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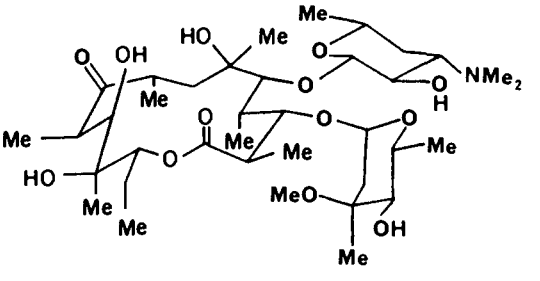
Erythromycin[1] (**1**), produced by a strain of *Streptomyces erythreus*, is the best known of the medicinally important macrolide antibiotics.[2] Structurally, this macrolide contains a 14-membered



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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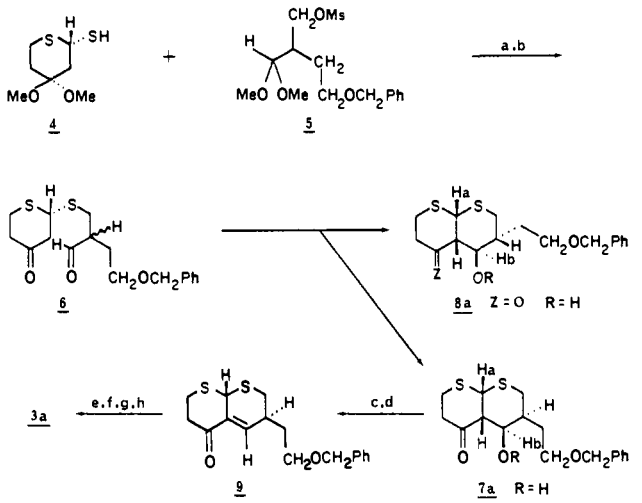
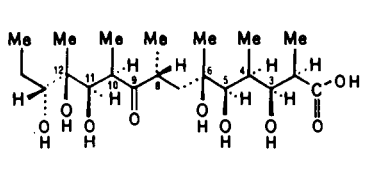
Scheme I[a]



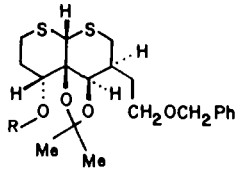
[a] (a) NaH, THF, Me_2SO, room temperature; (b) AcOH, H_2O, room temperature; (c) MsCl, Py, room temperature; (d) alumina, EtOAc, room temperature; (e) $NaBH_4$, MeOH, 0 °C; (f) $MeOCH_2I$, KH, THF, 0 °C; (g) OsO_4, ether, room temperature; $NaHSO_3$, aqueous Py, room temperature; (h) $Me_2C(OMe)_2$,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

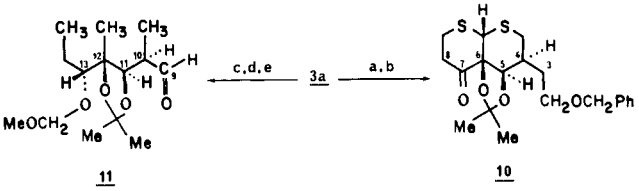


3a R = CH_2OCH_3

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).

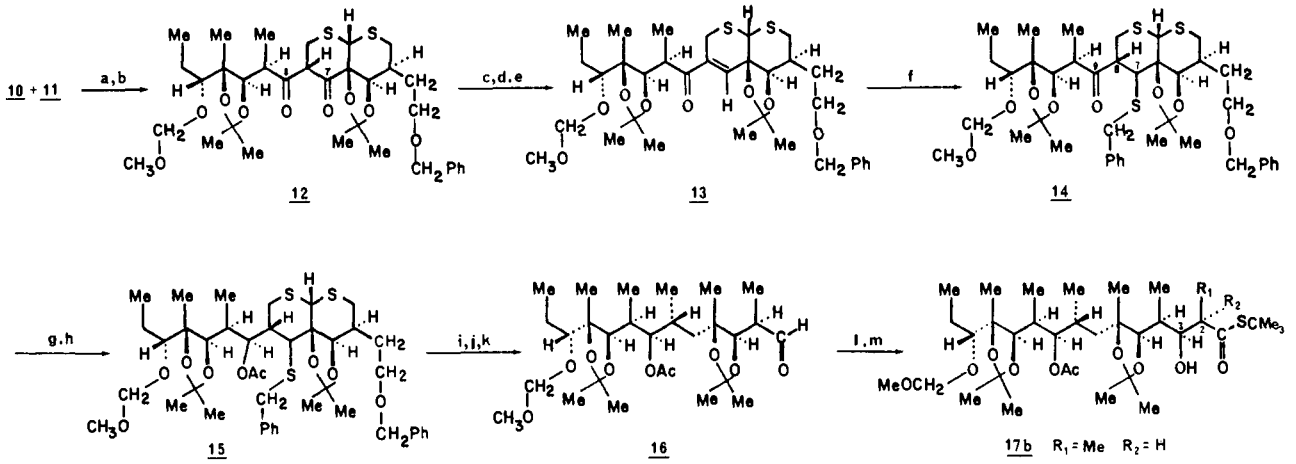
(9) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (c) Buchschacher, P.; