# Total Synthesis of Elfamycins: Aurodox and Efrotomycin. 2. Coupling of Key Intermediates and Completion of the Synthesis

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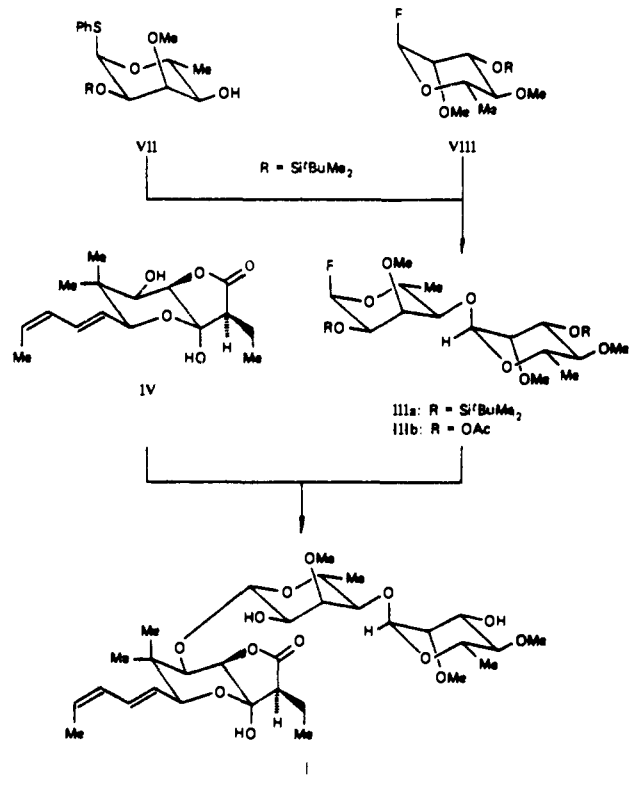
**Abstract:** The coupling of key intermediates IV–VIII and the completion of the total syntheses of aurodox (**1**) and efrotomycin (**2**) are described.

In the preceding paper in this issue, we reported the construction of key intermediates IV–VIII.[1] Described herein is the coupling of these key intermediates and the realization of the first total syntheses of the elfamycins aurodox (**1**) and efrotomycin (**2**).

The oligosaccharide fragment I of efrotomycin was assembled rapidly and efficiently from its three-component units as shown in Scheme I. Thus, applying our newly developed two-stage activation procedure for oligosaccharide construction.[2] units VII and VIII were joined under the influence of $AgClO_4$ (1.1 equiv) and $SnCl_2$ (1.1 equiv) in ether (4AMS, −15–25 °C)[2,3] during stage 2 activation, furnishing the expected (phenylthio)disaccharide in 75% yield and with the desired $\alpha$-glycosidic stereochemistry. Glycosyl fluoride IIIa was then smoothly generated (1.1 equiv of NBS, 1.2 equiv of $Et_2NSF_3$, $CH_2Cl_2$, −15 °C)[2] in 84% yield ($\alpha$:$\beta$, ca. 2:1, by $^1H$ NMR, inconsequential, however, for the present synthesis). Coupling of IIIa with goldinonolactone (IV) (1.1 equiv of $AgClO_4$, 1.1 equiv of $SnCl_2$, 4AMS, $Et_2O$, −15–0 °C)[2,3] proceeded chemoselectively to afford, after desilylation (2.2 equiv $n$-$Bu_4NF$, THF, 25°C), the advanced intermediate I in 75% overall yield but with the undesired $\alpha$ stereochemistry predominating at the newly formed O-glycosidic bond ($\alpha$:$\beta$, ca. 2:1 by $^1H$ NMR). However, this unsatisfactory stereochemical outcome was corrected by the strategic exchange of the silyl ethers of IIIa for acetoxy groups ((a) 2.2 equiv of $n$-$Bu_4NF$, THF, 0–25 °C; (b) 2.5 equiv of $Ac_2O$, DMAP catalyst, $CH_2Cl_2$, 25 °C, 80% overall yield) and utilizing the diacetate IIIb in the second glycosidation reaction. Indeed coupling of IIIb with goldinonolactone (IV) by the two-stage activation method as described above, furnished, after deacetylation (0.2 equiv of $K_2CO_3$, MeOH, 0–25 °C), exclusively the $\beta$-anomer *I* in 86% overall yield from IIIb. Thus, the 2-acetoxy group in IIIb, as expected, served favorably as a stereochemical director by internal participation in the glycosidation reaction.

