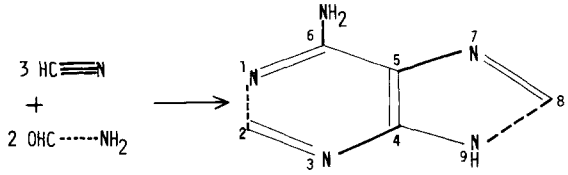
diluted 32-fold with formamide of natural abundance) and hydrogen cyanide of natural abundance (generated from 4.7 g of KCN) at 160 °C for 12 h, the two peaks, C_2 and C_8, were observed as enhanced peaks without ^{13}C–^{15}N coupling (Figure 1c). The presence of enhanced peaks instead of ^{13}C–^{15}N 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.



Acknowledgment. We thank Professor T. Okamoto (University of Tokyo) and Dr. K. Kubota (NIES) for their encouragements during the work.

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Hiroshi Yamada, Masaaki Hirobe
Faculty of Pharmaceutical Sciences
University of Tokyo, Hongo, Bunkyo-ku, Tokyo, Japan

Kimio Higashiyama, Hiroshi Takahashi
Hoshi College of Pharmacy, Ebara 2-4-41
Shinagawa-ku, Tokyo, Japan

Kazuo T. Suzuki*
National Institute for Environmental Studies
P.O. Yatabe, Ibaraki 300-21, Japan

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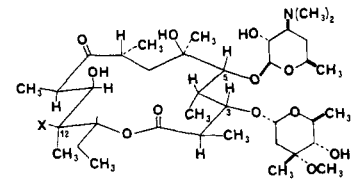
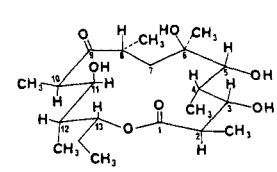
Total Synthesis of Erythromycins.[1] 3. Stereoselective Routes to Intermediates Corresponding to C(1) to C(9) and C(10) to C(13) Fragments of Erythronolide B

Sir:

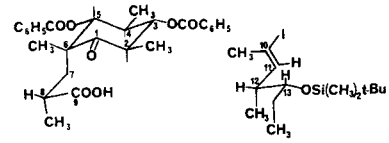
The erythromycins, produced by the fungus *Streptomyces erythreus*, constitute one of the most important of all known families of antibiotics. Their application in medicine over the past two decades has been both widespread and effective and has resulted in the saving of countless human lives. The two principal erythromycins, erythromycins A (**1a**) and B (**1b**) are closely related, differing only with respect to hydroxylation at



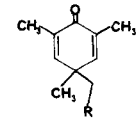
1a X = OH
1b X = H



2



3 **4**



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

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]

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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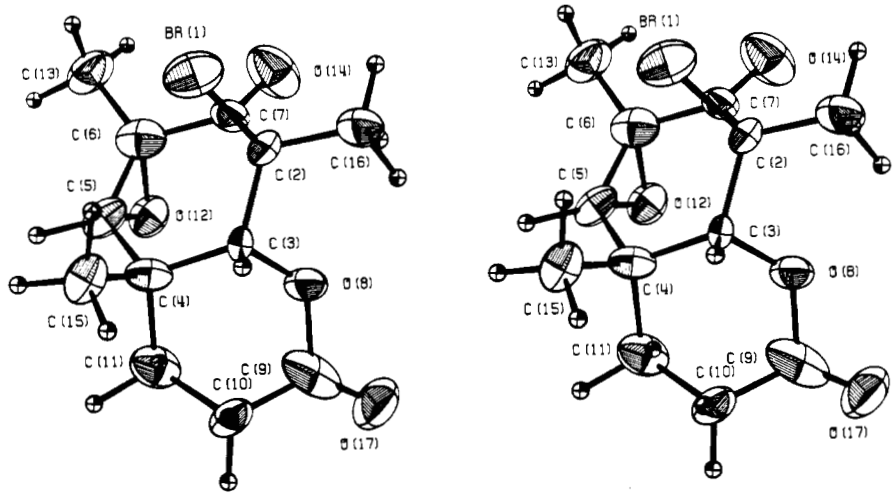
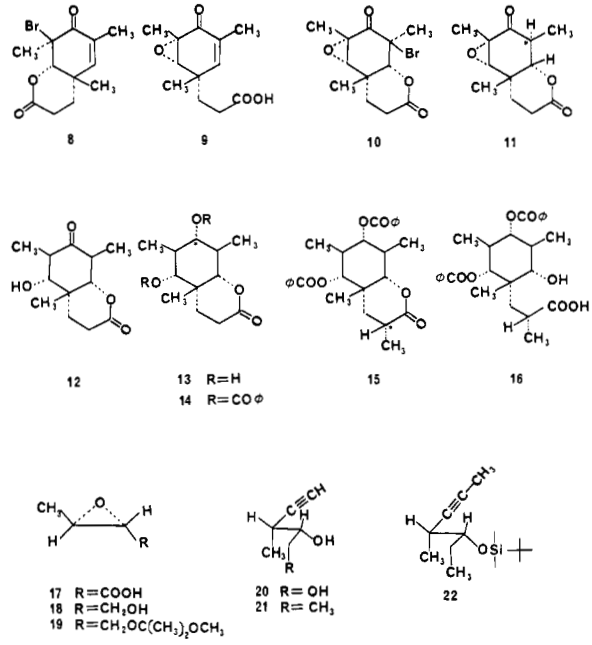


