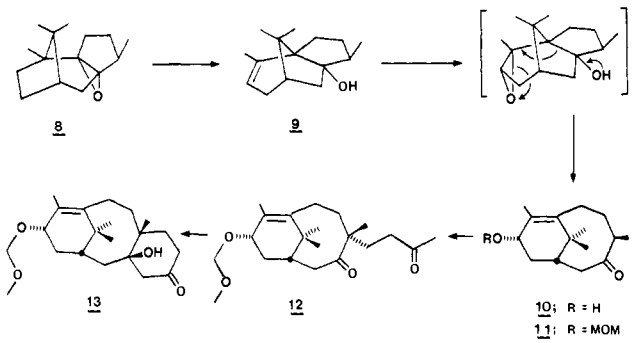
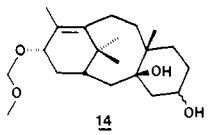
Treatment of **12** with KO-*t*-Bu in either *tert*-butyl alcohol or benzene at reflux resulted in retro Michael reaction to produce a mixture of **11** and its C8 epimer.[13] Cyclization of **12** to **13**[8]



could be carried out using a magnesium counterion: treatment of **12** with either BMDA[12] or bromomagnesium isopropylcyclohexylamide (BMICA)[15] (THF, -78 °C) gave **13** in 90% yield.[6] We have found **13** to be of modest stability, easily undergoing retroaldolization to **12** under mildly acidic or basic conditions.

To circumvent this problem, diketone **12** was treated with BMDA in THF at -78 °C for 30 min. Addition of excess Red-Al directly to the mixture at -78 °C afforded diol **14**[8] in high yield.



This provides a stable taxane derivative which can be utilized for further study.[16,17]

Formation of ketol **13**, embodying all of the skeletal features of the taxane diterpenes, *completes the first synthesis of this ring system. This synthesis requires five chemical steps* from readily available, optically active starting material **8** *and proceeds in 53% overall yield.*

The simplicity and efficiency of this process serve to underscore the viability of our fragmentation strategy for taxane synthesis. Having completed construction of the taxane skeleton, we have now turned our attention to modification of the route outlined here to allow for introduction of oxygen functionality at C9 and C10. Realization of this modification should make possible a simple and direct synthesis of taxusin (**4**). The results of this endeavor will be reported in due course.

Acknowledgment. We are particularly grateful to Robert Molino, Synfleur, Inc., for a generous gift of patchouli oil which enabled us to embark on this investigation. We also thank Dr. William Schrieber, International Flavors and Fragrances, Inc., who brought to our attention the fact that Patchino is an IFF product and later provided a generous donation of this substance. We appreciate the help of Professor Koji Nakanishi and John Termini, Columbia University, in the detailed ^{1}H NMR analysis (250 mHz) of hydroxy ketone **10**. Professor Harry C. Dorn provided valuable assistance in the ^{13}C NMR and ^{1}H NMR analysis of compounds **9-13**. Finally, we acknowledge financial support of this program by the National Cancer Institute.

Registry No. 8, 38337-32-5; **9**, 56143-63-6; **10**, 91606-42-7; **11**, 91606-43-8; **12**, 91606-44-9; **13**, 91606-45-0; **14**, 91606-46-1; trimethylsilyl methyl vinyl ketone, 43209-86-5.

(15) Prepared by treatment of isopropylcyclohexylamine with methylmagnesium bromide in THF at 25 °C for 24 h.

(16) This operation was carried out in response to a suggestion by the editor. We are grateful to Professor Meyers for providing the impetus for this finding.

(17) We thank Professor W. C. Still, in whose laboratory the **12** → **14** conversion was accomplished, for his hospitality and generosity. Although these are many potential solutions to this problem, we thank Professor P. L. Stotter for suggesting the use of Red-Al in this context.

Proton-Carbon NOE Difference Spectroscopy Studies of Carbon Microenvironments, Internuclear Distances, and Hydrogen Bonding in Rifamycin S

Neri Niccolai,[†] Claudio Rossi,[†] Vittorio Brizzi,[‡] and William A. Gibbons*[§]

Institute of General Chemistry and Institute of Pharmaceutical Chemistry University of Siena, 53100 Siena, Italy Department of Pharmaceutical Chemistry School of Pharmacy, University of London London, England WC1N 1AX

Received April 3, 1984

Proton-proton distance measurement[1] by (^{1}H:^{1}H) difference spectroscopy[2] and proton relaxation[3,4] are now well-established approaches for the study of conformation and dynamics of natural products[5] and biopolymers.[6] An alternative complementary approach was recently demonstrated on model compounds using (^{1}H:^{13}C) NOE difference spectroscopy.[7] This latter approach can (i) simultaneously delineate the carbon microenvironment and hence hydrogen bond pairs, (ii) yield proton-carbon distances, and (iii) provide criteria for distinguishing conformations of natural products and biopolymers.

