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SYNTHETIC STUDIES OF RIFAMYCINS. VI.[1] PREPARATION AND ELABORATION OF THE AROMATIC SEGMENT FOR THE SYNTHESIS OF RIFAMYCIN W

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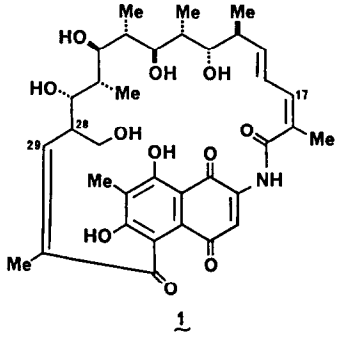
Summary: A convenient preparation of the aromatic segment 3 starting from 3,5-dibromo-2,6-dimethoxytoluene 5 and furan was described along with the elaboration of 3 by the aldol coupling with the aliphatic segment 2 to the synthetic precursor 4 of rifamycin W.

During the course of our synthetic studies of rifamycins, a family of ansamycin antibiotics, we have been interested in rifamycin W (1)[2,3] which had been suggested to be the biosynthetic progenitor of all the rifamycins.[4] The aliphatic segment 2[5] for the C-17-C-29 portion of 1 has recently been synthesized from D-glucose in these laboratories.[1] The successful synthesis of the aromatic segments of rifamycins has recently been reported from two research groups.[6] Herein, we wish to report a simple and convenient preparation of the aromatic segment 3, which could be coupled with 2 in good yield to afford the intermediate 4,



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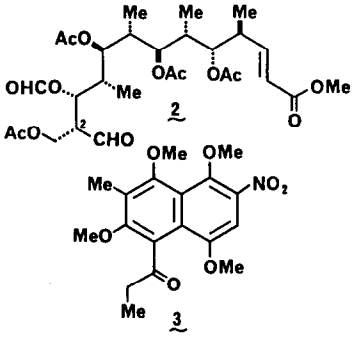

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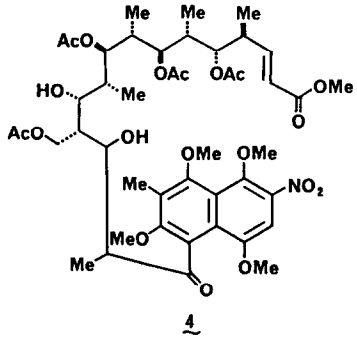
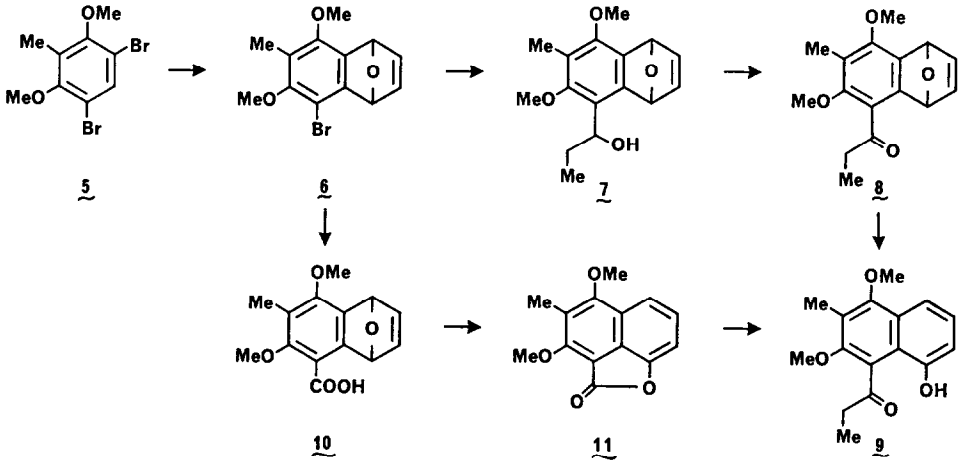