Scheme II depicts the coupling of the tetrahydrofuran and 2-pyridone fragments V and VI and the elaboration to advanced intermediate II. Thus, treatment of phosphonium bromide VI with $NaN(SiMe_3)_2$ (1.0 eq., toluene, 0°C) formed a bright cherry-red ylide solution which cleanly reacted with aldehyde V (toluene, −78–0 °C), leading to product **3** in 85% yield and better than 20:1 *E*:*Z* stereoselectivity (by $^1H$ NMR and isolation) at the newly generated double bond. At this stage, a number of protecting group manipulations were deemed necessary, in view of the anticipated sensitivity of the target molecules and their immediate precursors. Thus, exchange of the benzyl ether for a *p*-methoxybenzyl ether (easily removable by DDQ)[4] and removal of the acetonide and trichloroethoxycarbonyl protecting groups was achieved by treatment with (i) $Me_3SiI$ (1.0 equiv, $CH_2Cl_2$, 0 °C, 2 min, debenzylation) (ii) amberlyst-15 (DMF–$H_2O$, 25 °C, deacetonization) (iii) *p*-$MeOC_6H_4CH_2Cl$ (5.0 equiv)–$n$-$Bu_4NI$ (2.0 equiv) (THF, 25 °C), and (iv) Zn dust (excess, THF, pH

**Scheme I**




7.2 phosphate buffer, 25 °C), leading to compound **4** (40% overall yield from **3**). Persilylation of **4** (excess $Me_3Si$-imidazole, $CH_2Cl_2$, 25 °C) followed by aqueous workup and flash column chromatography furnished the desired advanced intermediate allylamine II in 80% overall yield.

Scheme III presents the final coupling reactions and the final targets of this synthetic work, audorox (**1**) and efrotomycin (**2**). Thus, allylamine II, after activation with $AlMe_3$ (1.0 equiv, $CH_2Cl_2$, −40–25 °C)[5] engaged goldinonolactone IV (0.2 equiv, toluene, $CH_2Cl_2$, 25°C), furnishing, after deprotection ((a) excess HF·pyr, THF, 0–25 °C; (b) 1.1 equiv of DDQ, MeOH, 25 °C), aurodox (**1**) in 33% overall yield based on (IV). A similar sequence with the oligosaccharide fragment I resulted in the total synthesis of efrotomycin (**2**) in 26% overall yield based on I. Both synthetic aurodox (**1**) and efrotomycin (**2**) as their acetate derivatives[6] **1′**

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[‡] Recipient of a Camille and Henry Dreyfus Teacher-Scholor Award, 1980-1985. J. S. Guggenheim Fellow, 1984.

(1) Dolle, R. E.; Nicolaou, K. C. *J. Am. Chem. Soc.*, paper in this issue.
(2) Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D.; Randall, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 4189.
(3) Mukaiyama, T.; Murai, Y.; Shoda, S. *Chem. Lett.* **1981**, *431*, 935.
(4) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.
(5) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *48*, 4171.

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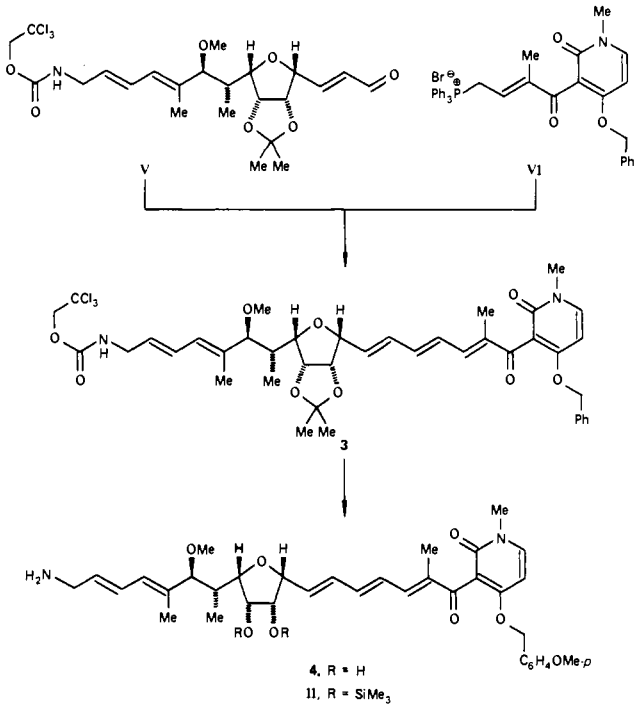
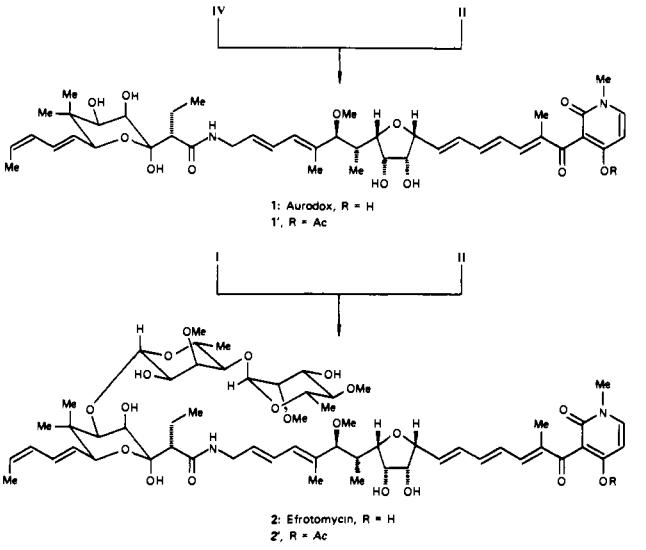
**Scheme II**



