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TOTAL SYNTHESIS OF RIFAMYCIN W

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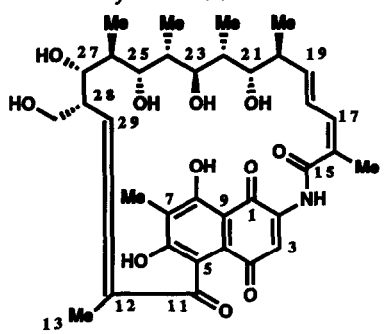
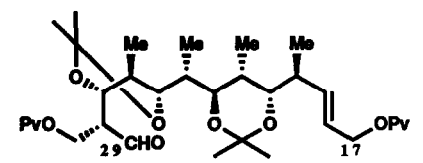
Summary: The first total synthesis of rifamycin W (1) has been accomplished by coupling two segments of the aliphatic ansa-chain 2 and the aromatic chromophore 3, elucidating the absolute structure completely.

Rifamycins are the first family of ansamycin antibiotics[1] characterized by the structure of aliphatic ansa-chain bridging an aromatic chromophore. Among them, only rifamycin S has been totally synthesized by Kishi and co-workers.[2] During the course of our synthetic studies of rifamycins,[3] we have been interested in rifamycin W (1),[4] which is the biosynthetic intermediate of all the rifamycin families.[4a] The structure was estimated[4b] on the basis of spectroscopic studies in comparison with rifamycin S, but the configurations of the C28 position and the C12 - C29 double bond remained undetermined. We wish to describe here the first total synthesis of rifamycin W (1) and elucidate the whole stereochemistry of 1 as depicted.



1 : rifamycin W



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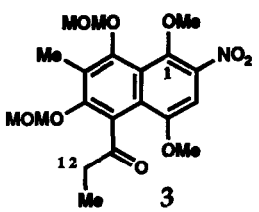

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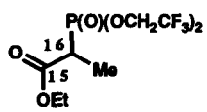
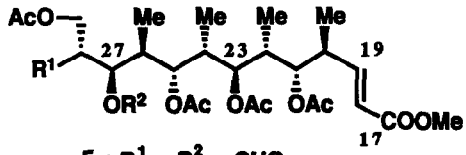


4

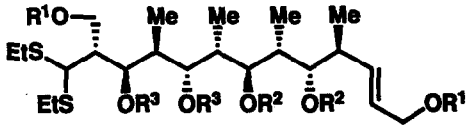
The crucial step for construction of 1 was the effective connection between the aliphatic ansa-chain and the aromatic chromophore and was accomplished by an aldol condensation[5] between the ansa-chain aldehyde 2 having (28*R*)-configuration[6] and the enolate of the aromatic segment 3. The aldehyde 2 was obtained from the ansa-chain compound 5, which had been previously prepared in enantiomerically pure form by using "two-stage coupling process" as a key step.[3,7] The aromatic segment 3 has been prepared from 3,5-dibromo-2,6-toluenediol by us.[8]

Treatment of 5 with ethanethiol and a catalytic amount of camphorsulfonic acid (30°C, 2d) gave the de-O-formylated dithioacetal 6[9] [70%; $[\alpha]_D^{27}$ -8° (c 0.12, $CHCl_3$)]. This was converted into the hexaol 7 by a three-step sequence in 95% yield [i) excess DIBAL/toluene, -78°C, 0.5 h;



