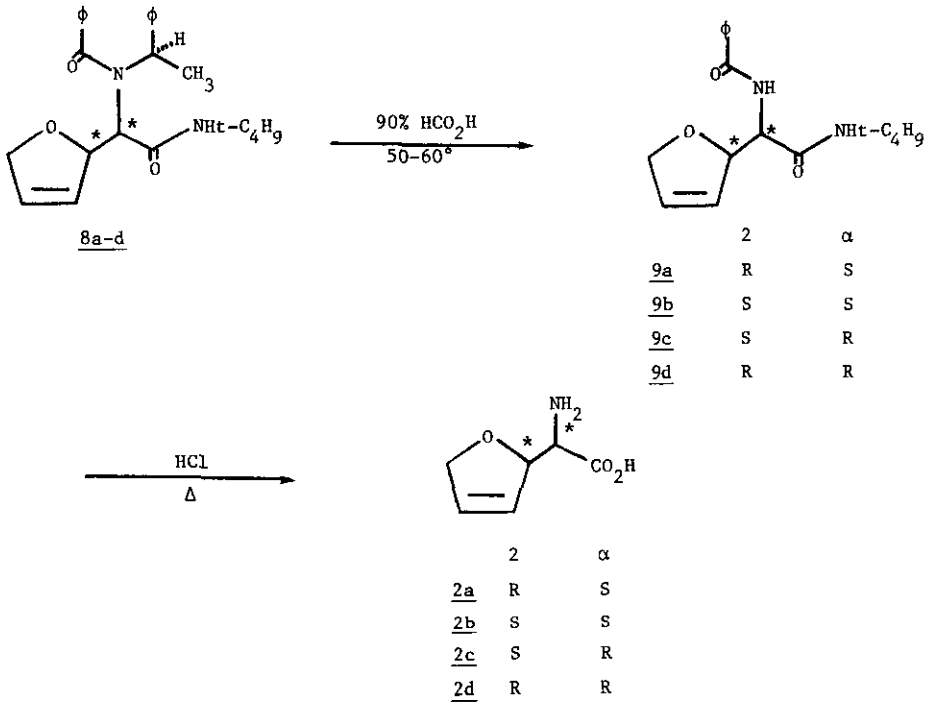
	2	α
8a	R	S
8b	S	S
8c	S	R
8d	R	R

Scheme 1

The total yield for compounds 8a-d was 78% based on 4. The physical properties of these

derivatives are shown in Table 1. An X-ray crystallographic structure of 8a and 8b showed the absolute configurations at their chiral centers to be 2R, αS, and 2S, αS, respectively.[5] These determinations were based on the absolute configuration of d-(+)-α-methylbenzylamine as being R (Figure 1).[6]

Compounds 8a-d were subsequently debenzylated with 95% formic acid at 50-60°C to afford the corresponding products 9a-d in yields of 90% or higher (Scheme 2). The spectral and physical properties of 9a and 9c were identical except for their optical rotations, i.e., $[\alpha]_{EtOH}^{D}$ = +23.0°



8a-d

	2	α
9a	R	S
9b	S	S
9c	S	R
9d	R	R

	2	α
2a	R	S
2b	S	S
2c	S	R
2d	R	R

Scheme 2

for 9a and $[\alpha]_{EtOH}^{D}$ = -39.4° for 9c. Debenzylated compounds 9b and 9d also exhibited identical physical and spectral properties. Their optical rotations, however, were -123.3° for 9b and +138.3° for 9d. These data indicate that 9a and 9c are enantiomers as are 9b and 9d. The assignment of the absolute stereochemistry of the chiral centers of the subsequent products was based on these results.

The hydrolysis of the debenzylated products (9a-d) proceeded smoothly to afford the corresponding amino acids (2a-d). This reaction was carried out by refluxing compounds 9a-d in 12N hydrochloric

Table. Physical and Spectral Data for Compounds 8a-b, 9a-b and 2a-b.