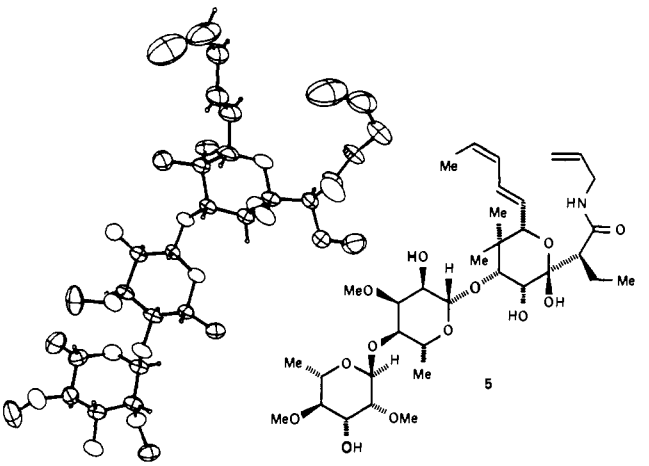
**Scheme III**



and **2'** were identical with the respective naturally derived samples by $^1$H NMR, MS, IR, UV, $[\alpha]_D$, and TLC.

As a final and independent structural confirmation of efrotomycin (**2**), the molecular structure of which was recently proposed by a Merck group on the basis of spectroscopic, chemical degradation, and comparisons with aurodox (**1**),[7] we prepared the colorless crystalline allylamine derivative **5** (Scheme IV), mp 80–81 °C (ether–hexane), from synthetic or degradatively derived oligosaccharide I (6.0 equiv of $H_2NCH_2CH{=}CH_2$, 6.0 equiv of $AlMe_3$, toluene, 25 °C, 65% yield) and subjected it to X-ray crystallographic analysis.[8] Scheme IV presents an optex view

**Scheme IV**



of this derivative as derived from this analysis, clearly demonstrating the absolute structure of this part of efrotomycin (**2**) in full accord with the Merck group's results.[7] Since the remaining half was found[7] to be identical with the fragment derived from aurodox (**1**) whose structure was fully established by Maer et al.,[9] both the structural confirmation and the total synthesis of efrotomycin (**2**) in its naturally occurring enantiomeric form have now been fully established.

The described sequences in these syntheses demonstrate the power and usefulness of important synthetic concepts and new methods including (a) the utilization of carbohydrate precursors in total synthesis of chirally rich complex natural products, (b) the Sharpless asymmetric epoxidation procedure, (c) the utilization of oligoepoxides in organic synthesis, particularly in the construction of oxygen-rich ring systems, and (d) the two-stage activation oligosaccharide synthesis via (phenylthio)glycosides and glycosyl fluorides in building saccharide chains and attaching them onto appropriate aglycons. Further applications of these new reactions in the total synthesis of complex molecules are in progress.[10]

## Experimental Section

**General.** $^1$H NMR spectra were recorded on a Bruker WH-250-MHz spectrometer in $CDCl_3$ and are reported in $\delta$ from $Me_4Si$. IR spectra were recorded on Perkin-Elmer Model 281B or 781 infrared spectrophotometer, and the IR figures reported are $\nu_{max}$ in inverse centimeter.

All reactions were monitored by thin-layer chromatography carried out on 0.25-mm E. Merck silica gel plates (60F–254) using UV light and 7% phosphomolybdic acid in ethanol heat as developing agent. Preparative-layer chromatography was performed on 0.5 mm × 20 cm × 20 cm E. Merck silica gel plates (60F–254). E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography.

All reactions were carried out under an argon atmosphere by using dry freshly distilled solvents under anhydrous conditions unless otherwise noted. Ethereal solvents were dried and distilled under nitrogen from sodium benzophenone ketyl. Methylene chloride was distilled under nitrogen from calcium hydride. Amines were distilled under argon from calcium hydride. Reaction temperatures were externaly measured. NMR multiplicities are reported by using the following abbreviations: s, singlet; d, doublet; triplet; q, quartet; m, multiplet; br, broad; J = coupling constant (hertz). Only strongest and/or structurally most important peaks are reported for the IR. All yields refer to chromatographically and spectroscopically ($^1$H NMR) homogeneous materials.

**Coupling of Key Intermediates VII and VIII. Preparation of Disaccharide IIIb.** To a cold suspension (−15 °C) of stannous chloride (21 mg, 0.11 mmol), silver perchlorate (23 mg, 0.11 mmol), and 4-Å molecular sieves (100 mg) in ether (2 mL) was added alcohol **VII** (42 mg, 0.11 mmol) in ether (1 mL) followed by the fluoride **VIII** (34 mg, 0.11

(6) The monoacetate derivatives **1'** and **2'** were prepared from **1** and **2**, respectively, by conversion to the sodium salt followed by reaction with acetic anhydride according to: Maehr, H.; Leach, M.; Yarmchuk, L.; Mitrovic, M. *J. Antibiot.* **1979**, *32*, 361.

