affected by the temperature of ageing (0 and 50 °C) prior to mixing of the two stock solutions. On the other hand, the temperature of ageing after mixing of the two stock solutions influenced the reaction rate. Table II shows the influence of the ageing procedure on the rate constant.[10] k_{obsd} increases from 0.0024 to 0.0091 s^{-1} when the mixed stock solution was kept at 21 °C for 30 min after having been kept at 0 °C. Further ageing at 61 °C (10 min) raised k_{obsd} by a factor of seven, but additional ageing at 0 °C did not change k_{obsd}. Since the hydrolysis starts only when pH of the reaction medium is adjusted to alkaline by buffer, the results of Table II are explained by redistribution of catalyst and substrate molecules among vesicles during ageing at higher temperatures. The ageing at 0 °C does not seem to promote the redistribution. This is consistent with the phase transition temperature of aqueous $2C_{12}N^+2C_1Br^-$ (13 ± 2 °C) as determined by differential scanning calorimetry.[11]

Figure 1 shows the influence of the solvent composition (aqueous ethanol) on k_{obsd}. In series A experiment (intervesicle reaction), k_{obsd} increased with increasing ethanol contents. The intervesicle reaction is facilitated because ethanol loosens the vesicle structure. In the intravesicle reaction where distribution of the reacting species is completely equilibrated (series B), ethanol rather diminishes k_{obsd}. The latter trend is similar to that observed for the CTAB system in the series A experiment.

In conclusion, the rate difference between intervesicle and intravesicle reactions can be made very large by selecting appropriate reactants which tightly bind to vesicles. The conventional micellar system is too soft for this purpose. The present system may find many interesting applications.

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Detection of ^{13}C–^{15}N Coupled Units in Adenine Derived from Doubly Labeled Hydrogen Cyanide or Formamide

Sir:

The formation of the nucleic acid base, adenine, by a simple heating procedure involving formamide and hydrogen cyanide[1] is of interest from the viewpoint of chemical evolution.[2] Although the formation of adenine from hydrogen cyanide has been reported and reaction mechanisms proposed,[3] there has been no direct experimental evidence as to the mechanism. Feeding experiments with doubly enriched precursors have been successfully applied to solve detailed reaction pathways during the biosyntheses of natural products.[4]

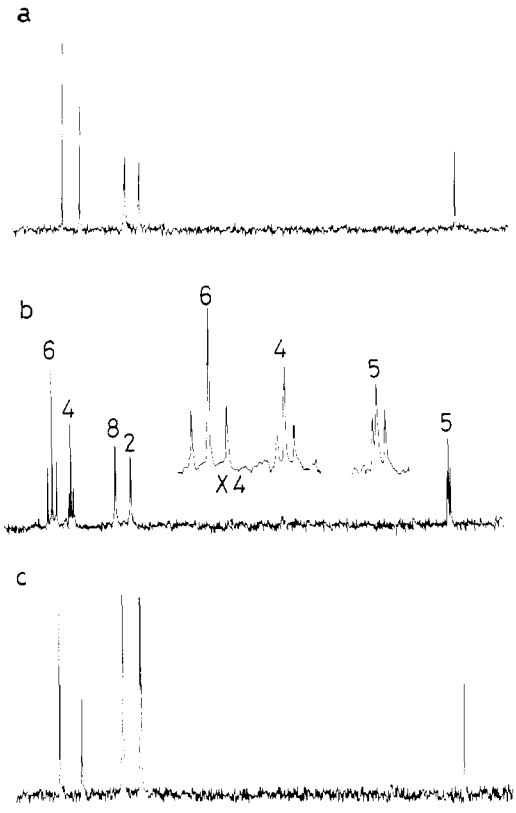

Figure 1. ^{13}C NMR spectra of labeled adenines. Adenine was dissolved in acidified Me_2SO solution (0.5 mL) with 1 drop of concentrated HCl. The spectra were recorded on a JEOL FX-100 NMR spectrometer equipped with a JEOL JEC-980B computer for Fourier transform operation at 25.05 MHz (data points, 4K; spectral width, 1.5 KHz; flip angle, 36°; 3 s between pulses) in a proton-noise decoupled mode: (a) adenine of natural abundance (11 mg), 20 000 pulses; (b) labeled adenine with $H^{13}C^{15}N$ (10.8 mg), 20 000 pulses; (c) labeled adenine with $H^{13}CO^{15}NH_2$ (8.3 mg), 30 000 pulses.

