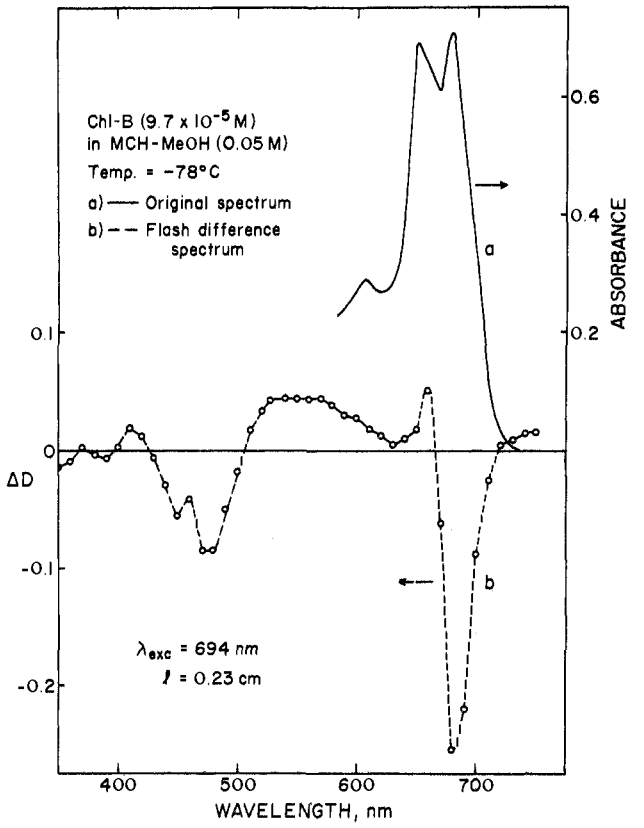
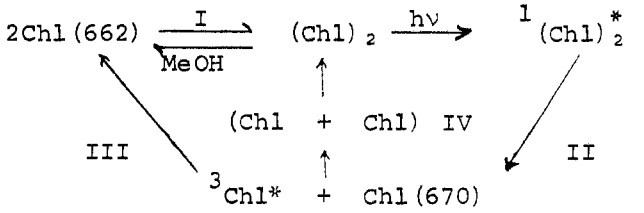


Figure 3. Absorption spectrum (curve a) and flash difference spectrum (curve b) immediately after laser flash (694.3 nm) excitation of deoxygenated chlorophyll *b* (9.5×10^{-5} M) in methylcyclohexane–methanol (0.05 M) at −78 °C; l = 0.23 cm. Arrows indicate absorbance scales for curves a and b.

Scheme I



ferent mode of solvent coordination. The disaggregation demonstrated in Figure 1 accompanies a decrease in acidity of Mg^{2+} in the excited state.[1]

Figure 3 shows similar results with Chl *b*. In methylcyclohexane–methanol (0.05 M) the room temperature monomer band at 644 shifts to 652 nm at −78 °C and is partially converted to dimer at 680 nm. Flashing (absorption in the dimer tail at 694 nm) selectively bleaches the 680-nm band, giving a broad triplet absorption[9] and red-shifted ground-state peak at 660 nm.

The transient absorption at 520 (Chl *a*, Figures 1 and 2) decays with mixed kinetics, as expected for a triplet.[9] However, the recovery at 695 nm is faster (Figure 2) and is close to first order throughout. In a typical experiment at ~0.01 M methanol, initial half-lives were 190 μs at 520 nm and 85 μs at 695 nm. In addition, at low methanol concentrations, a slight bleaching *after* the flash, followed by recovery, is seen around 660 nm (Figure 2). These observations fit Scheme I. The rapid recovery at 695 nm and slight reversible loss at 660 nm is interpreted as initial relaxation, via reaction I, of the perturbed monomer–dimer equilibrium. This will approach first order for small displacements from equilibrium, although the changes in Figure 1 are appreciable.

