The specific incorporation per C_4 unit, 3.3%, calculated from ^{13}C NMR data (Table I), is identical with that obtained from ^{14}C radioactivity measurements.

The signals due to the ^{13}C-enriched carbon atoms in the proton decoupled ^{13}C NMR spectrum of labeled retronecine appear as multiplets (Table II, Figure 2D), due to superposition of a doublet [^{13}C–^{15}N (C-3,N; C-5,N) or C^{13}–C^{13} (C-9, C-8) coupling] on a singlet. This multiplicity represents the various enriched species present in the labeled retronecine. The contribution of the various species can be calculated from the difference spectrum (Figure 2F).

Thus, the signal due to C-3 (62.7 ppm) consists of a doublet (73 ± 9% of the total area in the difference spectrum) due to the contribution of a species containing the intact ^{13}C–^{15}N bond transferred from the starting material superimposed on a singlet (27 ± 12%) representing a species containing ^{13}C adjacent to ^{14}N. Similarly, the signal due to C-5 (55.3 ppm) consists of 71 ± 9% doublet and 29 ± 12% singlet. It is evident that the ^{13}C–^{15}N bond of putrescine is conserved to an equal extent at C-3,N and C-5,N of retronecine. A "symmetrical dimeric" intermediate, such as **6**, on the route from putrescine into retronecine (route A, Scheme I) is thus strongly indicated. A "nonsymmetrical" route to the product (e.g., route B) would have resulted in a distribution of label, yielding a difference spectrum in which the signal due to C-5 would be a doublet, since all species labeled with ^{13}C at this carbon are also labeled with ^{15}N, whereas the signal due to C-3 would be a multiplet due to the superposition of a $^{13}C,^{15}N$ doublet on a $^{13}C,^{14}N$ singlet. The doublet/singlet ratio would be 1 or less, depending on the extent of dilution of the intramolecularly doubly labeled putrescine used as a precursor by endogenous, natural abundance material.

The signal due to C-9 (Table II, Figure 2F) appears as a doublet (28 ± 4% of signal area in the difference spectrum) superimposed on a singlet (72 ± 19%). The doublet is due to ^{13}C–^{13}C coupling between C-8 and C-9. The area of the doublet, relative to that of the singlet it straddles, is a measure of the contribution to the retronecine of the species which carries ^{13}C in both halves of the molecule.[22] If the administered putrescine (90 atom % ^{13}C at C-1) entered the product without dilution by endogenous material, the ratio of the areas of doublet and singlet of the signal due to C-9 in the difference spectrum of the product would be 45:55. The observed result corresponds to that expected if the enriched precursor had been diluted with ca. 60% of its own weight of endogenous material.

The coupling between C-8 and C-9 gives rise to a corresponding signal at C-8. This is poorly resolved, presumably due to superimposed low intensity coupling to C-3 and ^{15}N.[23]

The ^{13}C NMR spectrum of retronecine, obtained from intramolecularly $^{13}C,^{15}N$-doubly labeled putrescine, thus shows signals due to C-3 and C-5 which, within experimental error, are of equal intensity and multiplicity. This observation eliminates from further consideration a pathway such as route B. It suggests that a "symmetrical dimeric" intermediate, i.e., one with C_{2v} symmetry, such as **6**, lies on the pathway.[24]

Acknowledgment. This work was supported by a grant from the Natural Sciences and Engineering Research Council of Canada. We are indebted to Thelma Leech, M.Sc., Greenhouse Supervisor, McMaster University, for her cooperation in propagating the plant material for our experiments and Brian G. Sayer, Department of Chemistry, for recording the ^{13}C NMR spectra.

(22) The average enrichment in ^{13}C at carbon atoms C-9 and C-8 as well as at C-3 and C-5 of the retronecine hydrochloride actually biosynthesized during the 13 days of the feeding experiment is thus 28 atom %. The sample of retronecine hydrochloride which was isolated constitutes a mixture of this enriched material and natural abundance material present in the plants at the start of the feeding experiment. The average enrichment at each of C-3, -5, -8, and -9 of the isolated sample can be calculated from data given in Table I: $[^1/_4(1.17 + 1.50 + 1.61 + 1.58) + 1.1] = 2.57$ atom % ^{13}C. Let the isolated sample consist of x% enriched material (28 atom % ^{13}C, on average, at each of C-3, -5, -8, -9) and (100 − x)% natural abundance material (1.1 atom % ^{13}C at each carbon atom). It follows that $2.57 = 0.28x + 0.011\ (100 - x)$ and $x = 5.5$, i.e., the isolated sample contained 5.5% of enriched material, with 28 atom % ^{13}C, on average, at C-3, -5, -8, and -9. The extent of dilution of the enriched putrescine (90 atom % ^{13}C at C-1) by endogenous putrescine before incorporation into retronecine can be calculated from the equation $(45 + 0.011y)/(100 + y) = 0.28$, where 45 is the average enrichment (atom % ^{13}C) at a terminal carbon atom of the administered putrescine, 0.011 is the mol fraction of ^{13}C in endogenous putrescine, and y is percent endogenous putrescine added to the administered enriched sample. The dilution, y, is 63%.

(23) The mode of incorporation of the doubly labeled putrescine dictates that whereas molecules intramolecularly doubly ^{13}C labeled at C-8 and C-3 make a contribution to the product, there is no species which is similarly labeled at C-9 and C-3. Therefore long-range coupling between these two carbons cannot occur.

(24) Two other possibilities cannot be eliminated on the basis of the results. One is the intermediacy of a structure without C_{2v} symmetry but capable of undergoing a degenerate sigmatropic rearrangement (e.g., $NH_2CH_2CH_2CH_2CH{=}NCH_2CH_2CH_2CH_2NH_2$). Another is the occurrence of two different pathways, each involving "nonsymmetrical dimeric" intermediates, which coincidentally lead to identical enrichment of ^{13}C–^{15}N at C-3 and C-5.

Asymmetric Total Synthesis of Erythromycin. 1. Synthesis of an Erythronolide A Seco Acid Derivative via Asymmetric Induction

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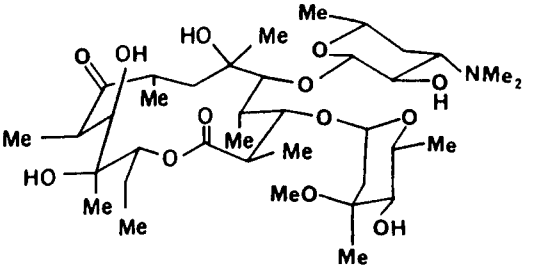
Erythromycin[1] (**1**), produced by a strain of *Streptomyces erythreus*, is the best known of the medicinally important macrolide antibiotics.[2] Structurally, this macrolide contains a 14-membered



1: erythromycin

† Deceased July 8, 1979.

‡ This manuscript was prepared by E.L., K.P.N., K.S., and D.E.W.

§ Address correspondence to this author at the Department of Chemistry, Carnegie-Melon University, Pittsburgh, PA 15213.

(1) (a) Isolation: McGuire, J. M.; Bunch, R. L.; Anderson, R. C.; Boaz, H. E.; Flynn, E. H.; Powell, H. M.; Smith, J. W. *Antibiot. Chemother.* **1952**, *2*, 281. (b) Structure (chemical degradation): Wiley, P. F.; Gerzon, K.; Flynn, E. H.; Sigal, M. V., Jr.; Weaver, O.; Quarck, U. C.; Chauvette, R. R.; Monahan, R. *J. Am. Chem. Soc.* **1957**, *79*, 6062. (c) Structure (X-ray): Harris, D. R.; McGeachin, S. G.; Mills, H. H. *Tetrahedron Lett.* **1965**, 679. (d) Synthesis (erythronolide B): Corey, E. J.; Kim, S.; Yoo, S.; Nicolaou, K. C.; Melvin, L. S., Jr.; Brunelle, D. J.; Falck, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4620. (e) Synthesis (erythronolide A): Corey, E. J.; Hopkins, P. B.; Kim, S.; Yoo, S.; Nambiar, K. P.; Falck, J. R. *Ibid.* **1979**, *101*, 7131.