Figure 1. Stereorepresentation of structure and absolute configuration of levorotatory bromo lactone **10** (courtesy of Dr. Jon Bordner[12]).



10 in benzene at 75 °C over 45 min, complete exclusion of air and moisture from all solutions being essential. The product obtained in 93% yield consisted of a mixture of the desired keto lactone **11** (87%)[10] together with 13% of the epimer at C*. Separation was unnecessary since a simple purification was possible at the next stage. Reduction of crude **11** in THF–water with excess aluminum amalgam at 0 to −10 °C for ~4.5 h, isolation of crude product, and recrystallization from ethyl acetate afforded the crystalline hydroxy ketone (±)-**12,** mp 164–166 °C, in 76% yield.[10] Hydrogenation of keto alcohol **12** using neutral Raney nickel[11] in dry dimethoxyethane at −20 °C and 1 atm of H_2 proceeded quantitatively to form the diol **13**[10] together with a small amount (~14%) of the epimer at C*. Although the two epimers could be separated chromatographically and the minor by-product could be recycled to the starting keto alcohol **12,** in practice it was convenient to benzoylate the mixture (4 equiv of benzoyl chloride in pyridine at 20 °C for 8 h) and to purify the resulting product by recrystallization from ether which led to the isolation of pure dibenzoate (±)-**14,** mp 207–208 °C, in 75% overall yield from **12.**

Addition of a solution of the lactone dibenzoate **14** in THF to 1.02 equiv of lithium diisopropylamide in THF at −78 °C over 45 min and treatment of the resulting solution with 10 equiv of methyl iodide and 1.2 equiv of hexamethylphosphoramide (first at −78 °C and then at −45 °C for 40 min) yielded (95%) the methylated lactone **15** (mp 261–262 °C) admixed with minor amounts of the epimer at C* (mp 243–244 °C), which is thermodynamically less stable. The formation of the epimer of **15** fortunately causes no complication in the next step, since both lactone **15** and its epimer are hydrolyzed by aqueous lithium hydroxide to the same hydroxy acid (**16**). Treatment of **16** with carbonyldiimidazole in THF at 25 °C afforded **15** specifically with no trace of the epimer at C*. Oxidation of **16** using Jones reagent at −10 °C afforded in 80% yield the corresponding keto acid (±)-**3,** mp 157 °C.

Resolution of an intermediate for the above synthetic sequence could be accomplished at an early stage and, further, even the antipode corresponding to *ent*-erythronolide B could be used in the synthesis. The epoxy acid (±)-**9** formed a nicely crystalline salt with (±)-1-α-naphthylethylamine which could be purified to a constant rotation of $[\alpha]^{26}_D$ −74° (CH_3OH) by recrystallization from ethanol–water (85:15). The epoxy acid obtained from this salt which had $[\alpha]^{28}_D$ −127° (CH_3OH) was shown to have the absolute configuration shown in **9** by conversion to the bromo lactone **10,** mp 136.5 °C, $[\alpha]^{20}_D$ −25° (CH_3OH), and x-ray crystallographic analysis.[12] The molecular geometry of the bromo lactone **10** is unusual and involves two skew ring conformations as shown in Figure 1.[12] The optically active lactone **12,** $[\alpha]^{27}_D$ +15° (CH_3OH), mp 151–153 °C, obtained from (−)-**9** showed a positive Cotton effect in the optical rotatory dispersion curve (CH_3OH), as expected for the absolute configuration shown in **12.** Finally the epoxy acid **9** which was not resolved (i.e., which was obtained from mother liquors during the resolution) could be recycled easily and effectively through deoxygenation with chromous ion to form the dienone acid **7.**