Here we report the actual extension of this approach from model compounds to rifamycin S, a natural product whose ^{1}H and ^{13}C spectral assignments have been reported.[8,9]

The on-resonance carbon-13 spectrum (Figure 1A) obtained by selective saturation of the hydroxyl proton attached to C_8 and the corresponding (^{1}H:^{13}C) NOE difference spectrum (Figure 1C) obtained by subtraction showed four NOE enhancements of carbon resonances: the magnitudes of these NOEs and ^{13}C relaxation rates are given in Table I.

Qualitative Information from (^{1}H:^{13}C) NOEs: Carbon Skeleton Mapping, Sequencing, and Hydrogen Bonds. One large NOE is attributed to the geminal H-O-$^{13}C_8$ dipolar interaction and the two small NOEs at C_7 and C_9 to dihedral H-O-C-^{13}C dipolar interactions. The fourth NOE clearly delineates the acceptor $^{13}C_1$ carbonyl group "hydrogen bonded" to the donor C_8-O-H group. The detection of only four NOEs qualitatively delineates the carbon microenvironment of the proton irradiated, and the relative size of the $^{13}C_7$ and $^{13}C_9$ NOEs is proof that the hydroxyl proton does not significantly populate the conformation cis to the $^{13}C_7$ atoms. This is confirmed by the lack of NOEs to $^{13}C_{14}$. The corrollary to these is that by irradiating individual protons and summing the carbon microenvironments such as that of the C_8-O-H one can map the carbon skeletons of a natural product or biopolymer.

Quantitative Proton-Carbon Distances Measurement. A com-

[†] Institute of General Chemistry.
[‡] Institute of Pharmaceutical Chemistry.
[§] University of London.

(1) Jones, C. R.; Sikakana, C. T.; Hehir, S.; Kuo, M.; Gibbons, W. A. *J. Am. Chem. Soc.* **1978**, *100*, 5960-5961.
(2) Gibbons, W. A.; Crepeaux, D.; Delayre, J.; Dunand, J. J.; Hadfukovic, G.; Wyssbrod, H. R. "Peptides: Chemistry, Structure, Biology"; Walter, R., Meienhofer, J., Eds.; Ann Arbor Science Publications: Ann Arbor, MI, 1975; pp 127-137.
(3) (a) Noggle, J. H.; Schirmer, R. E. "The Nuclear Overhauser Effect"; Academic Press: New York, 1971; Chapter 3, pp 44-76. (b) Campbell, I. D.; Freeman, R. *J. Chem. Phys.* **1973**, *58*, 2666-2667. (c) Hall, L. D.; Hill, D. W. *J. Am. Chem. Soc.* **1976**, *98*, 1269-1270.
(4) Jones, C. R.; Sikakana, C. T.; Kuo, M.; Gibbons, W. A. *Biophys. J.* **1978**, *24*, 815-832.
(5) Niccolai, N.; Schnoes, H. K.; Gibbons, W. A. *J. Am. Chem. Soc.* **1980**, *102*, 1513-1517.
(6) Kuo, M.; Drakenburg, T.; Gibbons, W. A. *J. Am. Chem. Soc.* **1980**, *102*, 520-524.
(7) Ford, J. J.; Gibbons, W. A.; Niccolai, N. *J. Magn. Reson.* **1982**, *47*, 522-527. The theory used in this reference had very limited applicability since it assumed all ^{13}C atoms exhibiting NOEs had similar spin-lattice relaxation rates. The theory used here incorporates the differing carbon relaxation rates.
(8) Oppolzer, W.; Prelog, V. *Helv. Chim. Acta* **1973**, *56*, 2287.
(9) Fuhrer, H. *Helv. Chim. Acta* **1973**, *56*, 2377.
(10) Unpublished results.