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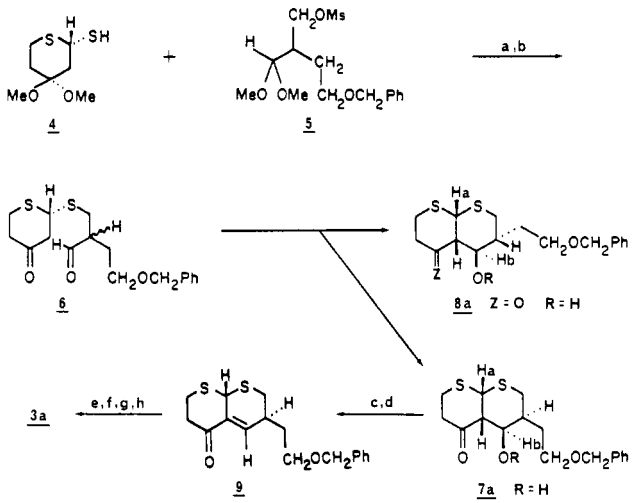
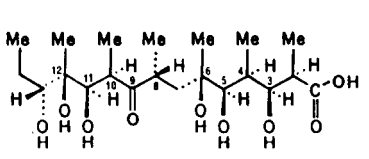
Scheme I[a]



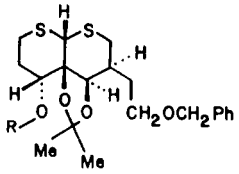
[a] (a) NaH, THF, Me_2SO, room temperature; (b) AcOH, H_2O, room temperature; (c) MsCl, Py, room temperature; (d) alumina, EtOAc, room temperature; (e) $NaBH_4$, MeOH, 0 °C; (f) $MeOCH_2I$, KH, THF, 0 °C; (g) OsO_4, ether, room temperature; $NaHSO_3$, aqueous Py, room temperature; (h) $Me_2C(OMe)_2$, TsOH, CH_2Cl_2, 0 °C.

lactone ring with 10 asymmetric centers and 2 unusual sugars, L-cladinose and D-desosamine. We now wish to record the first total synthesis of erythromycin, detailing the stereocontrolled asymmetric synthesis of the erythronolide A seco acid derivative **17b** in the present paper,[3] cyclization of this seco acid to the erythronolide A lactone system in the second paper,[4a] and the total synthesis of erythromycin in the third.[4b]

Assuming that a macrolactonization was feasible, we initially reduced the synthetic problem to the construction of an appropriate derivative of the erythronolide A seco acid (**2**). Recognizing the



2: erythronolide A seco acid

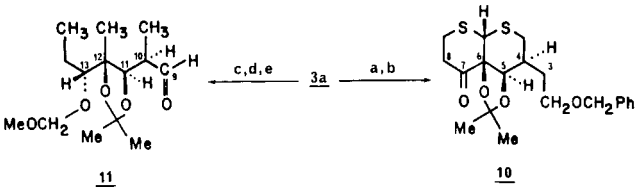


3a R = CH_2OCH_3

similarity in substitution and stereochemistry, we considered that a common intermediate such as the cis fused dithiadecalin **3a** could be used for the construction of the C-3–C-8 and C-9–C-13 portions of the seco acid **2**. Desulfurization of **3a** should provide the desired acyclic system possessing methyl groups at the required locations, while the bridging sulfur atoms introduce sufficient structural rigidity to permit the stereospecific operations required for its synthesis.

Preparation of the optically active dithiadecalin **3a** having the absolute configuration necessary for the synthesis of erythromycin was first investigated using enantiomerically resolved (+)-**4**[5a,b] of desired absolute configuration [$[\alpha]^{25}_D$ +21.7° (*c* 0.3, $CHCl_3$)] and racemic **5**[5c] as starting materials (Scheme I). Coupling of (+)-**4** and **5** followed by hydrolysis gave keto aldehyde **6** as an inseparable 1:1 diastereomeric mixture. Stereospecific[6] aldolization

Scheme II[a]



[a] (a) CF_3COOH, CH_2Cl_2, room temperature; (b) $(CF_3CO)_2O$, Me_2SO, CH_2Cl_2, −60 °C; (*i*-Pr)$_2$NEt, from −60 to 0 °C; (c) Ra(Ni)-(W-2), EtOH, reflux; (d) *o*-$NO_2C_6H_4SeCN$, P(*n*-Bu)$_3$, THF, room temperature; 30% H_2O, THF, room temperature; (e) O_3, MeOH, CH_2Cl_2, −78 °C; Me_2S, $NaHCO_3$, from −78 °C to room temperature.

of **6** was originally catalyzed by silica gel to provide a 1:1[7] mixture of the readily separable diastereomeric aldols[8] (+)-**7a** [mp 71–73 °C, $[\alpha]^{25}_D$ +11.8° (*c* 1.1, $CHCl_3$)] and (−)-**8a** [mp 111.5–113.5 °C, $[\alpha]^{25}_D$ −6.4° (*c* 1.48, $CHCl_3$)] in 70% combined yield from (+)-**4**. Subsequently we found that the reaction when catalyzed by proline[9] was equally effective. However, when **6** was submitted to aldolization by using L-proline (PhH/MeOH, 25 °C), *the aldols obtained were virtually racemic*![10] In contrast, the use of D-proline gave aldols of high optical purity.[11] These remarkable observations suggested the use of racemic **6**[5d] for aldolization, with D-proline as catalyst. Indeed, a marked degree of asymmetric induction was observed (in CH_3CN, 25 °C[12]), leading to a 1:1 mixture (70% yield) of aldols with the desired enantiomeric enrichment [(+)-**7a** and (−)-**8a**, both in 36% ee[10a,b]).[13] Enantiom-

(2) Recent reviews: (a) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. (b) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. (c) Back, T. G. *Ibid.* **1977**, *33*, 3041.

(3) Part of the work described in this paper was presented as a lecture by R. B. Woodward and recounted in: "Frontiers in Bioorganic Chemistry and Molecular Biology"; Ovchinnikov, Y. A.; Kolosov, M. N., Eds.; Elsevier/North Holland Biomedical Press: Amsterdam, 1979; pp 39–58.

(4) (a) Woodward, R. B., et al. *J. Am. Chem. Soc.*, following paper in this issue. (b) *Ibid.*, third paper in this series.

(5) (a) Racemic **4** was prepared (cf. ref 3 and Gais, H.-J. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 196) in 65% yield from tetrahydrothiapyran-4-one via the sequence: $(CH_2OH)_2$/TsOH/PhH, reflux; *N*-chlorosuccinimide/CCl_4, 0 °C; thiourea/acetone, 25 °C; aqueous NaOH, 25 °C; aqueous HCl/THF, 25 °C; $(MeO)_3CH$/TsOH/MeOH, 25 °C. (b) The resolution of **4** into (+)-**4** (cf. ref 3) involved (i) conversion of **4** to diastereomeric thioesters by (−)-camphanyl chloride (Gerlach, H. *Helv. Chim. Acta* **1968**, *51*, 1587), (ii) isolation, by crystallization, of a thioester [mp 134–135 °C, $[\alpha]^{25}_D$ +31.5° (c 1.0, $CHCl_3$)] which was shown to have the desired absolute configuration by X-ray crystallographic analysis,[21] and (iii) generation, by MeONa/MeOH, of (+)-**4**, which, surprisingly, was shown to be configurationally stable. (c) Mesylate **5** was prepared (cf. ref 3) in 60% yield from 4-benzyloxybutyric acid (Bennett, G. M.; Hock, A. L. *J. Chem. Soc.* **1927**, 472. Sudo, R.; Kaneda, A.; Itoh, N. *J. Org. Chem.* **1967**, *32*, 1844) via the sequence: MeOH/concentrated H_2SO_4, 25 °C; (*i*-Pr)$_2$NLi/THF, HCOOMe, −78 °C (Rathke, M. W.; Deitch, J. *Tetrahedron Lett.* **1971**, 2953); $(MeO)_3CH$/MeOH/concentrated H_2SO_4, 25 °C; $LiAlH_4$/ether, −20 → 0 °C; MsCl/Py, 0 °C. (d) Racemic substances corresponding to all synthetic intermediates reported in this paper have also been prepared (cf. ref 3) from racemic **4** and **5** by the same method described for the optically active intermediates (silica gel was used as the catalyst for aldolization of racemic **6**).

(6) For similar stereospecific cyclizations in carbocyclic systems, see: Marshall, J. A.; Wuts, P. G. M. *J. Org. Chem.* **1977**, *42*, 1794.

(7) Although the observed ratio was 1:1, we believe that partial epimerization at the carbon α to the aldehyde in **6** occurs prior to C–C bond formation: (a) an approximately 2:1 mixture of **7a** and **8a** was obtained upon aldolization (D-proline as catalyst) of **6** derived from (+)-**4** (100% ee) and optically active **5** (80% ee). The latter compound was prepared from the known 1,2-acetonide of (2*S*)-1,2,4-butanetriol (Corey, E. J.; Niwa, H.; Knolle, J. *J. Am. Chem. Soc.* **1978**, *100*, 1942). (b) Both (+)-**7a** and (−)-**8a** were chemically and configurationally stable under the aldolization conditions.

(8) The structure of **7a** and **8a** was assigned primarily by ^1H NMR evidence obtained from **7a** and **8a** as well as from suitable derivatives thereof, assuming an equatorial orientation of the side chain bearing the benzyloxy group. Relevant ^1H NMR ($CDCl_3$) data include the following. **7a**: δ 4.65 (H_a, d, *J* = 3 Hz); **7b** (R = Ms): 4.60 (H_a, d, *J* = 3 Hz), 5.40 (H_b, dd, *J* = 2, 3 Hz); **8a**: 4.26 (H_a, d, *J* = 3 Hz); **8b** [Z = $(OMe)_2$, R = Ac]: 4.45 (H_a, d, *J* = 3 Hz), 5.70 (H_b, t, *J* = 10 Hz).