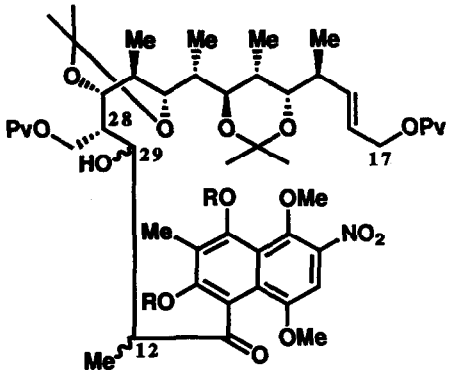
5 : $R^1 = R^2 = CHO$

6 : $R^1 = CH(SEt)_2$, $R^2 = H$

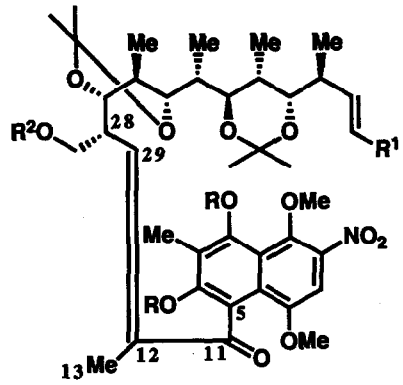


7 : $R^1 = R^2 = R^3 = H$

8 : R^1 = Pv, $R^2 = R^3$ = acetonide



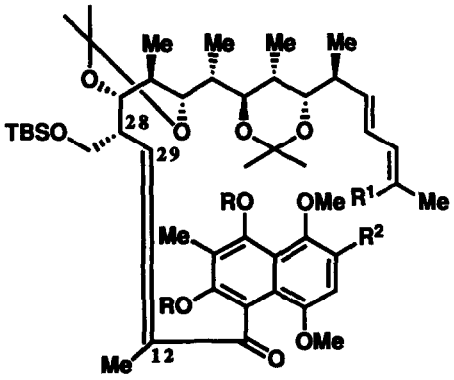
9 : R = MOM



10 : R = MOM, $R^1 = CH_2OH$, $R^2 = H$

11 : R = MOM, $R^1 = CHO$, $R^2 = H$

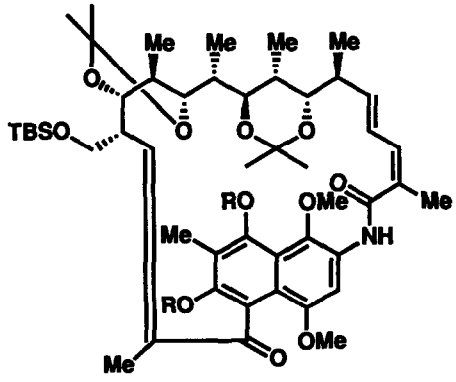
12 : R = MOM, $R^1 = CHO$, $R^2 = TBS$



13 : R = MOM, R^1 = COOEt, $R^2 = NO_2$

14 : R = MOM, R^1 = COOH, $R^2 = NO_2$

15 : R = MOM, R^1 = COOH, $R^2 = NH_2$



16 : R = MOM

ii) Ac_2O/4-dimethylaminopyridine/EtOAc, 25°C, 0.5 h; iii) NaOMe/MeOH, 25°C, 17 h]. After pivaloylation (PvCl/Py, 0°C, 4 h) of the two primary alcohols in **7**, the resultant tetraol was acetonized (2,2-dimethoxypropane/cat H_2SO_4/acetone, 25°C, 2 h) to afford **8**[9] [81%; $[\alpha]_D^{27}$ -16° (c 0.66, $CHCl_3$)]. Dethioacetalization of **8** ($HgCl_2$/HgO/80% aq acetone/ 25°C, 0.5 h) gave the ansa-chain aldehyde **2** in quantitative yield.

The coupling of the aldehyde **2** and the aromatic segment **3** was realized using a slightly modified House's conditions.[10] Anhydrous $ZnCl_2$ (3 equiv) in ether was added at -30°C to a THF solution of a lithium enolate of **3**, which was prepared from **3** (3 equiv) and lithium bis(trimethylsilyl)amide (3 equiv) at -30°C for 0.5 h. After 10 min at 0°C, the aldehyde **2** (1 equiv) in ether was added to the resulting zinc enolate of **3**. After 0.5 h at 0°C, usual work-up and silica-gel chromatographycal purification gave a mixture of the two separable adducts **9** in 86% yield in a ratio of 7 : 1. The major adduct was still a 1.2 : 1 inseparable mixture whereas the minor one was a 3 : 1 inseparable mixture.[11] Both the separated adducts were independently dehydrated (0.7% methanolic KOH, 40°C, 40 h) to afford the same α,β-unsaturated ketone **10** (85%). The ^1H NMR spectrum, however, showed that **10** consisted of a 3 : 1 inseparable mixture. Irradiation at 2.05 and 2.09 ppm (Me-13 peaks of the minor and the major **10**, respectively) gave no NOE enhancement at the olefinic region (5.60 ~ 6.00 ppm), thus establishing the *E*-configuration of the C12 - C29 double bond in **10**.[12] Therefore, it is reasonable to assume that this inseparable mixture should be due to the atropisomers because of hindered rotation around the C5 - C11 bond.[13] On the basis of molecular model studies, we expected that the free rotation about the C5 - C11 bond could be possible after the aromatic portion would be transformed into the intact structure present in **1**.

