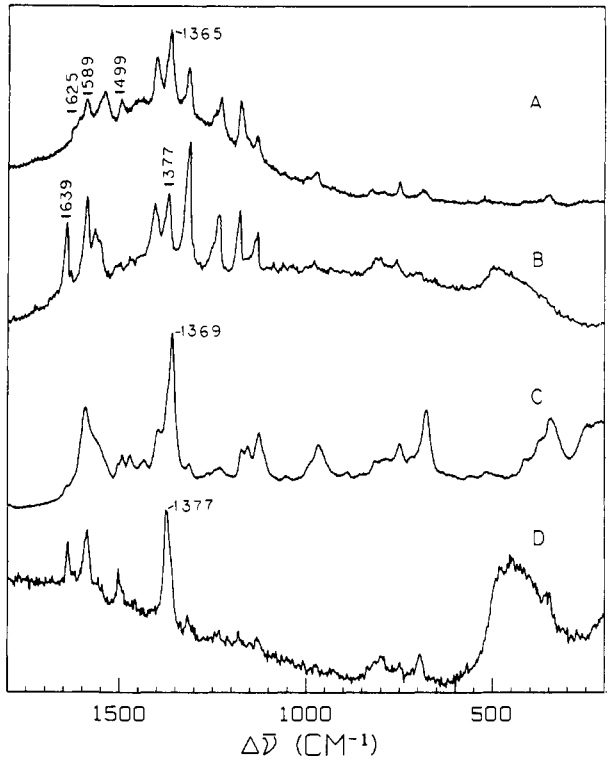

Figure 2. Comparison of the surface-enhanced RR spectra of cytochrome *c* with that in solution. (A) Cytochrome *c* spontaneously adsorbed from a 1×10^{-6} M solution on a Ag electrode at −0.6 V vs. SCE—laser excitation wavelength was 514.5 nm; (B) 1×10^{-3} M solution of ferricytochrome *c*—laser excitation wavelength was 514.5 nm; (C) same as (A) except laser excitation wavelength was 457.9 nm; (D) same as (B) except laser excitation wavelength was 457.9 nm. The laser power in all of the above experiments was approximately 40 mW. The scan parameters were as follows: slit width = 5 cm^{-1} for solution and 2 cm^{-1} for surface spectra; scan rate = 0.20 Å/s for solution and 0.3333 Å/s for surface spectra. The broad feature between 350 and 500 cm^{-1} in (D) is due to Raman scatter from the glass sample tube. For simplicity, only those bands discussed in the text are labeled.

c at the electrode appears unlikely on the basis of the close correspondence of the surface and solution spectra. Also, the surface spectra were reproducible on repeated cycling of the electrode from negative to positive potentials, suggesting that little denatured and insoluble protein remained on the electrode at the positive potentials. In contrast, the possibility of heme loss or protein denaturation in the case of Mb appears more probable. Direct interaction of the heme with the electrode could explain possible spin-state changes and/or large differences in the marker-band frequencies in comparison to their values for Mb in solution. Shifts on the order of 10 cm^{-1} are usually encountered in the vibrational frequencies of small molecules adsorbed at Ag electrodes.[1-7] Further experimentation is needed to determine the possibility and extent of denaturation in both proteins.

Surface spectra of Cyt *c* which are obtained by using laser excitation wavelengths closer in resonance with the Soret transitions are even more intense than those observed by using 514.5-nm light. Figure 2 compares the surface (A) and solution (B) spectra of Cyt *c* resulting from 514.5-nm excitation with the respective surface (C) and solution (D) spectra resulting from 457.9-nm excitation. The improvement in the signal-to-noise ratio in the 457.9-nm surface spectrum (C) suggests that an even lower detection limit for surface adsorbed heme proteins may be achievable by using deep-blue excitation. For both excitation wavelengths, a comparison of the solution spectra with those at the surface at −0.6 V clearly shows a shift in the oxidation-state band from approximately 1365 to 1377 cm^{-1}. The data again suggest the surface-bound Cyt *c* is reduced at this potential.

It should be noted that some decrease in surface signal strength is observed for both proteins with prolonged irradiation. The loss in intensity does not appear to be caused by extensive photodegradation of the protein, since no new bands are produced in the RR spectrum. The original signal intensity can be regenerated in the dark at −0.6 V, which suggests that the signal decrease is caused by thermally induced protein desorption at the electrode.