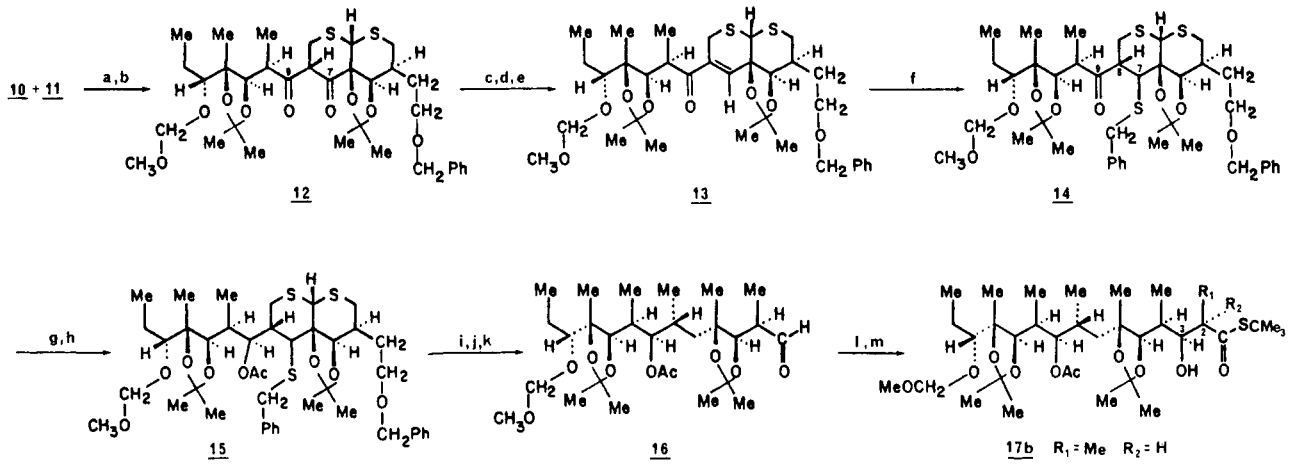
(9) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (c) Buchschacher, P.; Cassal, J. M.; Fürst, A.; Meier, W. *Helv. Chim. Acta* **1977**, *60*, 2747.

(10) The isolated aldols had (+)-**7a** and (−)-**8a** in 12–21% ee and 20–29% ee, respectively, (a) by comparison with optical rotations of optically pure (+)-**7a** and (−)-**8a** and (b) by ^1H NMR study employing an optically active shift reagent [Eu(hfc)$_3$] (cf. ref 7b).

(11) The isolated aldols had (+)-**7a** and (−)-**8a** in 80–82% ee and 84–86% ee,[10a] respectively (cf. ref 7b).

(12) The highest degree of asymmetric induction without any decrease in yield was observed in CH_3CN.

Scheme III[a]



[a] (a) Mesityllithium, THF, −50 °C; (b) $(CF_3CO)_2O$, Me_2SO, CH_2Cl_2, −60 °C; (*i*-Pr)$_2$NEt, from −60 to 0 °C; (c) KH, HMPA, THF, from 0 to −78 °C; AcCl, −78 °C; (d) $NaBH_4$, MeOH, CH_2Cl_2, −20 °C; (e) MsCl, Py, 0 °C; DMAP, Py, MeOH, 30 °C; (f) $PhCH_2SH$, *n*-BuLi, THF, −50 °C; (g) $LiAlH_4$, ether, −20 °C; (h) Ac_2O, DMAP, CH_2Cl_2, 0 °C; (i) Ra(Ni)-(W-2), EtOH, DMF, reflux; (j) *o*-$NO_2C_6H_4SeCN$, P(*n*-Bu)$_3$, THF, room temperature; 30% H_2O_2, THF, room temperature; (k) O_3, MeOH, CH_2Cl_2, −78 °C; Me_2S, $NaHCO_3$, from −78 °C to room temperature; (l) $EtCOSCMe_3$, LDA, THF, −110 °C; (m) *t*-BuLi, $(CH_2NMe_2)_2$, THF, −110 °C; AcOH, −110 °C.

erically enriched **7a** obtained from racemic **6** was dehydrated, producing enantiomerically enriched enone **9**, from which the desired enantiomer (+)-**9** [mp 74.5–75 °C, $[\alpha]^{25}_D$ +135.7° (*c* 1.2, $CHCl_3$)] could be isolated in optically pure form by an effective crystallization from benzene–hexane (97% recovery of the excess enantiomer). In this way *optically pure* (+)-**9** was obtained in a 10–12% overall yield from *racemic* **4** and **5**. Enone (+)-**9** thus obtained was transformed to (+)-**3a** [oil, $[\alpha]^{25}_D$ +25.8° (*c* 0.71, $CHCl_3$); 74% yield from (+)-**9**]; as expected, the sodium borohydride reduction and the osmium tetroxide oxidation took place stereospecifically.[14]

As summarized in Scheme II, the optically active dithiadecalin **3a** was converted to the ketone **10** [mp 69.5–70 °C, $[\alpha]^{25}_D$ −1.84° (*c* 1.41, $CHCl_3$); 85% yield from **3a**] and aldehyde **11**[15] [oil, $[\alpha]^{25}_D$ +31.6° (*c* 1.03, $CHCl_3$); 80% yield from **3a**] which served as the key segments comprising C-3–C-8 and C-9–C-13 of seco acid **2**, respectively.

Connection of the key segments was carried out, with the formation of the C-8/C-9 bond (Scheme III), by aldol condensation of the enolate of **10** (generated by mesityllithium[16]) with **11**, yielding diastereomeric aldols, which on oxidation gave a single 1,3-diketone **12**[17] [oil, $[\alpha]^{25}_D$ +34.6° (*c* 1.03, $CHCl_3$); 76% yield from **11**]. Regiospecific transformation of **12** (via the 9-enol acetate) to enone **13**, followed by addition of benzyl thiol,[18] furnished a single product **14** [oil, $[\alpha]^{25}_D$ +77.7° (*c* 1.02, $CHCl_3$); 83% yield from **12**] with the desired configuration at C-8 (and unknown stereochemistry at C-7). This stereochemical outcome at C-8 was anticipated from the following consideration: protonation at C-8 was expected to occur from the convex face of the dithiadecalin system, so as to bring the bulky substituents at C-4 and C-8 into equatorial positions as shown in Figure 1. The 9-keto group of **14** was reduced stereospecifically and converted to the acetate **15** (92% yield from **14**). The aldehyde **16** was obtained in 66% yield from **15** (cf. **3a** → **11**).

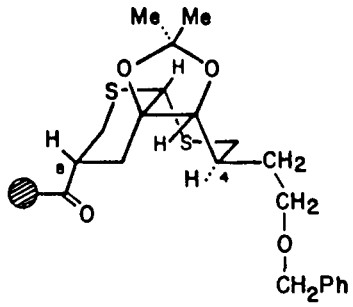
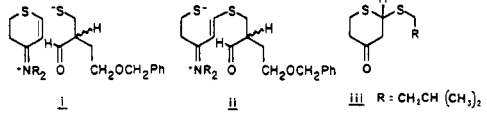


Figure 1.

The elaboration of the remaining C-1–C-2 portion of the erythronolide A seco acid (**2**) was accomplished by coupling **16** with the enolate of *tert*-butyl thiopropionate,[19] providing exclusively the "Cram"[20] product **17a** (R_1 = H, R_2 = Me; 85% yield), which possessed the undesired stereochemistry at C-2. The desired stereochemistry at C-2 was subsequently obtained by kinetic protonation of the presumed trianion of **17a** (generated by *t*-BuLi), which yielded **17b** [mp 121–123 °C, $[\alpha]^{25}_D$ −6.5° (*c* 0.99, $CHCl_3$); 90% yield] and recovered **17a** (8% yield). The structure of **17b** was confirmed by X-ray crystallographic analysis[21] on the racemic **17b** (mp 136–137 °C).[5d]

Having thus prepared an optically active intermediate (**17b**) possessing the carbon skeleton and all asymmetric centers of the erythronolide A seco acid, we were now prepared to study the problem of lactonization of derivatives of **17b**. These investigations

(13) Regarding the mechanism of the observed asymmetric induction (with racemic **6**), and the racemization (with optically active **6**), it is highly likely that species such as *i* (and possibly also *ii*) are involved as intermediates prior to C–C bond formation (cf. ref 7b).



The probable intermediacy of *i* is suggested by the observation that when iii (prepared from **4** and isoamyl methanesulfonate) was submitted to the aldolization conditions (L-proline/PhH/MeOH) in the presence of benzyl thiol (1 equiv), iv was produced (40% yield) in addition to recovered iii (43% yield).

(14) Confirmation of structure **3a** was provided by X-ray crystallographic analysis[21] on the racemic **3b** (R = Ac; mp 101–101.5 °C) prepared from racemic **3a**[5d] via the sequence: CF_3COOH/CH_2Cl_2, °C; Ac_2O/DMAP/CH_2Cl_2, 25 °C.

(15) It was less practical to prepare compounds having the required chain length at the outset, due to low yield of aldolization (cf. **6** → **7a**) of such substrates.

