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TOTAL SYNTHESIS OF RIFAMYCIN S

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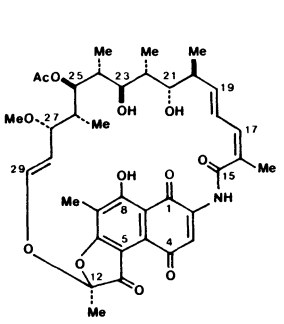
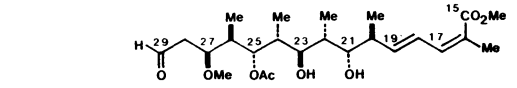
Abstract - The first total synthesis of rifamycin S is described.

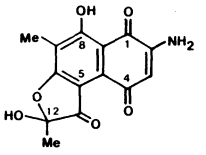
Rifamycins (originally spelled rifomycins),[1,2] isolated from the fermentation medium of Norcardia mediterranei by Senti, Greco and Ballotta in 1959, were the first examples of a novel class of antibiotics, ansamycins, characterized by an aliphatic bridge linking two non-adjacent positions of an aromatic 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 Oppolzer, and X-ray crystallographically by Brufani, Fedeli, Gliacomello and Vaciago. In this article, we would like to review our efforts in the total synthesis of rifamycin S (1).



1 : Rifamycin S



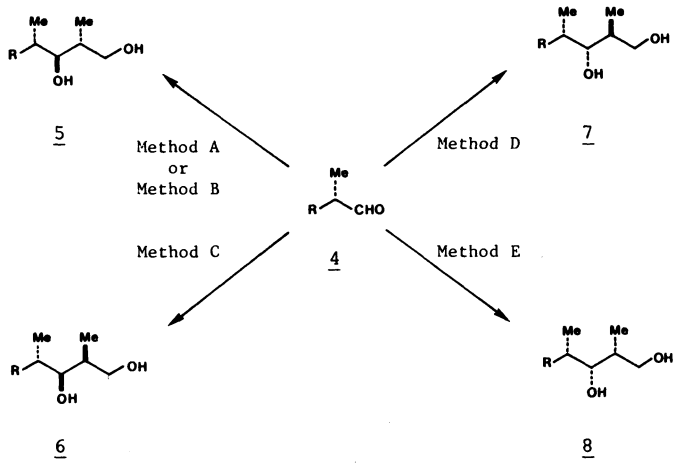
2



3

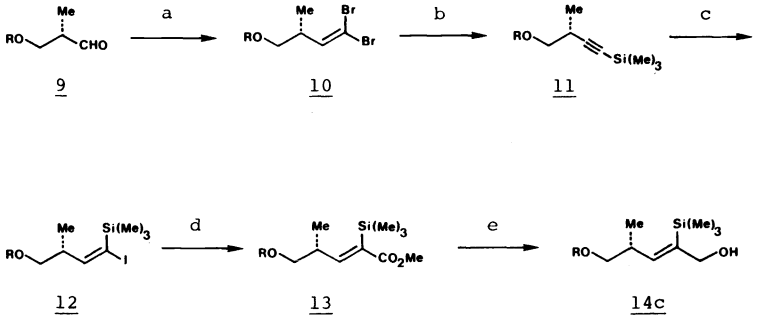
Disconnection of rifamycin S at the two carbon-hetero atom bonds yields the aliphatic segment 2 and the aromatic segment 3. Structure analysis of the aliphatic segment 2 reveals two important characteristics; first, the -CH(Me)-CH(OH)- structural unit appears repeatedly four times at the C-20[3] through C-27 positions, and second, with respect to its stereochemistry, there is a symmetry element at the C-23 position, ignoring the asymmetric center at the C-27 position. In connection with our interest in the synthesis of polyketide-derived natural products such as polyether, ansamycin and macrolide antibiotics, we have recently developed methods to synthesize stereoselectively the four diastereomers 5, 6, 7 and 8, respectively, from the aldehyde 4 (Scheme 1).[4] The overall stereoselectivity from 4 to 5 or 6 was perfect in a practical sense, while that from 4 to 7 or 8 was (12:1) ∿ (3:1) depending on the substituent R. These methods have been used successfully in controlling the stereochemistry at the C-20 through C-26 positions of the aliphatic segment 2, as is briefly illustrated in the following paragraphs.

Scheme 1



We chose the aldehyde 9 as the starting material for the synthesis of the aliphatic segment 2. Although this aldehyde is available in an optically active form as well,[5] the following experiments were carried out by using racemic starting material.[6] The aldehyde 9 was stereospecifically converted to the allylic alcohol 14c in about 45% overall yield by the sequence of reactions summarized in Scheme 2. The stereochemistry of the olefinic bond of 12 was controlled by applying the hydralumination reaction discovered by Nozaki and his co-workers[7] to the acetylene 11.

Scheme 2

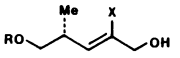


Reagents R = $CH_2C_6H_5$ or $CH_2OCH_2C_6H_5$

a. $CBr_4/(C_6H_5)_3P/CH_2Cl_2/0^oC$. b. *n*-BuLi/THF/-78°C, and then $(Me)_3SiCl$. c. DIBAL/heptane-ether/RT,[7] and then I_2/-78°C. e. 1. *n*-BuLi/THF/-78°C, and then $ClCO_2Me$. 2. DIBAL/CH_2Cl_2-$C_6H_5CH_3$/-78°C.

The conformations of the allylic alcohols 14a-c deserve comment. In the studies of the total synthesis of monensin, we recognized that consideration of the preferred, eclipsed conformation with respect to the sp^3-sp^2 system of such allylic alcohols is valuable in solving various problems.[4] Three eclipsed conformations, A, B and C, can be drawn for the allylic alcohols 14a-c, among which conformation A is considered most stable since conformations B and C will meet with steric compression due to the X group with the methyl group in B or with the alkoxymethyl group in C. The stereochemistry outcome of certain reactions on 14 can conventionally be predicted by counting the steric factors of the conformation A. For example, hydroboration of 14b was found to take place preferentially from the less sterically hindered β-face. On the other hand, epoxidation of 14a was expected to occur preferably from the α-face due to the directing effect of the alkoxyl and hydroxyl groups. Indeed, this was

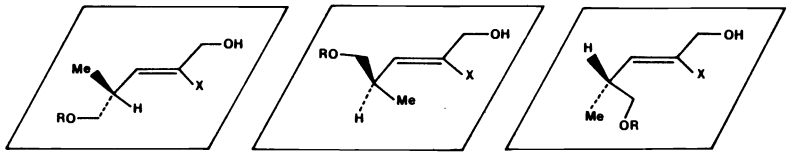
found to be the case, but the stereoselectivity of this epoxidation of 14a was disappointingly low, i.e. 3:2. In order to improve this poor stereoselectivity, the allylic alcohol 14c was synthesized with the hope that the bulky trimethylsilyl group would make conformation A far more stable than conformations B and C, which might be reflected in the relative stability of the transition states and hence in the product ratio. Epoxidation of 14c with m-chloroperbenzoic acid yielded the single epoxide 15!



14a : X = H

14b : X = Me

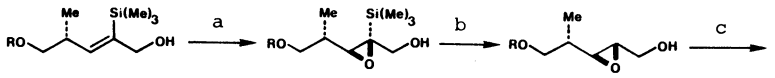
14c : X = $Si(Me)_3$



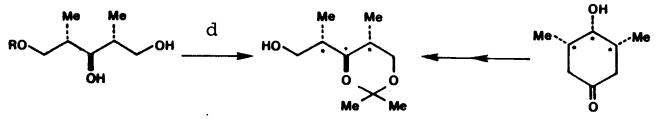
A B C

On treatment with fluoride anion, the trimethylsilyl group of the epoxide 15 was cleanly replaced by hydrogen. This type of reaction is known to take place with retention of stereochemistry.[8] The overall stereoselectivity from 14c to 16 was excellent; no signals due to the diastereomeric epoxide were detected in the NMR spectrum of the crude product. The epoxide ring of 16 was regio- and stereospecifically opened with lithium dimethylcuprate to yield the diol 17. The major reason for the observed remarkable regiospecificity proved to be mainly due to the steric hindrance from the methyl group for the incoming reagent.[4] The diol 17 was then converted to the acetonide alcohol 18 by routine synthetic operations. The stereochemistry of 18 was firmly established on comparison with the authentic sample, prepared from the stereochemically well-defined cyclohexanone 19. The overall yield from 14c to 18 was about 70%. The acetonide alcohol 18 was also obtained stereospecifically in slightly low overall yield by using Method B in Scheme 1.[4]

Scheme 3



14c 15 16



17 18 19

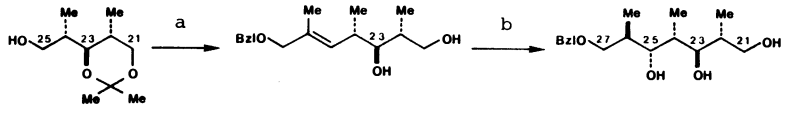
R = $CH_2C_6H_5$ or $CH_2OCH_2C_6H_5$

Reagents

a. MCPBA/CH_2Cl_2/0°C. b. $(n\text{-Bu})_4NF$/DMF/RT.[8] c. $LiCu(Me)_2/Et_2O$/-20°C. d. 1. acetone/CSA/$MgSO_4$/RT. 2. Li/liq. NH_3.

The plan was that the three chiral centers of 18 would become those at the C-22 through C-24 positions of the aliphatic segment 2. Introduction of the chiral centers at the C-25 and C-26 positions was realized by using the previously mentioned Method D in Scheme 1; hydroboration of the benzyl ether 20, prepared from 18 straightforwardly, yielded the desired tetrol monobenzyl ether 21 as the major product. The overall yield from 18 to 21 was 36% with about 4.5:1 overall stereoselectivity.

Scheme 4



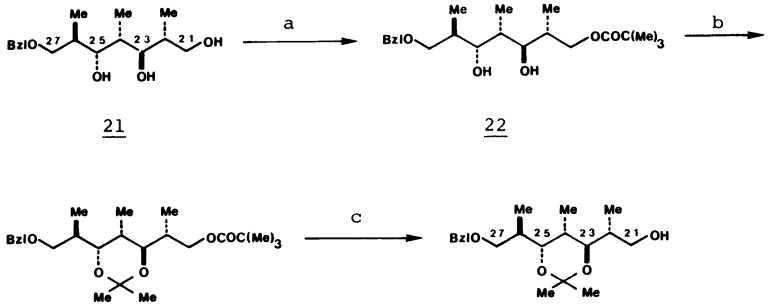
18 20 21

Reagents

a. 1. DMSO/$(COCl)_2$/CH_2Cl_2/-60°C, and then Et_3N.[9] 2. $(C_6H_5)_3P{=}C(Me)CO_2Et$/$ClCH_2CH_2Cl$/90°C. 3. $LiAlH_4$/Et_2O/0°C. 4. $C_6H_5CH_2Br$/KH/THF-DMF/0°C. 5. HCl/aq. MeOH/RT. b. B_2H_6/THF/0°C, and then H_2O_2/aq. NaOH-THF/RT.

The chiral centers at the C-20 and C-21 positions should be introduced by repeating the same sequence of reactions on the tetrol monobenzyl ether 21. For this purpose, selective protection of the secondary alcoholic groups over the primary was necessary, which was performed by prior selective protection of the primary alcoholic group with pivaloyl chloride treatment in 90% overall yield. There was no scrambling of the pivaloyl or the acetonide group observed in this sequence of reactions.

Scheme 5



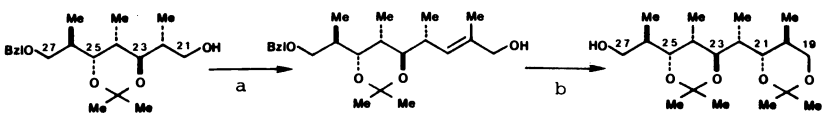
21 22 23 24

Reagents

a. $(Me)_3CCOCl$/Py/0°C → RT. b. acetone/CSA/$MgSO_4$/RT. c. $LiAlH_4$/Et_2O/0°C.

Application of the same sequence of reactions as the one outlined in Scheme 4 was now possible for the acetonide alcohol 24. Thus, the diacetonide 26 was synthesized from 24 in 34% overall yield with about 4.5:1 overall stereoselectivity.

Scheme 6



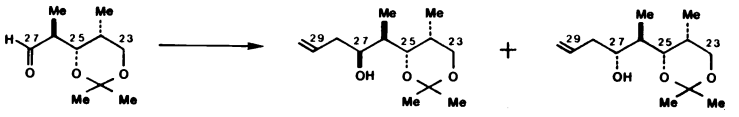
24 25 26

Reagents

a. 1. DMSO/$(COCl)_2$/CH_2Cl_2/-60°C, and then Et_3N.[9] 2. $(C_6H_5)_3P{=}C(Me)CO_2Et$/$ClCH_2CH_2Cl$/90°C 3. $LiAlH_4$/Et_2O/0°C. b. 1. HCl/aq. MeOH/RT. 2. B_2H_6/THF/0°C, and then H_2O_2/aq. NaOH-THF/RT. 3. 2,2-dimethoxypropane/acetone/CSA/RT. 4. Li/liq. NH_3.

A method to control the stereochemistry at the C-27 position was studied by using the acetonide aldehyde 27[10] as a model compound. After numerous attempts, it was experimentally discovered that diallylzinc[11] in ether at -78°C yielded a 4.3:1 mixture of the two possible alcohols, favoring the desired product 28 (Table 1).

Table 1

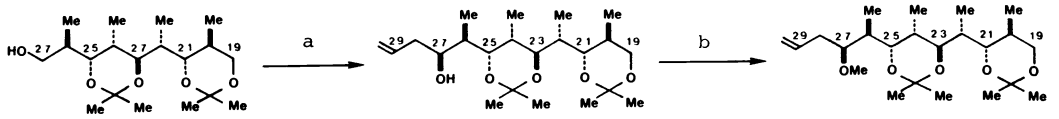


27 28 29

Reagent	Desired		Undesired
$CH_2=CHCH_2MgBr/Et_2O/-78^oC$	1.0	:	1.1
$(CH_2=CHCH_2)_2Zn/Et_2O/-78^oC$	4.3	:	1.0
$(CH_2=CHCH_2)_2Mn/Et_2O/-20^oC$	no reaction		
$(CH_2=CHCH_2)_2Cd/Et_2O/-20^oC$	no reaction		
cf. Real System			
$(CH_2=CHCH_2)_2Zn/Et_2O/-78^oC$	4.6	:	1.0

Using this method, the acetonide 26 was efficiently converted to the olefin 30. The stereoselectivity observed for the real system was about 4.6:1. There are four hydroxyl groups in the aliphatic segment 2, two of which exist as masked forms. It was, therefore, necessary to differentiate the hydroxyl groups at the C-25 and C-27 positions from those at the C-21 and C-23 positions. There was no problem selectively methylating the C-27 hydroxyl group of 30. The overall yield from 26 to 31 was 66%.

Scheme 7



26 30 31

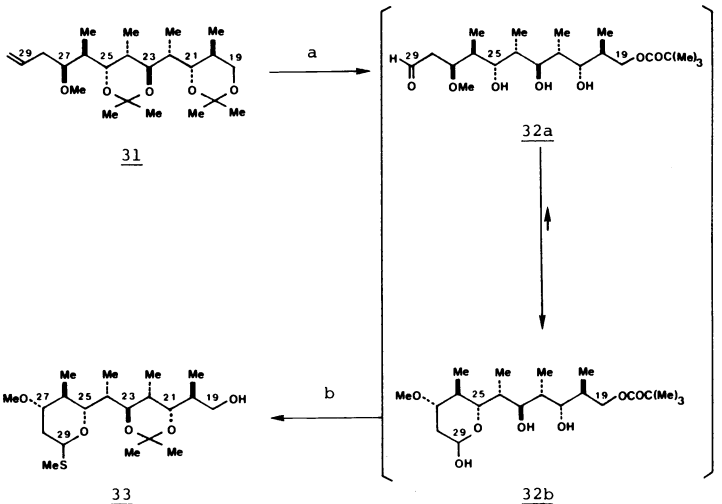
Reagents

a. 1. DMSO/$(COCl)_2/CH_2Cl_2/-60^oC$, and then Et_3N.[9] 2. $(CH_2=CHCH_2)_2Zn/Et_2O/-78^oC$.[11]

b. MeI/KH/THF-DMF/0^oC.

Differentiation of the C-25 hydroxyl group was cleanly achieved by using the C-29 aldehyde group. After hydrolysis of the acetonide groups of 31 and then selective protection of the primary alcohol, the vinyl group of 31 was oxidatively cleaved by osmium tetroxide-potassium periodate combination to yield the aldehyde 32a, which existed as the tetrahydropyranyl form 32b. This allowed the achievement of a unique differentiation of the C-25 hydroxyl group from the C-21 and C-23. Thus, the hemithioacetal acetonide 33[12] was synthesized in 56% overall yield from 31.

Scheme 8

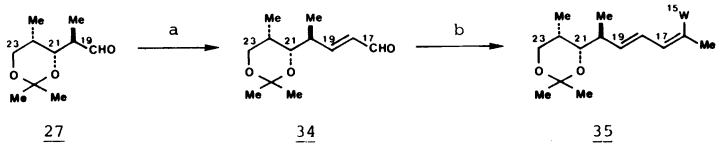


Reagents

a. 1. HCl/aq. MeOH/RT. 2. $(Me)_3CCOCl/Py/0^oC \rightarrow RT$. 3. OsO_4/KIO_4/aq. dioxane/RT. b. 1. $MeSH/BF_3 \cdot Et_2O/CH_2Cl_2/0^oC$. 2. 2,2-dimethoxypropane/acetone/CSA/RT. 3. $LiAlH_4/Et_2O/0^oC$.

We planned to introduce the trans,cis-diene system of the aliphatic segment 2 by two Wittig reactions, the feasibility of which was examined first by using again the acetonide aldehyde 27 as a model compound.[13] These results are summarized in Table 2. There was no problem introducing the trans-double bond at the C-19 position by using a stabilized ylid. The best reagent for the second Wittig reaction in terms of the overall stereoselectivity as well as practicality was $(MeO)_2P(O)CH(Me)CN$.[14] It is interesting to note that $(EtO)_2P(O)CH(Me)CN$[15] gave less satisfactory stereoselectivity.

Table 2



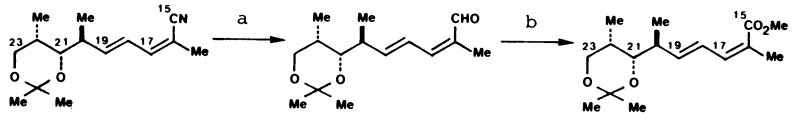
Reagents

a. 1. $(C_6H_5)_3P{=}CHCO_2Et/C_6H_6$/reflux. 2. $DIBAL/CH_2Cl_2$-$C_6H_5CH_3/-78^oC$. 3. $PDC/CH_2Cl_2/RT$.[16]

b. Reagent and Conditions	Desired (trans,cis)		Undesired (trans,trans)
$(C_6H_5)_3P{=}C(Me)CO_2Me/C_6H_6$/reflux	trace		major
$(MeO)_2P(O)CH(Me)CO_2Me/NaH/THF/-50^oC$[5a]	trace		major
$(EtO)_2P(O)CH(Me)CN/KOBu^t/THF/-78^oC$[15]	2.9	:	1.0
$(MeO)_2P(O)CH(Me)CN/KOBu^t/THF/-78^oC$[14]	5.0	:	1.0
cf. Real System			
$(EtO)_2P(O)CH(Me)CN/KOBu^t/THF/-78^oC$[15]	4.9	:	1.0
$(MeO)_2P(O)CH(Me)CN/KOBu^t/THF/-78^oC$[14]	10.	:	1.0

The nitrile 35 was converted to the trans,cis-diene ester 37 in excellent yield by the method summarized in Scheme 9. There would be no special comment necessary for this transformation except that the trans,cis-diene aldehyde 36 was found to isomerize easily to the corresponding trans,trans-diene aldehyde; careful handling of 36 was necessary to keep the stereoselectivity realized in the second Wittig reaction.

Scheme 9



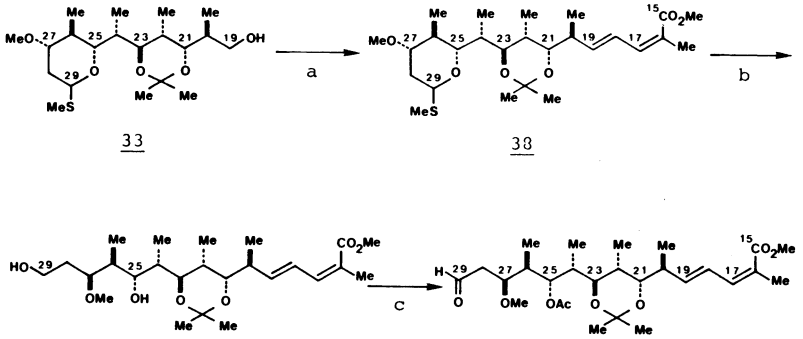
35 36 37

Reagents

a. DIBAL/$C_6H_5CH_3$/-78°C. b. NaCN/MnO_2/AcOH/MeOH/RT.[17]

The cyano Wittig reagent was successfully applied to the real system, where the stereoselectivity was cis:trans = 10:1. Thus, the ester 38[12] was obtained in 45% overall yield from 33. The functionalization at the C-25 and C-29 positions of 38 was achieved by the methods summarized in Scheme 10. After the hemithioacetal group was hydrolyzed to the corresponding hemiacetal, the tetrahydropyranyl ring of 38 was reductively opened. Selective acetylation at the C-25 hydroxyl group of 39 was performed via prior selective silylation of the C-29 primary hydroxyl group with tert-butyldiphenylsilyl chloride treatment. The overall yield from 38 to 2 was 74%.

Scheme 10



33 38

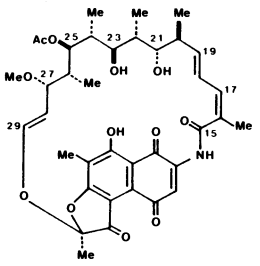
39 2

Reagents

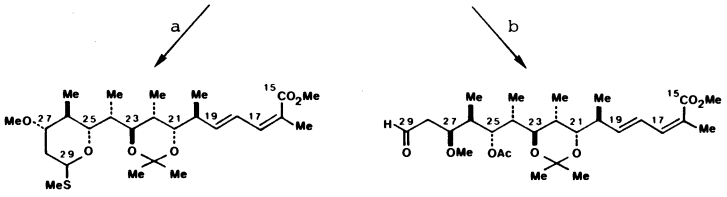
a. 1. PDC/CH_2Cl_2/RT.[16] 2. $(C_6H_5)_3P{=}CHCO_2Et$/$ClCH_2CH_2Cl$/90°C. 3. DIBAL/CH_2Cl_2-$C_6H_5CH_3$/-78°C. 4. PDC/CH_2Cl_2/RT.[16] 5. $(MeO)_2P(O)CH(Me)CN$/KOBu^t/THF/-78°C.[14] 6. DIBAL/$C_6H_5CH_3$/-78°C. 7. NaCN/MnO_2/AcOH/MeOH/RT.[17] b. 1. $HgCl_2$/$CaCO_3$/aq. acetone/RT. 2. $NaBH_4$/MeOH/RT. c. 1. Bu$^t(C_6H_5)_2SiCl$/imidazole/DMF/RT. 2. Ac_2O/Py/70°C. 3. $(n\text{-Bu})_4NF$/THF/RT. 4. DMSO/$(COCl)_2$/CH_2Cl_2/-60°C, and then Et_3N.[9]

We were confident of the structure of the totally synthetic aliphatic segment 2 since all the chiral centers were introduced by carefully studied methods. Nevertheless, it was beyond question that the structure, the stereochemistry in particular, of the synthetic substance needed to be firmly established. For this purpose, we studied the degradation reactions of rifamycin S (1). In spite of extensive studies by several groups, the intact aliphatic segment 2 had never been obtained from naturally occurring rifamycins. A practical, highly reproducible method to prepare this substance in 30-35% overall yield from rifamycin S (1) was developed in our laboratory (Scheme 11). On the other hand, the hemithioacetal 38 was straightforwardly prepared from one of the degradation products of rifamycin S, described by Kinoshita, Tatsuta and Nakata.[18]

Scheme 11



1 : Rifamycin S



38 2

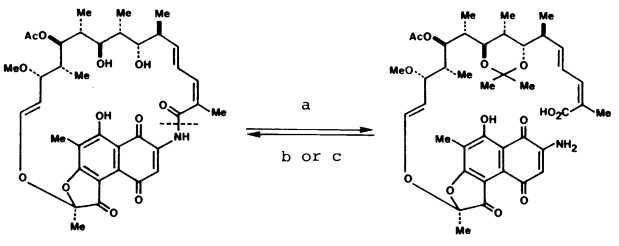
Reagents

a. 1. NaOH/aq. dioxane/0°C. 2. NBS/MeCN/RT. 3. NaOH/aq. MeOH/RT. 4. HCl/MeOH/RT. 5. $(n\text{-Bu})_3SnH/AIBN/C_6H_6$.[18] 6. $MeSH/ZnCl_2/CH_2Cl_2/0°C$. 7. 2,2-dimethoxypropane/acetone/CSA/RT. b. 1. 2,2-dimethoxypropane/acetone/CSA/RT. 2. NaOH/MeOH/RT. 3. MCPBA/THF/5% aq. $NaHCO_3/0°C$, followed by treatment with Et_2O/aq. Na_2SO_3/5% $NaHCO_3$/RT.

As expected, the totally synthetic aliphatic segment 2 and hemithioacetal 38 were found to be identical with the authentic substances, respectively, on comparison of spectroscopic and tlc data.

Having the totally synthetic aliphatic segment 2 in hand, we now turned our attention to methods to effect the ansa ring construction. We first investigated the lactam ring formation by using the amino acid 40, prepared from natural rifamycin S (1).[19] The desired lactam bond was cleanly formed by the methods summarized in Scheme 12. Reduction of the naphthoquinone moiety, i.e. Step 1 under Sequence b or Step 2 under Sequence c, was necessary to increase the nucleophilicity of the C-2 amino group.[20] Lindlar catalyst at low temperature was used for this purpose to avoid reduction of the olefinic bonds. Both methods tested were found effective for formation of the lactam bond, but the mixed anhydride procedure gave a slightly better overall yield.[21]

Scheme 12



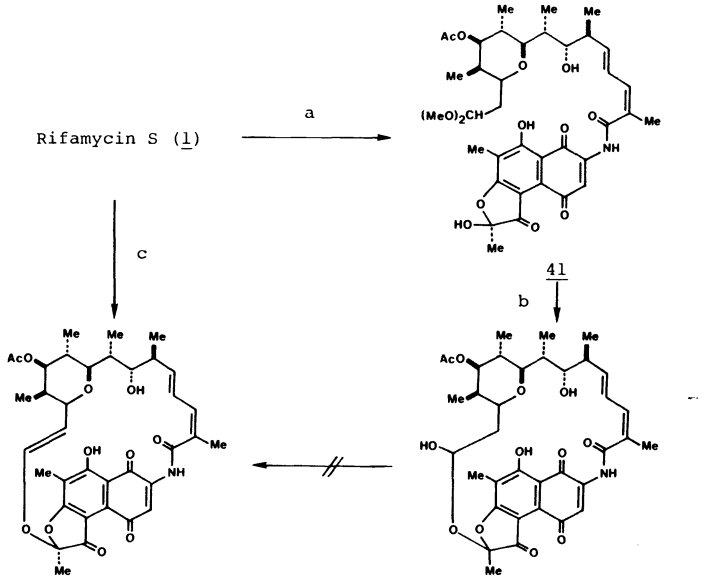
1 : Rifamycin S 40

Reagents

a. 1. 2,2-dimethoxypropane/CSA/RT. 2. NaOH/MeOH/RT. 3. sodium ascorbate/aq. DME/RT, followed by treatment with aq. NaOH/DME/RT, then $K_3Fe(CN)_6$ work-up. b. 1. H_2/Lindlar cat./THF/-20°C. 2. $(EtO)_2P(O)CN/Et_3N/DMF/RT$,[22] followed by $K_3Fe(CN)_6$ work-up. 3. HCl/aq. THF/RT. c. 1. $ClCO_2Et/Et_3N/CH_2Cl_2$/RT. 2. H_2/Lindlar cat./THF/-20°C. 3. THF/50°C, followed by $K_3Fe(CN)_6$ work-up. 4. HCl/aq. THF/RT.

The alternative possibility for the ansa ring construction, the intramolecular enol ether formation, seemed more attractive as there was the possibility that the relative stereochemistry at the C-12 and C-27 positions might be controlled in this approach. The feasibility of this plan was tested by using the acetal 41 and the corresponding thioacetal, prepared from rifamycin S (1).[23] The expected ansa product 42 from these compounds is known to be a degradation product on formic acid treatment of rifamycin S.[24] Numerous attempts were uniformly fruitless, however, among which the following observations are worth mention. On acid treatment (CSA/benzene/reflux), the acetal 41 yielded a new product which was isolated by flash silica gel chromatography in about 15% yield. The NMR spectrum of this product was very characteristic; one of the methyl group doublets appear at 0.35 ppm. Based on the NMR spectrum,[25] one of the most likely structures for the new product seemed to be the ansa hemiacetal 43, but all efforts to convert this substance to 42 were unsuccessful. Under these circumstances the approach involving the intermolecular enol ether formation was studied.[26]

Scheme 13

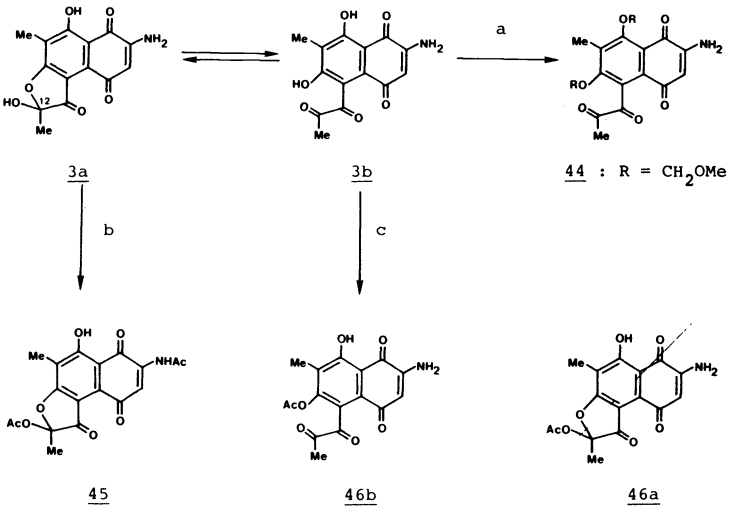


Reagents

a. HCl/MeOH/RT. b. CSA/C_6H_6/reflux. c. HCO_2H/RT.[24]

Although the aromatic segment 3 exists primarily as its closed tautomeric form — see 3a ⇄ 3b in Scheme 14 — particularly under acidic conditions, all attempts on acid- or metal ion-catalyzed enol ether formation were unsuccessful. It seemed hopeless to aklylate the tertiary alcoholic group of the closed form in the presence of a base. Indeed, 3 reacted smoothly with chloromethylmethyl ether in methylene chloride containing diisopropylethylamine, to yield exclusively the open-form product 44.[27] The NMR spectrum is most useful in determining the structure of open- or closed-form products; namely, the chemical shift for the C-13 methyl group of the closed-form product is observed uniformly around 1.7 ppm, while that of the open-form product is around 2.5 ppm.

Scheme 14



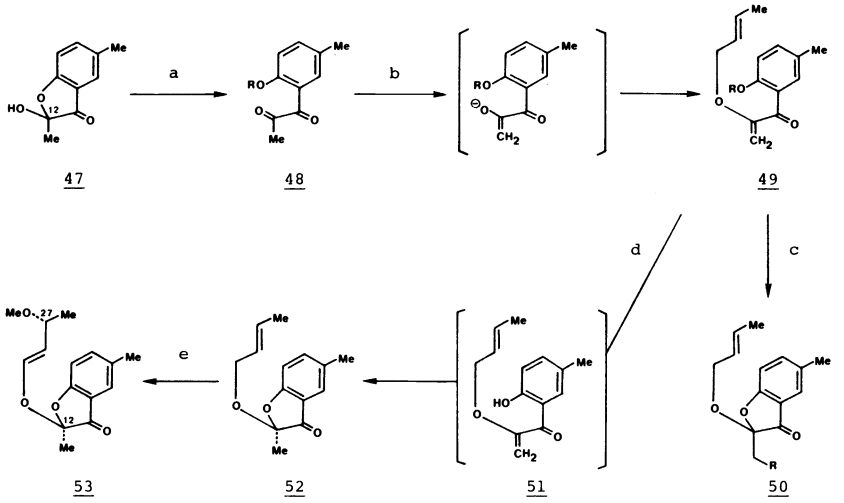
Reagents

a. $ClCH_2OMe/N(i\text{-}Pr)_2(Et)/CH_2Cl_2/RT$. b. $AcCl/ZnCl_2/CHCl_3/reflux$.[24] c. AcOH/DCC/DMF/RT.[24]

Kump and Bickel reported interesting observations on the reactivity of 3.[24] Namely, on treatment with acetyl chloride in the presence of zinc chloride, 3 yielded the diacetate of the closed form, i.e. 45. However, it seemed that there would be almost no chance to apply this type of reaction to our synthesis since the aliphatic segment 2 has rather acid-sensitive functionalities. On treatment with acetic acid and DCC, 3 yielded the monoacetate of 3, the structure of which had been assigned as 46a. This was exciting for our present purposes since there was the possibility of putting the aliphatic segment on the tertiary alcoholic group of the closed form under neutral conditions. However, we soon realized that the structure of 46a should be revised to the monoacetate of the open form, i.e. 46b, on the basis of NMR (δ 2.47 ppm) and IR (ν 1785 cm^{-1}) data. Thus, there were no examples known for acylation or alkylation on the tertiary alcoholic group of the closed form under basic or neutral conditions.

The open-form product of alkylation, cf. 44, would not necessarily lead to a dead end. One of the possibilities to utilize this type of product was examined by using the ketone 47[36] as a model compound. The anion of the open-form product 48 reacted smoothly with crotyl bromide to give cleanly the O-alkylated product 49. The protecting group of the phenolic function was chosen in such a way that it could be removed under mild acidic conditions without disturbing the enol ether group of 49. Indeed, upon brief treatment with trifluoroacetic acid in benzene at room temperature, 49 was found to produce the desired product 52 in excellent yield. This reaction seemed to involve 51 as an intermediate, since on treatment with boron trifluoride etherate, 49 cyclized in a different way to yield 50. Compound 52 was successfully converted to the methoxy compound 53, isolated as a diastereomeric mixture with respect to the C-12 and C-27 positions, as summarized in Scheme 15. It is interesting to point out that transformation of 52 to 53 took place in a highly regio- and stereoselective manner. This sequence of reactions had seemed quite promising, but we were unable to utilize it for the real synthesis partially because, although possible, the alkylation reaction was technically difficult particularly on a small scale, and partially because the chemoselectivity of the oxidation reaction in the real system, corresponding to Step 1 under e in the model system, was poor.

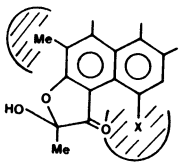
Scheme 15



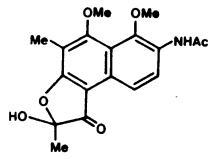
Reagents R = $CH_2C_6H_4OMe(p)$

a. p-$MeOC_6H_4CH_2Br/K_2CO_3$/DME-DMF/RT. b. LDA/HMPA-THF/-78°C, and then $MeCH{=}CHCH_2Br$/ -78°C → 0°C. c. $BF_3{\cdot}Et_2O/C_6H_5CH_3$/-20°C. d. TFA/$C_6H_6$/RT. e. 1. $(CH_2CO)_2NSeC_6H_5$/ CSA/MeOH.[28] 2. H_2O_2/CH_2Cl_2/RT, and then $CHCl_3$/Py/60°C.

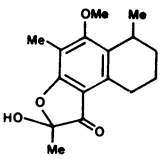
Under these circumstances, we decided to re-examine the possibility of alkylating the tertiary alcoholic group of the closed form with the hope that structural modification at the C-4 position of 3 might change the nature of the alkylation reaction; for example, the steric compression from the "X" and methyl groups might affect the amount of the desired, closed-form product — see Structure 54. Among numerous derivatives of 3 tested, the behavior of the following three compounds, 55, 56 and 57, towards alkylating reagents in the presence of a base was of interest. Upon treatment with various alkyl halides and alkyl mesylates in dimethylformamide in the presence of potassium carbonate, compounds 55 and 56 yielded exclusively the desired, closed-form product in excellent yield! However, compound 57 gave exclusively the undesired, open-form product under the same conditions.



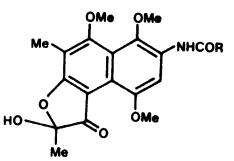
54



55



56

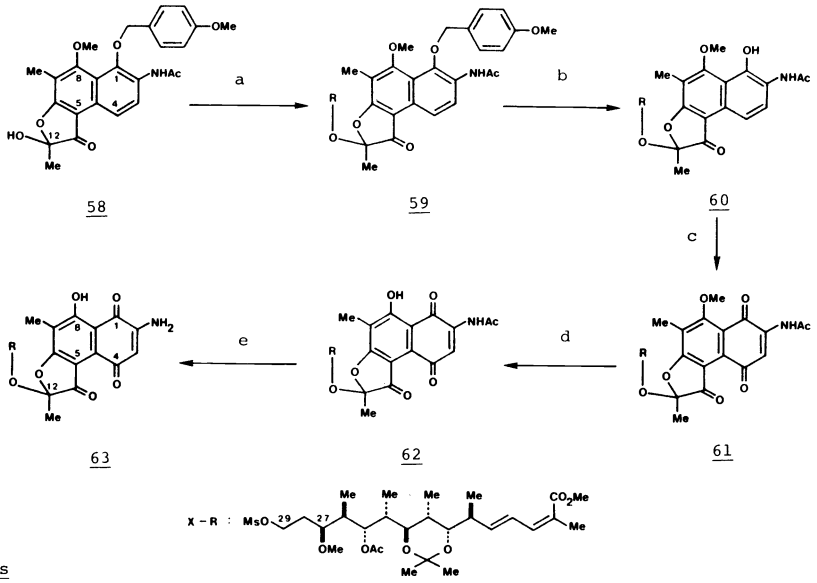


57

Encouraged by these exciting discoveries, we studied the final refinement of the protecting groups of the naphthalene 55. Thus, the naphthalene 58 was found to satisfy all the requirements for the present purposes. Namely, alkylation of 58 took place smoothly to give exclusively a closed-form product. The protecting groups of 58 were chosen in such a way

that the necessary functionalization of the naphthalene ring after the alkylation could be realized without disturbing the fragile functionalities. This was demonstrated by using the dihydrorifamycin S series as an example. The hydrolysis of the C-1 p-methoxybenzyl group was achieved under acidic conditions mild enough not to affect the C-12 ketal group. Fremy's salt was found to be perfect for oxidation of the phenol 60 to the naphthoquinone 61. Because of the C-1 carbonyl group, the hydrolysis of the C-8 methoxy group was possible under mild conditions. The acetyl group at the C-2 position was removed under mild basic conditions — note a sort of vinylogous diacylamine system. No undesired side reaction was observed in any step of this sequence.

Scheme 16



Reagents

a. 58 (1 eq.) + RX (1 eq.)/K_2CO_3/60°C. b. TFA/2,2-dimethoxypropane/acetone/CSA/RT.

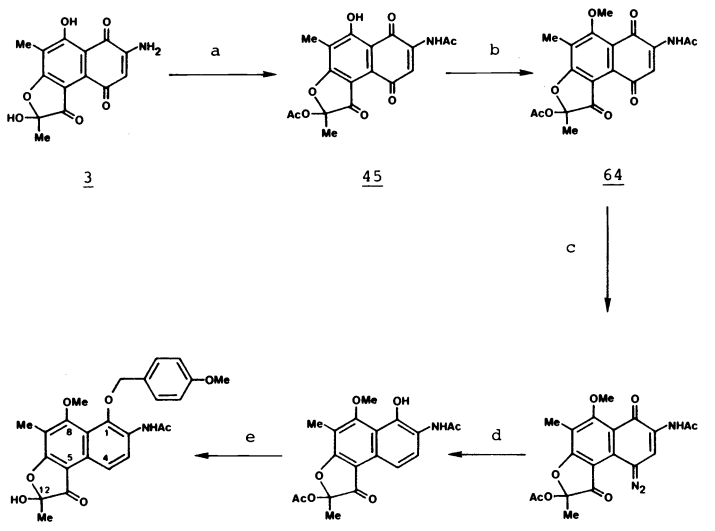
c. Fremy's salt/acetone/phosphate buffer (pH = 7)/RT. d. $MgI_2 \cdot Et_2O/C_6H_6$/RT.[29]

e. NaOH/MeOH/RT.

Let us now turn our attention to the synthesis of the naphthalene 58. At the early stage of this study the naphthalene 58 was prepared from the aromatic segment 3, which was in turn obtained from natural rifamycin S (1).[19] This synthesis is summarized in Scheme 17. The overall yield of 58 from 3 by this sequence of reactions was about 55%.

An alternative synthesis of the naphthalene 58 from 2-methylresorcinol monomethyl ether (67) is outlined in Scheme 18. The conjugated addition of pentenylmagnesium bromide to the cyclohexadienone 68, prepared from 67,[30] gave the phenol 69 in excellent yield.[31] There was no problem converting 69 to the tetralone 71 by using routine synthetic operations. The second Friedel-Craft reaction was found to take place smoothly on 71, but not on the corresponding monomethyl ether, i.e. the product of Step 1 under d. Thus, the tetralone 72 was obtained in almost quantitative yield from 71. The next stage of the synthesis was the adjustment of the oxidation level of 72, which was effectively realized by using selenium dioxide. The introduction of the C-2 amino group to the o-quinone 73 was achieved by applying a reaction discovered in the 19th century to this case.[32] Finally, the oxidation

Scheme 17

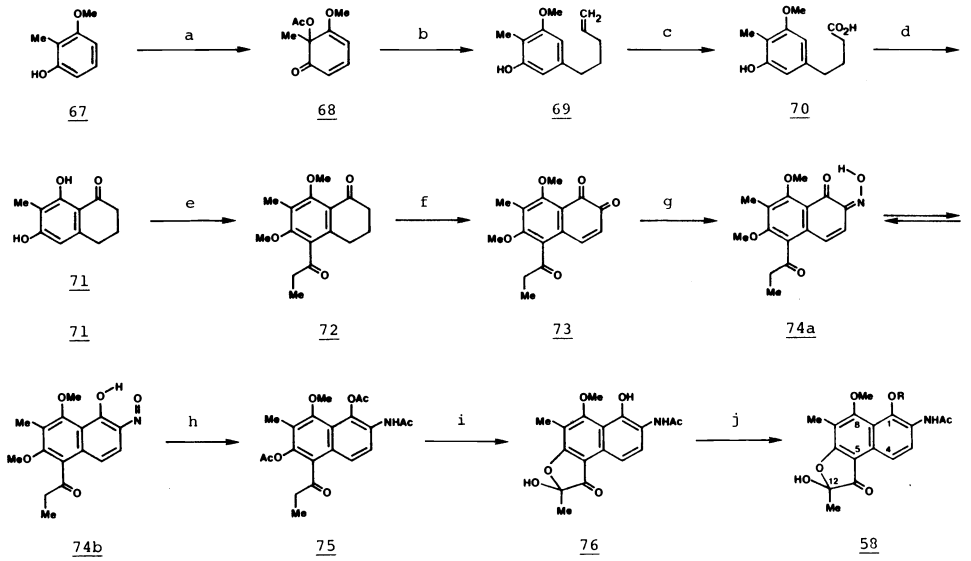


Reagents

a. $AcCl/ZnCl_2/CHCl_3$/reflux.[24] b. MeI/Ag_2O/MeOH-$CHCl_3$/60°C. c. $TsNHNH_2/MgSO_4$/MeCN/60°C.[25] d. H_2/Pd-C/EtOAc-CH_2Cl_2/RT. e. 1. *p*-$MeOC_6H_4CH_2Br/K_2CO_3$/DMF/RT. 2. 5% aq. Na_2CO_3/MeOH/RT.

of the C-12 carbon was realized by selenium dioxide oxidation at elevated temperature. The efficiency of this sequence of reactions was excellent except for the second selenium dioxide oxidation reaction, the conditions of which still need to be optimized.