The synthesis of the optically active intermediate **4** was accomplished as follows. (±)-*trans*-2,3-Epoxybutyric acid, conveniently available by oxidation of *trans*-crotyl alcohol with aqueous hydrogen peroxide–sodium tungstate at pH 5–5.5 and 55–60 °C,[13] had been resolved previously with brucine to afford the 2*R*,3*S* antipode,[14] the opposite of what we required. The 2*S*,3*R* antipode of *trans*-2,3-epoxybutyric acid (**17**), $[\alpha]^{22}_D$ +82.1° (C_6H_6), mp 61 °C, could be obtained readily from the racemic acid by resolution involving recrystallization of the salt with (−)-1-α-naphthylethylamine from absolute ethanol.[15] The acid **17** was reduced to the primary alcohol **18,** $[\alpha]^{25}_D$ +47° (C_6H_6), by conversion to the mixed carbonic anhydride (1.1 equiv of triethylamine and 1.1 equiv of ethyl chloroformate in THF at 0 °C initially and then at 20 °C for 36 h, addition of methylal (dimethoxymethane), and filtration to remove triethylamine hydrochloride) and subsequent reduction using excess sodium borohydride in methylal at 25 °C

with stirring. The alcohol **18** was then transformed into the 2-methoxy-2-propyl ether **19** (76% overall from 17) by reaction with 2-methoxypropene[16] in CCl_4 in the presence of a trace of phosphorus oxychloride and exposed to 3 equiv of lithium acetylide–ethylenediamine complex in dimethyl sulfoxide at 25 °C for 36 h. After workup and stirring with Amberlite IRC-50 resin in methanol, the acetylenic diol **20** could be obtained as major product (90% yield) contaminated by a small amount (~10% yield) of the position isomeric 1,3-diol resulting from the alternative cleavage of the 3-membered ring in **19**; the mixture was used for the remaining steps since purification at a later stage was advantageous.[17] The pure acetylenic alcohol **21**, $[\alpha]^{22}_D$ +32.4° (CH_3OH), was obtained in 75% overall yield from the mixture by (1) conversion to the primary mesitylsulfonate (1.05 equiv of mesitylenesulfonyl chloride in dry pyridine at −20 °C for 12 h) and (2) coupling[18] with dimethylcopperlithium (excess) in ether at −15 to −20 °C for 20 h, and (3) chromatography on silica gel (pentane–ether for elution).[19] The alcohol **21** was then silylated[20] (*tert*-butyldimethylsilyl chloride–imidazole–DMF, 18 h at 25 °C) and methylated (1.1 equiv of lithium diisopropylamide in THF followed by 3 equiv of CH_3I at −78 to 25 °C over 1 h and 25 °C for 2 h) to afford in 88% overall yield the protected acetylene **22**. Sequential hydrozirconation[21] of **22** with dicyclopentadienylchlorohydridozirconium (1 equiv) in benzene under argon at 43 °C for 2 h and iodination (addition to a small excess of iodine in CCl_4 at 25 °C) afforded in 84% yield a single isomeric iodo olefin, the required intermediate **4**,[22] $[\alpha]^{20}_D$ +24.9° ($CHCl_3$).

With the successful synthesis of intermediates **3** and **4** the stage was thus set for the elaboration of the structure of erythronolide B as described in the following publication.[23,24]

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(4) Of the synthetic challenge R. B. Woodward has written "Erythromycin, with all our advantages, looks at present hopelessly complex, particularly in view of its plethora of asymmetric centers . . ." (in "Perspectives in Organic Chemistry", A. Todd, Ed., Interscience Publishers, New York, N.Y., 1956, p 160).

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(8) B. Miller, *J. Am. Chem. Soc.*, **92**, 6246 (1970).

(9) Satisfactory infrared, proton magnetic resonance, and mass spectral data were obtained for each synthetic intermediate using purified and chromatographically homogeneous samples. All chemical reactions were conducted under an inert atmosphere unless otherwise indicated.

(10) The stereochemistry of this substance is clear from the NMR spectrum which unambiguously indicates that the proton at the newly created stereocenter is axial.