(16) Use of (*i*-Pr)$_2$NLi resulted in a complex mixture probably containing aldols derived from reaction of the α epimer of aldehyde **11** with **10**.

(17) In the racemic series a mixture of two diastereomeric diketones was obtained, in which the desired **12** predominated (5:1).

(18) All attempts to achieve a direct reduction of **13** to the corresponding saturated ketone were fruitless.

(19) Wemple, J. *Tetrahedron Lett.* **1975**, 3255.

(20) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828.

(21) The X-ray analysis was carried out by G. Rihs (CIBA-GEIGY, Basel, Switzerland). We are indebted to her for her expert assistance.

are described in the following paper.[4a]

Acknowledgment. We are indebted to Professor Yoshito Kishi for his help and encouragement and, in particular, for his acceptance of the role of principal investigator upon Professor Woodward's death. Financial assistance from the National Institutes of Health (GMO4229) is gratefully acknowledged.

Supplementary Material Available: Physical properties (IR and ^{1}H NMR spectra, etc.) of selected synthetic intermediates (including **3a,b**, **4**, **5**, **7a**, **8a**, **9–16**, and **17a,b**) and three dimensional views of the (−)-camphanyl thioester of (+)-**4**, **3b**, and **17b** as determined by X-ray crystallographic analysis, including crystallographic data and final atomic and anisotropic thermal parameters (29 pages). Ordering information is given on any current masthead page.

Asymmetric Total Synthesis of Erythromycin. 2. Synthesis of an Erythronolide A Lactone System

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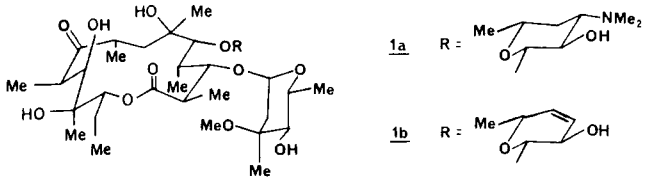
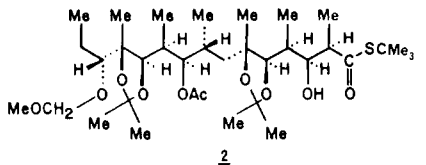
Received February 23, 1981

In reporting a total synthesis of erythromycin (**1a**) we described in the preceding paper[1] the synthesis of the erythronolide A seco acid derivative **2** in optically active form. In this paper we wish to report a successful transformation of **2** to **12** (synthetically equivalent to erythronolide A) via lactonization and also demonstrate that the proper functionalization of a substrate is critical for the successful lactonization.



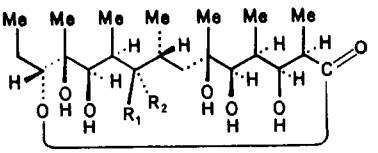
1a R =

1b R =



2

All attempts to lactonize substrates **3a** (X = OH, *S*-*t*-Bu) and **4a** (X = OH, *S*-*t*-Bu) (Table I), both readily available from **2**,[2] using several of the known methods[3] were uniformly unsuccessful. In view of these results, we decided to investigate extensively the structure/reactivity relationships of the lactonization. We chose to study the lactonization of substrates having not only the 9*R* configuration as in **2**, but also the 9*S* configuration, since the stereochemistry at C-9 is irrelevant to the overall synthesis; a keto group occupies the C-9 position of erythromycin. From (9*R*)- or (9*S*)-dihydroerythronolide A[4a,b] (**10a,b**), readily obtainable from natural erythromycin,[5] we prepared various substrates[4c,6] (**3b**, **4b–e** and **5a,b** of 9*R* configuration and **6a**, **7a–d**, **8a,b**, and **9** of 9*S* configuration) and subjected them to Corey's method[3a] of lactonization [2-pyridyl thioester, refluxing xylene (140 °C)].[7] These results are summarized in Table I.



10a R_1 = OH R_2 = H
10b R_1 = H R_2 = OH
10c R_1 = H R_2 = NH_2
10d R_1 = R_2 = O

Among the many substrates tested, only three compounds, **5b**, **7d**, and **9**, afforded lactones; with regard to the efficiency of lactonization, **5b** and **7d** gave disappointing yields, while **9** gave a remarkable 70% yield of lactone! These observations seemed to indicate that certain structural features such as (1) *S* configuration at C-9 and (2) cyclic protecting groups at C-3/C-5 and C-9/C-11 (as in **9**) are required for efficient lactonization.[8]

† Deceased July 8, 1979.

‡ This manuscript was prepared by E.L., K.P.N., K.S., and D.E.W.

§ Address correspondence to this author at the Department of Chemistry, Carnegie-Mellon University, Pittsburgh, PA 15213.

(1) Woodward, R. B., et al., *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) (a) The reaction sequence used for **2** → **3a** (X = *S*-*t*-Bu): Ac_2O/DMAP/CH_2Cl_2, 25 °C; $Me_3SiCl/Et_4NBr/CH_2Cl_2$, 0 °C;[2b] for **2** → **4a** (X = *S*-*t*-Bu): Conia's method (CF_3CO_2H);[2c] $Me_3SiCl/Et_4NBr/CH_2Cl_2$, 0 °C; mesitaldehyde dimethyl acetal/10-camphorsulfonic acid/CH_2Cl_2, 0 °C;[13] for **3a** (X = *S*-*t*-Bu) → **3a** (X = OH) and **4a** (X = *S*-*t*-Bu) → **4a** (X = OH): $Hg(CF_3CO_2)_2/Na_2HPO_4$/aqueous CH_3CN, 25 °C.[3d] (b) The reagent Me_3SiCl/Et_4NBr was found to be highly effective in selective removal of a methoxy methyl ether group in the presence of an acetonide. (c) Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J. M. *Synthesis* **1978**, 63.

(3) The methods examined include: (a) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614. (b) Corey, E. J.; Brunelle, D. J. *Tetrahedron Lett.* **1976**, 3409. (c) Gerlach, H.; Thalmann, A. *Helv. Chim. Acta* **1974**, *57*, 2661. (d) Masamune, S.; Kamata, S.; Schilling, W. *J. Am. Chem. Soc.* **1975**, *97*, 3515. (e) Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *Ibid.*, **1977**, *99*, 6756. (f) Taub, D.; Girotra, N. N.; Hoffsommer, R. D.; Kuo, C. H.; Slates, H. L.; Weber, S.; Wendler, N. L. *Tetrahedron* **1968**, *24*, 2443. (g) Staab, H. A. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 351.

(4) (a) Lactone **10a** was prepared by two routes—from **1b**[10] in 52% yield via the sequence: $NaAlH_2(OCH_2CH_2OMe)_2$/THF/PhMe, −78 → 30 °C; HCl/MeOH, 25 °C; and from erythronolide A (**10d**)[4d,e] in 80% yield by BH_3/THF, −78 → 25 °C. (b) Lactone **10b**[4f,g] was prepared by two routes—from **1b**[10] in 65% yield via the sequence: $NaBH_4$/alumina/THF, 25 °C; HCl/MeOH, 25 °C; and from **10d** in 95% yield by $NaBH_4$/alumina/THF, 25 °C. (c) All lactonization substrates except **3b** and **6a** were prepared[14] from the corresponding lactones (**4bl–el**, **5al,bl**, **7al–dl**, **8al,bl**, and **9l**). The lactones of 9*R* and 9*S* configuration were, in turn, prepared from **10a** and **10b**, respectively. Thioesters **3b** and **6a** were prepared from **10a** and **10b** via **3cl** [lactone corresponding to **3c** (R_1 = R_2 = H, X = OH)] and **6bl** [lactone corresponding to **6b** (R = H, X = OH)], respectively. (d) LeMahieu, R. A.; Carson, M.; Kierstead, R. W.; Fern, L. M.; Grunberg, E. *J. Med. Chem.* **1974**, *17*, 953. (e) We are grateful to Dr. R. A. LeMahieu (Hoffmann-LaRoche) for generously supplying the **10d** used in the present study. (f) Sigal, M. V., Jr.; Wiley, P. F.; Gerzon, K.; Flynn, E. W.; Quarck, U. C.; Weaver, O. *J. Am. Chem. Soc.* **1956**, *78*, 388 and ref 10. For the C-9 stereochemistry, see: Demarco, P. V. *Tetrahedron Lett.* **1969**, 383 and ref 6a. (g) We are grateful to Drs. T. J. Perun (Abbott Laboratories) and N. Neuss (Lilly Research Laboratories) for generously providing the **10b** used in the present study. (h) Santaniello, E.; Ponti, F.; Manzocchi, A. *Synthesis* **1978**, 891.