Product No.	Configuration 2	Configuration α	Yield [%]	m.p. °C	$[\alpha]^{D}_{solvent}$[b] °	IR (KBr) $\nu_{max}[cm^{-1}]$	^{1}H NMR (solvent)[c] δ ppm
8a	R	S	18	106-107	+22.9	3500, 3200, 1660, 1615, 1535 (NH, CO, C=C)	1.38(s, 9H, t-Bu), 1.56(d, 3H, Me), 3.45 (d, 1H, α-H), 3.8-4.5(m, 2H, =CH), 5.12 (q, 1H, -CH(Me)), 5.60-5.90(m, 2H, =CH), 5.7 5.90(m, 1H, 2-H), 7.10-7.60(m, 10H, ϕ, 7 (bs, 1H, NH)
8b	S	S	21	114-115	-4.5	3300, 1675, 1625, 1530, (NH, CO. C=C)	1.40(s, 9H, t-Bu), 1.55(d, 3H, Me), 3.45 (d, 1H, α-H), 4.30(m, 2H, CH_2), 5.05 (q, 1H, -CH(Me)), 5.20(m, 2H, =CH), 5.50- 5.82(m, 1H, 2-H), 7.00-7.70(m, 11H, ϕ)
8c	S	R	18	163-164	-45.2	3150, 1655, 1610, 1535 (NH, CO, C=C)	1.10(s, 9H, t-Bu), 1.55(d, 3H, Me), 3.45 (d, 1H, α-H), 4.65(m, 2H, CH_2), 5.10 (q, 1H, -CH(Me)), 5.60-6.00(m, 1H, 2-H), 5.80-6.00 (m, 2H, =CH), 7.20-7.50 (m, 11H, ϕ)
8d	R	R	22	125.5-126	+109.0	3320, 3200, 1675, 1625, 1535 (NH, CO, C=C)	1.15(s, 9H, t-Bu), 1.55(d, 3H, Me), 3.65 (d, 1H, α-H), 4.60-4.80(m, 2H, CH_2), 5.12 (q, 1H, -CH(Me)), 5.60-6.20(m, 1H, 2-H), 5.90-6.00(m, 2H), 7.20-7.60(m, 11H, ϕ)

9a	R	S	95	127-128	+23.0	3200, 1640, 1525 (NH, CO, C=C)	1.32(s, 9H, t-Bu). 4.55-4.70(m, 2H, CH_2-CO-N-), 4.75(α, 1H, -CH-), 5.10-5.35 (m, 1H, 2-H), 5.70-6.00(m, 2H, =CH), 6.25(bs, 1H, NH-COφ), 7.10-7.90 (m, 6H, NHt-Bu and φ)
9b	S	S	90	174-175	-123.3	3250, 1645, 1540 (NH, CO, C=C)	1.32(s, 9H, t-Bu), 4.55-4.70(m, 2H, CH_2-CO-N-), 4.80(d, 1H, -CH-), 4.75-5.20(m, 1H, 2-H) 5.85-6.02(m, 2H, =CH), 6.60(bs, 1H, NH), 7.15(bs, 1H, NH), 7.20-7.90(m, 5H, φ)
9c	S	R	95	128-129	-39.4	3200, 1640 1525 (NH, CO, C=C)	Same as 8a
9d	R	R	90	173-174	+138.3	3200, 1640 1530 (NH, CO C=C)	Same as 8b
2a	R	S	45	214-216 (dec.)	+36.6	3100b, 1600b, 1490, 1390, 1330 (NH_4^+, CO_2^-, C=C)	3.90(d, 1H, α-H), 4.60-4.80(m, 2H, CH_2), 5.20-5.50(m, 1H, 2-H), 5.75-5.60(m, 1H, =CH), 6.10-6.40(m, 1H, =CH)
2b	S	S	40	209 (dec.)	-122.5	2900b, 1600b, 1500, 1400, 1310 (NH_4^+, CO_2^-, C=C)	4.00(d, 1H, α-H), 4.55-4.85(m, 2H, CH_2), 5.18-5.40(m, 1H, 2-H), 5.55-5.68 (m, 1H, =CH), 6.05-6.30(m, 1H, =CH)

2c	S	R	50	215-217 (dec.)	-35.8	3150b, 1600b, 1500, 1390, 1330 (NH_4^+, CO_2^-, C=C)	same as 2a
2d	R	R	30	209-210 (dec.)	+109.0	2900b, 1600b, 1500, 1400, 1310 (NH_4^+, CO_2^-, C=C)	same as 2b

[a]The configuration of the α-methylbenzyl group in compounds 8a-b is R.