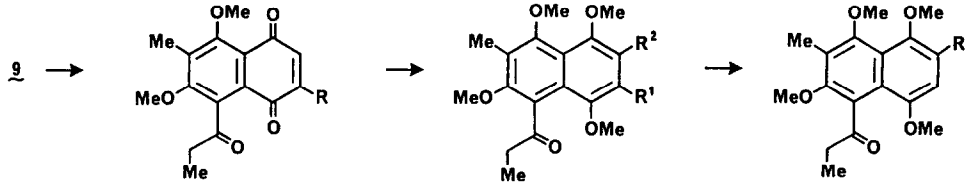
4

a synthetic precursor of rifamycin W. The starting material 5,[7] readily available from 2,6-dimethoxytoluene (Aldrich), was treated with 1.35 equiv of sodium amide and 15 equiv of furan (THF, 45°C, 15 h) to give the bromoepoxide 6[8] (94%, mp 58-59°C). Lithiation of 6 with 1.2 equiv of butyllithium (THF, -78°C, 10 min) followed by treatment with 1.2 equiv of propanal (-78→20°C, 6 h) afforded 7[8] (82%, mp 133-134°C). Jones oxidation of 7 furnished the epoxy ketone 8[8] (80%, mp 74-75°C), which was subjected to the epoxide ring opening reaction [60% $HClO_4$-THF(1:84 v/v), 50°C, 50 min] to give the naphthol 9[8] [86%, mp 179-181°C,

IR(KBr) ν_{max} 1675 cm^{-1}, UV(0.01N HCl in EtOH) λ_{max} nm(log ε) 224(4.59), 240(4.58), 305(3.85)] as a sole product. The structure shown for 9 was established by the following manner. The aforesaid lithiation of 6 (in Et_2O) followed by carboxylation (CO_2, -78°C, 10 min) afforded the naphthoic acid 10[8] (90%, mp 107-108°C). Treatment of 10 with 60% $HClO_4$-THF (1:67 v/v) (70°C, 5 h) yielded the lactone 11[8] (83%, mp 107-108°C subl, IR(KBr) ν_{max} 1762 cm^{-1}), which was treated with 1.05 equiv of ethyllithium (Et_2O, 0°C, 1.5 h) to give 9. This sample of 9 proved to be identical with the specimen of 9 derived from 8 in all respects. Oxidation of 9



with 3 equiv of N-bromosuccinimide[9] (AcOH-aq, 25°C, 1 h) gave the isomerically pure bromonaphthoquinone 12[8] (61%, mp 144-145°C) and naphthoquinone 13[8] (17%, mp 145-150°C dec). The structure 12 shown for the major product was assumed based on the experimental result[9] that 2-bromo-5-acetoxy-1,4-naphthoquinone was regiospecifically formed upon the reaction between N-bromosuccinimide and 1,5-diacetoxynaphthalene. Catalytic hydrogenation of 12 (H_2, 5% Pd-C, acetone) afforded the air sensitive hydronaphthoquinone, which was immediately methylated



with dimethyl sulfate and potassium carbonate to give 14[8] (74%, mp 87-88°C). Debromination[10] of 14 [Zn powder, 10% aq-NaOH-dioxane (1:2 v/v), 70°C, 12 h] afforded the tetramethoxynaphthalene 15[8] (100%, mp 76-77°C). The product 15 also was obtained from 13 by the reductive methylation as described above in 60% yield; the total yield of 15 from 9 amounted to 55%. Nitration of 15 proceeded smoothly with copper(II) nitrate[11] (Ac_2O, -20°C) to give

regiospecifically the nitronaphthalene 3[8] [80%, yellow prisms from hexane, mp 126-127°C, IR(KBr) ν_{max} 1710 cm^{-1}, UV(EtOH) λ_{max} nm(log ε) 232(4.57), 266(4.07), 378(3.58)], the structure of which was determined by X-ray crystallographic analysis as follows.

CRYSTAL DATA $C_{18}H_{21}O_7N$, MW 363.4, triclinic, $P\bar{1}$, a=10.056(2), b=12.901(5), c=7.359(2) Å, α=88.27(3), β=107.58(2), γ=89.67(3)°, V=909.6(5) $Å^3$, Z=2, D_x=1.33, D_m=1.30 g cm^{-3}, μ(Mo K_α)=0.096 mm^{-1}. The intensity mesurements were performed on a Rigaku automated four-circle diffractometer AFC-5 for 2θ(Mo K_α) ≤55°. The structure was solved by direct methods and refined to a final R value of 0.060 for 2266 observed reflections.[12] The structure was disordered. There were two possible orientations for the nitro group around the C(2)-N bond axis.