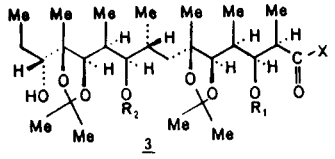
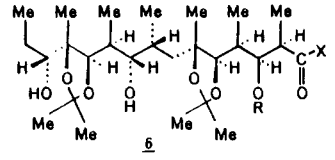
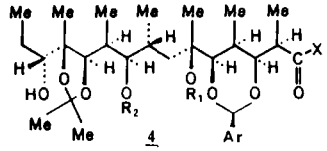
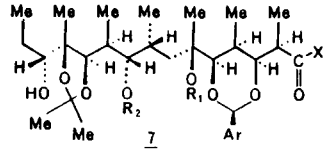
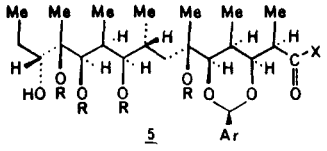
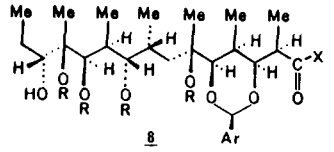
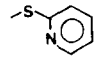
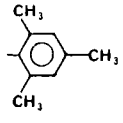
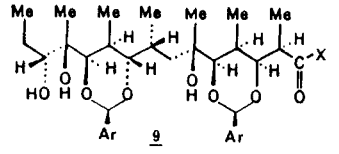
(5) We are grateful to Dr. N. Neuss (Lilly Research Laboratories) for generously providing all of the natural erythromycin used in the present study.

(6) Structures assigned to the lactonization substrates are based primarily on ^{1}H NMR evidence and chemical correlations (**3b**, **4b–e**, and **7a–d**) with suitable derivatives of structurally established[1] **2**. The structural types exemplified by **5al,bl**, **8al,bl**, and **9l** are known: (a) Perun, T. J.; Egan, R. S.; Martin, J. R. *Tetrahedron Lett.* **1969**, 4501.

(7) In contrast to most known methods (cf. ref 3) for lactonization, this method permits the isolation and purification of the activated esters and does not require any additives. This allowed us to study the lactonization in the absence of any contaminants, thus minimizing potential complications.

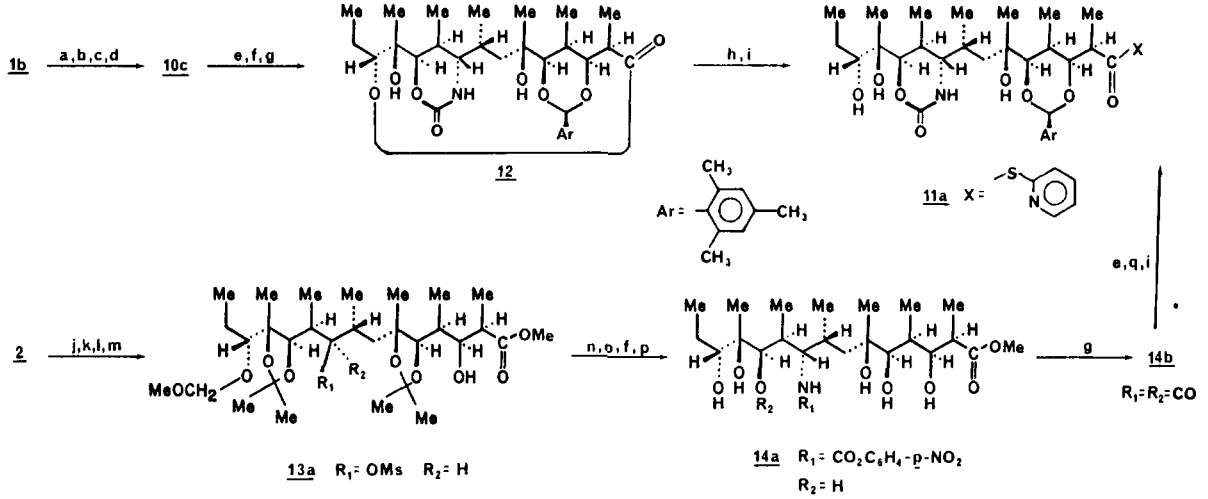
0002-7863/81/1503-3213$01.25/0

Table I. Results of Lactonization Study

9*R* substrates	lactone, %	9*S* substrates	lactone, %
 3	a R_1, R_2 = Ac: 0[a] b R_1, R_2 = MM: 0	 6	a R = MM: 0
 4	a R_1 = H R_2 = Ac: 0[a] b R_1, R_2 = H: 0 c R_1 = MM R_2 = H: 0 d R_1 = H R_2 = MM: 0 e R_1, R_2 = MM: 0	 7	a R_1, R_2 = H: 0 b R_1 = H R_2 = MM: 0 c R_1 = MM R_2 = H: 0 d R_1, R_2 = MM: 10
 5	a R = H: 0 b R = MM: 15	 8	a R = H: 0 b R = MM: 0
X =  Ar =  MM = $-CH_2OCH_3$		 9	70

[a] Compounds where X = OH and $SCMe_3$ were also attempted.

Scheme I[a]



[a] (a) NH_2NH_2, MeOH, reflux; (b) $NaNO_2$, AcOH, aqueous MeOH, 0 °C; (c) $NaBH_4$, MeOH, room temperature; (d) HCl, MeOH, room temperature; (e) mesitaldehyde dimethyl acetal, CF_3COOH, CH_2Cl_2, 0 °C; (f) $ClCOOC_6H_4$-*p*-NO_2, CH_2Cl_2, aqueous $NaHCO_3$, room temperature; (g) Et_3N, CH_2Cl_2, room temperature; (h) NaOH, EtOH, *t*-BuOH, room temperature;[14a] (i) ClCOS-2-Py, Et_3N, CH_2Cl_2, 0 °C; (j) Na_2CO_3, MeOH, room temperature; (k) $(PhOCH_2CO)_2O$, Py, DMAP, CH_2Cl_2, 0 °C; (l) MsCl, Py, 0 °C; (m) LiOH, 30% H_2O_2, THF, room temperature; (n) LiN_3, aqueous HMPA, 60 °C; (o) H_2 (1 atm), PtO_2, THF, room temperature; (p) NH_2OH·HCl, KH_2PO_4, aqueous MeOH, reflux; (q) EtSLi, HMPA, 30 °C.

Since synthetic **2** lacked these structural features, it was necessary to carry out a structural modification involving inversion of the stereochemistry at C-9 and site-specific introduction of cyclic protecting groups at the required locations. However, instead of **9**, we envisioned a nitrogen analogue such as **11a** as a lactonization substrate for the following considerations: (1) compound **11a** possesses the structural features which should facilitate its lactonization and (2) the amine functionality at C-9 might be expected to play a pivotal role in the later stages of the synthesis[9] by permitting highly site-selective operations.

Before proceeding further we tested the predicted efficacy of **11a** as a lactonization substrate. The substrate **11a** was prepared from natural erythromycin via **1b**[10] (Scheme I). Conversion of **1b** to the corresponding (9*S*)-amino derivative[11] and subsequent glycolysis yielded (9*S*)-aminoerythronolide A[12] (**10c**). Selective

(8) These structural requirements probably arise from conformational requirements for lactonization. In particular, the required pattern of cyclic protecting groups in a 9*S* substrate may assist it in adopting a conformation sufficiently resembling that of the corresponding lactone to facilitate ring closure. While the protection pattern as in **9** can be readily achieved with erythronolide derivatives having 9*S* configuration, such protection was unobtainable for (9*R*)-lactones (cf. ref 6a).

(9) Woodward, R. B., *et al. J. Am. Chem. Soc.*, following paper in this issue.

(10) Jones, P. H.; Rowley, E. K. *J. Org. Chem.* **1968**, *33*, 665.

(11) For a similar conversion, see: Wildsmith, E. *Tetrahedron Lett.* **1972**, 29.

acetalization of **10c** (using mesitaldehyde dimethyl acetal[13]), followed by introduction of a cyclic carbamate at C-9/C-11, furnished **12** [mp 260.5–262 °C, $[\alpha]^{25}_D$ – 40.7° (*c* 0.99, $CHCl_3$)]. Carbamate **12** thus obtained was transformed by saponification[14a] and thioesterification[14b] to **11a**. Subjection of **11a** to Corey's method[3a] of lactonization (xylene, 140 °C) furnished **12** in 40% yield. However, under milder conditions (toluene, 110 °C), the yield of **12** increased to 70%.[15] These results substantiated the usefulness of our conclusions from the study of the structure/reactivity relationships pertaining to the lactonization reaction.

At this point it remained for us to develop an efficient preparation of **11a** from our synthetic intermediate **2** (Scheme I). To this end, **2** was transformed in 75% yield to the mesylate **13a** in four steps: (1) deprotection of the C-9 hydroxyl (with concomitant ester exchange at C-1), (2) selective phenoxyacetylation at C-3, (3) mesylation at C-9, and (4) deprotection[16] at C-3. Treatment of **13a** with LiN_3 furnished the inverted azide **13b** [R_1 = H, R_2 = N_3; mp 81–82 °C, $[\alpha]^{25}_D$ +19.7° (*c* 2.2, $CHCl_3$)] in 75% yield after chromatography.[17] Carbamate **13c** (R_1 = H, R_2 = $NHCO_2C_6H_4$-*p*-NO_2), derived from azide **13b**, was smoothly deprotected to furnish the hexaol **14a** contaminated with a minor byproduct.[18] Crude **14a** underwent selective cyclization to the 9,11-cyclic carbamate **14b** (mp 164.5–165.5 °C; 70% yield from **13b**), which was readily purified by chromatography. Acetalization[13] of **14b** under thermodynamically controlled conditions led to the desired **11b** (X = OCH_3; 85% yield).[19] The thioester **11a** obtained from **11b** was identical to **11a**, derived from natural erythromycin (vide supra), and was lactonized in 70% yield to **12** [mp 260.5–262 °C, $[\alpha]^{25}_D$ –40.0° (*c* 0.94, $CHCl_3$)] by the previously established method.