[b]Ethanol (8a-d, 9a-d), 1N HCl (2a-d).

[c]$CDCl_3$ (8a-d, 9a-d), D_2O (2a-d).

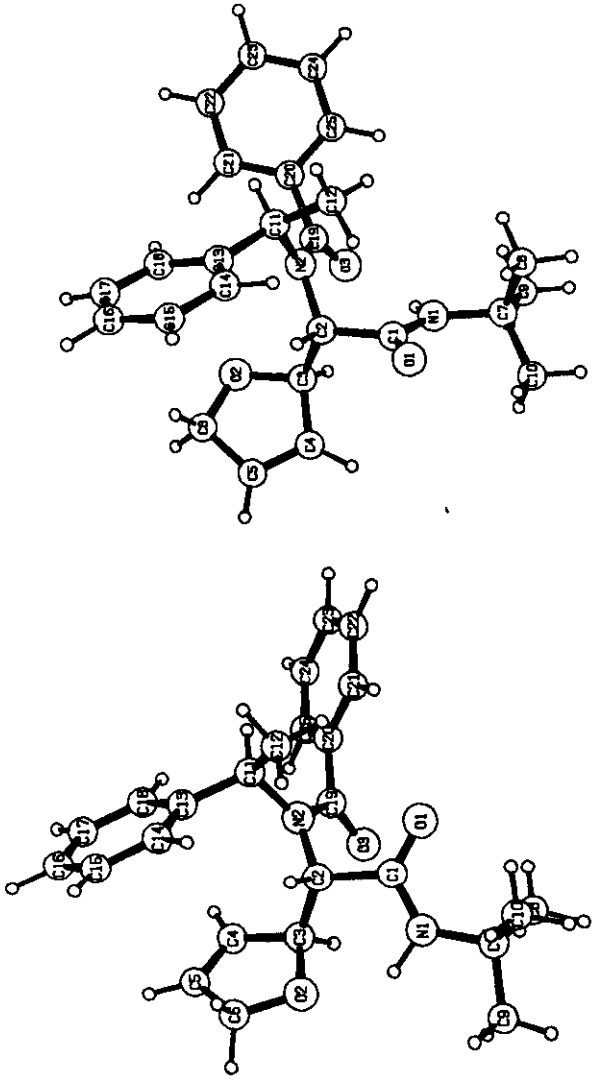


Figure 1. Perspective drawings of 8b (2S,αS) and 8a (2R,αS).

acid (Scheme 2). Chromatography on silica gel using 15% aqueous propanol gave the isomeric norfuranomycins (2a-d). These amino acids gave a reddish brown color when heated with ninhydrin. Norfuranomycins 2a-d exhibited antimicrobial activity against some Pseudomonas and Klebsiella strains of bacteria and also against E. coli.[7]

Experimental Procedure - Melting points are uncorrected and were determined on a Thomas Hoover Unimelt capillary melting point apparatus. Elemental microanalyses were carried out by Robertson Laboratory, Florham Park, New Jersey and by the Analytical Department of the Dow Chemical Company, Midland, Michigan. Infrared spectra were obtained on a Perkin-Elmer 137 spectrophotometer (KBr pellets). The ^{1}H NMR were recorded at 60 MHz in the designated solvents using tetramethylsilane (TMS) as internal reference standard. Chemical shifts are expressed in δ (ppm) downfield from TMS. Where deuterium oxide was employed as the solvent, sodium 3-(trimethylsilyl)tetradeuteriopropionate was used as the internal standard. Specific rotations were obtained on a Perkin Elmer model 141 polarimeter and are reported as $[\alpha]_D$ in units of degrees (°).

Preparation of 2,5-Dihydro-2-furaldehyde 2,4-Dinitrophenyl Hydrazone (6):

A solution (1.5 M) of diisobutylaluminum hydride in toluene (10.4 ml, 16 mmol) was added dropwise over a period of 30 min to a solution of methyl 2,5-dihydro-2-furoate (2.04 g, 16 mmol) in 40 ml of anhydrous ether at -78°C. The reaction mixture was stirred 30 min longer at -78°C, treated with 1 ml of methanol, and warmed gradually to ambient temperature. The gelatinous product that formed was diluted by addition of 80 ml of 5% hydrochloric acid and treated with a solution of 2,4-dinitrophenylhydrazine in 15 ml of concentrated sulfuric acid, 20 ml of water and 70 ml of ethanol. After 10 min, the ethereal layer was separated, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to afford 3.28 g of yellow crystals (6) which were further purified by recrystallization from ethanol, m.p. 150-151°C, 74% yield.