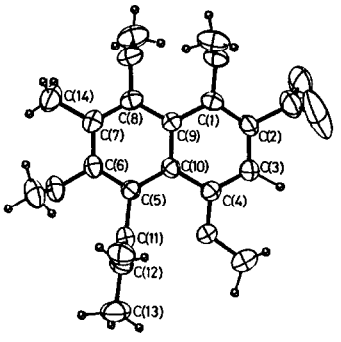
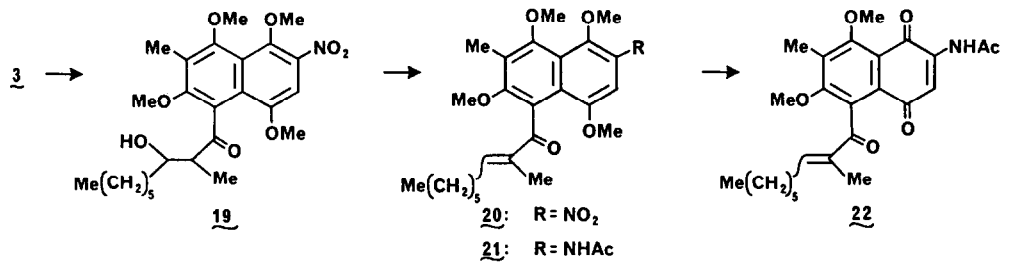


Fig. 1. Molecular structure of nitro compound 3

In Fig. 1 the molecular structure of 3 is shown, where the nitro O atoms having the assigned population parameter 0.9 are presented. Nitration of 14 with copper(II) nitrate (Ac_2O, -20°C, 2 h) afforded 16[8] (56%, mp 154-155°C), which was debrominated with sodium formate[13] [$(Ph_3P)_4Pd$, DMF, 100°C, 3 h] to give the product proved to be identical with 3. By these results, the assumed structures of 12 and 14 were verified. Catalytic reduction of 3 (H_2, 5% Pd-C, MeOH) afforded the amine 17,[14] which was acetylated (Ac_2O, Py) to give 18[8] (95%, mp 193-194°C).

The possible elaboration of 3 or 18 by the cross aldol coupling with the aliphatic segment 2 was tested using heptanal as a model. Among various conditions studied, modified conditions



of the Mukaiyama's aldol reaction via divalent tin enolate,[15] gave the best result to date when the nitro compound 3 was used. Treatment of 3 with 1.3 equiv of stannous triflate and 1.4 equiv of 1-ethylpiperidine (CH_2Cl_2, 0°C, 30 min) led to the tin enolate,[15] which reacted at 0°C with 1.3 equiv of heptanal to afford 19 as a 1.7: 1 diastereomeric mixture in 84% yield based on 3. By contraries, the acetamide 18 could not be fruitfully elaborated by the same type of aldol reaction; the amide group of 18 appeared to impede the enolization of 18 with stannous triflate and base. Dehydration of both the diastereoisomers[14] isolated from 19 (0.7% methanolic KOH, 20°C, 24 h) gave the same unsaturated ketone 20[14] in 90% yield as a single product. Selective reduction of 20 (H_2, Lindlar catalyst, MeOH, 30°C) followed by

acetylation afforded 21[14] in 98% yield. Oxidative demethylation of 21 with ammonium cerium(IV) nitrate[16] provided the naphthoquinone 22[8] [73%, mp 143-145°C, UV(EtOH) λ_{max} nm (log ε) 231(4.42), 256(4.38), 301(4.10), 367(3.54)]. The nitro compound 3 thus seems to be a promising aromatic segment for the rifamycin W synthesis. Practically, the ansa-chain compound 2 (1 equiv) was treated at 0°C for 20 h with the tin enolate prepared from 3 equiv of 3 with 3.9 equiv of stannous triflate and 4.3 equiv of 1-ethylpiperidine (CH_2Cl_2, 0°C, 30 min) to give the aldol product 4[14] as a diastereomeric mixture in 87% yield based on 2. The further elabolation of 4 is now in progress in our laboratories.

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