Kirk-Othmer Encyclopedia of Chemical Technology.

ELFAMYCINS

The elfamycins are so named because they exhibit antimicrobial activity through the inhibition of protein biosynthesis via binding to the *el*ongation *fac*tor Tu (1). All of the known elfamycins are listed in Table 1 and the structures are given in Figure 1. These antibiotics are distinguished by low mammalian toxicity, narrow-range antimicrobial activity, and positive effects on feed utilization and growth promotion in farm animals. Elfamycins also improve milk production in lactating ruminants.

Elfamycins are natural products. Aurodox (**1**, R = CH_3) and efrotomycin (**2**, R = CH_3) have been synthesized chemically.

1. Properties

Elfamycins are slightly acidic because of the 4-hydroxy-2-pyridone or the carboxylic acid moiety. They are soluble in most polar organic solvents and the alkali and ammonium salts are water-soluble. The extractability of the free acids from aqueous solution into solvents such as dichloromethane and ethyl acetate is utilized in their isolation from fermentation broths.

Purifications of elfamycins have been described in the literature using Craig distribution (2, 34), chromatography on Sephadex LH-20 (2, 14, 26) and Amberlite XAD-2 (10, 17, 19, 26), supercritical fluid extraction (37), and chromatography on an Ito multilayer coil planet centrifuge (26, 38). ^{1}H and ^{13}C nmr assignments of most elfamycins have been accomplished (3, 24, 26, 32). The characteristic uv spectra permits some differentiation (12) and bathochromic shifts associated with Al^{3+} complexation have been used to quantify efrotomycin (**2**, R = CH_3) in feed premixes (39, 40).

1.1. Structures

The first structure to be elucidated was that of aurodox (**1**, R = CH_3), the oldest member of the elfamycin family. The elfamycins are amorphous and crystalline derivatives are as yet unknown. A combination of degradation reactions and the spectroscopic and Roentgen crystallographic analyses of the products was used to determine structure (4). The discovery that the amide linkage in aurodox could be disconnected under extremely mild conditions permitted a sequence of controlled cleavages, the products of which provided the structural and stereochemical information required to permit complete stereochemical assignments of the parent molecule. As shown in Figure 2**a,** treatment of aurodox using acetic acid at room temperature gave several products. One, termed goldinonic acid in view of the aurodox-producing microorganism's name, represented the carboxylic acid component of the amide and was isolated as the γ-lactone (**13**) (41). Periodate oxidation gave 3(*S*)-4(*E*)-6(*Z*)-3-hydroxy-2,2-dimethyl-4,6-octadienal (**14**), the absolute configuration of which was ascertained crystallographically (40) and by further degradation via (**15**) and (**16**) to the retrosynthetically significant (*R*)-(—)-pantolactone (**17**). Repetition of the acetic acid treatment using aurodox (4-bromobenzyl)ether (**19**) as

Table 1. Elfamycins

Antibiotic	CAS Registry Number	Molecular formula	Producing organism	Structure no.	Refs.
aurodox	[12704-90-4]	$C_{44}H_{62}N_2O_{12}$	*Streptomyces goldiniensis var. goldiniensis*	(**1**, R = CH_3)	(2–4)
kirromycin[a]	[50935-71-2]	$C_{43}H_{60}N_2O_{12}$	*S. collinus Tü 365*	(**1**, R = H)	(3, 5–7)
azdimycin	[57035-45-7]	unknown	*S. diastatochromogenes* ATCC 31013		8
efrotomycin	[56592-32-6]	$C_{59}H_{88}N_2O_{20}$	*S. lactamdurans* NRRL 3802	(**2**, R = CH_3)	(9–13)
dihydromocimycin	[61994-74-9]	$C_{43}H_{62}N_2O_{12}$	*S. ramocissimus* CBS190.69 CBS190.69	(**3**)	(12, 14)
heneicomycin	[66170-37-4]	$C_{44}H_{62}N_2O_{11}$	*S. filipinensis* NRRL 11044	(**4**, R = CH_3, R′ = C_2H_5, R″ = CH_3)	(12, 15, 16)
kirrothricin	[79190-00-4]	$C_{44}H_{64}N_2O_{10}$	*S. cinnamomeus* Tü 89	(**5**)	(12, 17, 18)
factumycin	[84600-89-5]	$C_{44}H_{62}N_2O_{10}$	*S. lavendulae* ATCC 31312	(**6**)	(12, 19)
MSD A63A	[81209-82-7]	unknown	*Streptoverticillum hiroshimense*		20
L681,217	[93522-10-2]	$C_{36}H_{53}N_1O_{10}$	*S. cattleya* ATCC 39203	(**7**)	(12, 21, 22)
SB22484, factor 3	[97328-80-8]	$C_{41}H_{56}N_2O_{11}$	*S. strain* NRRL 15496	(**4**, R = H, R′ = CH_3, R″ = H)	(12, 23, 24)
SB22484, factor 4	[97328-81-9]	$C_{42}H_{58}N_2O_{11}$	*S. strain* NRRL 15496	(**4**, R = H, R′ = C_2H_5, R″ = H)	(12, 23, 24)
phenelfamycin A	[118498-91-2]	$C_{51}H_{71}N_1O_{15}$	*S. violaceoniger* str. AB999F-80, AB1047T-33	(**8**, R = H, R′ = $COCH_2C_6H_5$)	(12, 25, 26)
phenelfamycin B	[118498-91-3]	$C_{61}H_{71}N_1O_{15}$	*S. violaceoniger* str. AB999F-80, AB1047T-33	(**8**, R = $COCH_2C_6H_5$, R′ = H)	(12, 26, 27)
phenelfamycin C	[118498-91-4]	$C_{58}H_{83}N_1O_{18}$	*S. violaceoniger* str. AB999F-80, AB1047T-33	(**9**, R = H, R′ = $COCH_2C_6H_5$)	(12, 26, 27)
phenelfamycin D	[118498-91-5]	$C_{58}H_{83}N_1O_{18}$	*S. violaceoniger* str. AB999F-80, AB1047T-33	(**9**, R = $COCH_2C_6H_5$, R′ = H)	(12, 26, 27)
phenelfamycin E	[114451-31-9]	$C_{65}H_{95}N_1O_{21}$	*S. violaceoniger* str. AB999F-80, AB1047T-33	(**10**, R = H, R′ = $COCH_2C_6H_5$)	(12, 26, 27)
phenelfamycin F	[114451-30-8]	$C_{65}H_{95}N_1O_{21}$	*S. violaceoniger* str. AB999F-80, AB1047T-33	(**10**, R = $COCH_2C_6H_5$, R′ = H)	(12, 26, 27)
unphenelfamycin	[118117-42-3]	$C_{43}H_{65}N_1O_{14}$	*S. violaceoniger* str. AB999F-80, AB1047T-33	(**8**, R = R′ = H)	(12, 26, 27)
LL-E19020α	[114451-31-9]	$C_{65}H_{95}N_1O_{21}$	*S. lydicus sp. tanzanius* NRRL 18036	(**11**, R = H, R′ = $COCH_2C_6H_5$)	(28–32)
LL-E19020β	[114451-30-8]	$C_{65}H_{95}N_1O_{21}$	*S. lydicus sp. tanzanius* NRRL 18036	(**11**, R = $COCH_2C_6H_5$, R′ = H)	(28–32)
UK-69,753	[118117-42-3]	$C_{58}H_{86}N_2O_{18}$	*Amycolatopsis orientalis* ATCC 53550	(**12**)	(12, 31, 33, 34)
N-demethylefrotomycin	[124846-41-9]	$C_{58}H_{86}N_2O_{20}$	*Nocardia* ATCC 53758	(**2**, R = H)	35

[a]Identical to mocimycin which was isolated from *S. ramocissimus* CB5190.69 (6, 36).

substrate minimized side reactions and gave goldinonolactone (**13**) and the amine component, goldinamine (4-bromobenzyl)ether (**20**), thus accounting for all skeletal elements of the antibiotic.

The goldinamine bromobenzyl ether (**20**) gave rise to a series of useful degradation products. The most significant fragments are summarized in Figure 2**b.** The spectroscopic analysis of the trienone moiety was supplemented crystallographically via its derivative (**23**) (42), and the absolute configuration of (**13**) was confirmed by crystallographic analysis of the 4-bromobenzoate (**21**) (4, 41).