0002-7863/84/1506-5732$01.50/0

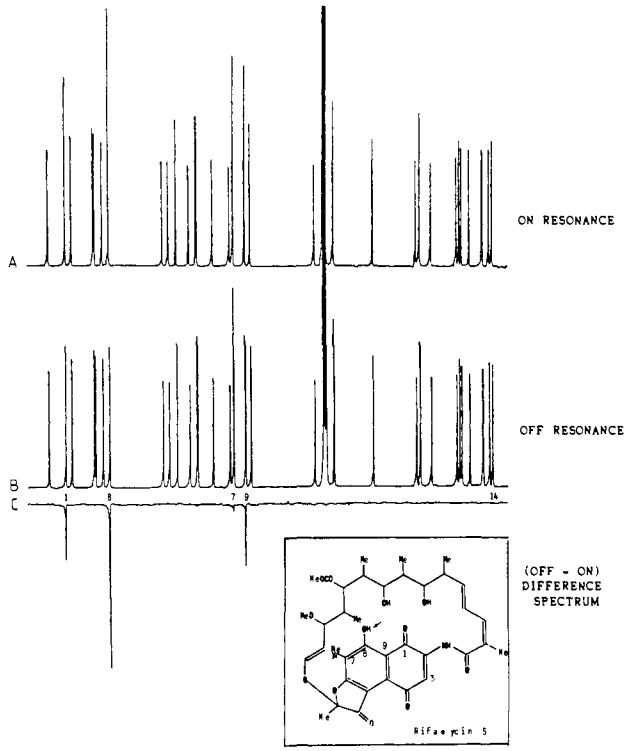


Figure 1. ^{13}C spectra of 0.5 M rifamycin S in $CDCl_3$ recorded on an XL-200 Varian spectrometer at 23 °C: (A) ^{13}C spectrum after irradiation of the phenolic hydroxyl proton, (B) as (A) but with the decoupler set "off" resonance. (C) difference spectrum (A - B). The presaturation selective pulse on the phenolic hydroxyl proton had a 10-s duration and 0.5-W power. During the acquisition of the FIDs the decoupler was on with a power of 4 W in the broad-band mode. The structure of rifamycin S is inset. Only those carbon atoms relevant to the discussion are numbered.

Table I

C_n	δ^a	$NOE_{C_n}(H_8)$	R_{C_n},[b] s^{-1}	r_o-$(H-C_n)$[c]	r_A-(H_8-C_n)[d]	r_B-(H_8-C_n)[e]
C_1	184.57	0.35	0.35	2.38A	2.27	2.30
C_8	166.59	0.89	0.17	2.02A		2.05
C_7	114.31	0.05	0.27	3.26A	3.01	3.05
C_9	110.51	0.34	0.23	2.54A	2.45	2.5

[a] ppm from external Me_4Si. [b] ^{13}C spin-lattice relaxation rates obtained by using the inversion recovery method. [c] Proton-carbon internuclear distances calculated by computer modeling. [d] Proton-carbon internuclear distances calculated by using method A and $r(C_8-H_8)$ as the calibration. [e] Proton-carbon internuclear distances calculated using method B and $\tau_c = 1.7 \times 10^{-10}$ s^{-1}. This value was evaluated from the dipolar contribution of the protonated C_3 relaxation rate ($R_{C_3} = 3.9$ s^{-1}).

bination of NOE and ^{13}C relaxation rate measurements yielded information on single proton-carbon distances since

$$NOE_{C_m}(H_n)R_{C_m} = (\gamma_H/\gamma_C)/\delta_{mn} \quad (1)$$

The internuclear distance (r_{m-n}) between the carbon atom (C_m) and the H_n proton can be obtained by two independent methods.

Method A: When the saturation of H_n gives Overhauser effects on two or more carbon resonances, internuclear distances can be calculated from the following type of relationship:

$$\frac{NOE_{C_1}(H_n)R_{C_1}}{NOE_{C_2}(H_n)R_{C_2}} = \frac{r_{2-n}^6}{r_{1-n}^6} \quad (2)$$

In order to evaluate r's from eq 2, a knowledge of correlation times is not required, but one of the two distances has to be used as a calibration one.

Method B: If both the correlation time and the cross-relaxation term are known, an absolute determination of r_{mn} is possible with use of eq 3.

$$r_{m-n}^6 = \frac{h^2\gamma_H{}^3\gamma_C}{10NOE_{C_m}(H_n)R_{C_m}}\left[\frac{6\tau_c}{1+(\omega_H+\omega_C)^2\tau_c^2} - \frac{\tau_c}{1+(\omega_H-\omega_C)^2\tau_c^2}\right] \quad (3)$$

The use of either of the methods depends on the particular system being investigated, but it seems reasonable that, as in the present work, they can be used simultaneously, thus allowing a double check on calculated r values and hence the assumptions behind the data in Table I.