Scheme 18



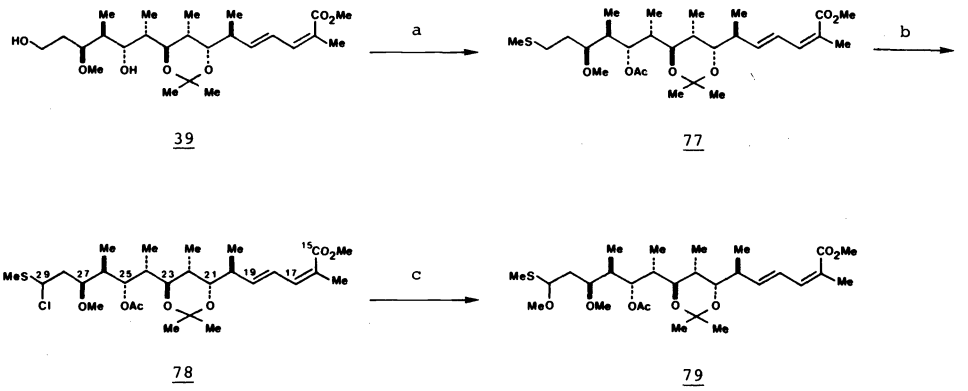
Reagents

R = $CH_2C_6H_4OMe(p)$

a. $Pb(OAc)_4/AcOH/60°C$. b. $CH_2=CH(CH_2)_3MgBr/Et_2O/0°C$. c. $OsO_4/NaIO_4$/aq. dioxane/RT. 2. Jones oxidation. d. 1. $AcCl/AlCl_3/CCl_4$/RT, and then aq. Na_2CO_3 work-up. 2. Py·HCl/200°C. e. $MeCH_2CO_2H/BF_3/90°C$, and then aq. Na_2CO_3 work-up. 2. MeI/K_2CO_3/acetone/100°C. f. SeO_2/AcOH/70°C. g. NH_2OH·HCl/EtOH/RT. h. 1. H_2/Pd-C/THF/RT. 2. $AcCl/Et_3N$/THF/0°C. 3. $BCl_3/CH_2Cl_2/0°C$. 4. $AcCl/Et_3N/CH_2Cl_2/0°C$. i. 1. SeO_2/xylene/180°C, and then aq. Na_2CO_3 work-up. j. *p*-$MeOC_6H_4CH_2Br/N(i\text{-}Pr)_2(Et)/CH_2Cl_2$/RT.

Turning to the preparation of the properly functionalized aliphatic segment, an α-halo sulfide appeared to be one of the best choices. The N-chlorosuccinimide chlorination of the sulfide 77, prepared from the diol 39, yielded an about 4:3 diastereomeric mixture of the reactive α-chloro sulfide 78,[33] the structure of which was established by two experiments: first, the NMR spectrum of 78 in deuterated benzene showed a triplet (J = 7 Hz) at 5.01 ppm and a doublet-of-doublets (J = 9 and 5 Hz) at 5.14 ppm, and second, the treatment of 78 with methanol in the presence of potassium carbonate yielded the dimethyl hemithioacetal 79 in about 70% overall yield from 77.

Scheme 19

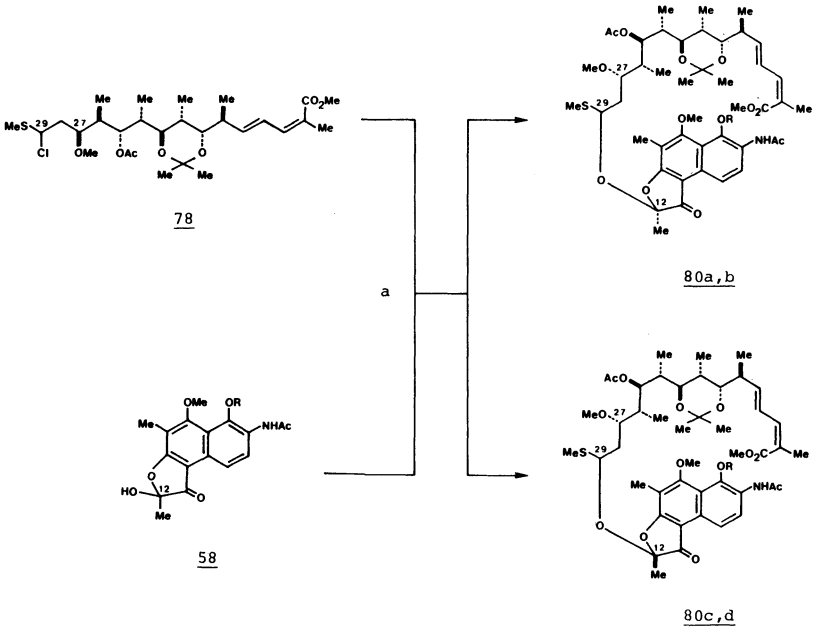


Reagents

a. 1. $Bu^t(C_6H_5)_2SiCl$/imidazole/DMF/RT. 2. Ac_2O/Py/70°C. 3. $(n\text{-Bu})_4NF$/THF/RT. 4. MsCl/Et_3N/CH_2Cl_2/0°C. 5. MeSNa/THF/RT. b. NCS/C_6H_6/RT. c. MeOH/K_2CO_3/RT.

Treatment of 58 (1 eq.) with 78 (1 eq.) in dimethylformamide in the presence of potassium carbonate at room temperature yielded a mixture of the four possible diastereomers 80a-d with respect to the C-12, C-27 and C-29 positions in about equal amount. The yield based on the consumed aromatic segment 58 was 86%, while the yield based on the aliphatic

Scheme 20



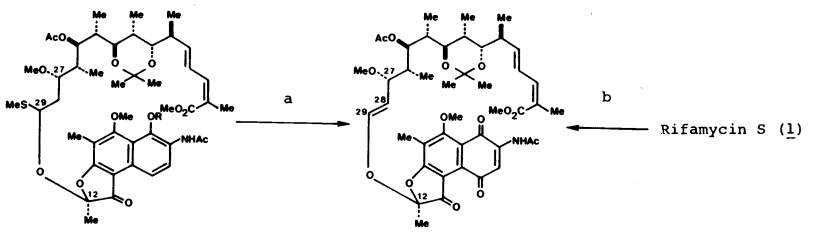
Reagents

a. 1. 58 (1 eq.) + 78 (1 eq.)/K_2CO_3/DMF/RT. 2. TLC separation.

segment 78 was 31%, due to the gradual decomposition of 78 to the corresponding vinyl sulfide under these conditions. By preparative thin layer chromatography, 80a and 80b were isolated as pure form, but the remaining two diastereomers 80c and 80d were as an inseparable mixture. Fortunately, the two diastereomers 80a and 80b, isolated as pure form, were shown to have the natural relative stereochemistry with respect to the C-12 and C-27 positions, while the two inseparable diastereomers 80c and 80d to have the unnatural relative stereochemistry (vide infra). Therefore, in order to continue the synthesis, it was sufficient to separate the mixture of 80a and 80b from that of 80c and 80d.