The diene side of (**20**) was first obtained from its *N*-acetyl derivative by periodate oxidation in the form of 2(*R*)-3(*S*)-4(*E*)-6(*E*)-8-amino-3-methoxy-2,4-dimethyl-4,6-octadienal (4, 43). The threo configuration of this product was ascertained by ir spectroscopy (4) and by crystallographic analysis of the *N*-dinitrophenyl (DNP)

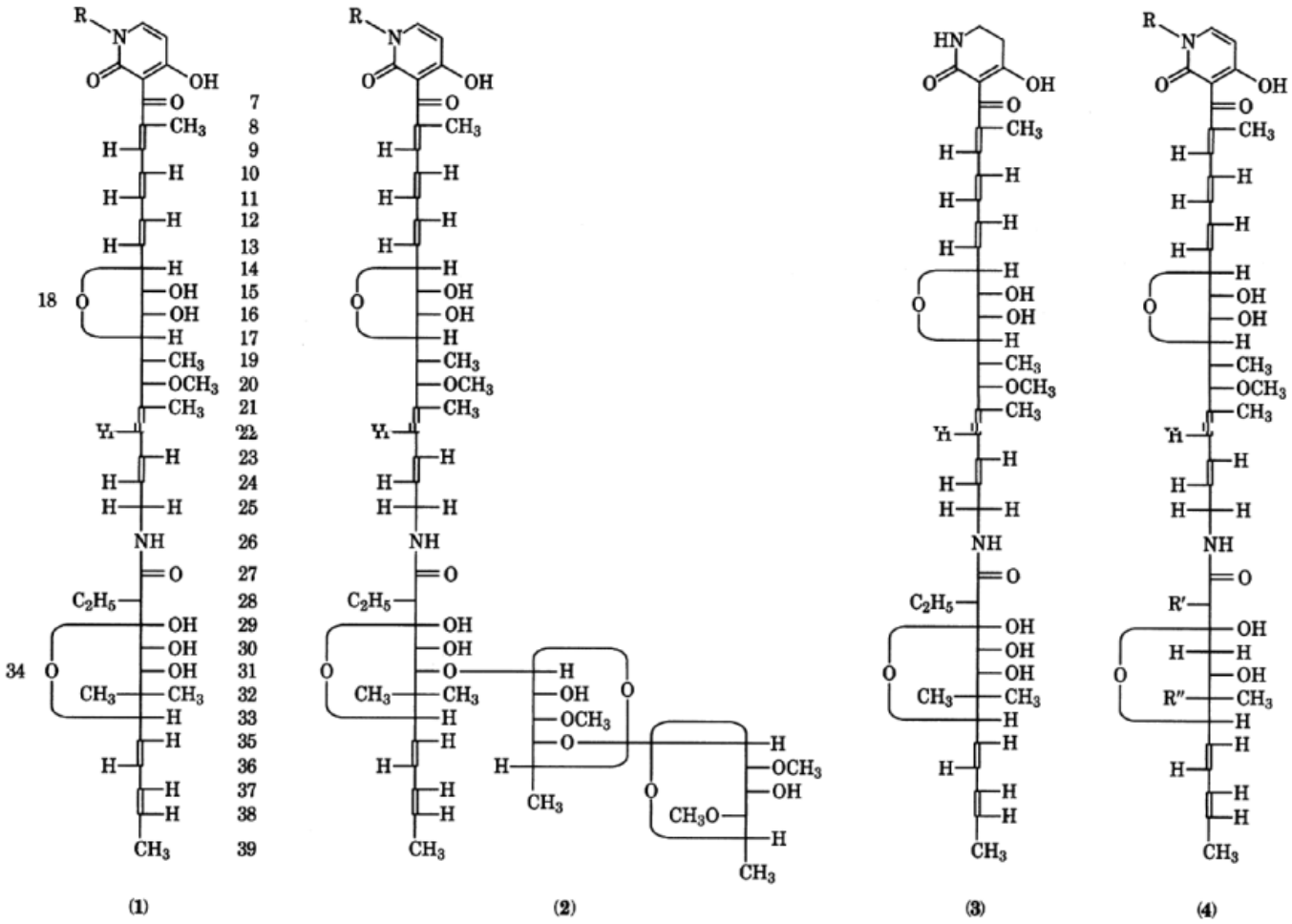

Fig. 1. Structures of the elfamycins given in Table 1 where the carbon skeleton numbering scheme is shown for structure (**1**) only.

derivative of its dimethyl acetal (43). Anomalous scatter in the analysis of (**22**) made the determination of absolute configuration possible (44). The configuration of the central tetrahydrofuran ring in (**20**) was originally determined spectroscopically (43, 45) and its topography was revealed by several degradation products (4). Most significant was the isolation of (**24**) which included not only the two stereocenters of (**22**), but also the four carbons in the tetrahydrofuran ring. Aldehyde (**24**) was converted to the crystalline tricyclic acetal (**25**). The topographic assignment of (**25**) also resulted from a crystallographic analysis (46), so that aurodox (**1**, R = CH_3) became known in complete stereochemical detail.

Similar degradation reactions were used to establish the absolute configuration of mocimycin (kirromycin) (**1**, R = H) (46), the constitution of which had been described previously (7, 47). The chemical structures of most other subsequently discovered elfamycins have been determined spectroscopically and assignments of absolute configurations are not complete. The elfamycin structures shown in Figure 1 have complete stereochemical details that have been in part ascertained experimentally and in part are assumed to correspond to the aurodox topography.

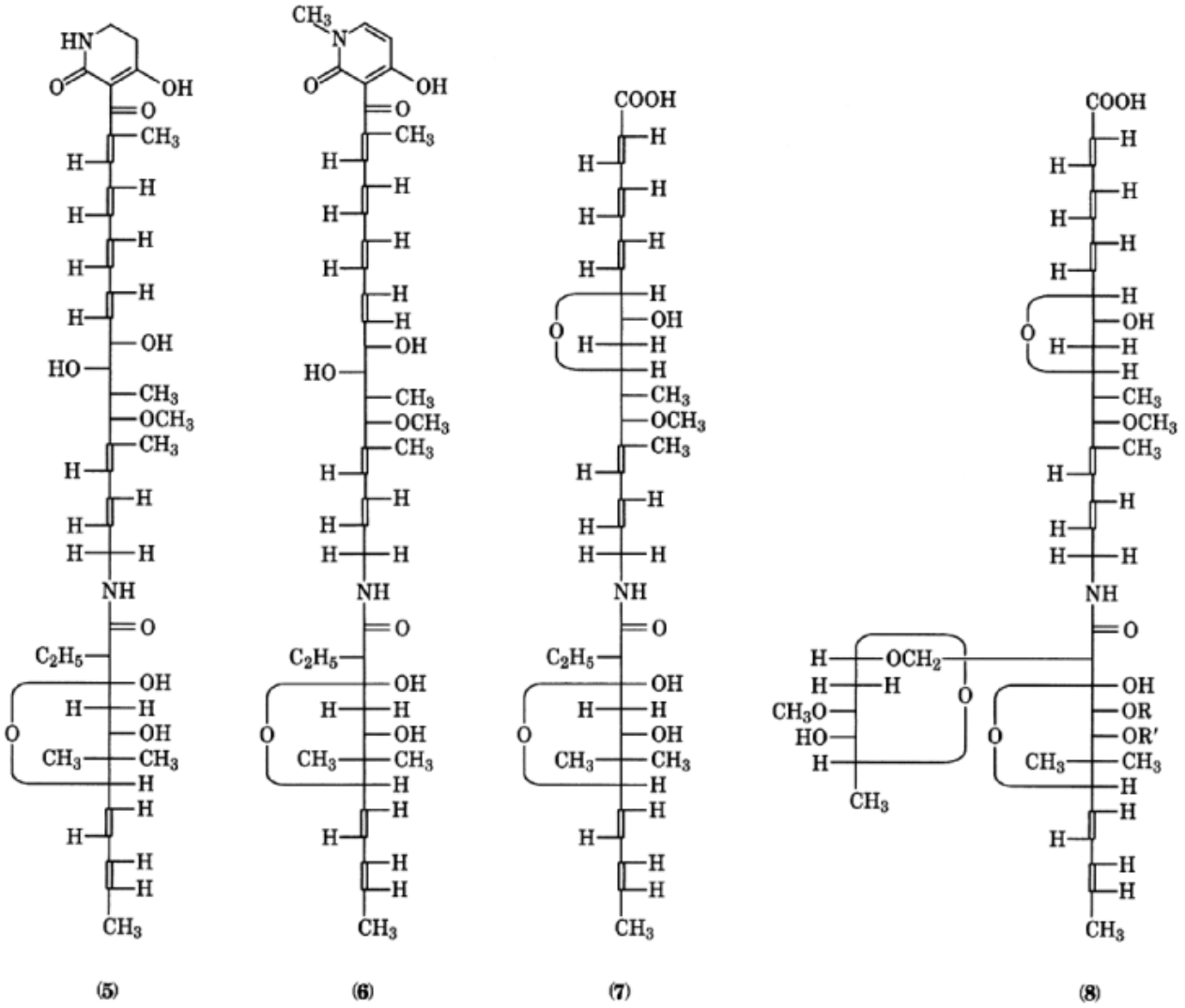

Fig. 1. Continued.