It can be said with certainty that the RR spectra observed for Cyt *c* and Mb are of molecules adsorbed at the electrode surface and that the underlying surface enhancement has a basis similar to that for SERS of small molecules. The criteria on which this conclusion is based include the following: (1) the signal intensity is dependent upon anodization of the Ag electrode; (2) the signal intensity is potential dependent; (3) depolarization ratios for all of the Cyt *c* and Mb vibrations are near 0.5, in contrast to the range of values exhibited in solution (from 0.1 to ∞); (4) detectable enhancement of the RR spectra of these proteins could not be observed at a Pt electrode by using conventional Raman spectrometers. These observations will be further explored in a future publication.

In conclusion, the data presented, though of a preliminary nature, are highly encouraging with regard to possible applications of SERS to bioanalytical problems. Surface-enhanced RR spectra were obtained for highly dilute solutions of the heme-containing proteins Cyt *c* and Mb, indicating that SERS has potential for detecting RR scattering from extremely small amounts of biological materials. Besides the enhancement effect, the electrode may serve as a scavenger and concentrate the species of interest in the laser beam. The observation of redox changes in the heme group of these two proteins substantiates that it will be possible to study electron-transfer processes in biological systems at the electrode surface. Furthermore, the sensitivity of the RR spectrum of heme to its environment should enable a detailed investigation of the state of the protein at the electrode surface. This type of structural information is not available in conventional electrochemical experiments. With the development of methodology for preserving the native state of proteins at the electrode surface, the combination of SERS and RRS techniques may well prove to be one of the most sensitive and selective probes of biomolecular structure yet devised.

Acknowledgment. Professors Brian Hoffman and Emanuel Margoliash generously provided the samples of myoglobin and cytochrome *c* used in this study. Dr. Haya Zemel and Dr. Willem Koppenol were extremely helpful in their discussions regarding the properties of myoglobin and cytochrome *c*. The support of NIH Grant 5R01GM27498-02 and NSF Grant CHE-7824866 is gratefully acknowledged.

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Total Synthesis of Rifamycins. 1. Stereocontrolled Synthesis of the Aliphatic Building Block

Sir:

Rifamycins,[1,2] isolated from the fermentation medium of *Norcardia mediterranei* by Senti, Greco, and Ballotta in 1959,

(1) For reviews on ansamycin antibiotics including rifamycins, see: (a) Prelog, V. *Pure Appl. Chem.* **1963**, *7*, 551. (b) Rinehart, K. L., Jr. *Acc. Chem. Res.* **1972**, *5*, 57. (c) Sensi, P. *Pure Appl. Chem.* **1975**, *41*, 15. (d) Rinehart, K. L., Jr.; Shield, L. S. *Prog. Chem. Org. Nat. Prod.* **1976**, *33*, 231. (e) Wehrli, W. *Top. Curr. Chem.* **1977**, *72*, 22.

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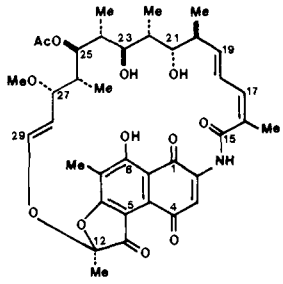
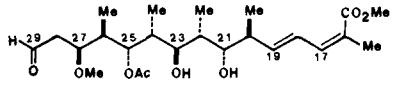
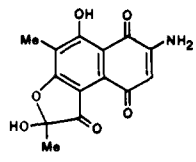
were the first examples of a novel class of antibiotics, ansamycins, characterized by an aliphatic bridge linking two nonadjacent positions of an aromatic nucleus. The great number of antibiotics belonging to this class can be divided into two subclasses: those whose ansa bridge is attached to a naphthoquinone or naphthalene nucleus, represented by rifamycin S, and those whose ansa bridge is attached to a benzoquinone or benzene nucleus, represented by maytansine. Rifampicin, a derivative of rifamycins, is a widely used, orally active tuberculostatic agent. The structure of rifamycins has been elucidated chemically by Prelog and Oppolzer, and X-ray crystallographically by Brufani, Fedeli, Gliacomello, and Vaciago. In reporting the first total synthesis of rifamycin S (**1**), we describe a stereocontrolled synthesis of the aliphatic