Attempts to isolate reaction I were made by using reversible quenchers to shorten the triplet lifetime. However, dimer recovery at 695 nm kept pace with triplet decay even down to lifetimes of 10 μs (with chloranil) or 1 μs (in presence of oxygen) and at methanol concentrations of ~0.01 M. This indicates another pathway for dimerization via geminate monomers (reaction IV), which appear to diffuse apart relatively slowly forming a Chl population distinct from the 662-nm species.

These experiments show that photodisaggregation of the 700-nm dimer in fluid hydrocarbon solvent occurs in <50 ns after excitation both at room temperature and −78 °C. However, reaction II is slow enough to permit observation of dimer fluorescence[6] even at room temperature.[2] Whether these results apply to P-700 is, of course, an open question and depends on both the validity of the model[2,3] and speed of P-700 oxidation in vivo.[10] Until this is resolved, the possibility of complications arising from dimer cleavage and shifted monomer bands should be recognized in interpreting light–dark difference spectra of algae or chloroplasts, particularly those which show positive transients or complex spectral shifts in the red, accompanying bleaching of P-700.[11] A blocked electron-transport path from P-700 may also permit unfolding to the triplet,[12] offering a possible means of short-term energy storage. Photodisaggregation may function in mediating the response of chloroplast membranes to light.

The photodissociation of pheophytin *a* aggregates has been described by Sagun and Dhzagarov.[13]

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Total Synthesis of (R_C)-Sparsomycin[1]

Sir:

Seventeen years have passed since the isolation of sparsomycin (**1**) from *Streptomyces sparsogenes* was reported by Argoudelis and Herr.[2] This compound exhibits anticancer activity[4,5] and is active against various bacteria,[3,4] fungi,[6] and viruses.[7] Wiley and MacKellar, through their structure proof of **1**, demonstrated that the chiral carbon atom has the *S* configuration,[8] but the configuration of the sulfinyl group has not been determined. Several analogues of **1** have been syn-

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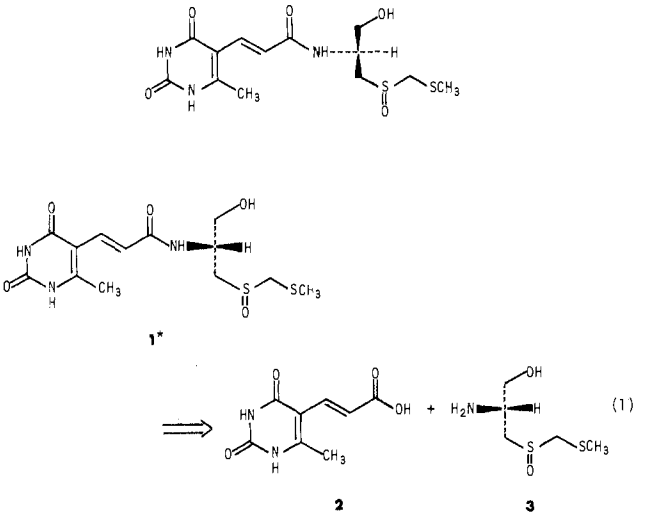


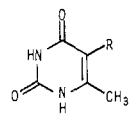
1*

(1)

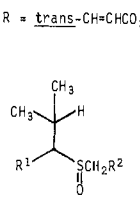
2 3

thesized,[9] but no total synthesis of this system had been performed until recently when first Ottenheijm[10] and now our group successfully developed routes to the R_C enantiomer (**1***) of sparsomycin. In this communication we report our route to this enantiomer.

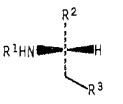
Our basic strategy (eq 1) employs a convergent approach to **1*** in which the carboxylic acid (**2**)[8,9] and a derivative of the amine component (**3**) are synthesized separately followed by amide formation to give the final product. Through a modification of the procedure of Wiley and MacKellar,[8] the acid **2** was prepared from commercially available 6-methyluracil (**4**) by a four-step procedure involving (1) hydroxymethylation (3 equiv of 37% aqueous H_2CO, 2.75 equiv of 1.25 N NaOH, 25 °C, 82%) to give **5**,[11] (2) oxidation ($Ce(NH_4)_2(NO_3)_6$, H_2O, 25 °C, 67%) to produce the aldehyde **6**, (3) Wittig condensation ($Ph_3P{=}CHCO_2Et$, Me_2SO, 25 °C, 76%) to afford the unsaturated ester **7**, and (4) hydrolysis (NaOH, dioxane–CH_3OH–H_2O, 25 °C) followed by acidification (aqueous HCl) to give the desired acid **2** in 96% yield.