2. Production, Biosynthesis, and Chemistry

The production of elfamycins is described in the references cited in Table 1. Fermentation yield improvements with aurodox (**1**, R = CH_3) proved difficult because of feedback inhibition (48). Aurodox-resistant strains (49), however, responded positively to conventional mutagenic methods leading to yield increases from 0.4 to 2.5 g/L (50). Scale-up of efrotomycin (**7**, R = CH_3) fermentations were found to be particularly sensitive to small changes in sterilization conditions of the oil-containing medium used (51).

Biosynthetic studies using acetate (Ac), propionate (Pr), and butyrate (Bu) revealed the polyketide nature of aurodox which has the composition $Pr(Ac)_8$ for the goldinamine skeleton C-7 to C-25 and the composition $Bu(Ac)_5$ for the C-27 to C-39 carbon chain of goldinonic acid. In contrast to the methyl branch at C-8, those at

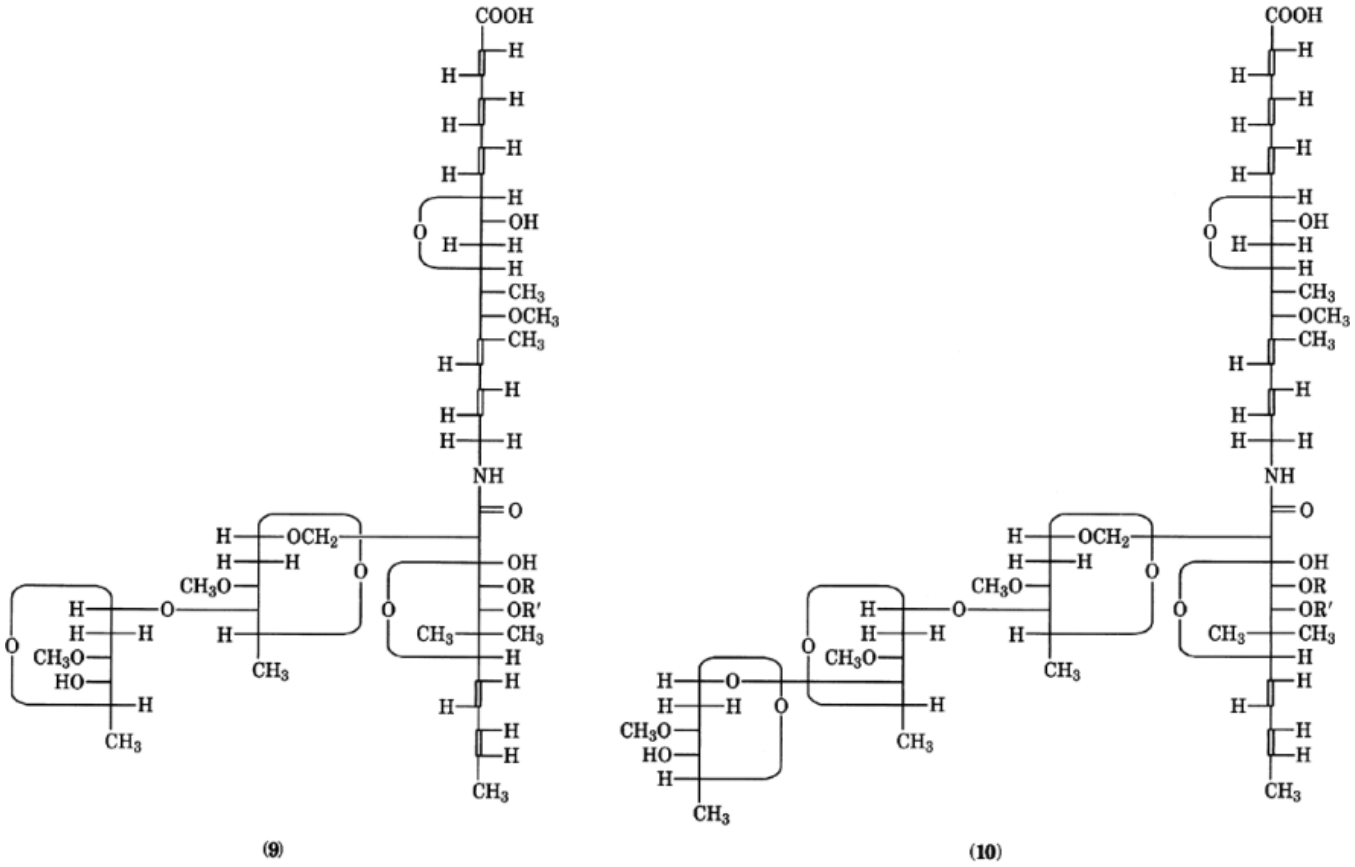

Fig. 1. Continued.

C-19 and C-21 are methionine-derived as are all remaining methyl groups (52, 53). The biogenetic origin of the pyridone moiety is not clear.

Desmethylefrotomycin (**2**, R = H) is a product of microbial transformation of mocimycin (**1**, R = H) by *Nocardia ATCC 53758* (35). Efrotomycin (**2**, R = CH_3) biosynthesis was studied in a resting cell system of *Nocardia lactamdurans* by glycosylation of aurodox (**1**, R = CH_3) via 6′-deoxyallosyl aurodox (54).

Mocimycin has been chemically converted to aurodox by protection of the 4-hydroxy group at the pyridone moiety as the benzoylformate, followed by *N*-methylation and hydrolytic removal of the protective group (1, 55). Whereas aurodox esters are active growth promotors in animals, goldinamines that are *N*-acylated by acids other than goldinonic acid, such as acetic, benzoic, or arylsulfonic acids, lack useful antimicrobial or growth-promoting activity (1).

Mocimycin was prepared from dihydromocimycin (**3**) by oxidation with selenium dioxide (14, 56). 4-Amino-4-dehydroxyefrotomycins were obtained by aminolysis of efrotomycin-4-*O*-phenylchlorophosphate (57).

Elfamycins having 4-hydroxy-2-pyridone moieties (**1–6,12**) readily undergo reversible internal cyclizations by conjugate addition of either oxygen functionality on the pyridone ring at C-9. These products can be isolated as exemplified by isoefrotomycin (58).

Aurodox and efrotomycin have been chemically synthesized (59). In analogy to the degradation studies shown in Figure 2, goldinonolactone (**13**) was synthesized from (**17**) by enantioselective reduction of ketolactone

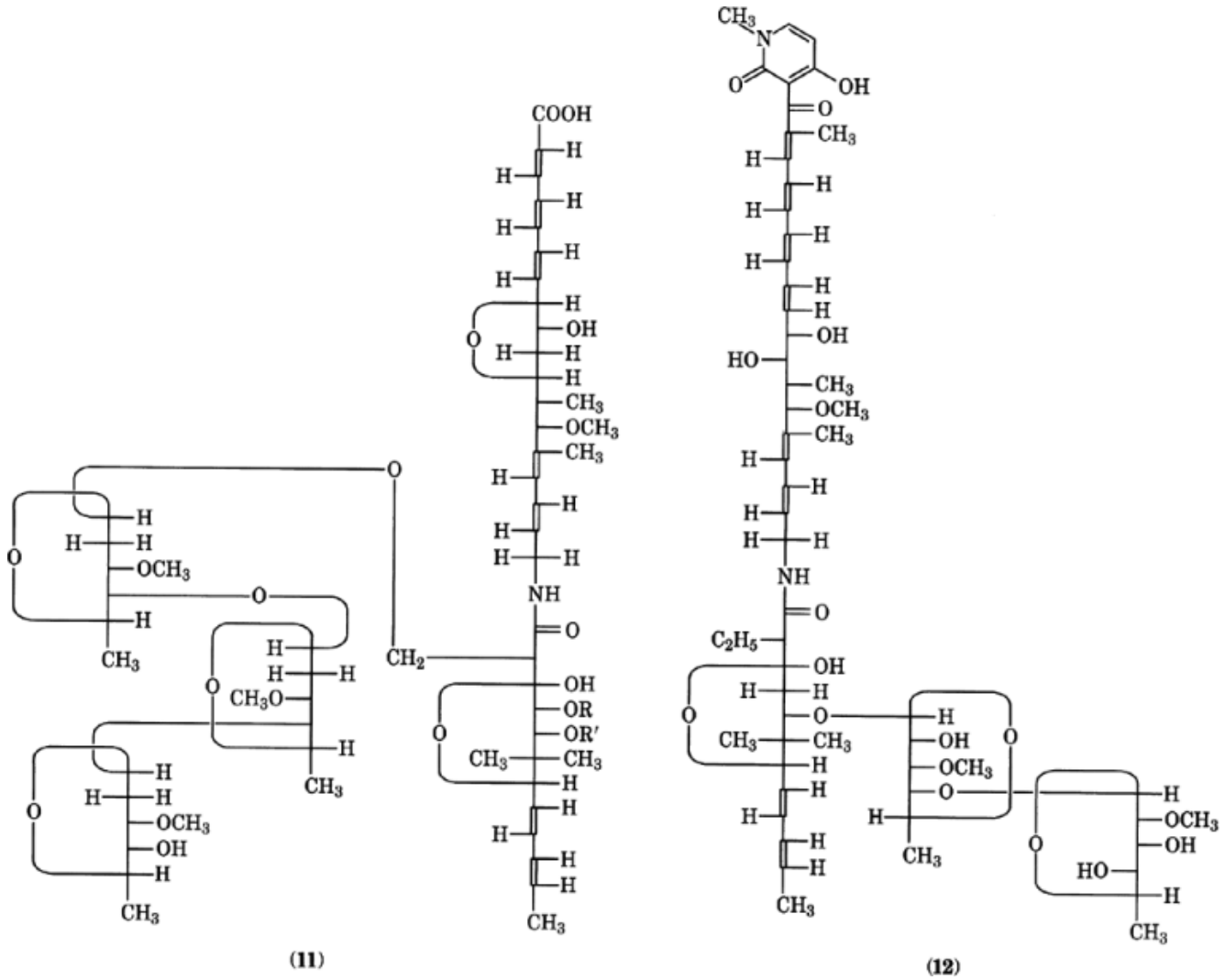

Fig. 1. Continued.