1: Rifamycin S



2

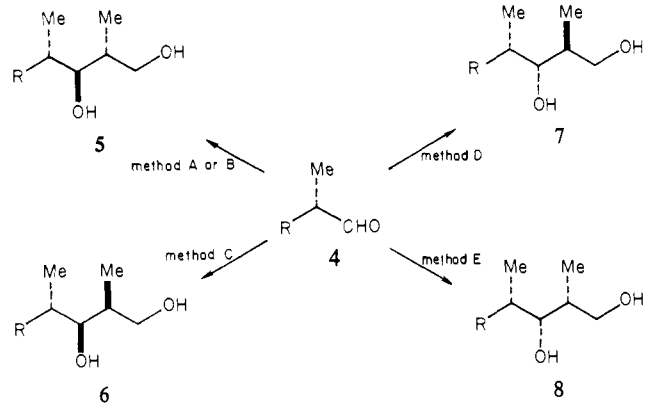


3

building block **17** in this communication and a total synthesis in the following paper.[3]

Disconnection of rifamycin S at the two carbon–heteroatom 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[4] through C-27 positions; 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 I).[5] The recognition of the preferred, eclipsed conformation with respect to the sp^3–sp^2 system played a major role in developing these methods. When these methods were used, the diacetonide **12**[6] [NMR ($CDCl_3$) δ 1.38 (6 H, s), 1.36 (3 H, s), 1.32 (3 H, s)] was straightforwardly synthesized from the aldehyde **9**[7] (Scheme II). The overall stereoselectivity from **9** to **10** was completely stereospecific[8] in a practical sense while that from **10** to **11** and also from **11** to **12** was about 4.5:1.[8] Selective protection of the secondary alcoholic group over the primary, required in the transformation of **10** to **11** and also of **13** to **14**, was efficiently performed via prior selective protection of the primary alcoholic group with pivaloyl chloride treatment.

Scheme I[a]



[a] Method A:[5c] (1) $CBr_4/(C_6H_5)_3P/CH_2Cl_2/0$ °C; (2) *n*-BuLi/THF/−78 °C and then $(Me)_3SiCl$; (3) DIBAL/heptane–ether/room temperature,[19] and then I_2/−78 °C; (4) *n*-BuLi/THF/−78 °C and then $ClCO_2Me$; (5) DIBAL/CH_2Cl_2–$C_6H_5CH_3$/−78 °C; (6) MCPBA/CH_2Cl_2/0 °C; (7) $(n\text{-Bu})_4NF$/DMF/room temperature; (8) $LiCu(Me)_2/Et_2O$/−20 °C. The overall yield of this sequence of reactions was about 35%, and the overall stereoselectivity was completely stereospecific in a practical sense. Method B:[5b] (1) $CBr_4/(C_6H_5)_3P/CH_2Cl_2$/0 °C; (2) *n*-BuLi/THF/−78 °C, and then $ClCO_2Me$; (3) H_2/Pd–$CaCO_3$/quinoline/hexane; (4) DIBAL/CH_2Cl_2–$C_6H_5CH_3$/−78 °C; (5) MCPBA/CH_2Cl_2/0 °C; (6) CH_2=CHMgBr/CuI/Et_2O/−20 °C; (7) MsCl/Py/0 °C; (8) $LiAlH_4/Et_2O$/0 °C; (9) O_3/MeOH/−78 °C or $OsO_4/NaIO_4$/MeOH/0 °C; (10) $NaBH_4$/MeOH/0 °C. The overall yield of this sequence of reactions was about 25%, and the overall stereoselectivity was completely stereospecific in a practical sense. Method C:[5b] Steps 1 through 5 are the same as those under method B. (6) $LiCu(Me)_2/Et_2O$/−20 °C. The overall yield of this sequence of reactions was about 40%, and the overall stereoselectivity was completely stereospecific in a practical sense. Method D:[5a,b] (1) $(C_6H_5)_3P{=}C(Me)CO_2Et$/$ClCH_2CH_2Cl$/90 °C; (2) $LiAlH_4/Et_2O$/0 °C; (3) B_2H_6/THF/0 °C and then H_2O_2/aqueous NaOH–THF/room temperature. The overall yield of this sequence of reactions was about 70%, and the overall stereoselectivity was 10:1–3:1, depending on the substituent R. Method E:[5a,b] (1) $(MeO)_2P(O)CH(Me)CO_2Me$/NaH/THF/−78 °C → −50 °C; (2) $LiAlH_4/Et_2O$/0 °C; (3) B_2H_6/THF/0 °C, and then H_2O_2/aqueous NaOH–THF/room temperature. The overall yield of this sequence of reactions was about 70%, and the overall stereoselectivity was 12:1–2.5:1, depending on the substituent R.