(7) Dewey, R. S.; Arison, B. H.; Hannah, J.; Shih, D. H.; Albers Schonberg, G. *J. Antibiot.*, in press. We thank Dr. G. Albers Schonberg of Merck, Sharp + Dohme, Rahway, NJ 07065, for sharing information on efrotomycin with us and for a manuscript prior to publication.

(8) This analysis was carried out by Dr. P. Carroll of this Department.

(9) Maehr, H.; Leach, M.; Williams, T. H.; Blount, J. F. *Can. J. Chem.* **1980**, *58*, 501.

(10) All new compounds described in this and the preceding paper in this issue were characterized by full spectroscopic and analytical and/or exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.

mmol) also in ether (1 mL). The reaction mixture was brought to room temperature over a 2-h period, diluted with ether (5 mL), and filtered through celite. The filtrate was washed with saturated $NaHCO_3$ (3 × 5 mL), dried over $MgSO_4$, and again filtered. Removal of solvents in vacuo and flash column chromatography (silica, 20% ether in petroleum ether) of the residue gave exclusively the bis(silyl) disaccharide (62 mg, 84%). A solution of this disaccharide (43 mg, 0.064 mmol) in tetrahydrofuran (1 mL) containing tetra-*n*-butylammonium fluoride (1 mmol) was stirred at room temperature for 3 h and then concentrated. Purification of the residue by passage through a small column of silica gel (70% ether in petroleum ether; 5% methanol in ether) provided the corresponding diol which was dissolved in methylene chloride (0.2 mL) and treated with 4-(dimethylamino)pyridine (29 mg, 0.24 mmol) and acetic anhydride (0.012 mL, 0.18 mmol) at 0 °C. After 2 min the solution was concentrated under a gentle stream of argon and flash-chromatographed (60% ether in petroleum ether) to afford the bis(acetyl) disaccharide (32 mg, 96%). A methylene chloride solution (2 mL) of this disaccharide (30 mg, 0.057 mmol) and (diethylamino)sulfur trifluoride (0.013 mL, 0.08 mmol) at 0 °C was treated with *N*-bromosuccinimide (14 mg, 0.08 mmol). The reaction mixture became yellow as the solution was warmed to room temperature. After 1 h the solution was diluted with saturated $NaHCO_3$ (2 mL) and ether (10 mL). Separation of the organic phase and purification of the crude product using flash column chromatography (silica, 60% ether in petroleum ether) provided glycosyl fluoride IIIb (21 mg, 83%). IIIb: $R_f$ = 0.54 (silica, ether); $[\alpha]^{24}_D$ −23.94° (*c* 1.42, $CHCl_3$); IR (neat) $\nu_{max}$ 2940, 1740 (OAc), 1375, 1235, 1105, 1075, 735 $cm^{-1}$; $^1H$ NMR δ 5.54 dd, J = 50.0, 7.0 Hz, 1 H, H-1), 5.10 (dd, *J* = 4.0, 9.0 Hz, 1 H, H-3′), 4.80 (m, 2 H, H-2, −1′), 4.0. (m, 1 H, H-5), 3.88 (m, 1 H, H-3), 3.79 (m, 1H, H-5′), 3.62 (m, 1 H, H-2′), 3.54, 3.48, and 3.45 (singlets, 3 H each, OMe), 3.47 (m, 1 H, H-4), 3.24 (t, *J* = 9.0Hz, 1 H, H-4′), 2.16 and 2.14 (singlets, 3 H each, OAc), 1.32 (d, *J* = 6.0Hz, 6 H, H-6, H-6′); HRMS calculated for $C_{19}H_{31}FO_{10}$ ($M^+$) 438.1899, found 438.1879.