With the intermediate lactone **12** in hand, we were ready to proceed with the conclusion of our synthesis of erythromycin, which is described in the following paper.[9]

Acknowledgment. We are indebted to Professor Yoshito Kishi for his help and encouragement and, in particular, for his acceptance of the role of principal investigator upon Professor Woodward's death. Financial assistance from the National Institutes of Health (GM04229) is gratefully acknowledged. Mass spectra were provided by the facility supported by the National Science Foundation (Grant CHE-7908590).

Supplementary Material Available: Physical properties (IR and ^1H NMR spectra, etc.) of selected synthetic intermediates (including **11a,b**, **12**, **13a–c**, and **14b**) and schemes used for the preparation of (1) lactones (**3cl**, **4bl–el**, **5al,bl**, **6bl**, **7al–dl**, **8al,bl**, and **9l**) from **10a** or **10b** and (2) thioesters **3b** and **6a** from **3cl** and **6bl**, respectively (13 pages). Ordering information is given on any current masthead page.

(12) It should be noted that the reported[12a] preparation of **10c** was subsequently shown[12b] to be incorrect: (a) Djokic, S.; Tamburasev, A. *Tetrahedron Lett.* **1967**, 1645. (b) Massey, E. H.; Kitchell, B.; Martin, L. D.; Gerzon, K.; Murphy, H. W. *Ibid.* **1970**, 157.

(13) Selective protection of the 1,3-diol portion of a 1,3,4-triol was most effectively achieved via the mesitaldehyde acetal, even in cases where commonly used acetals failed.

(14) (a) The saponification method [NaOH in *t*-BuOH/EtOH (4/1)] employed was most effective in avoiding (i) epimerization at C-2 and (ii) formation of 12,13-epoxy acids when a free C-12 hydroxyl group was present. (b) Corey, E. J.; Clark, D. A. *Tetrahedron Lett.* **1979**, 2875.

(15) The observed temperature effect can be explained mainly by the formation of byproducts only under the 140 °C conditions. The major byproduct, identified as the 2-*epi*-thioester (probably produced via a ketene), decomposed primarily to unidentified compounds under the 140 °C conditions and did not lactonize to give a 2-*epi*-lactone. The formation of such 2-*epi*-thioesters appears to be general under the 140 °C conditions and was also observed in other cases.

(16) The deprotection of the C-3 hydroxyl group is required; otherwise elimination leading to unsaturation at C-2/C-3 takes place under the subsequent displacement conditions.

(17) Unidentified elimination products were also formed in 20% yield.

(18) This byproduct is probably the corresponding δ-lactone of **14a**. It is the exclusive product under the usual acidic conditions used for such deprotections.

(19) Other acetals were also formed as minor products but were reequilibrated to **11b** after separation. The yield of **11b** is based on two such reequilibrations.

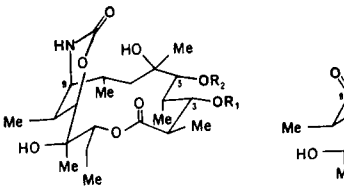
Asymmetric Total Synthesis of Erythromycin. 3. Total Synthesis of Erythromycin

R. B. Woodward,† E. Logusch,‡ K. P. Nambiar,‡ K. Sakan,§,‡ D. E. Ward,‡ B.-W. Au-Yeung, P. Balaram, L. J. Browne, P. J. Card, C. H. Chen, R. B. Chênevert, A. Fliri, K. Frobel, H.-J. Gais, D. G. Garratt, K. Hayakawa, W. Heggie, D. P. Hesson, D. Hoppe, I. Hoppe, J. A. Hyatt, D. Ikeda, P. A. Jacobi, K. S. Kim, Y. Kobuke, K. Kojima, K. Krowicki, V. J. Lee, T. Leutert, S. Malchenko, J. Martens, R. S. Matthews, B. S. Ong, J. B. Press, T. V. Rajan Babu, G. Rousseau, H. M. Sauter, M. Suzuki, K. Tatsuta, L. M. Tolbert, E. A. Truesdale, I. Uchida, Y. Ueda, T. Uyehara, A. T. Vasella, W. C. Vladuchick, P. A. Wade, R. M. Williams, and H. N.-C. Wong

Department of Chemistry, Harvard University Cambridge, Massachusetts 02138

Received February 23, 1981

In the preceding paper[1] we described the preparation of the key lactone intermediate **1a** in optically active form. In this paper we report the synthesis of erythromycin (**2**) from **1a**. In essence,



1a R_1=R_2= mesitaldehyde acetal

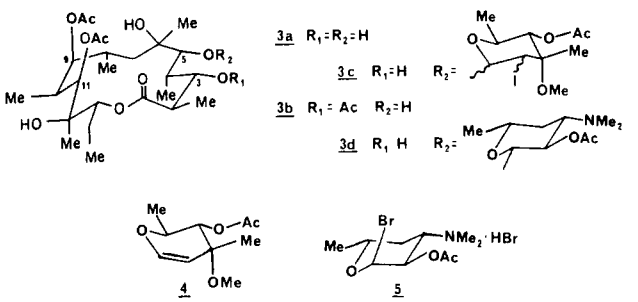
1b R_1=R_2=H

2

this transformation involves the glycosidation of a suitable derivative of **1a** with L-cladinose and D-desosamine and the generation of the C-9 ketone functionality.

In planning our work we were aware that glycosidation, in particular, demanded highly specific operations, in terms of both site- and stereoselectivity: cladinose must be attached at the C-3 hydroxyl group with α-anomeric stereochemistry and desosamine at C-5 with β stereochemistry. We felt that once appropriate solutions were available to the site-specific operations, the stereochemical control of the glycosidation reactions should be manageable. We, therefore, examined the relative reactivities of the C-3 and C-5 hydroxyl groups toward glycosidation; if there were a practical difference in reactivity, such an observation would naturally suggest a sequence of sugar attachment as well as minimize the need of protecting groups.

Initially we chose the lactone **3a**,[2,3] derived from natural er-



3a R_1=R_2=H

3c R_1=H R_2=

3b R_1= Ac R_2=H

3d R_1 H R_2=

4

5

† Deceased July 8, 1979.

‡ This manuscript was prepared by E.L., K.P.N., K.S., and D.E.W.

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(1) Woodward, R. B., et al. *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) Diacetate **3a** was prepared by two independent routes—from (9*S*)-3′-de(dimethylamino)dihydroerythromycin[2a] via the sequence: Ac_2O/DMAP/CH_2Cl_2, 25 °C; HCl/MeOH, 25 °C; and from (9*S*)-dihydroerythronolide A 3,5-mesitaldehyde acetal[1] in 90% yield via the sequence: Ac_2O/DMAP/CH_2Cl_2, 25 °C; Conia's method (CF_3COOH).[2b] (a) Jones, P. H.; Rowley, E. K. *J. Org. Chem.* **1968**, *33*, 665. (b) Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J. M. *Synthesis* **1978**, 63.

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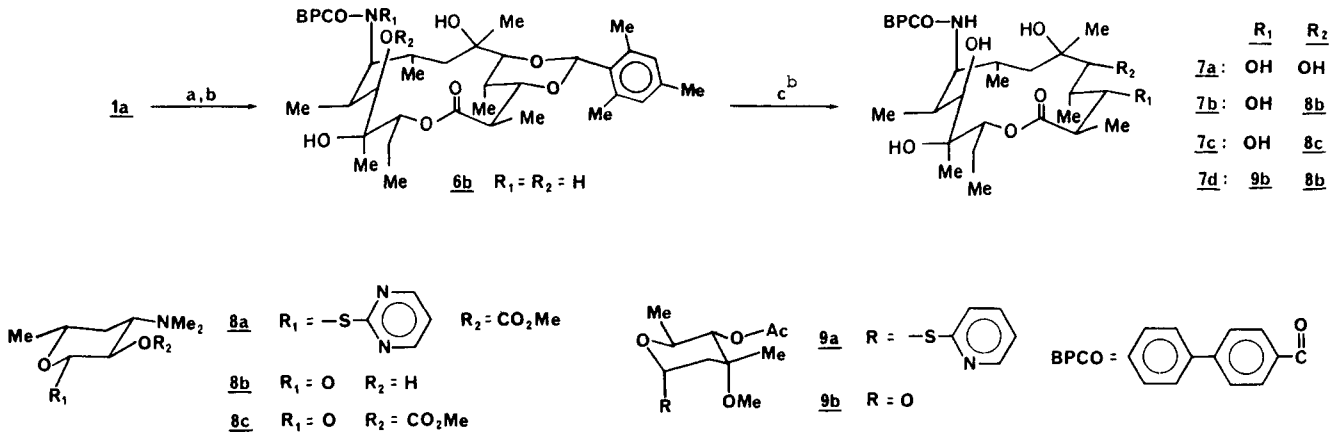
Scheme I[a]