Registry No. Rifamycin S, 13553-79-2.

Origin of the Rate Acceleration in the Ireland-Claisen Rearrangement

Joseph J. Gajewski* and Jahangir Emrani

Department of Chemistry, Indiana University
Bloomington, Indiana 47405
Received May 21, 1984

The synthetically useful,[1] mechanistically intriguing[2] aliphatic Claisen rearrangement (thermal [3,3]-sigmatropic shift of allyl vinyl ethers to γ,δ-unsaturated carbonyl compounds) is a concerted reaction which proceeds via a transition state that is chairlike, as revealed from stereochemical studies,[3] that more resembles reactant than product, and that resembles an oxaallyl radical-allyl radical pair than a 2-oxacyclohexane-1,4-diyl, as revealed from secondary deuterium kinetic isotope effects (2° DKIEs).[4]

Trimethylsiloxy substitution at C-2 of the parent ether lowers the activation free energy by roughly 9 kcal/mol relative to that of allyl vinyl ether itself.[5] Despite the qualitative rationalization by Carpenter,[6] the magnitude of the effect is not well understood. Significantly, the rate-accelerating effect is not observed in the 3,3-rearrangement of 2-(trimethylsiloxy)-3-methyl-1,5-hexadiene, which requires heating to 210 °C to achieve a 2-h half-life,[7] so the effect of Me_3SiO substitution is not universal. The mechanistic question therefore is which of the two "perpendicular" alternatives,[8] 2-oxacyclohexane-1,4-diyl or oxaallyl-allyl radical pair, is stabilized by 2-Me_3SiO in the aliphatic Claisen rearrangement.

Table I records the DKIEs for the 3,3-shift of 2-(trimethylsiloxy)-3-oxa-1,5-hexadiene obtained from the kinetics of rearrangement in carbon tetrachloride of the vacuum-distilled ketene acetals. The reaction rates are independent of solvent polarity ($k(CH_3CN) = 1.33k(CCl_4)$); thus, mechanistic interpretation must focus on a neutral transition state and not on the effect of solvents including that of THF, the usual solvent for the reaction.

The KIEs provide a measure of the progress along the two structural coordinates, O,C-4 bond breaking and C-1,C-6 bond making, assuming the linear free energy relationship, KIE = EIE^d, where the EIEs are the H/D fractionation factors between O—$CH_2(D_2)$—C and C=$CH_2(D_2)$ and C=$CH_2(D_2)$ and C—C-$H_2(D_2)$—C, respectively.[9,10] This assumes that the factors af-

(1) (a) Claisen, L. *Ber.* **1912**, *45*, 3157. (b) Claisen, L.; Tietze, E. *Ibid.* **1925**, *58*, 275. (c) Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 1. (d) Bennett, G. B. *Synthesis* **1977**, 589. (e) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227.
(2) (a) Hurd, C. D.; Pollack, M. A. *J. Org. Chem.* **1939**, *3*, 550. (b) Cope, A. C.; Hardy, E. M. *J. Am. Chem. Soc.* **1940**, *62*, 441. (c) Gajewski, J. J. *Acc. Chem. Res.* **1980**, *13*, 142.
(3) Vitorelli, v. P.; Winkler, T.; Hansen, H.-J., Schmid, H. *Helv. Chim. Acta* **1968**, *51*, 1457.
(4) Gajewski, J. J.; Conrad, N. D. *J. Am. Chem. Soc.* **1979**, *101*, 6693.
(5) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.
(6) Carpenter, B. K.; Burrows, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 6984.
(7) The enolate of 3-methyl-5-hexen-2-one was treated with Me_3SiCl and pyrolyzed in hexachlorobutadiene at 211.4 °C.; the first-order rate constant was 4.94 (0.02) × 10^{-4} s.
(8) Thornton, E. R. *J. Am. Chem. Soc.* **1967**, *89*, 2915.
(9) Hartshorn, S. R.; Shiner, V. J. *J. Am. Chem. Soc.* **1972**, *94*, 9002.
(10) Conrad, N. D. Ph.D. Thesis, Indiana University, Bloomington, 1979.

0002-7863/84/1506-5733$01.50/0