The mixture of diastereomers 80a and 80b was successfully converted to the methyl ester 81a primarily by applying the previously outlined method to this case. The initial step of this sequence of reactions was the oxidation of the sulfide group of 80 to the corresponding sulfoxide, which was found more acid stable. The hydrolysis of the p-methoxybenzyl group was again realized in a mixture of acetone and 2,2-dimethoxypropane containing camphorsulfonic acid to avoid the hydrolysis of the acetonide group. Olefin formation from the sulfoxide was smoothly effected in o-dichlorobenzene containing diisopropylamine at 160°C, to give an approximately 1:1 mixture of the trans and cis olefins. Oxidation of this mixture with Fremy's salt yielded an about 1:1 mixture of the trans and cis olefin methyl esters 81a and 81b, which could be separated by preparative thin layer chromatography. The overall yield from 80a,b to 81a,b was 65-70%. The trans olefin methyl ester 81a was found identical with the authentic substance, prepared from natural rifamycin S (1),[14,34] on comparison of spectroscopic and tlc data. The structure of the cis olefin methyl ester 81b was concluded from its spectroscopic data, in particular the spin-spin coupling constant (J = 6 Hz) of the C-28 and C-29 olefinic protons. By the same sequence of reactions, the mixture of the two inseparable diastereomers 80c and 80d was also converted to an about 1:1 mixture of the trans and cis olefin methyl esters 81c and 81d, which could be separated by preparative thin layer chromatography. The trans olefin methyl ester 81c was found very similar to 81a, although definitely different, on comparison of spectroscopic and tlc data. The same was found for the relationship between the cis olefin methyl esters 81b and 81d. Thus the relative stereochemistry at the C-12 and C-27 positions of the previously mentioned four diastereomers was established.

Scheme 21



80a,b* 81a**

R = $CH_2C_6H_4OMe(p)$

*80c and 80d are the diastereomers at the C-29 position, having the unnatural relative stereochemistry with respect to the C-12 and -27 positions.

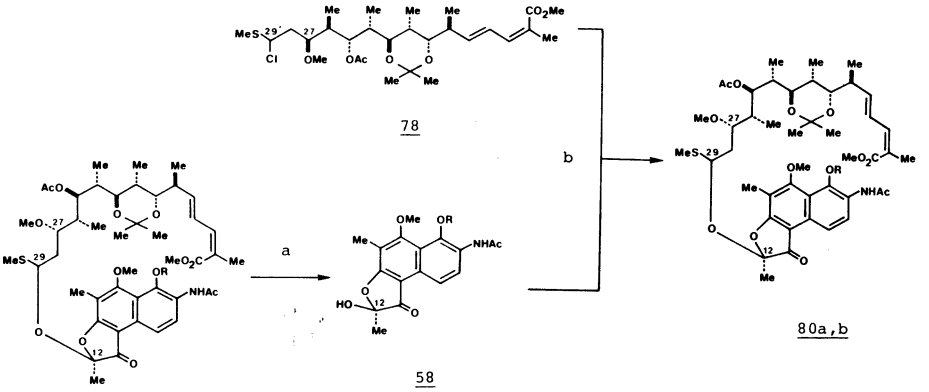
**81b is the *cis* isomer of 81a at the C-28 and -29 double bond. 81c and 81d are the *trans* and *cis* isomers at the C-28 and -29 double bond, having the unnatural relative stereochemistry with respect to the C-12 and -27 positions.

Reagents

a. 1. MCPBA/CH_2Cl_2/-78°C. 2. 2,2-dimethoxypropane/acetone/CSA/RT. 3. diisopropylamine/$C_6H_4Cl_2(o)$/160°C/30 min. 4. Fremy's salt/acetone/phosphate buffer (pH = 7)/RT. b. 2,2-dimethoxypropane/acetone/CSA/RT. 2. NaOH/MeOH/RT. 3. H_2/Lindlar cat./THF/-20°C, followed by treatment with AcCl/Et_3N/-78°C → RT and $K_3Fe(CN)_6$ work-up. 4. MeI/Ag_2O/MeOH-$CHCl_3$/60°C.

This sequence of reactions outlined in Scheme 20 and 21 not only provided the key intermediate 81a for the total synthesis of rifamycin S (1), but also gave an opportunity to investigate one of the possibilities for controlling the relative stereochemistry at the C-12 and C-27 positions. By using optically active aliphatic segment 78, prepared from natural rifamycin S,[19,35] the optical resolution of the aromatic segment 58 was examined. Thus, hydrolysis of the mixture of the diastereomers 80a and 80b was effected in wet acetone in the presence of mercuric chloride and mercuric oxide. The aromatic segment 58 was isolated by silica gel thin layer chromatography, and immediately subjected to a coupling reaction with the optically active aliphatic segment 78. Although these experiments were carried out only on a small scale several times, it seemed safe to conclude that the coupling reaction yielded the desired diastereomers 80a and 80b but not the undesired diastereomers 80c and 80d!

Scheme 22

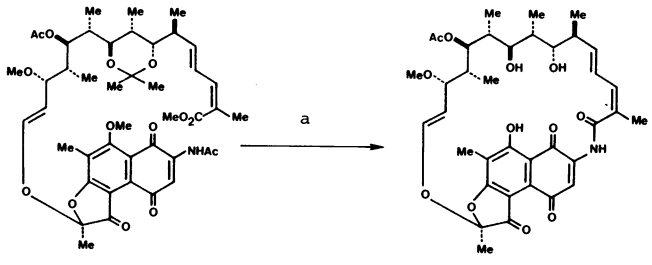


Reagents

a. $HgCl_2/HgO$/aq. acetone/RT. b. 58 + 78/K_2CO_3/DMF/RT.

By using the previously described method, the trans olefin methyl ester 81a was successfully converted to rifamycin S (1) in about 55% overall yield. Comparisons of the spectroscopic and tlc data of the totally synthetic and natural substances left no doubt that the totally synthetic substance was identical with the natural. Thus, the first total synthesis of rifamycin S was achieved.

Scheme 23



Reagents

a. 1. $MgI_2 \cdot Et_2O/C_6H_6$/RT.[29] 2. sodium ascorbate/aq. DME/RT, followed by treatment with aq. NaOH/DME/RT, then $K_3Fe(CN)_6$ work-up. 3. NaOH/MeOH/RT/5 min. 4. $ClCO_2Et/Et_3N/CH_2Cl_2$/RT. 5. H_2/Lindlar cat./THF/-20°C. 6. THF/50°C, followed by $K_3Fe(CN)_6$ work-up. 7. HCl/aq. THF/RT.

I would like to express my sincere appreciation for the exciting, stimulating and fruitful work done by Drs. Hideo Iio, Hiroto Nagaoka, Werner Rutsch, Gerard Schmid and Mark R. Johnson, whose devoted efforts have brought this synthesis to its successful conclusion. Financial support from the National Institutes of Health and National Science Foundation is gratefully acknowledged.

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19. We are indebted to Drs. Bickel and Scartazzini, CIBA-GEIGY, Basel, for a generous gift of rifamycin S and a sample of the aromatic segment 3.
20. This type of chemistry was discussed in relation to the mitomycin synthesis: see Y. Kishi, J. Nat. Prod., 42, 549 (1979).
21. Recently, Corey and Clark reported results almost identical to Method C; E. J. Corey and D. A. Clark, Tetrahedron Lett., 2045 (1980).
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23. The acetal 41 was synthesized from rifamycin S by HCl-MeOH treatment; see the papers quoted under reference 25. The thioacetal was synthesized from rifamycin S by $BF_3 \cdot Et_2O$-MeSH treatment.
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26. After having recognized dramatic difference in chemical behavior between compounds like 55 and 57, we attempted the intramolecular enol ether formation on compounds with the same naphthalene moiety as 55 without fruitful results.
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35. See Schemes 11 and 19.
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