**Coupling of Key Intermediates IV and IIIb. Preparation of Advanced Intermediate I.** To a cold (−15 °C) suspension of stannous chloride (11 mg, 0.06 mmol), silver perchlorate (12 mg, 0.06 mmol), and 4-Å molecular sieves (50 mg) in ether (1 mL) was added goldinonolactone IV (18 mg, 0.06 mmol) in ether (0.5 mL) followed after 2 min by fluoride IIIb (22 mg, 0.05 mmol) also in ether (1 mL). The temperature was brought up to 0 °C and stirred for 6 h, after which time the milky white reaction mixture was diluted with ether (10 mL) and filtered through celite. The filtrate was washed with saturated $NaHCO_3$ (3 × 3 mL) and dried over $MgSO_4$. Filtration and evaporation of solvent in vacuo gave the crude glycoside. This glycoside was then azeotropically dried with benzene (3 × 5 mL), dissolved in dry methanol (1 mL), and treated with a catalytic amount of triethylamine. Stirring for 48 h, removal of methanol in vacuo, and flash column chromatography (silica, 2% methanol in ether) of the residue furnished anomerically pure I (24 mg, 78%) identical with an authentic sample derived from efrotomycin by degradation (IR, $^1H$ NMR, MS, $[\alpha]_D$, TLC). I: $R_f$ = 0.13 (2% methanol in ether); $[\alpha]^{24}_D$ −37.44° (*c* 0.17, $CHCl_3$), IR ($CCl_4$ film) $\nu_{max}$ 3560, 3010, 2980, 2940, 1780, 1470, 1455, 1380, 1080, 1030, 680 $cm^{-1}$; $^1H$ NMR δ 6.55 (dd, *J* = 15.0, 11.0 Hz, 1 H, H-2′), 6.02 (t, J = 11.0 Hz, 1 H, H-3′), 5.55 (m, 2 H, H-1′, −4′), 4.90 (s, 1 H, H-1‴), 4.86 (d, *J* = 7.5 H, 1 H, H-1″), 4.42 (d, *J* = 4.0 Hz, 1 H, H-7a), 4.20 (m, 2 H, H-5, −5″), 3.80–3.40 (m, 6 H, H-5″, −3‴, −2‴, −3″, −2″, −7), 3.62, 3.58, and 3.46 (singlets, 3 H each, OMe), 3.36 (dd, *J* = 9.0, 2.5 Hz, 1 H, H-4″), 3.00 (m, 2 H, H-4‴, OH), 2.60 (m, 2 H, H-3, OH), 2.35 (d, *J* = 7.0 Hz, 1 H, OH), 1.88 (m, 2 H, $CH_2$), 1.79 (dd, *J* = 7.0, 1.5 Hz, 3 H, H-5′), 1.32 (d, *J* = 5.5 Hz, 3 H, H-6‴), 1.22 (d, *J* = 5.0 Hz, 3 H, H-6″), 1.16 (t, *J* = 7.5Hz, 3 H, $CH_2CH_3$), 0.98 and 0.90 (singlets, 3 H each, 6-Me); HRMS calculated for $C_{31}H_{50}O_{13}$ ($M^+$) 630.3251, found 630.3241.

**Coupling of Key Intermediates V and VI. Preparation of Advanced Intermediate 3.** A solution of the phosphonium salt VI (26 mg, 0.041 mmol) in toluene (0.5 mL) was cooled to −20 °C and sodium bis(trimethylsilyl) amide (5 mg, 0.039 mmol) was added in one portion. After stirring for 30 min the deep red anion solution was further cooled to −78 °C, and aldehyde V (21 mg, 0.039 mmol) in toluene (0.2 mL) was added with magnetic stirring. Warming the solution to −10°C over a period of 30 min followed by quenching with saturated $NH_4Cl$ (1 mL) gave, following standard workup procedures and flash column chromatography (silica, 10:10:1; ethyl acetate, methylene chloride, methanol), compound **3** (27 mg, 87%). **3**: $R_f$ = 0.61 (silica, 5:5:1; methylene chloride, ethyl acetate, methanol); $[\alpha]^{24}_D$ −14.32° (*c* 1.32, $CHCl_3$); IR ($CHCl_3$ film) $\nu_{max}$ 3450, 3000, 1740 (carbamate), 1650 (amide), 1595, 1230, 1090, 990 $cm^{-1}$; $^1H$ NMr δ 7.30 (m, 6 H, Ph, H-6‴), 6.90 (d, *J* = 11.0 Hz, 1 H, H-11″), 6.54 (m, 4H, H-8″, −9″, −10″, −5), 5.02 (d, *J* = 7.5 Hz, 1 H, H-5‴), 5.96 (m, 2 H, H-4,−7″), 5.65 (dt, *J* = 15.0, 6.0 Hz, 1 H, H-6), 5.05 (s, 3 H, benzyl, NH), 4.72 (s, 2 H, $OCH_2CCl_3$), 4.70 (m, 1 H, H-3′), 4.60 (m, 1 H, H-4′), 3.92 (m, 3 H, H-2′, −7), 3.56 (m, 1 H, H-5′), 3.50 (s, 3 H, N-Me), 3.31 (d, *J* = 9.0Hz, 1 H, H-2), 3.12 (s, 3 H, OMe), 2.30 (m, 1 H, H-1), 2.1 (s, 3 H, 12″-Me), 1.68 (s, 3 H, 3-Me), 1.40 and 1.25 (singlets, 3H each, acetonide), 0.89 (d, *J* = 7.0Hz, 3 H, 1-Me). Anal. ($C_{41}H_{49}Cl_3N_2O_9$) C,H,N.