(**26**) followed by a sequence of acyclic stereoselective reactions shown in Figure 3. The stereocenters C-30 and C-31 in goldinonic acid (**1**) were generated by a Sharpless epoxidation of (**29**) followed by inversion at C-2 in epoxyalcohol (**31**). The (*E*),(*Z*)-geometry of the pentadienyl substituent was constructed from (**35**) by oxidation and addition of the anion derived from (*Z*)-crotyl diphenylphosphine oxide. Addition of butyrate to lactone (**36**) afforded a mixture of lactols which, after acetal hydrolysis, recyclization, and base-catalyzed epimerization, gave a mixture of C-3-epimeric dihydroxylactols from which pure goldinonolactone (**13**) could be isolated chromatographically (60).

The all-cis tetrahydrofuran ring of goldinamine was synthesized by the consecutive epoxide opening of the ester enolate derived from (**42**) according to an old concept as shown in Figure 4 (61). The five adjacent stereocenters in (**42**) were assembled by a kinetic resolution of alcohol (**38**) via its epoxide (**39**). One of the newly gained stereocenters was sacrificed to gain the allylic alcohol (**40**) which was subjected to a Sharpless

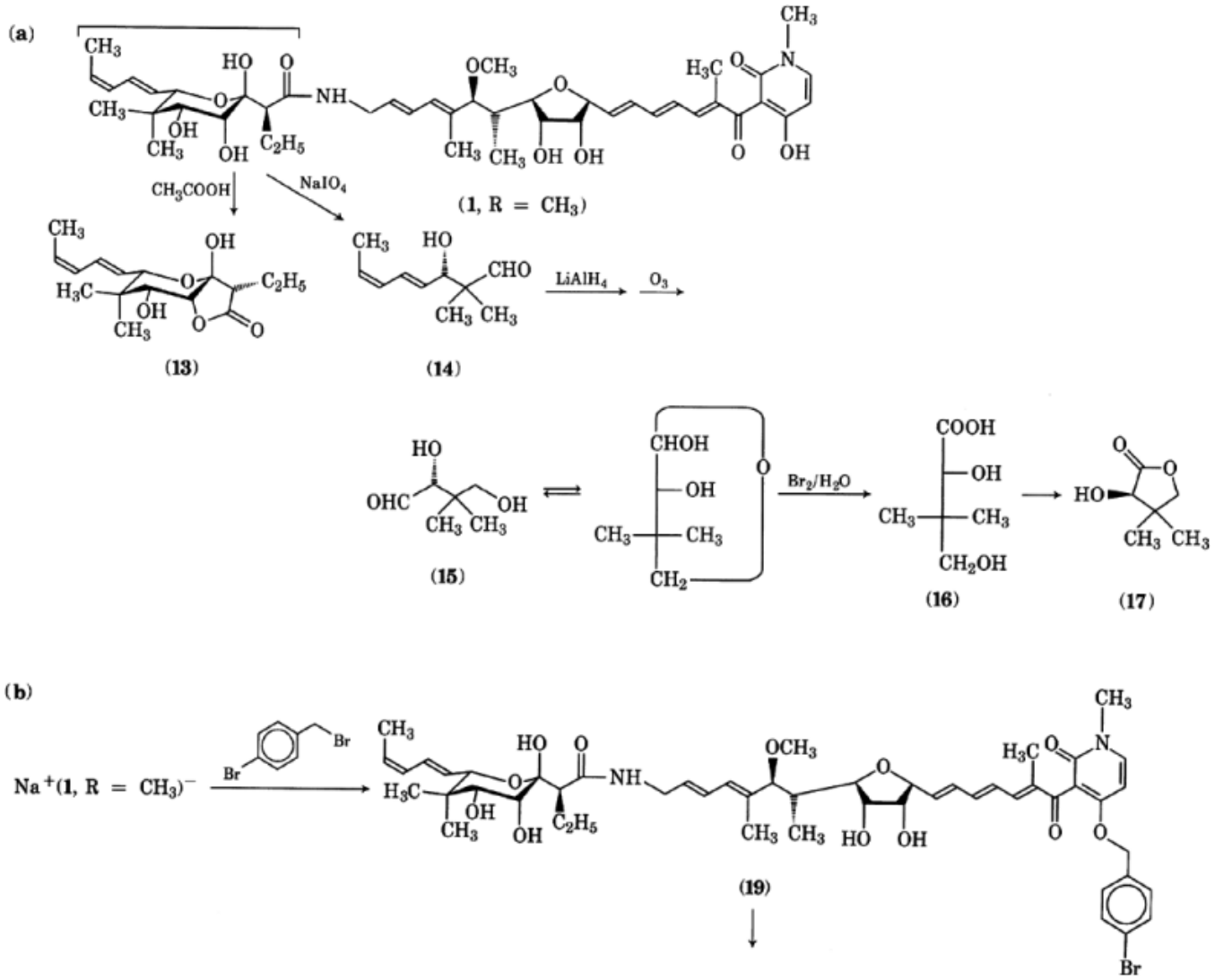

Fig. 2. Chemical degradation of aurodox: (**a**), goldinonic acid; (**b**), goldinamine.

epoxidation to introduce the third stereocenter. An epoxidation of the homoallylic alcohol (**41**) using *m*-chloroperbenzoic acid generated the two additional stereocenters with a diastereoselectivity of 94%. Hydrogenolysis of the benzyl ether, hydrolysis of the silyl ether, protection of the resulting diol, and oxidation of the primary alcohol gave a carboxylic acid which, after deprotonation, generated an alkoxide ion that opened the terminal epoxide to furnish the desired tetrahydrofuran (**43**). Further elaboration via (**44**) and (**45**) gave the terminal alkene (**46**) which was subjected to a stereoselective hydroboration to introduce the fifth consecutive stereocenter. A Swern oxidation of the resulting alcohol, followed by reaction with lithium di(α-methoxyvinyl)cuprate, led to the vinyl ether (**48**), the hydrolysis of which gave (**49**) with the sixth stereocenter in 73% de. A Wittig-Horner reaction using trimethyl phosphonoacetate established the (*E*)-geometry of the alkene with a stereoselectivity of 78%. An additional reduction step led to aldehyde (**50**).

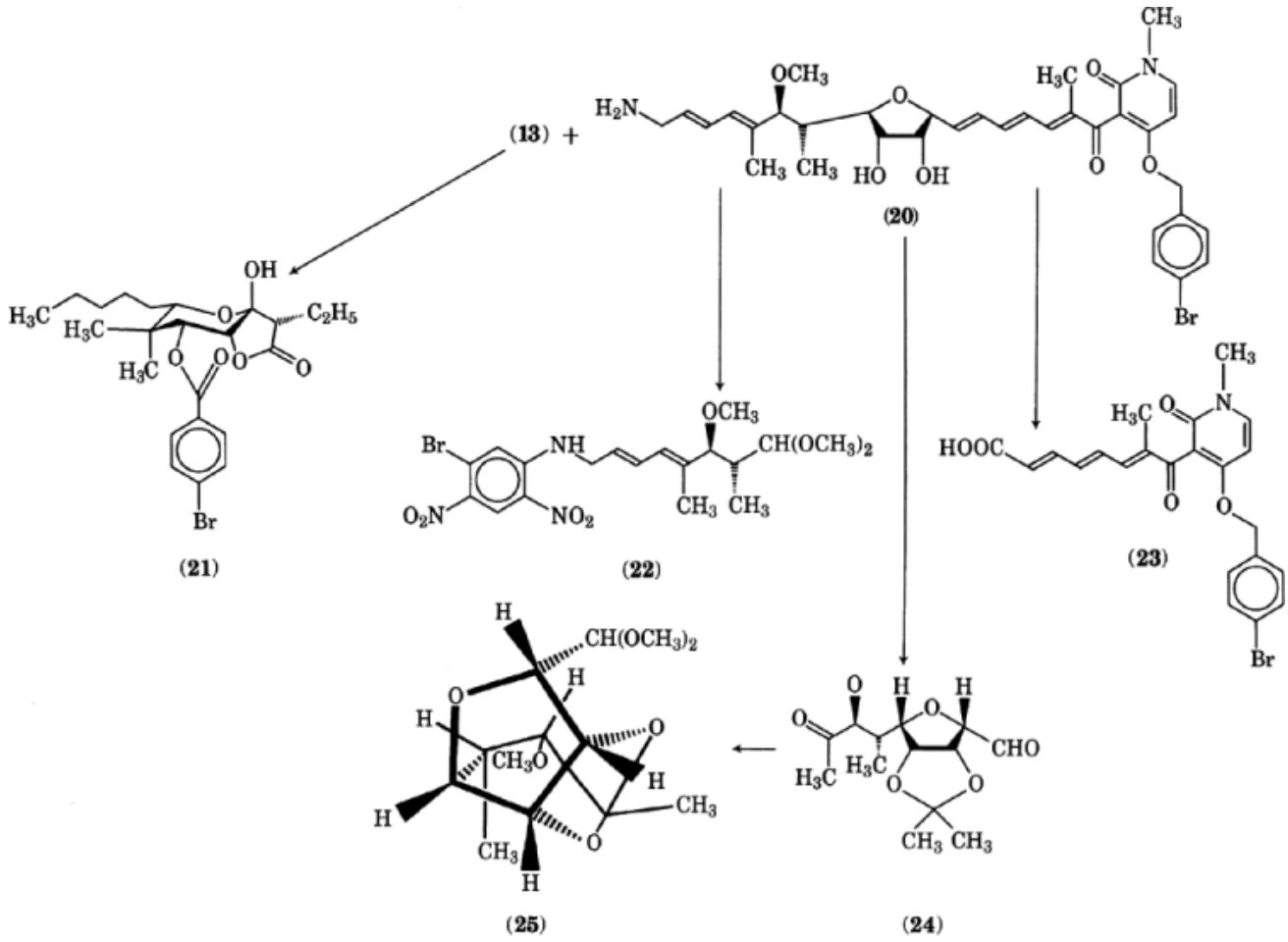

Fig. 2. Continued.

Condensation of (**50**) with diisopropyl phosphonoacetonitrile established the second (*E*)-alkene with 82% stereoselectivity as shown in Figure 5. The third (*E*)-alkene, as shown in (**52**), was prepared from (**51**) after desilylation and oxidation of the resulting primary alcohol, followed by an additional Wittig-Horner reaction with 75% stereoselectivity. The missing (*E*),(*E*)-diene portion was generated by a Wittig-Horner condensation where one of the double bonds was provided by the reactant (*E*)-3-methyl-4-[4-(benzyloxy)-1,2-dihydro-1-methyl-2-oxo-3-pyridyl]-4-oxo-2-butenyl-1-triphenyl phosphonium bromide. Goldinamine derivative (**55**), derived from (**54**) by changing the protective groups, served as a suitable substrate for the final condensation with (**13**) to furnish aurodox (1, R = CH_3), after removal of the silyl and benzyl ether groups (62).

Goldinonolactone and the tetrahydrofuran moiety of goldinamine were also synthesized from L- and D-mannose, respectively (63). The synthesis of efrotomycin has also been effected (62).

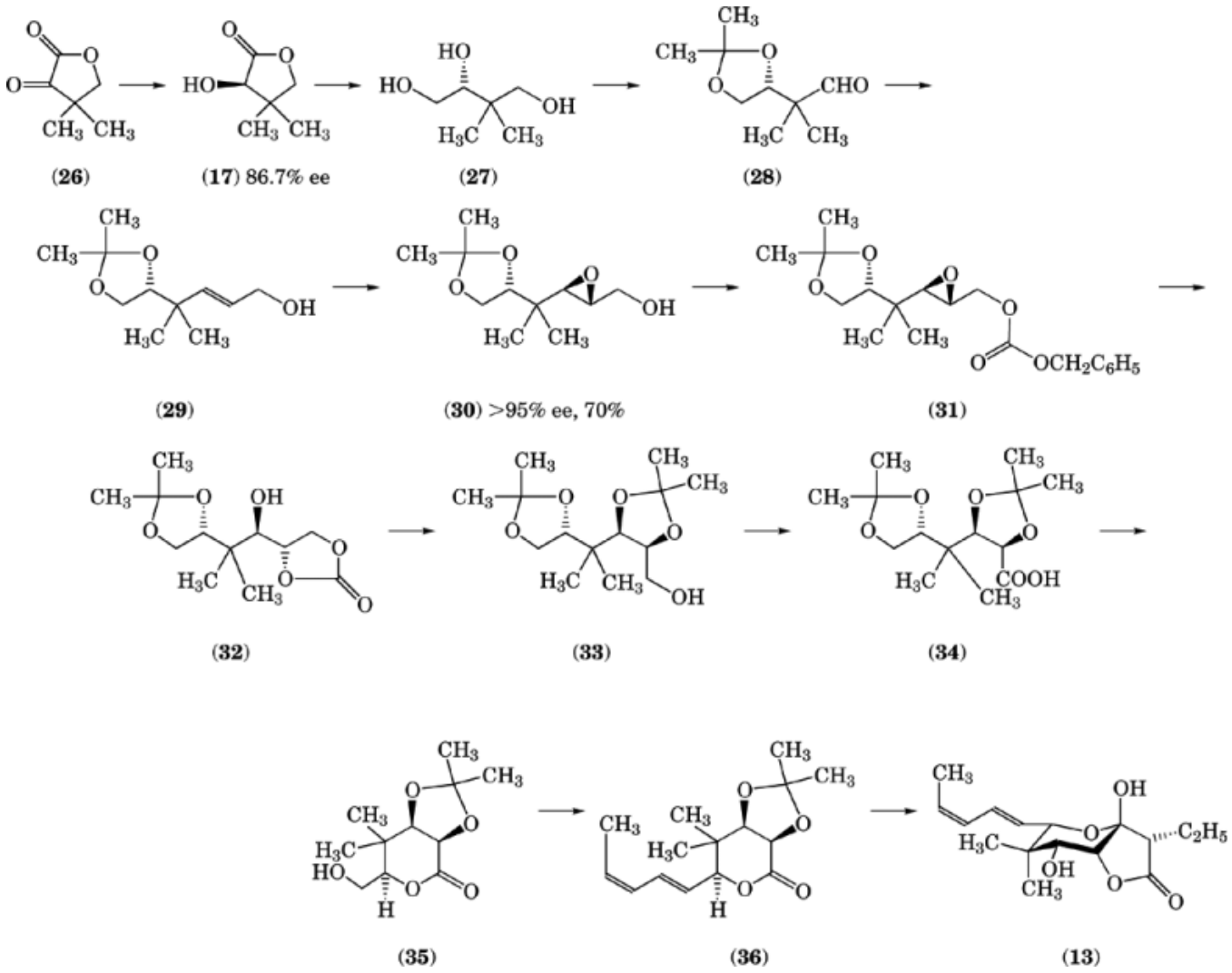

Fig. 3. Synthesis of goldinonolactone (**13**).

3. Biological Properties

3.1. Mode of Action

Elfamycins block bacterial protein biosynthesis at the level of elongation factor Tu (EF-Tu) (64–66). The biosynthesis of protein proceeds in four major stages, commencing with activation, which involves the synthesis of aminoacyl-*t*RNA (aa-*t*RNA) in the cytoplasm, followed by initiation, elongation, and termination. Binding of the ternary complex $\mathrm{EF-Tu{\cdot}GTP{\cdot}aa{-}}t\mathrm{RNA}$, where GTP is guanosine triphosphate, in the ribosomal *A*-site initiates the elongation phase. After hydrolysis of GTP to guanosine diphosphate (GDP) and the subsequent release of EF-Tu, peptide bond formation takes place. Elfamycins prevent the release of the $\mathrm{EF-Tu{\cdot}GDP}$ complex from the ribosome and hence debilitate peptidyl transfer and peptide synthesis. This mode of action

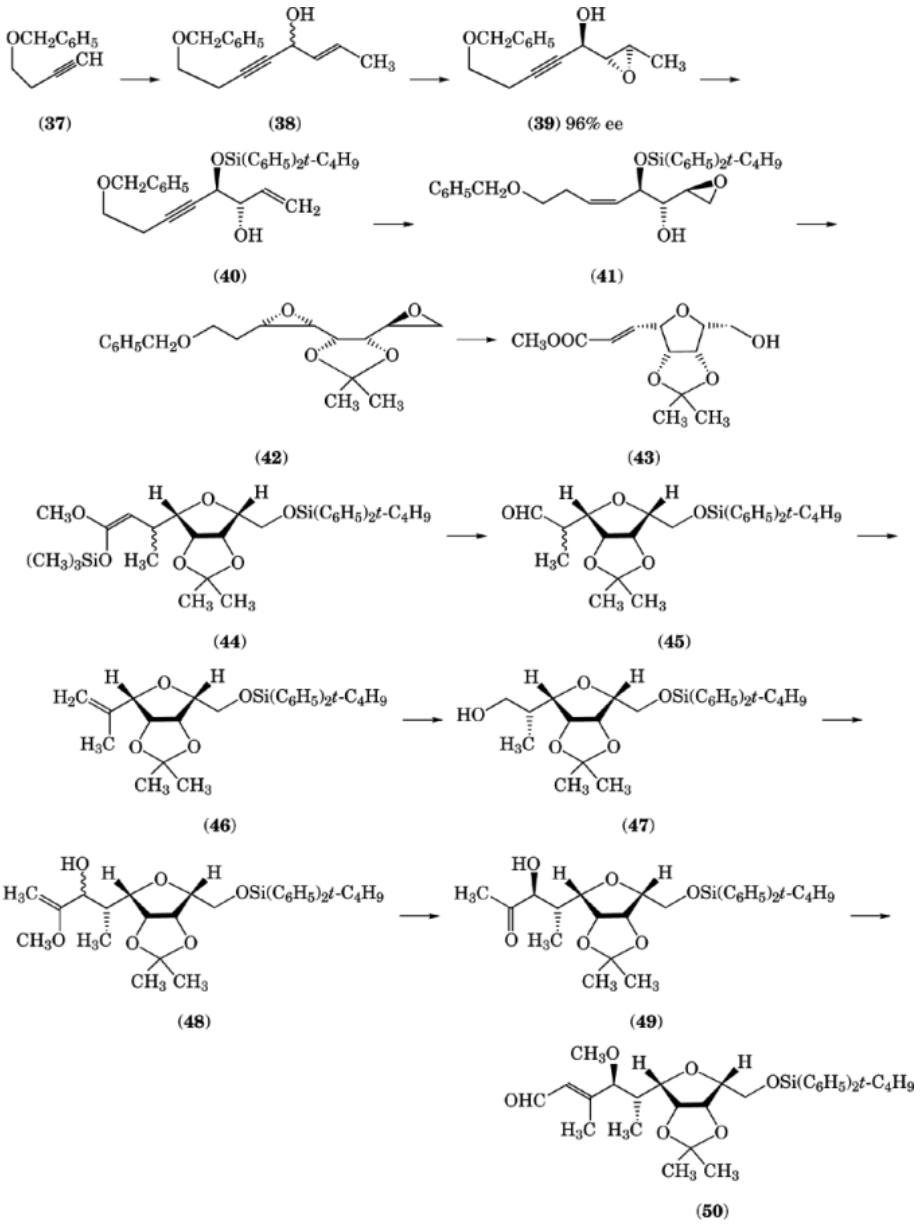

Fig. 4. Synthesis of the tetrahydrofuran moiety in goldinamine.

stands in unique contrast to that of other antibiotics which also interfere with the elongation phase of protein biosynthesis (60).

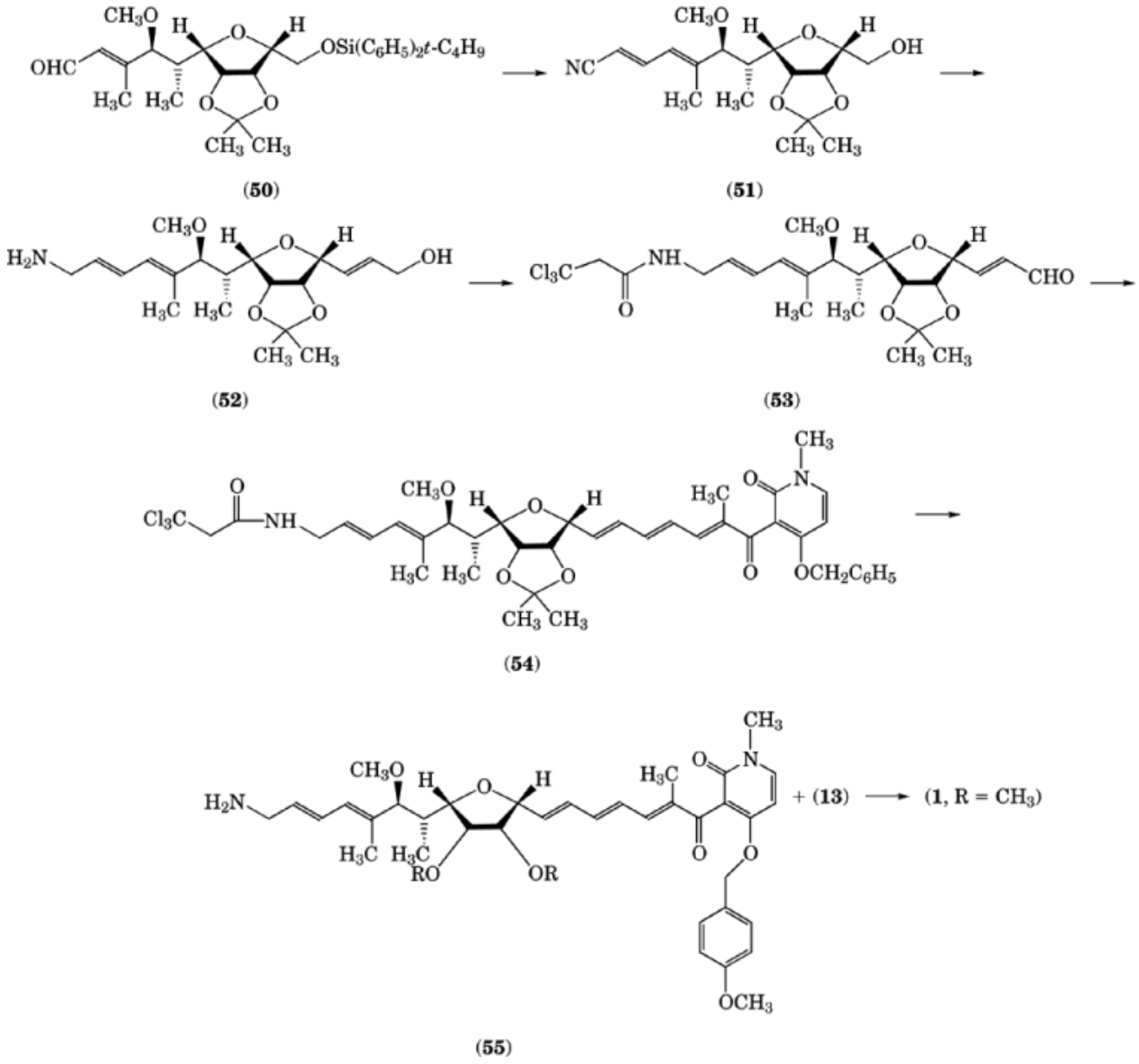

Fig. 5. Synthesis of goldinamine derivatives and aurodox when R′ is trimethylsilane.

3.2. Antimicrobial Activity

The elfamycins' antimicrobial specificity and lack of toxicity in animals can be explained in view of species-dependent specificity of elfamycin binding to EF-Tu. Inefficient cellular uptake or the presence of a nonresponding EF-Tu were cited as responsible factors for the natural resistance in *Halobacterium cutirubrum* (67), *Lactobacillus brevis* (68), and in actinomycetes (5, 69). The low activity of elfamycins against *S. aureus* was

also attributed to an elfamycin-resistant EF-Tu system (70). However, cross-resistance with other antibacterial agents has not been observed (71).

Elfamycins have similar *in vitro* antimicrobial spectra and the activity against *Moraxella*, *Pasteurella*, *Yersinia*, *Haemophilus*, *Streptococcus*, *Corynebacterium*, and *Neisseria* appears to be common (2, 23, 72). Aurodox (**1**, R = CH_3) (2), azdimycin (8), LL-E19020α(**11**, R = H, R′ = $COCH_2C_6H_5$), LL-E19020β (**11**, R = $COCH_2C_6H_5$, R′ = H) (29), efrotomycin (**2**, R = CH_3), and heneicomycin (**4**, R = R″ = CH_3, R′ = C_2H_5) (72) have shown activity *in vivo* against *Streptococcus pyogenes* and the latter two antibiotics exhibited similar activity against *Moraxella bovis* (73, 74).

Kirrothricin (**5**), aurodox, and efrotomycin were found to be active as protozoacids against the parasite *Eucoccidium dinophili* (75), and LL-E19020α and LL-E19020β were active against *Babesia* (see Antiparasitic agents). The latter two antibiotics acted as nematocides toward *Caenorhabditis elegans* and as anthelmintics (see Antiparasitic agents, anthelmintics) toward *Trichostrongylus colubiformis* (28).

Mocimycin (kirromycin) (**1**, R = CH_3) and tylosin [1401-69-0] (see Antibiotics, macrolides) exhibited similar activity against *Treponema hyodysenteria*, the causative microorganism of dysentery in swine. Dihydromocimycin (**3**), however, was more active against this microorganism than either mocimycin or tylosin (14). Moreover, dihydromocimycin was active against tylosin-resistant *treponema* strains and was used as a feed additive at levels of 20–40 ppm (see Feeds and feed additives) (14). The growth-promoting activity of mocimycin was not observed for dihydromocimycin (14).

Efrotomycin (**2**, R = CH_3) is active against mycoplasma (PPLO) of chicks, pigs, and cattle (9). A combination of efrotomycin and bottromycin [1393-68-6], a complex of macrolides, has been used as a therapeutic and prophylactic agent to control mycoplasma infections and dysentery in swine (76). *Mycoplasma gallisepticum S-6* was the most susceptible organism tested against heneicomycin (**4**, R = R″ = CH_3, R′ = C_2H_5) (15, 16). Additionally, *M. gallisepticum* infected chicks receiving feed containing 50 ppm of LL-E19020α (**11**, R = H, R′ = $COCH_2C_6H_5$) had better weight gain, improved feed conversion, and less mortality than infected, nonmedicated chicks (30).

Efrotomycin is effective against *Clostridium perfringens* (77) and is much more active against 29 clinical isolates of *Clostridium difficile* than ciprofloxacin [85721-33-1] (78, 79) (see Antibacterial agents, synthetic, quinolones). Activity against gram-positive anaerobes, especially *Clostridium difficile*, was also noted for all phenelfamycins and unphenelfamycin (**8**, R = R′ = H). Phenelfamycin A (**8**, R = H, R′ = $COCH_2C_6H_5$) prolonged the survival of *C. difficile enterocolitis* in infected hamsters and was active against *Neisseria gonorrhoeae* and *streptococci* (80). Aurodox (**1**, R = CH_3) exhibited similar activity in the hamster model (81).

Antibiotic LL-E19020α and LL-E19020β are described as useful agents for the treatment of chronic respiratory disease, fowl cholera, and necrotic enteritis in birds (76) and as anthelmintics in monogastric and ruminant animals (28).

3.3. Growth Promotion

Elfamycins, in general, enhance the growth of farm animals (see Growth regulators, animal). Growth improvement and feed conversion was studied using aurodox (**1**, R = CH_3) in chicks and turkeys. Effective drug levels were established to be 1–10 mg/kg of feed for chicks. The effective dose for turkeys was 5–10 times higher (82). The growth promoting ability of aurodox (**1**, R = CH_3) and mocimycin (**1**, R = H) was compared with other antibiotics and hormonal anabolic agents in chicks (83). Maximum weight improvement of 23% and enhanced feed efficiency of 13% in chicks was obtained with efrotomycin (**2**, R = CH_3) levels of 11 ppm (77). Antibiotics LL-E19020α and LL-E19020β proved to be more effective growth promotors in chicks than bacitracin [1405-87-4] and virginiamycin (see Antibiotics, peptides) (32) and also improved feed efficiency for meat-producing animals and fish. When given at 100 ppm in feed they caused weight gain by 6.1% in chicks. Feed efficiency was also increased, and during the first week of feeding an 8% increase was observed (84). Antibiotics LL-E19020α and LL-E19020β are more effective growth promotors than aurodox (32). The growth promoting effect of zinc

bacitracin was potentiated by mocimycin (85). The improvement of weight gain and feed conversion by subtherapeutic antibiotic levels were shown to occur concomitantly with decreased cholyltaurine hydrolase activity suggesting that the inhibition of this enzyme is responsible for weight gain and improvement in feed utilization (see Enzyme inhibition) (86).

Efrotomycin (**2**, R = CH_3) is being developed as a growth promoting agent for swine. Pigs on efrotomycin diets gained weight 5.9–8.9% faster and utilized feed 1.7–4.0% more efficiently than the control animals. Growth improvement was linear from 2 to 16 ppm of drug, and the plateau of feed efficiency was reached at 4 ppm of efrotomycin (87). The effect on the shedding of *Salmonella*, however, is a matter of primary concern in swine and fowl, not only with efrotomycin (88), but with other elfamycins as well.

Stable growth promoting feed additives were prepared by granulation of the drug with alginic acid [9005-32-7] and magnesium hydroxide and adding it to oiled rice hulls (89) or by adsorption of elfamycins onto corn cob grits and coating with 10% tristearin [555-43-1] (90). A molecular efrotomycin dispersion with (2-vinylpyridine)-styrene copolymer served as a postrumen effective dosage form for oral administration (91).

3.4. Improvement of Lactation

Qualitative and quantitative improvements in milk production (see Milk and milk products) are dependent upon changes of ruminal volatile fatty acid (VFA) production and VFA composition. Increased propionate production at the expense of acetate and butyrate is responsible for growth enhancement and is achieved by additives such as polyether antibiotics (see Antibiotics, polyethers). Relatively high levels of acetate and butyrate, however, are required to maintain adequate fat content in milk. Oral administration of elfamycins at concentrations of 1–10 mg/kg of animal body weight per day has been shown to increase milk volume from 2–15% relative to untreated animals without compromising fat content. The methods of administration to ruminants such as dairy cows and goats were similar to those employed for improving feed utilization and growth promotion (92).

4. Economic Aspects

The potential usefulness of elfamycins as growth promotors and feed-conversion enhancers is now generally recognized. Low original fermentation yields and difficulties in yield improvements discouraged early attempts to develop aurodox (**1**, R = CH_3) and mocimycin (kirromycin) (**1**, R = H) commercially. A development program for efrotomycin (**2**, R = CH_3), however, is ongoing as of this writing. Some of the newer elfamycins, such as the LL-E19020 pair, are considerably more active growth promotors than either aurodox or mocimycin, pointing toward the emergence of a second generation of elfamycins.

BIBLIOGRAPHY

Cited Publications

1. H. Maehr, M. Leach, L. Yarmchuk, and M. Mitrovic, *J. Antibiot.* **32**, 361 (1979).
2. Ger. Pat. 2,140,322 (Feb. 17, 1972), J. Berger (to Hoffmann-LaRoche); Pat. 3,657,421 (Apr. 18, 1972), reissue Jan. 27, 1976, J. Berger (to Hoffmann-LaRoche); J. Berger, H. H. Lehr, S. Teitel, H. Maehr, and E. Grunberg, *J. Antibiot.* **26**, 15 (1972).
3. J. Barber, and A. E. Derome, T. D. Howard, L. Lian, and G. Tebb, *Magn. Reson. Chem.* **27**, 748 (1989).