A method to control the C-27 sterochemistry was studied by using the acetonide aldehyde **18**[6,9] as a model compound (Scheme III). After many attempts, it was experimentally discovered that diallylzinc[10] in ether at −78 °C yielded a 4.3:1 mixture[8] of the two possible alcohols, favoring the desired product **19**.[6] When this method was used, the diacetonide **12** was effectively converted to the olefin **13**[6] [NMR ($CDCl_3$) δ 3.36 (3 H, s), 1.38 (3 H, s), 1.33 (3 H, s), 1.32 (3 H, s), 1.29 (3 H, s)]. The stereoselectivity observed for the real system was 4.6:1.[8] Formation of the tetrahydropyran ring [see the hemithioacetal **14**;[6] α anomer:[11] NMR ($CDCl_3$) δ 4.33 (1 H, dd, J = 12, 2 Hz), 3.35 (3 H, s), 2.17 (3 H, s), 1.35 (3 H, s), 1.30 (3 H, s); β anomer:[11] NMR ($CDCl_3$) δ 5.24 (br d, J = 6 Hz), 3.34 (3 H, s), 2.12 (3 H, s), 1.37 (3 H, s), 1.34 (3 H, s)] uniquely differentiated the C-25 hydroxyl group

(2) For synthetic studies on rifamycins, see: (a) Corey, E. J.; Clark, D. A. *Tetrahedron Lett.* **1980**, 2045 and references cited therein. (b) Kinoshita, M.; Nakata, M.; Sakai, T.; Tatsuta, K. American Chemical Society/Chemical Society of Japan Chemical Congress, Honolulu, April 2-6, 1979; American Chemical Society: Washington, DC, 1979; ORG 481.

(3) Iio, H.; Nagaoka, H.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, following paper in this issue.

(4) The numbering corresponds to that of rifamycin S—see structure **1**.

(5) (a) Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259. (b) Johnson, M. R.; Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4343. (c) Hasan, I.; Kishi, Y. *Ibid.* **1980**, 4229. (d) Kishi, Y. *Aldrichim. Acta*, **1980**, *13*, 23.

(6) Satisfactory spectroscopic data (NMR, MS, IR, UV) were obtained for this substance.

(7) Johnson, M. R.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4347.

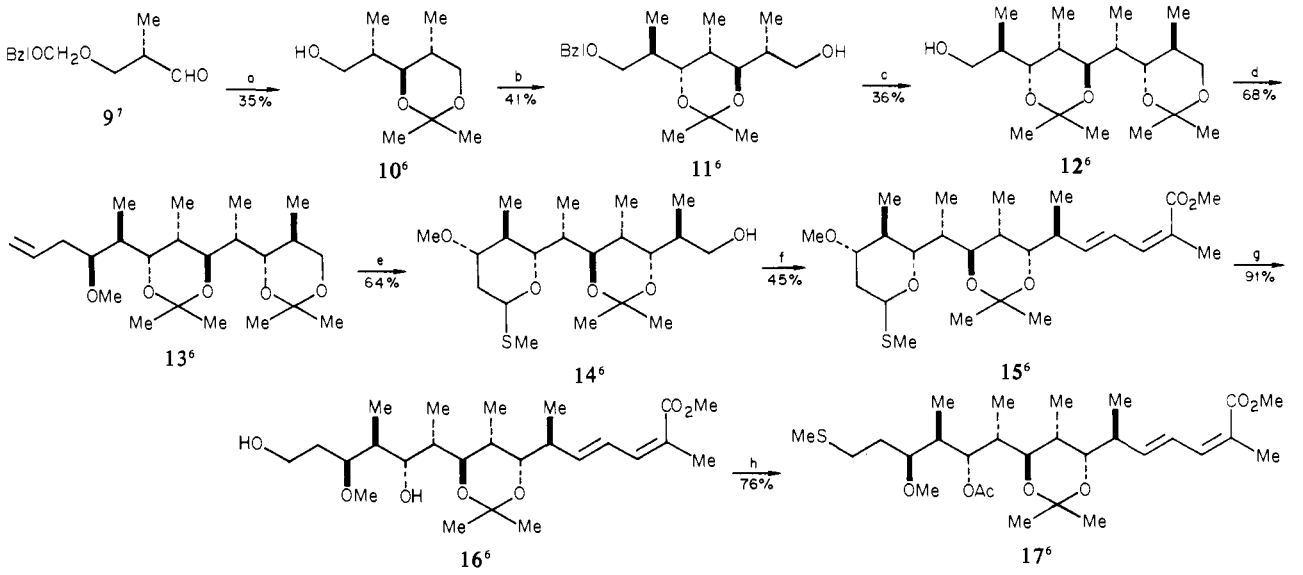
(8) This ratio was determined from analysis of the NMR spectrum of the crude product, which agreed with that of the isolated products.