(11) Prepared from Ni–Al alloy and aqueous sodium hydroxide at 75–80 °C (temperature is critical) followed by washing to neutrality, activation using a small amount of hydrazine, and further washing with a few small portions of dimethoxyethane (air free). The stereoselectivity of the reduction of **12** is quite sensitive to the conditions used for preparation of the catalyst.

(12) The single-crystal x-ray crystallographic analysis was kindly carried out by Professor Jon Bordner, Department of Chemistry, North Carolina State University, Raleigh, N.C., in 1976. Details of the analysis will be published in *Cryst. Struct. Commun.*

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(14) K. Harada and J. Oh-hashi, *Bull. Chem. Soc. Jpn.*, **39**, 2311 (1966).

(15) The optical rotation of fully resolved salt was found to be $[\alpha]^{22}_D$ +11.8° (CH_3OH). The acid **17** was recovered quantitatively from the salt by treatment with 1.0 equiv of methanesulfonic acid in ether, washing with a small amount of saturated Na_2SO_4, and evaporation of ether.

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(17) The selectivity of formation of **20** is due to the presence of the bulky ether group in the starting oxide **19**. Use of the epoxy alcohol **18** in the acetylide displacement yielded much inferior selectivity.

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(19) The optically active alcohol **21** was identical chromatographically and spectroscopically with racemic alcohol obtained by reaction of *trans*-2-pentene oxide with sodium acetylide.

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(21) (a) D. W. Hart, T. F. Blackburn, and J. Schwartz, *J. Am. Chem. Soc.*, **97**, 679 (1975); (b) J. Schwartz and J. A. Labinger, *Angew. Chem., Int. Ed. Engl.*, **15**, 333 (1976).

(22) The location of iodine in **4** is clear from the ^1H NMR spectrum (e.g., sharp CH_3 singlet at 2.38 ppm), and the stereochemistry about the double bond follows from the cis addition course of hydrozirconation. The formation of only one position isomer in hydrozirconation, though not unexpected, is noteworthy.

(23) This work was assisted financially by a grant from the National Institutes of Health.

(24) We are deeply indebted to Dr. Jon Bordner[12] for his important assistance to this work by x-ray analysis of the bromo lactone **10**. Mr. Istvan Székely helped in the preparation of some of the synthetic intermediates.

E. J. Corey,* Eugene J. Trybulski
Lawrence S. Melvin, Jr., K. C. Nicolaou
John A. Secrist, Robert Lett, Peter W. Sheldrake
J. R. Falck, Daniel J. Brunelle, Martin F. Haslanger
Sunggak Kim, Sung-eun Yoo

Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138

Received March 15, 1978

Total Synthesis of Erythromycins. 4. Total Synthesis of Erythronolide B[1]

Sir:

Described herein is the first total synthesis of an aglycone of the erythromycin family of antibiotics, erythronolide B (**1**), a naturally occurring substance which is the biosynthetic progenitor of all the erythromycins.[2] This work makes use of key intermediates described in the foregoing paper,[1] the keto acid **2** and the unsaturated iodide **3**.

Although both **2** and **3** are available in optically active form of the required absolute configuration, the initial demonstration of the approach as here outlined involved the use of racemic **2** and optically active **3** and the chromatographic separation of an unnatural diastereomer during the course of synthesis.

Baeyer–Villiger reaction of the keto acid (±)-**2** was surprisingly slow using customary procedures and required forcing conditions. The desired lactone **4** could be obtained, however, in ~70% yield by treatment with excess 25% peracetic acid in ethyl acetate (Union Carbide Co.) for 6 days at 55–58 °C after chromatographic removal of unchanged keto acid **2**.[3,4] Treatment of the lactone with 1.1 equiv of 2,2′-dipyridyl disulfide and 1.2 equiv of triphenylphosphine in THF at 20 °C[5] afforded, after removal of solvent and chromatography at +5 °C on silica gel, 65% of the pure thio ester **5** which was coupled[6] with the iodide **3** via a Grignard reaction. The dextrorotatory iodide **3**, $[\alpha]^{25}_D$ +24.9°, in THF at −78 °C was lithiated by treatment with 2 equiv of *tert*-butyllithium in pentane (−78 °C for 0.5 h and −50 °C for 0.5 h)[7] and, after addition of 1.0 equiv of anhydrous magnesium bromide in THF at −50 °C (from 1,2-dibromoethane and magnesium metal

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