4. H. Maehr, M. Leach, T. H. Williams, and J. F. Blount, *Can. J. Chem.* **58**, 501 (1980).
5. H. Wolf and H. Zähner, *Arch. Microbiol.* **83**, 147 (1972).
6. U.S. Pat. 3,923,981 (Dec. 2, 1975), C. Vos and J. den Admirant; U.S. Pat. 3,927,211 (Dec. 16, 1975), C. Vos and J. den Admirant.
7. C. Vos and P. E. J. Verwiel, *Tetrahedron Lett.* 5173 (1973).
8. U.S. Pat. 3,898,327 (Aug. 5, 1975), M. W. Nimeck, E. Meyers, and W.-C. Liu.
9. Ger. Pat. 2,450,813 (Apr. 30, 1985), R. G. Wax and W. M. Maiese.
10. R. Wax, W. Maise, R. Weston, and J. Birnbaum, *J. Antibiot.* **29**, 670 (1976).
11. J. D. Strong, *Analyst* **111**, 853 (1986).
12. E. Selva and co-workers, *J. Antibiot.* **43**, 1349 (1990).
13. R. S. Dewey, B. H. Arison, J. Hannah, D. H. Shih, and G. Albers-Schoenberg, *J. Antibiot.* **38**, 1691 (1985).
14. Ger. Pat. 2,621,615 (Nov. 25, 1976), H. M. Jongsma, H. J. Kooreman, J. L. van Os, and C. Vos.
15. U.S. Pat. 4,071,631 (Jan. 31, 1978),
16. S. B. Zimmerman, J. H. Chalmers, Jr., R. S. Dewey, E. O. Stapley, and S. Hernandez, *J. Antibiot.* **32**, 665 (1979).
17. I. Thein-Schranner, H. Zähner, H.-U. Hoppe, I. Hummel, and A. Zeeck, *J. Antibiot.* **35**, 948 (1982).
18. A. Zeeck, H. U. Hoppe, and I. Hummel, *Tetrahedron Lett.* **22**, 2357 (1981).
19. V. P. Gullo, S. B. Zimmerman, R. S. Dewey, O. Hensens, and P. J. Cassidy, *J. Antibiot.* **35**, 1705 (1982).
20. U.S. Pat. 4,311,693 (Jan. 19, 1982), S. Hernandez, S. B. Zimmerman, V. P. Gullo, and R. S. Dewey.
21. U.S. Pat. 4,476,139 (Oct. 9, 1984), A. J. Kempf and co-workers.
22. A. J. Kempf and co-workers, *J. Antibiot.* **39**, 1361 (1986).
23. Eur. Pat. 139,158 (May 2, 1985), E. Selva and co-workers.
24. P. Ferrari, D. Edwards, G. G. Gallo, and E. Selva, *J. Antibiot.* **43**, 1359 (1990).
25. D. R. Williams, G. T. Carter, F. Pinho, and D. B. Borders, *J. Chromatogr.* **484**, 381 (1989).
26. J. E. Hochlowski and co-workers, *J. Antibiot.* **41**, 1300 (1988).
27. M. Jackson, J. P. Karwowski, R. J. Theriault, M. L. Maus, and W. L. Kohl, *J. Antibiot.* **41**, 1293 (1988).
28. Eur. Pat. 252,380 (Jan. 13, 1988), G. T. Carter and co-workers.
29. W. M. Maiese and co-workers, *J. Antibiot.* **24**, 1489 (1989).
30. Eur. Pat. 313,846 (May 3, 1989), G. T. Carter and co-workers.
31. M. R. Jefson, J. Bordner, C. P. Reese, and E. B. Whipple, *J. Antibiot.* **42**, 1610 (1989).
32. G. T. Carter, D. W. Phillipson, J. J. Goodman, T. S. Dunne, and D. B. Borders, *J. Antibiot.* **41**, 1511 (1988).
33. U.S. Pat. 4,847,245 (July 11, 1989), M. R. Jefson, K. Kaneda, S. Nishiyama, and J. Tone.
34. M. S. Pacey and co-workers, *J. Antibiot.* **42**, 1453 (1989).
35. U.S. Pat. 4,847,245 (July 11, 1989), M. R. Jefson, J. Kaneda, S. Nishiyama, and J. Tone.
36. Ger. Pat. 2,140,674 (May 18, 1972), C. Vos and J. den Admirant.
37. K. A. Larson and M. L. King, *Biotechnol. Prog.* **2**, 73 (1986).
38. G. M. Brill, J. B. McAlpine, and J. E. Hochlowski, *J. Liq. Chromatogr.* **8**, 2259 (1985).
39. D. W. Fink and J. D. Stong, *Anal. Chem.* **56**, 2339 (1984).
40. L. Kaplan, D. W. Fink, and C. Halsey, *Anal. Chem.* **56**, 360 (1984).
41. H. Maehr and co-workers, *Helv. Chim. Acta* **55**, 3051 (1972).
42. H. Maehr, J. F. Blount, M. Leach, A. Stempel, and G. Büchi, *Helv. Chim. Acta* **55**, 3054 (1972).
43. H. Maehr and co-workers, *J. Am. Chem. Soc.* **95**, 8448 (1973).
44. H. Maehr, J. F. Blount, M. Leach, and A. Stempel, *Helv. Chim. Acta* **57**, 936 (1974).
45. H. Maehr, T. H. Williams, M. Leach, and A. Stempel, *Helv. Chim. Acta* **57**, 212 (1974).
46. H. Maehr, M. Leach, J. F. Blount, and A. Stempel, *J. Am. Chem. Soc.* **96**, 4034 (1974).
47. H. Maehr, M. Leach, L. Yarmchuk, and A. Stempel, *J. Am. Chem. Soc.* **95**, 8449 (1973).
48. C.-M. Liu, T. Hermann, and P. A. Miller, *J. Antibiot.* **30**, 244 (1977).
49. C.-M. Liu, T. Hermann, and P. A. Miller, *J. Antibiot.* **32**, 1025 (1979).
50. J. Unowsky and D. C. Hoppe, *J. Antibiot.* **31**, 662 (1978).
51. D. Jain and B. C. Buckland, *Bioprocess Eng.* **3**, 31 (1988).
52. C.-M. Liu, H. Maehr, M. Leach, M. Liu, and P. A. Miller, *J. Antibiot.* **30**, 616 (1977).
53. C.-M. Liu, T. H. Williams, and R. Pitcher, *J. Antibiot.* **32**, 414 (1979).
54. J. B. K. Nielsen and L. Kaplan, *J. Antibiot.* **42**, 944 (1989).

55. U.S. Pat. 4,112,216 (Sept. 5, 1978), H. Maehr; Neth. Pat. 7,607,573 (Jan. 10, 1976).
56. Ger. Pat. 2,658,977 (May 5, 1977), H. Jongsma, H. J. Kooreman, and J. L. van Os.
57. U.S. Pat. 4,515,783 (May 7, 1985), B. O. Linn and A. Lusi.
58. U.S. Pat. 4,482,545 (Nov. 13, 1984), R. J. Bochis and R. S. Dewey.
59. K. C. Nicolaou, *Chem. Br.* **21**, 813 (1985).
60. R. E. Dolle and K. C. Nicolaou, *J. Am. Chem. Soc.* **107**, 1691 (1985).
61. G. Ohloff, K.-H. Schulte-Elte, and B. Willhalm, *Helv. Chim. Acta.* **47**, 602 (1964).
62. R. E. Dolle and K. C. Nicolaou, *J. Am. Chem. Soc.* **107**, 1695 (1985).
63. R. E. Dolle and K. C. Nicolaou, *J. Chem. Soc., Chem. Commun.*, 1016 (1985).
64. D. L. Miller and H. Weissbach, *Arch. Biochem. Biophys.* **141**, 26 (1970).
65. A. Parmeggiani and G. W. M. Swart, *Ann. Rev. Microbiol.* **39**, 557 (1985).
66. A. Parmeggiani and G. Sander, *Top. Antibiot. Chem.* **5**, 159 (1980).
67. M. Kessel and F. Klink, *Eur. J. Biochem.* **114**, 481 (1981).
68. W. Wörner and H. Wolf, *Regard. Biochim.* **3**, 57 (1981).
69. C. Gloeckner and H. Wolf, *FEMS Microbiol. Lett.* **25**, 121 (1984).
70. C. C. Hall, J. D. Watkins, and N. H. Georgopapadakou, *Antimicrob. Agents Chemother.* **33**, 322 (1989).
71. T. M. Jacks, E. G. Frazier, G. K. Abruzzo, A. C. Graham, and R. A. Fromtling, *Methods Find. Exp. Clin. Pharmacol.* **11**, 697 (1989).
72. B. M. Frost, M. E. Valiant, B. Weissberger, and E. L. Dulaney, *J. Antibiot.* **29**, 1083 (1976).
73. U.S. Pat. 4,024,251 (May 17, 1977), W. M. Maiese and R. G. Wax.
74. B. M. Frost, M. E. Valiant, and E. L. Dulaney, *J. Antibiot.* **32**, 626 (1979).
75. L. Tejmar-Kolar and H. Zähner, *FEMS Microbiol. Lett.* **24**, 21 (1984).
76. Jpn. Pat. 61,165,332 (July 26, 1986), T. Konishi and K. Matsumoto.
77. M. W. Stutz, S. L. Johnson, F. R. Judith, and B. M. Miller, *Poult. Sci.* **62**, 1612 (1983).
78. S. W. B. Newsom, J. Matthews, and A. M. Rampling, *J. Antimicrob. Chemother.* **15**, 648 (1985).
79. C. R. Clabots, C. J. Shanholtzer, L. R. Peterson, and N. D. Gerding, *Diagn. Microbiol. Infect. Dis.* **6**, 49 (1987).
80. R. N. Swanson and co-workers, *J. Antibiot.* **42**, 94 (1989).
81. J. Unowsky, unpublished data, 1987.
82. M. L. Marusich, E. F. Ogrinz, and M. Mitrovic, *Poult. Sci.* **53**, 636 (1974).
83. W. L. Marusich, E. F. Ogrinz, N. Camerlengo, and M. Mitrovic, *Poult. Sci.* **57**, 1297 (1978).
84. U.S. Pat. 4,704,276 (Nov. 3, 1987), S. Kantor.
85. Ger. Pat. 2,406,164 (Aug. 14, 1974), T. van Eek and R. Beukers; Neth. Pat. 7,401,731 (Aug. 13, 1974).
86. S. D. Feighner and M. P. Dashkevicz, *Appl. Environ. Microbiol.* **53**, 331 (1987).
87. A. G. Foster, D. H. Baker, T. R. Cline, G. L. Cromwell, and T. Veum, *J. Anim. Sci.* **65**, 877 (1987).
88. T. M. Jacks, E. Frazier, F. R. Judith, and G. Oslon, *Am.J. Vet. Res.* **49**, 1832 (1988).
89. Eur. Pat. 91,767 (Oct. 19, 1983), R. J. Yarwood, H. C. Maxfield, and A. J. Phillips.
90. S. Afr. Pat. 8,706,440 (Apr. 27, 1988), M. H. Fisher and H. H. Mrozik.
91. U.S. Pat. 4,808,412 (Feb. 28, 1989), E. P. Smith and S. H. Wu.
92. U.S. Pat. 4,336,250 (June 22, 1982), C. C. Scheifinger.

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