(9) This substance was synthesized by using method C in Scheme I.

(10) Thiele, K.-H.; Zdunneck, P. *J. Organomet. Chem.* **1965**, *4*, 10. Abenhaim, D.; Henry-Basch, E.; Freon, P. *Bull. Soc. Chim. Fr.* **1969**, 4038. Allylmagnesium bromide in ether yielded a 1.1:1.0 mixture favoring the undesired product. Diallylcadmium and diallylmanganese failed to react with **18**.

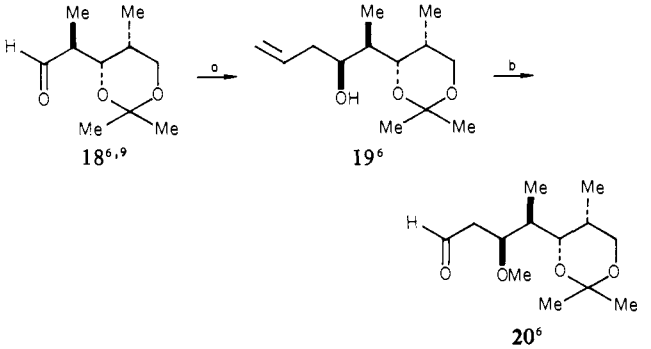
(11) The α and β anomers were cleanly separated by preparative thin-layer chromatography (silica gel).

Scheme II[a]



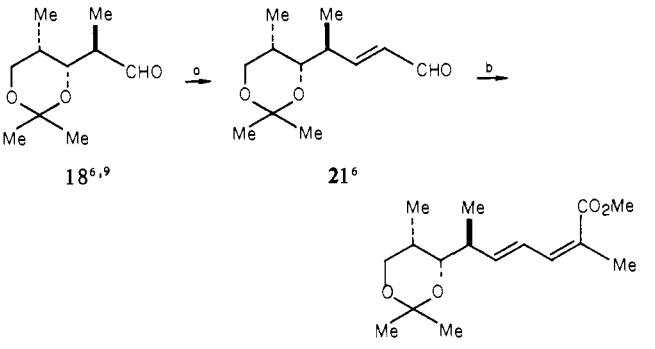
[a] (a) Steps 1 through 8 are the same as those under method A (or 1 through 10 under method B). (9) (or 11) Acetone/CSA/$MgSO_4$/room temperature; (10) (or 12) Li/liquid NH_3. (b) (1) Me_2SO/$(COCl)_2$/CH_2Cl_2/−60 °C and then Et_3N;[20] Steps 2 and 3 are the same as steps 1 and 2 under method D; (4) $C_6H_5CH_2Br$/KH/THF-DMF/0 °C; (5) HCl/aqueous MeOH/room temperature; (6) the same as step 3 under method D; (7) $(Me)_3CCOCl$/py/0 °C → room temperature; (8) acetone/CSA/$MgSO_4$/room temperature; (9) $LiAlH_4$/Et_2O/0 °C. (c) (1) Me_2SO/$(COCl)_2$/CH_2Cl_2/−60 °C and then Et_3N;[20] Steps 2 and 3 are the same as steps 1 and 2 under method D. (4) HCl/aqueous MeOH/room temperature; (5) the same as step 3 under method D; (6) 2,2-dimethoxypropane/acetone/CSA/room temperature; (7) Li/liquid NH_3. (d) (1) Me_2SO/$(COCl)_2$/CH_2Cl_2/−60 °C and then Et_3N;[20] (2) $(CH_2{=}CHCH_2)_2Zn$/Et_2O/−78 °C;[10] (3) MeI/KH/THF-DMF/0 °C. (e) (1) HCl/aqueous MeOH/room temperature; (2) $(Me)_3CCOCl$/py/0 °C → room temperature; (3) OsO_4/KIO_4/aqueous dioxane/room temperature; (4) MeSH/BF_3Et_2O/CH_2Cl_2/0 °C; (5) 2,2-dimethoxypropane/acetone/CSA/room temperature; (6) $LiAlH_4$/Et_2O/0 °C. (f) (1) PDC/CH_2Cl_2/room temperature;[21] (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/room tmperature;[21] (5) $(MeO)_2$-P(O)CH(Me)CN/KOBu-*t*/THF/−78 °C;[13] (6) DIBAL/$C_6H_5CH_3$/−78 °C; (7) NaCN/MnO_2/AcOH/MeOH/room temperature.[22] (g) (1) $HgCl_2$/$CaCO_3$/aqueous acetone/room temperature; (2) $NaBH_4$/MeOH/room temperature; (h) (1) Bu-*t* $(C_6H_5)_2SiCl$/imidazole/DMF/room temperature; (2) Ac_2O/py/70 °C; (3) (*n*-Bu)$_4$NF/THF/room temperature; (4) MsCl/Et_3N/CH_2Cl_2/0 °C; (5) MeSNa/THF/room temperature.