**Coupling of Advanced Intermediates IV and II. Preparation of Aurodox Acetate 1′.** Amine II (158 mg; 0.205 mmol) was dissolved in methylene chloride (3 mL) containing a small amount of dimethylformamide and treated with trimethyl aluminum (0.20 mL of a 1.0 M solution in toluene, 0.20 mmol) at −40 °C. After warming to 0 °C (15 min) a solution of lactone **IV** (12 mg; 0.041 mmol) in methylene chloride (0.2 mL) was added, and the reaction mixture was stirred at room temperature for 24 h. The solution was poured into saturated sodium potassium tartrate (3 mL) and extracted with methylene chloride (3 × 5 mL). Drying the combined extracts over $MgSO_4$ and filtering and removing the solvent in vacuo gave a crude product which was dissolved in methylene chloride (1 mL) and treated with excess HF·pyr at 0 °C. After 4 h at 0–25 °C the solution was diluted with methylene chloride (3 mL), washed with saturated $NaHCO_3$, dried, and concentrated to afford a residue which gave the following flash column chromatography (silica, 10:10:1; ethyl acetate, methylene chloride, methanol), 4-*O*-(*p*-methoxybenzyl)aurodox (3.2 mg, 33% based on IV). This *p*-methoxybenzyl ether (28 mg, 0.03 mmol) was dissolved in methanol (2 mL) and treated with DDQ (8 mg, 0.035 mmol, recrystallized). After stirring for 5 min, the solvent was gently removed in vacuo and the residue chromatographed on Sephadex LH-20 using acetone as the mobile phase. Combining and evaporation of the appropriate fractions gave a bright yellow foam which was treated with acetic anhydride (0.004 mL, 0.041 mmol) in pyridine (0.1 mL) at room temperature for 30 min. Direct flash column chromatography of the reaction mixture (silica, 40:40:1; ethyl acetate, methylene chloride, methanol, then 5:5:1 of the same solvents) provided aurodox monoacetate **1′** (21 mg, 82%) identical with an authentic sample derived from aurodox (IR, $^1H$ NMR, $[\alpha]^{24}_D$, TLC) **1′**: $R_f$ = 0.18 (silica, 5:5:1; methylene chloride, ethyl acetate, methanol): $[\alpha]^{24}_D$ −87.21° (*c* 0.82, $CHCl_3$); IR ($CHCl_3$ film) $\nu_{max}$ 3460, 3005, 1760 (m, C=O), 1655 (amide), 1600, 1190, 1100 $cm^{-1}$; $^1H$ NMR δ 7.38 (d, *J* = 7.0 Hz, 1 H, H-6), 6.89 (d, *J* = 10.0 Hz, 2 H, H-9), 6.70–6.35 (m, 5 H, H-10, −11, −12, −23, −36), 6.19 (d, *J* = 7.0 Hz, 1 H, H-5), 5.98 (m, 3 H, H-13, −22,−37), 5.89 (s, 1 H, 29-OH), 5.70–5.44 (m, 4 H, H-24,−35,−38, NH), 4.38 (m, 2 H, H-15,16), 4.28 (d, *J* = 7.0 Hz, 1 H, H-33), 4.20 (br s, 2 H, H-14, OH), 4.00 (m, 2 H, H-25), 3.75 (m, 2 H, H-3, −31), 3.48 (s, 3 H, NMe), 3.47 (obscured, 1 H, H-17), 3.24 (d, *J* = 10.0 Hz, 1 H, H-20), 3.18 (s, 3 H, 20-OMe), 1.92 (d, *J* = 7.5 Hz, 1 H, OH), 2.60 (dd, *J* = 10.0, 4.5 Hz, 1 H, H-28), 2.45 (s, 1 H, OH), 2.24 (m, 2 H, H-19, OH), 2.18 (s, 3 H, OAc), 2.02 (s, 3 H, 8-Me), 1.76 (dd, *J* = 7.0, 1.5 Hz, 3 H, H-39), 1.75 (obscured, 2H, H-45), 1.66 (s, 3 H, 21-Me), 0.97 and 0.94 (singlets, 3 H each, 32-Me), 0.95 (obscured, 3 H, H-46), 0.88 (d, *J* = 7.5 Hz, 3 H, 19-Me). Anal. ($C_{41}H_{64}N_2O_{13}$) C,H,N.