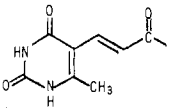
4, R = H
5, R = CH_2OH
6, R = CHO
7, R = trans-CH=$CHCO_2Et$



8, $R^1 = R^2 = H$
9, $R^1 = H$, $R^2 = SCH_3$
10, $R^1 = SCH_3$, $R^2 = H$



11, $R^1 = H$, $R^2 = CO_2H$, $R^3 = SH$
12, $R^1 = H$, $R^2 = CO_2H$, $R^3 = SCH_3$
13, $R^1 = H$, $R^2 = CH_2OH$, $R^3 = SCH_3$
14, $R^1 = H$, $R^2 = CH_2OH$, $R^3 = S(O)CH_3$
15, $R^1 = PhCH_2OCO$, $R^2 = CH_2OH$, $R^3 = SCH_3$
16, $R^1 = PhCH_2OCO$, $R^2 = CH_2OH$, $R^3 = S(O)CH_3$
17, $R^1 = PhCH_2OCO$, $R^2 = CH_2OTHP$, $R^3 = S(O)CH_3$
18, $R^1 = H$, $R^2 = CH_2OTHP$, $R^3 = S(O)CH_3$
19, $R^1 = H$, $R^2 = CH_2OTHP$, $R^3 = S(O)CH_2SCH_3$



20, R^1 =
$R^2 = CH_2OTHP$
$R^3 = S(O)CH_2SCH_3$

The synthesis of the amine component **3** was much more challenging, primarily because of the unusual dithioacetal *S*-oxide moiety for which we needed to develop new methodology. Whereas Ottenheijm employed the reaction of an α-chlorosulfoxide with sodium methylmercaptide,[10] we chose to use a quite different approach. Realizing that the sulfenylation of ketone enolates and related species has become a common transformation,[12] we wished to explore the extension of this reaction to the sulfenylation of α-sulfinyl carbanions; Trost had earlier reported the sulfenylation of allylic sulfoxides.[13] Because of its close stereochemical relationship to precursors of **3** (vide infra), methyl isobutyl sulfoxide (**8**) was chosen as a model compound. Treatment of **8** with 2 equiv of lithium diisopropylamide (LDA) in THF at −78 °C, followed by the addition of dimethyl disulfide (1 equiv) and warming to 0 °C, gives the sulfenylation product **9** in 65% yield (not optimized); none of the regioisomeric product **10** is detected. Next, a very short route to **3** was explored which has the advantage of avoiding the use of any protecting groups. As a prospective substrate for the sulfenylation reaction, the sulfoxide **14** was prepared from (*R*)-L-cysteine (**11**) by first methylation (NaOEt, CH_3I, C_2H_5OH, 25 °C, 88%) to give *S*-methylcysteine (**12**),[14] reduction ($LiAlH_4$, ether, reflux, 70%) to produce *S*-methylcysteinol (**13**), and finally oxidation (30% aqueous H_2O_2, CH_3OH, 25 °C, 100%) to afford **14**. Unfortunately, **14** is not sufficiently soluble in the ether-type solvents that are normally employed for generation of carbanions, and therefore the direct sulfenylation of **14** fails. Consequently, the need arose to prepare a derivative of **14** having more satisfactory solubility behavior. An important finding by Ottenheijm was that the tetrahydropyranyl (THP) protecting group may be removed from the masked hydroxyl group under very mildly acidic conditions[10] in the presence of the normally rather acid-labile dithioacetal *S*-oxide moiety.[15] Therefore, we chose to prepare the THP derivative **18** by the following sequence based upon Ottenheijm's work:[10] (1) reaction of **13** with benzyl chloroformate (NaOH, H_2O, 0–10 °C, 88%)[16] to give the *N*-benzyloxycarbonyl derivative **15**, (2) oxidation ($NaIO_4$, H_2O, CH_3CN, 0–25 °C, 90%)[17] to produce the sulfoxide **16** as an ~1:1 mixture (^1H NMR integration) of diastereomers, (3) reaction of **16** with 10 equiv of dihydropyran (0.01 equiv of p-$CH_3C_6H_4SO_3H$, THF, 0–25 °C, 93%) to afford the THP derivative **17**, and (4) reductive cleavage (2 mol equiv of Na, NH_3, reflux, 83%)[18] to give **18**[10] which, fortunately, is quite soluble in typical organic solvents. Under the same conditions employed for the model compound **8**, **18** undergoes sulfenylation to afford **19** in 70% yield.