[a] (a) BPCOCl, Et_3N, DMAP, CH_2Cl_2, room temperature; (b) aqueous NaOH, THF, *i*-PrOH, room temperature; (c) SiO_2, aqueous CF_3COOH, CH_2Cl_2, room temperature.[2b] [b] The conditions lead to **7a**.

ythromycin,[4] to study the relative reactivities of the hydroxyl groups. We first investigated attachment of L-cladinose to **3a**, since greater reactivity of the C-3 vs. the C-5 hydroxyl group was suggested by predominant formation of the 3,9,11-triacetate **3b**[5] from **3a** upon acetylation (Ac_2O/Py). However, glycosidation of **3a** with L-cladinal **4**[6] (3 equiv) under modified Tatsuta conditions[7] (3.1 equiv of *N*-iodosuccinimide in the presence of a radical scavenger[7b] in CH_3CN at −30 → 25 °C) unexpectedly yielded the C-5 glycoside **3c**[8] as the predominant product (34% yield based on consumed **3a**; 47% conversion).[9] The greater reactivity at C-5 was further confirmed by the site-selective attachment of D-desosamine to **3a**. Thus glycosidation of **3a** using **5**[10a] (5 equiv) under modified Koenigs–Knorr conditions[10b,c] (10 equiv of silver triflate, lutidine, CH_2Cl_2/THF at 25 °C) yielded a single isolable glycosidation product **3d**[11] (10% yield), the desired β-glycoside[12] at C-5. These experiments suggested that the C-5 hydroxyl group would be more reactive toward glycosidation, and hence protection of only the C-9 and C-11 hydroxyl groups would be sufficient for our purposes.

In light of these observations we decided to first attach desosamine to a suitable derivative of our synthetic intermediate **1a**. The 9,11-protected **1b** (mp > 300 °C), readily available from **1a** by CF_3COOH hydrolysis,[2b] appeared to be attractive in this regard, but insolubility in almost all solvents precluded its use. It therefore became necessary to first remove the cyclic carbamate (Scheme I). By acylation with *p*-phenylbenzoyl chloride,[13] carbamate **1a** was converted to **6a** ($R_1 = R_2 = CO$), hydrolysis of which afforded **6b** (70% yield[14] from **1a**). Deprotection of the C-3 and C-5 hydroxyl groups furnished the key glycosidation substrate **7a** in quantitative yield.

Glycosidation of **7a** employing D-desosaminide **8a**[15a,b] (5 equiv) and silver triflate[15c,d] (6 equiv) in CH_2Cl_2/PhMe at 25 °C provided the expected β-glycoside **7b**[12,16] [mp 172–176 °C, $[\alpha]^{25}_D$ −70.7° (*c* 0.63, $CHCl_3$); 36% yield] after methanolysis.[17a,b] Furthermore, glycosidation of **7c**, derived from **7b** ($ClCO_2Me/CH_2Cl_2$/aqueous $NaHCO_3$), with L-cladinoside **9a**[18a] (5.5 equiv) and $Pb(ClO_4)_2$[18b] (6.5 equiv) in CH_3CN at 25 °C, furnished after methanolysis[17a]

(3) In depicting **3a** and other lactones in this paper, we adopt the Perun–Celmer model as the conformation of the lactone system of erythromycin: (a) Celmer, W. D. *Pure Appl. Chem.* **1971**, *28*, 413. (b) Perun, T. J. In "Drug Action and Drug Resistance in Bacteria. 1. Macrolide Antibiotics and Lincomycin"; Mitsuhashi, S., Ed.; University Park Press: Baltimore, 1971; p 123.

(4) We are grateful to Dr. N. Neuss (Lilly Research Laboratories) for generously providing all of the natural erythromycin used in the present study.

(5) Relevant ^1H NMR ($CDCl_3$) data for **3b**: δ 5.55 (H_3, dd, *J* = 10.0, 4.0 Hz), 5.03 (1 H, d, *J* = 1.0 Hz), 4.80 (1 H, dd, *J* = 9.2, 3.6 Hz), 4.64 (1 H, dd, *J* = 9.6, 3.6 Hz).

(6) (a) Synthesis of L-cladinose: Lemal, D. M.; Pacht, P. D.; Woodward, R. B. *Tetrahedron* **1962**, *18*, 1275. (b) Cladinal **4** was prepared from 4-acetylcladinose[7a] in 88% yield by an improved sequence: 1-chloro-2,5-dioxophosphalan/$(i\text{-Pr})_2NEt$/ether, −40 → 25 °C; $MeSO_2N_3$, 25 °C. L-cladinose, used to prepare 4-acetylcladinose, was obtained quantitatively from natural erythromycin by glycolysis (continuous extraction: aqueous HCl/ether, reflux). For a less effective method, see: Wiley, P. F. *Methods Carbohydr. Chem.* **1962**, *1*, 264.

(7) (a) Tatsuta, K.; Fujimoto, K.; Kinoshita, M. *Carbohydr. Res.* **1977**, *54*, 85. (b) The use of butylidene-4,4′-bis-(6-*tert*-butyl-3-methylphenol) in a modified Tatsuta procedure significantly increased the yield of glycosidation. We thank Professor Y. Kishi for suggesting the use of radical scavengers and providing us with a number of such compounds.

(8) The assigned structure of **3c** is supported by the following observations: (a) ^1H NMR ($CDCl_3$) signal δ 4.13 (br m) due to the proton attached to C-3 sharpened (dd, *J* = 7.5, 2.0 Hz) when D_2O was added; (b) under forcing acetylation conditions (Ac_2O/DMAP), only one additional acetate was introduced at C-3 of **3c**, indicating the absence of any other free secondary hydroxyl groups in **3c**.

(9) Two minor unidentified glycosides were also isolated in 7 and 2% yield (based on consumed **3a**).

(10) (a) Masamume, S.; Yamamoto, H.; Kamata, K.; Fukuzawa, A. *J. Am. Chem. Soc.* **1975**, *97*, 3513. (b) Hanessian, S.; Banoub, J. *Carbohydr. Res.* **1977**, *53*, C13. (c) It should be noted that the previously reported method (ref 10a) for attachment of **5** failed in the present case.

(11) The glycoside **3d** thus obtained was identical with an authentic sample prepared from (9*S*)-dihydroerythromycin (derived in 82% yield from **2** by reduction with $NaBH_4$/alumina[11a]) via the sequence: Ac_2O/DMAP/CH_2Cl_2, 25 °C; HCl/MeOH, 25 °C; AcCl/CH_2Cl_2/aqueous $NaHCO_3$, 25 °C. (a) Santaniello, E.; Ponti, F.; Manzocchi, A. *Synthesis* **1978**, 891.

(12) The observed βanomeric stereochemistry was expected in view of the presence of a participating acyl group at the 2 position of the desosamine: see, for example, "Chemistry of the Glycosidic Bond"; Bochkov, Zaikov, Eds.; Pergamon Press: London, 1979.

(13) Scribner, R. M. *Tetrahedron Lett.* **1976**, 3853.

(14) Hydrolysis of **6a** afforded **6b** along with **1a** (3:2). The recovered **1a** was recycled twice to obtain the yield cited for **6b**.

(15) (a) Synthesis of D-desosamine: Richardson, A. C. *Proc. Chem. Soc.* **1963**, 131. (b) Thioglycoside **8a** was prepared in 63% yield from D-desosamine via the sequence: 2-mercaptopyrimidine/$(NCO_2Et)_2$/P(*n*-Bu)$_3$/PhMe, −30 → 25 °C; $ClCO_2Me/CH_2Cl_2$/aqueous $NaHCO_3$, 25 °C. We are indebted to Drs. W. D. Celmer (Pfizer) and N. Neuss (Lilly Research Laboratories) for generously providing us with D-desosamine hydrochloride used in this study. (c) Among the metal salts [Hg(II), Cu(II), Ag(I) and Pb(II)] investigated, silver triflate was most effective. The glycosidation method used for **3a** → **3d** was less effective in the present case. See also ref 10c. (d) For similar glycosidation methods, see: (e) Mukaiyama, T.; Nakatsuka, T.; Shoda, S. *Chem. Lett.* **1979**, 487. (f) Hanessian, S.; Bacquet, C.; Lehong, N. *Carbohydr. Res.* **1980**, *80*, C17.

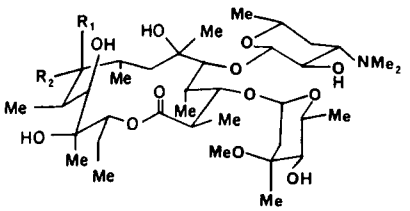
(16) The glycoside **7b**, obtained in the manner described, was identical with an authentic sample prepared from (9*S*)-erythromycylamine[20] via the sequence: HCl/MeOH, 25 °C; $ClCO_2C_6H_4$-*p*-Ph/Et_3N/CH_2Cl_2/aqueous $NaHCO_3$, 25 °C.