Anal. Calcd for $C_{11}H_{10}O_5N_4$: C, 47.49; H, 3.62; N, 20.14. Found: C, 47.52; H, 3.90; N, 20.05. IR (KBr): 3200, 1610, 1590, 1320 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 4.65-4.80 (m, 2H, 5-CH_2); 5.20-5.60 (m, 1H, 2-H); 5.91-6.21 (m, 1H, 4-H); 6.23-6.45 (m, 1H, 3-H); 7.83 (d, 1H, 6'-H); 7.97 (d, 1H, 5'-H); 8.23-8.45 (q, 1H, 3'-H); 8.85 (d, 1H, N=CH); 11.4 (s, 1H, NH).

Preparation of 2-(2,5-Dihydro-2-furyl)-1,3-diphenylimidazolidine (7):

A solution of 5 was generated as described for 6. To this solution was added a mixture of 3.4 g (16 mmol) of dianilinoethane in 100 ml of 5% aqueous hydrochloric acid. After 10 min, the ethereal layer was separated, dried over anhydrous sodium sulfate, filtered and evaporated in vacuo

to afford 3.27 g of crude 7 which was purified by recrystallization from 70% aqueous ethanol, m.p. 97.5-98.5°C, 70% yield.

Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05 H, 6.89 N, 9.58. Found: C, 78.10 H, 7.02 N, 9.53 IR (KBr): 1600, 1560, 1495, 1380 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.51 (s, 4H, CH_2 of imidazolidine); 4.28-4.46 (m, 2H, 5-CH_2); 5.10-5.43 (m, broad, 1H, 5-H); 5.53 (d, 1H, -N-CH-N); 5.63-5.76 (m, 2H, 3- and 4-H); 6.22-7.00 (m, 6H, m- and p-aromatic H); 7.00-7.40 (m, 4H, o-aromatic H).

Reduction of Methyl 2,5-Dihydrofuroate (4) and Four Component Condensation of Aldehyde (5):

A solution of methyl 2,5-dihydrofuroate (3.2 g, 0.025 mol) in 100 ml of anhydrous toluene was treated with a 2M solution of diisobutylaluminum hydride in toluene (6.25 ml, 0.025 mol), added dropwise, with stirring under nitrogen at -78°C. The reaction was maintained 2 h at -78°C and then treated with five 20 ml aliquots of 10% aqueous methanol. The reaction mixture was raised to 0°C and treated with R-α-methylbenzylamine (6.10 g, 6.4 ml, 0.05 mol), benzoic acid (6.10 g, 0.05 mol), tert-butylisonitrile (2.1 g, 0.025 mol) in a sequential addition. The resulting suspension was stirred at ambient temperature for 16 hr, diluted with methylene chloride and extracted consecutively with water, 0.2 N sodium hydroxide, 0.1 N hydrochloric acid, and saturated sodium chloride. The extracts were dried over anhydrous magnesium sulfate. The organic layer was concentrated in vacuo and the residue chromatographed on silica gel using ether-petroleum ether (1:2) to afford compounds 8a-d (7.93 g, 78% yield) with R_f values 0.70, 0.60, 0.40, and 0.33, respectively. Recrystallization of these isomers from ether-petroleum ether (1:3) gave four crystalline compounds with the following melting points: 8a, 106-107°C; 8b, 114-115°C; 8c, 163-164°C; 8d, 125-126°C.

Anal. Calcd for $C_{25}H_{30}N_2O_3$: C, 73.86; H, 7.44; N, 6.89. Found: 8a C, 73.54; H, 7.64; N, 6.59; 8b C, 73.50; H, 7.60; N, 6.70; 8c C, 73.88; H, 7.59; N, 6.73; 8d C, 73.86; H, 7.60; N, 6.95. The physical properties of 8a-d are summarized in Table 1.