Scheme III[a]



[a] Reagents: (a) $(CH_2{=}CHCH_2)_2Zn$/Et_2O/−78 °C.[10] (b) (1) MeI/KH/THF-DMF/0 °C; (2) OsO_4/KIO_4/aqueous dioxane/room temperature.

Scheme IV[a]



[a] (a) (1) $(C_6H_5)_3P{=}CHCO_2Et$/C_6H_6/reflux; (2) DIBAL/CH_2Cl_2-$C_6H_5CH_3$/−78 °C; (3) PDC/CH_2Cl_2/room temperature.[21] (b) (1) $(MeO)_2P(O)CH(Me)CN$/KOBu-*t*/THF/−78 °C;[13] (2) DIBAL/$C_6H_5CH_3$/−78 °C; (3) NaCN/MnO_2/AcOH/MeOH/room temperature.[22]

from the C-21 and C-23 hydroxyl groups.

It was planned to introduce the *cis,trans*-diene system by two Wittig reactions, the feasibility of which was examined first by using again the acetonide aldehyde **18**,[6,9] as a model compound (Scheme IV).[12] The best method in terms of overall stereoselectivity as well as practicability is summarized below. To obtain a good ratio (cis:trans = 5:1[8]) for the second Wittig reaction, it was important to use $(MeO)_2P(O)CH(Me)CN$.[13,14] Contrary to the results on the cyano series, the corresponding methyl ester, $(MeO)_2P(O)CH(Me)CO_2Me$,[5a] gave almost exclusively the trans ester. This cyano reagent was successfully applied to the real system, where stereoselectivity was cis:trans = 10:1.[8] The structure of the synthetic hemithioacetal **15**[6] [α anomer:[11] NMR ($CDCl_3$) δ 7.13 (1 H, dd, *J* = 16, 11 Hz), 6.40 (1 H, d, J = 11 Hz), 5.97 (1 H, dd, *J* = 16, 7 Hz), 3.75 (3 H, s), 3.35 (3 H, s), 2.18 (3 H, s), 1.94 (3 H, s), 1.27 (3 H, s), 1.25 (3 H, s); β anomer:[11] NMR

(12) For alternative solutions of this problem, see: Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 2317. See also the paper quoted in ref 2b.

(13) This reagent was prepared from $(MeO)_2P(O)CH_2CN$ by a standard method. It is interesting to add that $(EtO)_2P(O)CH(Me)CN$ (see: Deschaps, B.; Lampin, J. P.; Mathey, F.; Seyden-Penne, J. *Tetrahedron Lett.* **1977**, 1137; also: Breuer, E.; Bannet, D. M. *Ibid.* **1977**, 1141; *Tetrahedron* **1978**, *34*, 997) gave less satisfactory results; the stereoselectivity for the model system was cis:trans = 2.9:1 and that for the real system was cis:trans = 4.7:1.

(14) The *cis,trans*-diene aldehyde, the product of the DIBAL reduction of the *cis,trans*-diene nitrile, was found to isomerize easily to the corresponding *trans,trans*-diene aldehyde. Careful handling of this substance was necessary to keep the stereoselectivity realized in the Wittig reaction.