Oxidation of allylic alcohol **10** with MnO_2 in CH_2Cl_2 (25°C, 3 h) followed by silylation (TBSCl/imidazole/CH_2Cl_2, 25°C, 1 h) of the resultant allyl aldehyde **11** gave **12** (86% from **10**). Still's olefination[14] of **12** [**4**/$(Me_3Si)_2NK$/18-crown-6/THF, -78°C, 0.5 h) gave the desired (*Z,E*)-diene ester **13**[9] (82%) as a sole product. Hydrolysis of **13** with LiOH in 2 : 2 : 1 THF-MeOH-H_2O (40°C, 8 h) gave the carboxylic acid **14**[9](98%). Selective reduction of the nitro group in **14** was a troublesome step. After many unsuccessful results, sodium dithionite reduction[15] ($Na_2S_2O_4$/$NaHCO_3$/1 : 1 DMF-H_2O, 110°C, 10 min) gave the best result (100%). The resultant unstable aminocarboxylic acid **15** was cyclized under the Baker's conditions[16] [bis(2-oxo-3-oxazolidinyl)phosphinic chloride (4 equiv)/$^iPr_2NEt$ (10 equiv)/toluene (1.5 x 10^{-3}M), 85°C, 3 h] to afford the labile product, which was immediately oxidized with AgO in dioxane (1N HNO_3, 25°C, 1 h)[17] followed by deprotection (1 : 1 1N aq HCl-THF, 25°C, 2 d) to afford rifamycin W (**1**) in 30% yield from **14**. As expected, both atropisomers were converged into the single isomer **1**. All data (^1H NMR, IR, UV, TLC mobility) were identical with those of natural rifamycin W.[18] This goal indicates that the configurations of the C28 position having hydroxymethyl group and C12 - C29 double bond are *R* and *E*, respectively.

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b) E. Martinelli, G. G. Gallo, P. Antonini, and R. J. White, *Tetrahedron*, **30**, 3087 (1974).

5) We previously succeeded in the coupling between the ansa-chain aldehyde **5** and the Mukaiyama's tin enolate of the aromatic segment **3** (6,8-dimethyl ether in stead of 6,8-dimethoxymethyl ether) to give the aldol product as a diastereomeric mixture in 87% yield [M. Nakata, M. Kinoshita, S. Ohba, and Y. Saito, *Tetrahedron Lett.*, **25**, 1373 (1984)]. However, in the case of the aromatic segment having methoxymehyl protecting groups we could not obtain a good yield of the coupling product *via* a tin enolate.

6) We assumed conviniently the C28-hydroxymethyl configuration in **1** to be *R* by considering the facility of the synthesis. When the opposite stereochemistry was required, the chemical interchange of the pivaloyloxymethyl and aldehyde groups could be considered feasible.

7) The new route to the ansa-chain compound **5** from levoglucosan has been developed. The details will be published in a full account.

8) M. Nakata, S. Wada, K. Tatsuta, and M. Kinoshita, *Bull. Chem. Soc. Jpn.*, **58**, 1801 (1985).

9) All new compounds gave satisfactory spectroscopic data, including ^{1}H NMR, IR, and MS.

10) H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Am. Chem. Soc.*, **95**, 3310 (1973).

11) The stereochemistry of these four isomers has not been determined.

12) ^{1}H NMR experiment of natural rifamycin W (**1**) in our hands reveals no NOE between Me-13 and H-29, showing the *E*-configuration of the C12 - C29 double bond in **1**.

13) The atropisomers ratio of the compounds derived from **10** depends on whether the C28-hydroxymethyl group is protected or not (*e.g.*, **11**, 3 : 1; **12** ~ **15**, 1.2 : 1). The details will be published in a full account.

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18) We are indebted to Dr. Parenti, Gruppo Lepetit, Milano, for a generous gift of rifamycin W.

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