Debenzylation of (αR, 2S)-N-tert-Butyl-2,5-dihydro-α-[N-[(R)-α-methylbenzyl]benzamido]-2-furan-acetamide (8a):

A solution of 8a (2.00 g, 0.005 mol) in 50 ml of 95% formic acid was stirred at 50-60°C for 6 hr. The mixture was diluted with 150 ml of methylene chloride, extracted with 6 x 25 ml portions of water, dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo to afford crude 9a which was purified by recrystallization from methylene chloride-petroleum ether. Yield: 1.43 g (93%), m.p. 127-128°C, $[\alpha]^D_{EtOH}$ + 23.0°, R_f 0.45 (Merck silica gel 60, ether).

Anal. Calcd for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.34; N, 9.26. Found: C, 67.25; H, 7.05; N, 9.20. The same procedure was used to debenzylate 8b-d. The physical properties of 9a-d are given

in Table 1.

Preparation of (2R, αS)-Amino-2,5-dihydro-2-furanacetic Acid (2a):

A solution of compound 9a (1.50 g, 0.005 mol) in 50 ml of concentrated hydrochloric acid (12 N) was heated at reflux for 1 hr, cooled to ambient temperature, diluted with an equal volume of water, and extracted with methylene chloride. The aqueous solution was neutralized and treated with decolorizing carbon. Concentration of the aqueous solution and chromatography of the residue on silica gel using 15% aqueous propanol as the eluent afforded crude 2a (R_f 0.45, Merck silica gel-60, n-PrOH-H_2O 7:3), which was further purified by recrystallization from aqueous acetone. Yield: 0.321 g (45%), m.p. 215-216°C decomp.) $[\alpha]^D_{1NHCl}$ + 36.6°. Anal. Calcd for $C_6H_9NO_3$: C, 50.35; H, 6.34; N, 9.79. Found: C, 50.05; H, 5.95; N, 9.65. The same procedure was used to obtain amino acids 2b-d. The physical properties of these compounds are summarized in Table 1.

Acknowledgement - We thank Ms. Rita Madison of the Bioproducts Research Laboratory, the Dow Chemical Company, Midland, Michigan for the preliminary biological tests. Partial support from a grant from the Dow Research Foundation is gratefully acknowledged.

References -

1. K. Katagiri, K. Tori, Y. Kimura, T. Yoshida, T. Nagasaki, and H. Minato, J. Med. Chem., 1967, 10, 1149; K. Katagiri, U.S. Patent, 3,642,985 (1972).
2. J. E. Semple, P. C. Wang, Z. Lysenko, and M. M. Joullié, J. Am. Chem. Soc., 1980, 102, 7505.
3. H. R. Divanfard and M. M. Joullié, Org. Prep. Proceed. Int., 1978, 10, 94; H. R. Divanfard, Ph.D. Dissertation, 1978, pp. 127-131.
4. R. Urban, D. Marquarding, and I. Ugi, Z. Physiol. Chem., 1978, 359, 1541 and references cited therein.
5. The absolute stereochemistry of 8a and 8b has been determined from single crystal X-ray analyses. The intensity data were measured on a Hilger-Watts four circle diffractometer (Ni filtered Cu-Kα radiation, θ-2θ scans, pulse height discrimination). Crystal data: 8a: a = 11.243(6), b = 12.326(6), c = 16.993(7) Å, space group $P2_12_12_1$, Z=4; 8b: a = 8.521(2), b = 13.472(2), c = 20.728(3) Å, space group $P2_12_12_1$, Z=4. Both structures were solved by a multiple solution procedure (G. Germain, P. Main, and M. M. Woolfson, Acta Cryst., 1971, A27, 368.
6. W. Klyne and J. Buckingham, "Atlas of Stereochemistry. Absolute Configurations of Organic Molecules," Oxford University Press, New York, N.Y., 1974, p. 23.

7. Norfuranomycin isomers (2a-b) were assayed in Davis-Glucose Agar and had minimum inhibitory concentrations (MIC) in the range of 10-50 ppm.

8. tert-Butylisonitrile was prepared by a modification of the procedure of Ugi et al. (Org. Syn., Coll. Vol.V), John Wiley and Sons, New York, N.Y., 1973, p. 300. Diphenyl ether was used instead of petroleum ether.

Received, 22nd July, 1981