We wish to report the result of ^{13}C NMR experiments on the nucleic acid base, adenine, which was obtained from doubly enriched hydrogen cyanide or formamide.

Doubly enriched potassium cyanide (^{13}C, 90.5%; ^{15}N, 99.2%) was diluted fiftyfold with potassium cyanide of natural abundance (3.75 g) to differentiate newly formed C–N bonds from the labeled C–N bond. Hydrogen cyanide which was generated by acidifying the potassium cyanide with concentrated sulfuric acid was introduced into formamide (10 g) under ice cooling. The mixture was sealed and heated at 160 °C for 5 h. Adenine was extracted with and recrystallized from hot water.[1] ^{13}C NMR spectra of adenine were obtained in acidified Me_2SO-d_6 to improve the peak heights of nonprotonated carbons (C_4, C_5, and C_6.)[5] The chemical shifts of the five carbons of adenine in acidified Me_2SO solution (Figure 1a) were different from those in neutral Me_2SO solution (in parentheses) as follows:[6] C_2, 141.8 (152.2); C_4, 147.4 (151.1); C_5, 112.4 (117.3); C_6, 149.2 (155.1); and C_8, 143.2 (139.2) (parts per million downfield with respect to Me_4Si). Three ^{13}C–^{15}N coupled units were observed in the ^{13}C NMR spectrum of the product, adenine, derived from doubly labeled hydrogen cyanide (Figure 1b). Those are C_4 (J = 9.5 Hz), C_5 (J = 7.3 Hz), and C_6 (J = 20.5 Hz) and are shifted slightly to higher field (0.4, 1.5, and <0.1 Hz, respectively) than those of noncoupled peaks due to ^{15}N isotope shift.

On the other hand, when adenine was prepared by heating doubly enriched formamide (^{13}C, 91%; ^{15}N, 96%, 77 mg was

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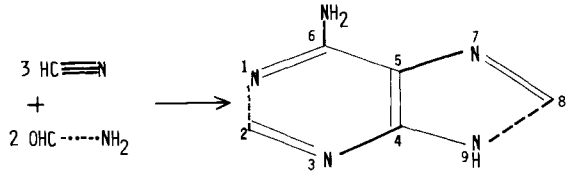
diluted 32-fold with formamide of natural abundance) and hydrogen cyanide of natural abundance (generated from 4.7 g of KCN) at 160 °C for 12 h, the two peaks, C_2 and C_8, were observed as enhanced peaks without $^{13}C-^{15}N$ coupling (Figure 1c). The presence of enhanced peaks instead of $^{13}C-^{15}N$ coupled peaks can be explained by the thermal fission and reformation of the C–N bond in formamide during the prolonged heating procedure.[7]

These results indicated that the adenine ring was constituted from two molecules of formamide and three molecules of hydrogen cyanide. Among the C–N units in adenine, C_5-N_7, C_6-NH_2, and probably C_4-N_3 originate from hydrogen cyanide while C_2-N_1 and C_8-N_9 are from formamide as shown below.