($CDCl_3$) δ 7.13 (1 H, dd, J = 16, 11 Hz), 6.40 (1H, d, J = 11 Hz), 5.97 (1 H, dd, J = 16, 7 Hz), 3.75 (3 H, s), 3.34 (3 H, s), 2.12 (3 H, s), 1.94 (3 H, s), 1.31 (3 H, s), 1.27 (3 H, s)] was established on comparison of spectroscopic (NMR, IR, UV, MS) and TLC data with those of the authentic substance prepared from natural rifamycin S.[15,16]

The hemithioacetal **15** was further converted to the sulfide **17**[6] [NMR ($CDCl_3$) δ 7.12 (1 H, dd, J = 16, 11 Hz), 6.39 (1 H, d, J = 11 Hz), 5.96 (1 H, dd, J = 16, 7 Hz), 3.74 (3 H, s), 3.32 (3 H, s), 2.50 (2 H, t, J = 7 Hz), 2.11 (3 H, s), 2.01 (3 H, s), 1.94 (3 H, s), 1.23 (6 H, s), 0.99 (3 H, d, J = 7 Hz), 0.95 (3 H, d, J = 7 Hz), 0.87 (3 H, d, J = 7 Hz), 0.85 (3 H, d, J = 7 Hz)]. After the hemithioacetal group was hydrolyzed to the corresponding hemiacetal, the tetrahydropyranyl ring of **15** was opened reductively. Selective acetylation of the C-25 hydroxyl group of **16**[6] was achieved via prior selective silylation of the C-29 primary hydroxyl group with *tert*-butyldiphenylsilyl chloride treatment.[17]

The synthesis of the optically active sulfide **17** from the optically active aldehyde **9**[7] via the route reported is currently in progress in our laboratory. A total synthesis of racemic rifamycin S (**1**) from the aliphatic building block **17** and the aromatic building block **3**[18] will be described in the following communication.

Acknowledgment. Financial assistance from the National Institutes of Health (NS 12108) and National Science Foundation (CHE 78-06296) is gratefully acknowledged. W.R. expresses his gratitude to the Swiss National Science Foundation for a postdoctoral research fellowship, and H.I. expresses his gratitude to the Yamada Science Foundation for the support of travel expenses from Japan to the U.S.

Supplementary Material Available: NMR spectra of new compounds described in this paper (20 pages). Ordering information is given on any current masthead page.

(15) The authentic substance was prepared from a degradation product of rifamycins, described by M. Kinoshita, K. Tatsuta, and M. Nakata (*J. Antibiot.* **1978**, *31*, 630), in two steps; i.e., compound **4** in the paper quoted was treated with $MeSH/ZnCl_2/CH_2Cl_2/0$ °C and then with 2,2-dimethoxypropane/acetone/CSA/room temperature.

(16) 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**.

(17) The alcohol **16** was successfully converted to the aldehyde **2**[6] [NMR ($CDCl_3$) δ 9.82 (1 H, t, J = 2 Hz), 7.11 (1 H, dd, J = 15, 11 Hz), 6.38 (1 H, d, J = 11 Hz), 5.94 (1 H, dd, J = 15, 7 Hz), 3.75 (3 H, s), 3.29 (3 H, s), 2.02 (3 H, s), 1.94 (3 H, s), 1.23 (6 H, s)] in excellent yield in four steps (i.e., steps 1 through 3 are the same as those under (h) in Scheme II; step 4: $Me_2SO/(COCl)_2/CH_2Cl_2/-60$ °C, and then Et_3N[20]). In spite of extensive degradation studies by many groups, the aldehyde **2** had never been obtained from naturally occurring rifamycins. A practical, highly reproducible method to prepare the aldehyde **2** in 30–35% overall yield from rifamycin S in three steps [i.e., (1) 2,2-dimethoxypropane/acetone/CSA/room temperature; (2) NaOH/MeOH/room temperature; (3) MCPBA/THF/5% aqueous $NaHCO_3$/0 °C, followed by treatment with Et_2O/aqueous Na_2SO_3/5% aqueous $NaHCO_3$/room temperature] was developed in our laboratory. The authentic aldehyde **2** was found identical with the synthetic substance on comparison of spectroscopic and TLC data. The aldehyde **2**, thus prepared, was converted to the sulfide **17** in three steps (i.e., (1) $NaBH_4$/MeOH/0 °C; (2) MsCl/Et_3N/CH_2Cl_2/0 °C; (3) MeSNa/THF/room temperature) which was found identical with the totally synthetic substance on comparison of spectroscopic and TLC data.