(17) (a) The methanolysis (Flynn, E. H.; Sigal, M. V., Jr.; Wiley, P. F.; Gerzon, K. *J. Am. Chem. Soc.* **1954**, *76*, 3121) facilitated isolation and purification of the products. (b) Three minor glycosides were also isolated in addition to **7b** in 13, 12, and 4% yield. (c) One minor glycoside was also isolated in addition to **7d** (1:3).

(18) (a) Cladinoside **9a** (mp 149–151 °C) was prepared in 72% yield from 4-acetylcladinose (cf. ref 6b) by (2-Py-S)$_2$/P(*n*-Bu)$_3$/CH_2Cl_2, 0 °C. (b) Among the metal salts [Ag(I), Cu(II), and Pb(II)] studied, $Pb(ClO_4)_2$ was best in terms of reaction yield, ease of workup, and purity of the product. The glycosidation method employed for **3a** → **3c** failed in the present case.

the glycoside **7d** (55% yield based on consumed **7b**; 37% conversion).[17c] The newly introduced anomeric stereochemistry of **7d** was shown to be of the desired α configuration (vide infra). This stereochemical outcome can be attributed largely to participation by the solvent, CH_3CN, which contributes to an overall double inversion during the course of the reaction.[19] These gratifying results enabled us to achieve site-selective introduction of both sugar moieties in a surprisingly simple manner, avoiding the extensive use of protecting groups.

Completion of the synthesis of erythromycin was carried out in the following manner. Simultaneous deprotection of both the C-4″ hydroxyl group of the cladinose moiety and the C-9 amino group in **7d** by Na–Hg/MeOH[13] furnished (9*S*)-erythromycylamine (**10a**) [mp 126–129 °C, $[\alpha]^{25}_D$ −48.1° (*c* 0.59, $CHCl_3$); 75% yield] which was found to be identical with an authentic



10a $R_1 = NH_2$ $R_2 = H$
10b $R_1 = NHCl$ $R_2 = H$
10c $R_1 = R_2 = NH$

sample prepared from natural erythromycin by a known method.[20] Treatment of **10a** with *N*-chlorosuccinimide (1 equiv) in pyridine at 25 °C gave **10b** (mp 166–170 °C with partial melting at 130–134 °C), which was dehydrochlorinated by AgF in HMPA at 70 °C to yield erythromycinimine (**10c**).[20a,b,21] Hydrolysis of **10c** in water at 5 °C afforded the corresponding ketone (40% overall yield from **10a**), which was found to be identical with erythromycin (**2**) in all respects (^1H NMR, mp, mmp, α_D, mass, IR and chromatographic mobility).[22]

Acknowledgment. We are indebted to Professor Yoshito Kishi for his help and encouragement and, in particular, for his acceptance of the role of principal investigator upon Professor Woodward's death. Financial assistance from the National Institutes of Health (GM04229) is gratefully acknowledged. Mass spectra and FT-IR spectra were provided by the facilities supported by the National Science Foundation (Grants CHE-7908590 and CHE-7805150, respectively). The 250-MHz ^1H NMR spectra were measured by the facility supported by the National Science Foundation (Grant CHE-8019562) at the Massachusetts Institute of Technology.

Supplementary Material Available: Physical properties (IR and ^1H NMR spectra, etc.) of selected synthetic substances (including **2**, **6a,b**, **7a–d**, **8a**, **9a**, and **10a,b**) and scheme used for the synthesis of **2** from **3d** (16 pages). Ordering information is given on any current masthead page.

(19) For sterically demanding glycosidation substrates such as **7c**, pronounced participation by CH_3CN was expected.[15f] The presumed intermediate nitrilium species was expected to have the β configuration, due to the "reverse anomeric effect": West, A. C.; Schuerch, C. *J. Am. Chem. Soc.* **1973**, *95*, 1333. Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2205.

(20) (a) Wildsmith, E. *Tetrahedron Lett.* **1972**, 29. For other known methods, see: (b) Timms, G. H.; Wildsmith, E. *Ibid.* **1971**, 195. (c) Massey, E. H.; Kitchell, B.; Martin, L. D.; Gerzon, K.; Murphy, H. W. *Ibid.* **1970**, 157.

(21) Commonly used methods for oxidation of an amine were unsuccessful when applied to **10a**: (a) Kahr, K.; Berther, C. *Chem. Ber.* **1960**, *93*, 132. (b) Corey, E. J.; Achiwa, K. *J. Am. Chem. Soc.* **1969**, *91*, 1429. (c) Bachmann, W. E.; Cava, M. P.; Dreiding, A. S. *Ibid.* **1954**, *76*, 5554. Ruschig, H.; Fritsch, W.; Schmidt-Thomé, J.; Haede, W. *Chem. Ber.* **1955**, *88*, 883. (d) Bacon, R. G. R.; Hanna, W. J. W. *J. Chem. Soc.* **1965**, 4962. We attribute this failure in part to the hindrance caused by the hydroxyl groups at C-6 and C-11, which are close spatially to the C-9 amino group in **10a**. Thus treatment of **10a** with 3,5-di-*tert*-butyl-1,2-benzoquinone[21b] furnished the corresponding perhydro-1,3-oxazine at C-9/C-11 as a stable product.

(22) The glycoside **3d** (see text) has also been successfully converted to erythromycin: for the sequence employed see the supplementary material. This transformation constitutes another total synthesis of erythromycin, since **3a** (the precursor to **3d**) is derived from erythronolide A[1,2] and the synthesis of erythronolide A has been reported by Corey et al.; see ref 1e in the first paper in this series.

Measurements of Degenerate Radical Ion–Neutral Molecule Electron Exchange by Microsecond Time-Resolved CIDNP. Determination of Relative Hyperfine Coupling Constants of Radical Cations of Chlorophylls and Derivatives[1]

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Chemically induced dynamic nuclear spin polarization (CIDNP) has been shown to be a good method to study photochemical electron transfer.[2] Electron transfer of an excited donor (D) or acceptor (A) molecule produces a geminate radical ion pair which may undergo a back-reaction leaving D and A in their ground states with polarized nuclear spins. It has been pointed out by one of us[3] that if the *only* reaction is electron transfer from D to A followed by back-transfer to regenerate ground states, it may be impossible to observe CIDNP unless the free paramagnetic ions have a relatively long life. This prediction arises directly from the radical pair theory of CIDNP which rigorously requires that at high field the nuclear polarization of the radicals undergoing geminate annihilation is of opposite sign and equal magnitude as that carried by the escaping free ions. If the free ions are converted to the same products as the geminate ions, no observable polarization results *unless* the free ions lose some of their polarization by relaxation, thus making the polarization generated in the geminate process dominant. The conversion of the polarized ions to polarized diamagnetic products can occur by ion annihilation and ion–neutral molecule electron exchange according to (1),

$$*D^+ + D \rightleftarrows *D + D^+ \quad (1)$$

where the asterisks denote nuclear spin polarization. Since the concentration of the neutral molecules is often much higher than that of the ions, this is frequently the most important pathway and leads to failure to observe CIDNP.

In this communciation, we wish to show that fast time-resolved CIDNP spectroscopy can get around this difficulty and give some information on electron exchange kinetics which are difficult to measure directly by other methods.[4] The basis for the success of the time-resolved method is the fact that geminate processes are complete in a fraction of a microsecond, while combination of free ions and/or exchange according to (1) may take tens or hundreds of microseconds depending on concentrations. Thus, if the magnetization is probed, say at 1 μs after the radical ions have been generated by a laser flash, the polarization of products that is probed originates almost exclusively from geminate processes and has not yet been annihilated by the opposite polarization derived from the free ions.

The utility of the method is demonstrated by the photooxidation of chlorophyll and derivatives using quinone. The system had been studied by Roth and collaborators,[5,6] but they failed to observe any polarization of chlorophyll presumably because of rapid exchange according to (1).

Figure 1 shows the pigment polarizations obtainable when a dilute solution ($<10^{-3}$ M) of pigment containing 5×10^{-3} M

*Argonne National Laboratory.

(1) Work performed under the auspices of the Division of Chemical Sciences, Office of Chemical Sciences, Office of Basic Energy Sciences of the U.S. Department of Energy.

(2) H. D. Roth, "Chemically Induced Magnetic Polarization"; L. T. Muus, P. W. Atkins, K. A. McLauchlan, and J. B. Peterson, Eds., D. Reidel, Dordrect, Holland 1977, pp 35–76.

(3) G. L. Closs, *Chem. Phys. Lett.*, **32**, 277 (1975).

(4) G. L. Closs and R. J. Miller, *J. Am. Chem. Soc.*, **101**, 1639 (1979).

(5) A. A. Lamola, M. L. Manion, H. D. Roth, and G. Tollin, *Proc. Natl. Acad. Sci., U.S.A.*, **72**, 3265 (1975).

(6) The polarized quinone signal is visible even in steady state if the solutions are slightly acidified, thus leading to the protonated semiquinone radical, which exchanges with the quinone on a time scale slow relative to relaxation.

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