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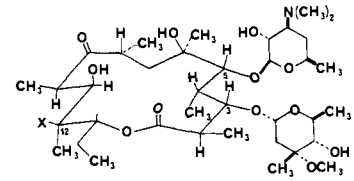
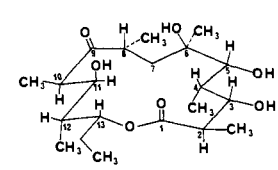
Total Synthesis of Erythromycins.[1] 3. Stereoselective Routes to Intermediates Corresponding to C(1) to C(9) and C(10) to C(13) Fragments of Erythronolide B

Sir:

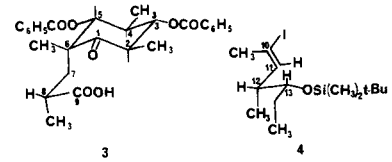
The erythromycins, produced by the fungus *Streptomyces erythreus*, constitute one of the most important of all known families of antibiotics. Their application in medicine over the past two decades has been both widespread and effective and has resulted in the saving of countless human lives. The two principal erythromycins, erythromycins A (**1a**) and B (**1b**) are closely related, differing only with respect to hydroxylation at C-12.[2] Present evidence indicates that the various erythromycins (including A and B) are produced in nature from the precursor erythronolide B (**2**) (the aglycone of erythromycin B) by a sequence involving glycosylation at the C(3) and C(5) hydroxyls.[3] The erythromycins and erythronolides stand in a quite unique position among natural products which have not been synthesized, because of their importance and their complexity.[4] In this communication we report the stereoselective synthesis of two key intermediates for erythromycin synthesis, one suitable for use as synthon for the C(1) to C(9) segment of erythronolides A and B (substance **3**) (after insertion of oxygen between the ring members labeled 1 and 6 in **3**), and the other (**4**) corresponding to the C(10) to C(13) section of erythronolide B. The publication immediately following details the use of these two intermediates in the first total synthesis of erythronolide B (**2**).[5]



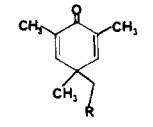
1a X = OH
1b X = H



2



3 **4**



5 R = CH=CH$_2$
6 R = CH$_2$CH$_2$OH
7 R = CH$_2$COOH

The overall plan was derived using the strategy of antithetic analysis and depended on the tactic of generating the macrocyclic unit by lactonization. In connection with the latter requirement, studies were initiated in these laboratories several years ago which were successful both in providing a new and effective method for the conversion of hydroxy acids to macrocyclic lactones[6] and for formation of the rigid[7] 14-membered ring of erythronolide B itself.[1a] Another major strategic element in the present approach is the use of 6-membered cyclic intermediates to establish and confirm the stereorelationships required for the C(1) to C(9) segment.

The synthesis of **3** was initiated from the dienone **5** (available[8] on large scale from 2,4,6-trimethylphenol and allyl bromide in 60% overall yield) by hydroboration (1.5 equiv of diborane in tetrahydrofuran (THF) at 0–10 °C) to the hydroxy dienone **6**[9] (85% yield) and subsequent oxidation at 0 to −10 °C with a small excess of Jones chromic acid reagent for ~30 min to form the dienone acid **7**, mp 98 °C, in 85% yield. Reaction of the potassium salt of **7** in water with a small excess of bromine–potassium bromide solution produced a precipitate of crystalline bromo lactone **8**, mp 126–128 °C, in 96% yield. The sequence **5** → **6** → **7** → **8** can be carried out easily in the laboratory on a 1-mol scale, and the intermediates **6** and **7** need not be purified. Treatment of the bromo lactone **8** in THF with 1.5 equiv of aqueous potassium hydroxide at 0 to 20 °C for ~2 h and isolation of acidic product provided the epoxy keto acid (±)-**9**, mp 88 °C, in 98% yield, the resolution of which is described below. The synthetic route as applied to racemic intermediates continues with bromolactonization of the potassium salt of **9** in aqueous solution to give the epoxy bromo keto lactone (±)-**10**, mp 108–109 °C, in 91% yield. Replacement of bromine in **10** by hydrogen was carried out by simultaneous addition of tri-*n*-butyltin hydride (1.25 equiv) in benzene and azobisisobutyronitrile (~1 mol %) in benzene to a solution of

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