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A SYNTHESIS OF THE AROMATIC SEGMENT OF RIFAMYCIN S

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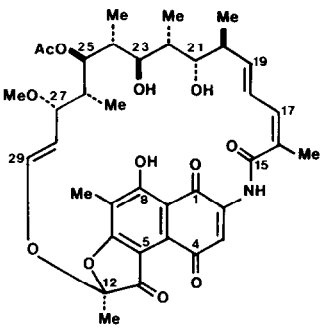
Abstract The aromatic segment 15 of rifamycin S (1) was synthesized from the cyclohexadienone 2 or ii in high overall yield.

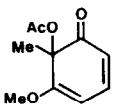
Rifamycins (originally spelled rifomycins),[1,2] isolated from the fermentation medium of Norcardia mediterranei by Senti, Greco and Ballotta in 1959, were the first examples of a novel class of antibiotics, ansamycins, characterized by an aliphatic bridge linking two non-adjacent positions of an aromatic nucleus. The great number of antibiotics belonging to this class can be divided into two sub-classes: those the ansa bridge of which is attached to a naphthoquinone or naphthalene nucleus, represented by rifamycin S, and those the ansa bridge of which is attached to a benzoquinone or benzene nucleus, represented by maytansine. Rifampicin (U.S.: rifampin), a derivative of rifamycins, is a widely-used, orally-active tuberculostatic agent. The structure of rifamycins was elucidated chemically by Prelog and Oppolozer, and X-ray crystallographically by Brufani, Fedeli, Gliacomello and Vaciago. We have recently reported the first total synthesis of rifamycin S (1), in which the aromatic segment 15 played the key role.[3] In this communication, we would like to outline the synthesis of this substance.



1 : Rifamycin S

The conjugated addition of pentenylmagnesium bromide (CH_2=CH(CH_2)$_3$MgBr/Et_2O/0°C) to the cyclohexadienone 2[4], prepared from 2-methylresorcinol monomethyl ether, gave the phenol 3[5] (oil; NMR ($CDCl_3$) δ 2.07 (3H, s), 3.80 (3H, s); 55% yield).[6] The phenol 3 was converted to the carboxylic acid 4[5] (oil) by 3 steps, i.e. (1) Ac_2O/110°C, (2) O_3/CH_3OH/-78°C, followed by

$(CH_3)_2S$ work-up, and (3) Jones oxidation, in almost quantitative yield. The Friedel-Craft reaction of 4 ($AcCl/AlCl_3/CCl_4$/RT), followed by aqueous acid treatment, yielded the tetralone 5[5] (mp 124-125°C; NMR ($CDCl_3$) δ 2.05 ppm (3H, s), 3.86 (3H, s), 6.25 (1H, s); 95% yield).[7] It was planned to introduce the side chain at the C-5 position[8] by acylation of the tetralone 5. However, 5 was found to be exceptionally inert towards various acylating reagents. To overcome this problem, 5 was hydrolyzed (Py·HCl/200°C) to the resorcinol 6[5] (mp 200-201°C), which was found to react smoothly with propionic acid at 90°C in the presence of borontrifluoride. Thus, the acylated tetralone 7[5] (mp 89-90°C) was isolated, after aqueous sodium carbonate work-up, in 92% overall yield from 5. The acylated tetralone 7 was converted to the corresponding dimethyl ether 8[5] (mp 76-77°C; NMR ($CDCl_3$) δ 1.17 (3H, t, J = 7.2 Hz), 2.19 (3H, s), 3.69 (3H, s), 3.79 (3H, s); 93% yield) under standard conditions (CH_3I/K_2CO_3/acetone/100°C).



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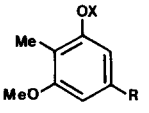
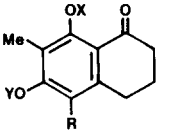
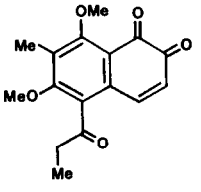


3 : X=H, R=$(CH_2)_3CH=CH_2$
4 : X=Ac, R=$(CH_2)_3CO_2H$



5 : X=H, Y=CH_3, R=H
6 : X=Y=H, R=H
7 : X=Y=H, R=$COCH_2CH_3$
8 : X=Y=CH_3, R=$COCH_2CH_3$



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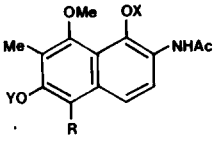
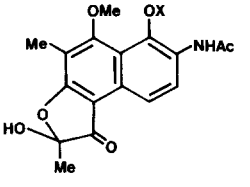