**Coupling of Advanced Intermediates I and II. Preparation of Efrotomycin Acetate 2′.** Amine II (158 mg; 0.205 mmol) was dissolved in methylene chloride (3 mL) containing a small amount of dimethylformamide and treated with trimethylaluminum (0.20 mL of a 1.0 M solution in toluene; 0.20 mmol) at −40 °C. After the solution was warmed to 0 °C (15 min), a solution of lactone I (16 mg, 0.025 mmol) in methylene chloride (0.2 mL) was added, and the reaction mixture was stirred for 48 h. The solution was poured into saturated sodium potassium tartrate (3 mL) and extracted with methylene chloride (3 × 5 mL). Drying of the combined extracts over $MgSO_4$ and filtering and removing of the solvents in vacuo gave a crude product which was dissolved in methylene chloride (1 mL) and treated with excess HF·pyr at 0 °C. After 4 h at 25 °C, the mixture was diluted with methylene chloride, washed with saturated $NaHCO_3$, dried, and evaporated to afford a residue which furnished the following flash column chromatography (silica, 10:10:3; ethyl acetate, methylene chloride, methanol), 4-*O*-(methoxybenzyl)efrotomycin (5 mg, 26% based on I). The *p*-methoxybenzyl ether (14 mg, 0.011 mmol) was dissolved in methanol (2 mL) and treated with recrystallized DDQ (3 mg, 0.013 mmol). After stirring for 5 min, the solvent was gently removed in vacuo and the residue chromatographed on Sephadex LH-20 by using acetone as the mobile phase. Combining and evaporation of the appropriate fractions gave a yellow foam which was treated with acetic anhydride (0.002 mL, 0.021 mmol) in pyridine (0.1 mL) at room temperature for 30 min. Direct flash column chromatography of the reaction mixture (silica, 40:40:1; methylene chloride, ethyl acetate, methanol and then 10:10:3 of the same solvents) provided efrotomycin monoacetate **2′** (11 mg, 86%) identical with an authentic sample obtained from natural efrotomycin (IR, $^1H$ NMR, $[\alpha]^{24}_D$, TLC). **2′**: $R_f$ = 0.18 (silica, 10:10:3; methylene chloride, ethyl acetate, methanol); $[\alpha]^{24}_D$ −87.60° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$ film) $\nu_{max}$ 3500, 3010, 2930, 1765 (C=O), 1655 (amide), 1600, 1185, 1100, 1020, 900 $cm^{-1}$; $^1H$ NMR δ 7.37 (d, *J* = 7.0 Hz, 1 H, H-6), 6.88 (d, *J* = 10.0 Hz, 1 H,

H-9), 6.60–6.35 (m, 5 H, H-10, -11, -12, -23, -36), 6.19 (d, $J$ = 7.0 Hz, 1 H, H-5), 5.95 (m, 3 H, H-13, -22, -37), 5.89 (s, 1 H, 29-OH), 5.70–5.44 (m, 4 H, H-24, -35, -38, NH), 4.90 (s, 1 H, H-1″), 4.64 (d, $J_{1',2'}$ = 7.5 Hz, 1 H, H-1′), 4.38 (m, 2 H, H-15, -16), 4.30 (d, $J$ = 7.0 Hz, 1 H, H-33), 4.20 (br s, 2 H, H-14, OH), 4.00–3.30 (series of multiplets, 2 H, H-17, -25, -30, -31, -2′, -3′, -4′, -5′, -2″, -3″, -5″), 3.62, 3.60 and 3.54 (singlets, 3H each, OMe), 3.48 (s, 3 H, NMe), 3.22 (d, $J$ = 9.5 Hz, 1 H, H-20), 3.20 (s, 3 H, 20-OMe), 3.01 (t, $J$ = 8.5 Hz, 1 H, H-4″), 2.90 (d, $J$ = 7.5 Hz, 1 H, OH), 2.64 (dd, $J$ = 10.0, 3.5 Hz, 1 H, H-28), 2.54 (s, 1 H, OH), 2.40 and 2.34 (doublets, $J$ = 7.0 Hz, 1 H each, OH), 2.15 (s, 3 H, OAc), 2.15 (m, 1 H, H-19), 2.02 (s, 3 H, 8-Me), 1.76 (dd, $J$ = 7.0, 1.5 Hz, 3 H, H-39), 1.75 (m, 2 H, H-45), 1.68 (s, 3 H, 21-Me), 1.32 and 1.23 (doublets, $J$ = 6.0 Hz, 3 H each, H-6′ and H-6″), 0.90 and 0.96 (singlets, 3 H each, 32-Me), 0.96 (obscured, 3 H, H-46), 0.88 (d, $J$ = 7.5 Hz, 3 H, 19-Me). Anal. ($C_{61}H_{91}N_2O_{21}$) C,H,N.