(18) A synthesis of the aromatic building block **3** has recently been completed in our laboratory; a paper has been submitted to *Tetrahedron Lett.*

(19) Uchida, K.; Uchimoto, K.; Nozaki, H. *J. Org. Chem.* **1976**, *41*, 2215.

(20) Mancuso, A. J.; Juang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(21) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 398.

(22) Corey, E. J.; Gilman, N. W.; Gariem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.

(23) A Guggenheim fellow (1980–81).

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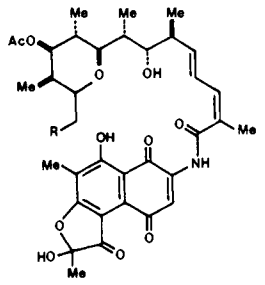
Total Synthesis of Rifamycins. 2. Total Synthesis of Racemic Rifamycin S

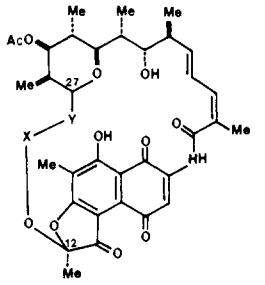
Sir:

Having the totally synthetic aliphatic building block for rifamycin in hand,[1] we have now turned our attention to methods to effect the ansa-ring construction. We first investigated the lactam-ring formation by using the amino acid **2**[2] [NMR ($CDCl_3$) δ 3.04 (3 H, s), 2.22 (3 H, s), 1.97 (6 H, s), 1.70 (3 H, s), 1.21 (6 H, s)], prepared from natural rifamycin S (**1**).[3] The desired lactam bond was cleanly formed by the methods summarized in Scheme I. Reduction of the naphthoquinone moiety was necessary to increase the nucleophilicity of the C-2[4] amino group.[5] 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.[6]

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 **3**[2] and the thioacetal **4**,[2] prepared from rifamycin S (**1**).[7] The expected ansa



3, R = $CH(OMe)_2$
4, R = $CH(SMe)_2$



5, X-Y = -CH=CH- (*trans*)
6, X-Y = $-CH(OH)CH_2-$

product **5** from these compounds is known to be a degradation product of formic acid treatment of rifamycin S.[8] Numerous attempts were uniformly fruitless, but the following observations are worth mentioning. On acid treatment (CSA/benzene/reflux), the acetal **3** 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 appears at 0.35 ppm. Based on the NMR spectrum,[9] one of the most likely structures for the new product seemed to be the ansa hemiacetal **6**, but all efforts to convert it to **5** were unsuccessful. Under these circumstances, the approach involving the *intermolecular* enol ether formation was studied.[10]

(1) Nagaoka, H.; Rutsch, W.; Schmid, G.; Iio, H.; Johnson, M. R.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, preceding paper in this issue.

(2) Satisfactory spectroscopic data (NMR, MS, IR, UV) were obtained for this substance.

(3) We are indebted to Drs. Bickel and Scartazzini, CIBA-GEIGY, Basel, for a generous gift of rifamycin S and a sample of the naphthoquinone **7**.

(4) The numbering corresponds to that of rifamycin S—see structure **1** in the preceding paper.

(5) This type of chemistry was discussed in relation to the mitomycin synthesis. See: Kishi, Y. *J. Nat. Prod.* **1979**, *42*, 549.

(6) Recently, Corey and Clark reported results almost identical with method C: Corey, E. J.; Clark, D. A. *Tetrahedron Lett.* **1980**, 2045.

(7) The acetal **3** was synthesized from rifamycin S by HCl–MeOH treatment. The thioacetal **4** was synthesized from rifamycin S by BF_3Et_2O–MeSH treatment.

(8) Kump, W.; Bickel, H. *Helv. Chim. Acta* **1973**, *56*, 2323.

(9) It is known that rifamycins and their derivatives with the ansa bridge give a methyl group doublet at unusually high magnetic field. See: Prelog, V. *Pure Appl. Chem.* **1963**, *7*, 551. Oppolzer, W.; Prelog, V. *Helv. Chim. Acta* **1973**, *56*, 2287.

(10) A possible alternative structure for this product, i.e., the hemiketal involving the C-11 ketonic and the C-29 hydroxyl groups in **6**, could not be excluded. After having recognized dramatic difference in chemical behavior between compounds like **9** and **7**, we attempted the intramolecular enol ether formation on compounds with the same naphthalene moiety as **9** without fruitful results.

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