At this point, the diastereomeric sulfoxides may be separated by LC (Waters Associates dual-pump flow-gradient system using CH_2Cl_2 and CH_3OH and a 30-cm × 3.9-mm μ-Porasil column).[19] A principal difference in the 80-MHz ^1H NMR spectra of these diastereomers is that the S(O)CH_2S-protons appear as two lines (AB doublet) with a separation of 2 Hz for one diastereomer and 9 Hz for the other. As reported by Ottenheijm,[10] the former diastereomer undergoes amide formation with the acid component **2** (DCC, 1-hydroxybenzotriazole,[20] DMF, 0–25 °C, 51%) to afford **20**. Hydrolysis of this THP derivative in a 100:1 (v:v) mixture of 95% ethanol and 1 N hydrochloric acid at reflux for 15 min affords the R_C enantiomer (**1***) of sparsomycin in a yield of 80%. This product is identical with an authentic sample of sparsomycin according to IR, ^1H NMR, and TLC, but, as expected, it possesses the opposite sign of optical rotation.

Further work is in progress to determine the configuration of the sulfinyl group of **1**, to synthesize the naturally occurring enantiomer of **1** from D-cysteine,[21] to prepare a series of analogues, and to investigate the scope of the sulfenylation reaction.

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Acid-Catalyzed Hydration of Di-*tert*-butylketene

Sir:

We report new evidence relevant to the mechanism of ketene hydration. Specifically di-*tert*-butylketene (**1**) undergoes hydration to the acid **2** in 50% water–acetonitrile with general acid catalysis and a solvent isotope effect k_{H^+}/k_{D^+} of 2.8. These facts indicate that the reaction occurs by rate-limiting proton transfer.

$$\underset{\mathbf{1}}{t\text{-}Bu_2C{=}C{=}O} + H_2O \xrightarrow{H^+} \underset{\mathbf{2}}{t\text{-}Bu_2CHCO_2H}$$

The reaction mechanisms of ketenes[1] are of interest because of their widespread use in acylations,[1] cycloadditions,[2] and other synthetic procedures.[3] Ketenes are also implicated as intermediates in reactions of various acyl derivatives with nucleophiles,[4] including reactions of biologically important molecules.[4c]

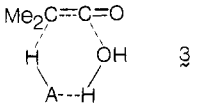
There has been intense recent interest in the protonation and hydration of ketenes. Studies on ketene itself include four independent measurements of the gas-phase proton affinity,[5] determination of gas-phase hydration kinetics,[6a] and a molecular orbital study of the site of protonation.[6b] The kinetics of hydration of dimethylketene in solution have been examined,[7] and the hydration of arylketenes in water have been studied.[8]

There was agreement on a value of the proton affinity of ketene of 194 ± 1 kcal/mol,[5] almost identical with that of isobutene (193.5 kcal/mol).[5b] There was some difference of opinion as to the site of protonation (eq 1): two groups favored

$$CH_2{=}C{=}O \xrightleftharpoons{H^+} CH_3\overset{+}{C}{=}O \quad \text{or} \quad CH_2{=}\overset{+}{C}OH \qquad (1)$$