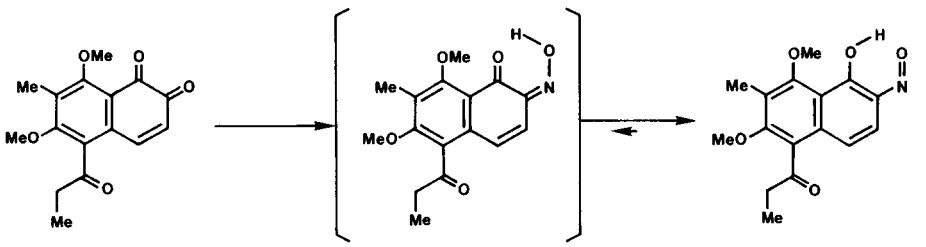
10 : X=Ac, Y=CH_3, R=$COCH_2CH_3$
11 : X=Y=H, R=$COCH_2CH_3$
12 : X=Y=CH_2OCH_3, R=$COCH_2CH_3$
13 : X=Y=CH_2OCH_3, R=$COCOCH_3$



14 : X=H
15 : X=$CH_2C_6H_4OCH_3$(p)

The next stage of the synthesis was the adjustment of the oxidation level of 8, which was realized by using selenium dioxide in acetic acid at 70°C; the o-naphthoquinone 9[5] (mp 117-118°C; NMR ($CDCl_3$) δ 1.21 (3H, t, J = 7.3 Hz), 2.24 (3H, s), 3.75 (3H, s), 3.88 (3H, s), 6.38 (1H, d, J = 10.4 Hz), 7.21 (1H, d, J = 10.4 Hz)) was isolated by silica gel chromatography in 53% yield. The intorduction of the C-2 amino group to the o-naphthoquinone 9 was achieved by applying a reaction discovered in the 19th century;[9] on treatment with hydroxylamine hydrochloride (excess)

in ethanol at room temperature, 9 selectively yielded the mono-oxime 16a, which exists as its tautomeric nitroso form 16b[5] (mp 139-140°C (dec.); NMR ($CDCl_3$) δ 1.21 (3H, t, J = 7.3 Hz), 2.27 (3H, s), 3.77 (3H, s), 3.89 (3H, s)). Hydrogenation of 16b (H_2/Pd-C/THF/RT), followed by acetylation ($AcCl/Et_3N$/THF/0°C), gave the diacetate 10[5] (mp 100-101°C; NMR ($CDCl_3$) δ 1.23 ppm (3H, t, J = 7.3 Hz), 2.16 (3H, s), 2.33 (3H, s), 2.42 (3H, s), 3.75 (6H, s)). The overall yield from 9 to 10 was 98%.



9 16a 16b

The remaining problems at this stage of the synthesis were (1) selective deprotection of the C-6 phenolic group, (2) the adjustment of the oxidation level of the C-5 side chain, and (3) the protection of the C-1 phenolic group as the p-methoxybenzyl ether. Selective cleavage of the C-6 methyl ether of 10 over the C-8 was realized by borontrichloride in methylene chloride at -20°C——note the effect of the C-6 carbonyl group; the naphthalene 11[5] (mp 119-123°C) was obtained, after aqueous sodium carbonate work-up, in 94% yield in this way. The oxidation of the C-5 side chain was initially realized by selenium dioxide oxidation at 180°C of the diacetate of 11 (i.e., X=Y=Ac in 11), but later air oxidation was found to be much more effective. Namely, the naphthalene 11 was converted to the corresponding dimethoxymethyl ether 12[5] ($CH_3OCH_2Br/(Pr^i)_2(Et)N/CH_2Cl_2/0°C$; mp 103-104°C; NMR ($CDCl_3$) δ 1.22 ppm (3H, t, J = 7.3 Hz), 2.23 (3H, s), 2.38 (3H, s), 3.53 (3H, s), 3.54 (3H, s), 3.76 (3H, s)) and then subjected to air oxidation ($O_2/KOBu^t/BuOH^t$-DME/-20°C) to yield the α-diketone 13[5] (mp 138-139°C; NMR ($CDCl_3$) δ 2.23 ppm (3H, s), 2.36 (3H, s), 2.54 (3H, s), 3.44 (3H, s), 3.55 (3H, s), 3.79 (3H, s)) in 95% overall yield. Acid treatment of 13 (CSA/CH_3OH/RT) yielded the naphthol 14[5] (mp 193-194°C; NMR ($CDCl_3$) δ 1.67 ppm (3H, s), 2.22 (3H, s), 2.32 (3H, s), 4.02 (3H, s), 7.84 (1H, d, J = 8.9 Hz), 8.68 (1H, d, J = 8.9 Hz)) in 92% yield. p-Methoxybenzylbromide treatment of 14 (p-$CH_3OC_6H_4$-$CH_2Br/(Pr^i)_2(Et)N/CH_2Cl_2$/RT) gave the aromatic segment 15[3,5] (amorphous solid; 80% yield), which was found to be identical with the authentic sample, prepared from rifamycin S, on comparison of spectroscopic (NMR, IR, UV, MS) and tlc data.