**Coupling of Advanced Intermediate I and Allylamine. Preparation of Compound 5.** Allylamine (0.08 mL, 1.10 mmol) in dry methylene chloride (2 mL) was treated with trimethylaluminum (0.50 mL of a 2 M solution in toluene; 1.0 mmol) at room temperature. The solution was stirred for 15 min and then slowly added to a solution of lactone **I** (113 mg, 0.18 mmol) at 0 °C. The reaction mixture was brought to room temperature and stirred at that temperature overnight, whereupon it was poured into ethyl acetate (10 mL) and saturated sodium potassium tartrate (5 mL). The aqueous layer was separated and extracted with ethyl acetate (2 × 10 mL). Combining the extracts, drying over $MgSO_4$, removing the solvents under reduced pressure, and recrystallizing the residue (ether–hexane) afforded compound **5** (81 mg, 67%). **5**: mp 156–158 °C (from ether–hexane); $R_f$ = 0.46 (silica, 5% methanol in ether); $[\alpha]^{24}_D$ -54.90° ($c$ 1.13, $CHCl_3$); IR ($CHCl_3$ film) $\nu_{max}$ 3560 and 3440 (NH, OH), 3000, 2960, 1640 (amide), 1525, 1450, 1370, 1080, 1020 $cm^{-1}$; $^1H$ NMR 4.29 6.45 (dd, $J$ = 15.0, 11.0 Hz, 1 H, H-2′), 6.00 (m, 3 H, H-4′, 3-OH, NH), 5.80 (m, 1 H, H-2″), 5.60 (dd, $J$ = 15.0, 7.0 Hz, 1 H, H-1′), 5.46 (dd, $J$ = 11.0, 7.5 Hz, 1 H, H-3′), 5.24 (dd, $J$ = 17.0 0.2 Hz, 1 H, H-3″), 5.10 (dd, $J$ = 10.0, 0.2 Hz, 1 H, H-3a″), 4.90 (d, $J$ = 0.1 Hz, 1 H, H-1‴), 4.65 (d, $J$ = 7.5 Hz, 1 H, H-1‴), 4.28 (d, $J$ = 7.0 Hz, 1 H, H-6), 4.00–3.45 (multiplets, 10 H, H-1″, -3,-4,-2‴,-3‴,-5‴,-2⁗,-3⁗, -5⁗), 4.60, 4.56 and 4.29 (singlets, 3 H each, OMe), 3.40 (dd, $J$ = 10.0, 2.0 Hz, 1 H, H-4‴), 3.02 (t, $J$ = 9.0 Hz, 1 H, H-4⁗), 2.65 (dd, $J$ = 10.0, 4.0 Hz, 1 H, $CHCH_2CH_3$), 2.58 (s, 1 H, OH), 2.50 and 2.38 (doublets, $J$ = 8.0Hz each, 1 H each, OH), 1.75 (dd, $J$ = 7.0, 1.5 Hz, 3 H, H-5′), 1.75 (obscured, 2 H, $CHCH_2CH_3$), 1.32 (d, $J$ = 7.0 Hz, 3 H, H-6⁗), 1.21 (d, $J$ = 7.0 Hz, 3 H, H-6‴), 0.98 and 0.91 (singlets, 3 H each, 5-Me), 0.89 (t, $J$ = 5.0 Hz, 3 H, $CHCH_2CH_3$); HRMS calculated for $C_{34}H_{57}NO_{13}$ ($M^+$) 671.3877, found 671.3876.

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# A Convenient Synthesis of 4-Unsubstituted β-Lactams

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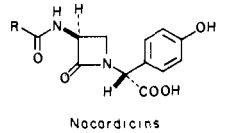
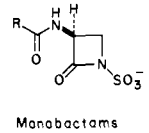
**Abstract:** The reaction of lithium ester enolates with *N*-(cyanomethyl)amines affords 4-unsubstituted β-lactams in good yields, see eq 1. The N-1 substituent can be varied widely, as can the C-3 substituents, which can be H, alkyl, SPh, $NH_2$, or NHCOR. The preparation of 3-amino-substituted β-lactams (**8–10**, **12**, **14–17**) in one step from *N*-(cyanomethyl)amines and esters of α-amino acids is a particularly significant feature of this new β-lactam synthesis. Enantiomerically pure 3-amino-substituted β-lactams, with either the 3*R* (**19** and **21**) or 3*S* (**23** and **24**) configuration, can also be prepared from the chiral, nonracemic, *N*-(cyanomethyl)amines. The asymmetric induction observed in the reactions of these latter *N*-(cyanomethyl)amines with the lithium enolate of **14** is rationalized by a chelated transition state **26**.

The powerful antibiotic activity of the nocardicins and monobactams[1] against Gram negative organisms has highlighted the importance of developing new efficient procedures for preparing monocyclic 4-unsubstituted β-lactams.[2] Gilman was the first to



Nocardicins



Monobactams

describe the formation of β-lactams from the reaction of ester enolates with imines.[3] Although this reaction has proven to be a useful method for preparing substituted β-lactams,[4,5] in particular β-lactams containing aryl substituents at *N*-1 and C-4, it has not been utilized to prepare 4-unsubstituted β-lactams[6] due to the inaccessibility of monomeric formaldehyde imines.[7] We recently disclosed that unstable formaldehyde imines could be generated

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(6) 4-Unsubstituted β-Lactams have been prepared from hexahydrotriazines by reaction with a Lewis acid followed by treatment with an acid chloride and pyridine,[6a] or from the reaction of the derived *N*-(chloromethyl)carbamates with silyl ketene acetals[6b]: (a) Kamiya, T.; Oku, T.; Nakaguchi, O.; Takeno, H.; Hashimoto, M. *Tetrahedron Lett.* **1978**, 5119. (b) Ikeda, K.; Terao, Y.; Sekiya, M. *Chem. Pharm. Bull.* **1981**, *29*, 1747.

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