C protonation,[5a,b] another reported that the position of protonation depended on the acidity of the proton donor,[5c] and one group favored O protonation.[5d]

In the studies of dimethylketene hydration in organic media, acid catalysis was observed[7] and a concerted addition of water involving the cyclic transition state **3** was proposed, where H–A represents the catalyzing acid. In the investigation of aryl-



3

ketenes the substrates were generated in situ by photochemical Wolff rearrangement and the rates of hydration were followed by the change in conductivity of the photolyzed solution (eq 2).[8]

$$ArC(=O)CHN_2 \xrightarrow{h\nu} ArCH{=}C{=}O \xrightarrow{H_2O} ArCH_2CO_2H \qquad (2)$$

In the latter study high rates of reaction were reported (first-order rate constants of 4×10^3 and 5×10^4 s^{-1} for *p*-tolyl- and *p*-nitrophenylketenes, respectively).[8] The reactions were reported to be independent of pH in the range 4–10.8, with solvent isotope effects k_{H_2O}/k_{D_2O} = 1.8–2.0, and the rates were correlated with σ_p^n constants with ρ = 1.19.

We have been able to correlate rates of alkene hydrations with considerable success.[9] In view of the interest in ketene hydration, and the indecisive nature of the previous studies of this reaction, further study appeared desirable.

Di-*tert*-butylketene (**1**)[10] offers great advantages for the study of mechanism of ketene hydration, in that it is stable to dimerization and to reaction with air and has both ultraviolet and visible chromophores which permit reliable spectral measurement of its rate of hydration. Rates of hydration of **1** were conveniently observed by monitoring the disappearance of its UV absorption maximum at 227 nm. In solutions of 50% aqueous acetonitrile at 25 °C in HCO_2H–HCO_2Na buffers at ionic strength 0.05 (NaCl) and a pH of 4.09, the rate law $k_{obsd} = k_{H^+}[H^+] + k_{HA}[HCO_2H]$ was closely followed, with k_{H^+} = 4.43 M^{-1} s^{-1} and k_{HA} = 2.38×10^{-2} M^{-1} s^{-1}. These rate constants gave a good fit to other rate data obtained for the pH range 3.67–4.50. At the pH value of 7.7 no reaction was discernible; so k_{H_2O} must be $<10^{-6}$ M^{-1} s^{-1}.

General acid catalysis was also observed at pH 3.30 using a HCl–KH_2PO_4 buffer in the same medium. The fit of the data was not so precise as in formic acid but gave values of k_{H^+} = 3.6 M^{-1} s^{-1} and $k_{HA'}$ = 0.90 M^{-1} s^{-1}.

Acid catalyzed hydration was also observed for H_2SO_4 in the range of 1.7×10^{-3} to 2.9×10^{-4} M H_2SO_4 in 50% water–acetonitrile. The acidity function of this medium has not been determined but k_{H^+} = 3.2 M^{-1} s^{-1} could be estimated,[10] and a solvent isotope effect of k_{H^+}/k_{D^+} = 2.8 at 9.00 $\times 10^{-4}$ M sulfuric acid was found. The observed values of k_{H^+} in the three acid systems are thus in reasonable agreement, with that in the formate buffers being the most reliable.

The observed general acid catalysis and the large solvent isotope effect unequivocally establish that **1** undergoes hydration by rate-limiting protonation. Carbon protonation to give the acylium ion is one likely path (eq 3), but protonation on oxygen (eq 4) is also possible.

$$t\text{-}Bu_2C{=}C{=}O \xrightarrow{H^+} t\text{-}Bu_2\overset{+}{C}HC{=}O \qquad (3)$$

$$t\text{-}Bu_2C{=}C{=}O \xrightarrow{H^+} t\text{-}Bu_2C{=}\overset{+}{C}OH \qquad (4)$$

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