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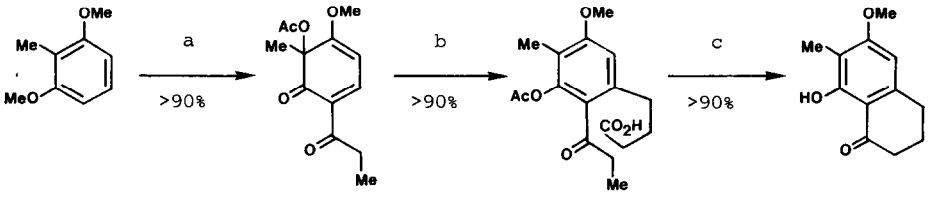
References and Footnotes

1. For reviews on ansamycin antibiotics including rifamycins, see, a. V. Prelog, Pure Appl. Chem., 7, 551 (1963). b. K. L. Rinehart, Jr., Acct. Chem. Res., 5, 57 (1972). c. P. Senti, Pure Appl. Chem., 41, 15 (1975). d. K. L. Rinehart, Jr. and L. S. Shield, Prog. Chem. Org. Nat. Prod., 33, 231 (1976). e. W. Wehrli, Top. Current Chem., 72, 22 (1977).
2. For synthetic studies on rifamycins, see, a. E. J. Corey and D. A. Clark, Tetrahedron Lett., 2045 (1980) and references cited therein. b. M. Kinoshita, M. Nakata, T. Sakai and K. Tatsuta, ACS/CSJ Chemical Congress, Paper No. 481, Honolulu, April 2-6, 1979.
3. H. Nagaoka, W. Rutsch, G. Schmid, H. Iio, M. R. Johnson and Y. Kishi, J. Am. Chem. Soc., in press; H. Iio, H. Nagaoka and Y. Kishi, J. Am. Chem. Soc., in press; Y. Kishi, Pure Appl. Chem., in press.
4. F. Wessely, J. Swoboda and V. Guth, Mh. Chem., 95, 650 (1964).
5. Satisfactory analytical and spectroscopic data were obtained for this substance.
6. A similar reaction was used in the synthesis of lasalocid A; T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smith-Palmer and Y. Kishi, J. Am. Chem. Soc., 100, 2933 (1978).
7. The tetralone 5 was synthesized also by the following sequence of reactions. The overall yield of this sequence was higher than that of the one described in the text, primarily due to the high yield for the conjugated addition of pentenylmagnesium bromide to the cyclohexadienone ii, readily prepared from dimethoxytoluene (i). It is interesting to mention that the Friedel-Craft reaction of iii under hydrogen fluoride conditions (HF/RT) yielded exclusively the tetralone 5, while the reaction under aluminum chloride conditions ($AlCl_3$/AcCl/nitrobenzene/RT) yielded a mixture of 5 and 5-propionyl-6-hydroxy-7-methyl-8-methoxytetralone.



i ii iii 5

Reagents

a. 1. $CH_3CH_2CO_2H/BF_3/90^oC$, followed by aqueous acid treatment. 2. $Pb(AcO)_4/AcOH/60^oC$.
b. 1. $CH_2=CH(CH_2)_3MgBr/Et_2O/0^oC$. 2. $Ac_2O/110^oC$. 3. $O_3/CH_3OH/-78^oC$, followed by $(CH_3)_2S$ work-up. 4. Jones oxidation. c. HF/RT.

8. The numbering corresponds to that of rifamycin S (1).
9. H. Goldschmidt, Chem. Ber., 17, 213 and 2066 (1884).

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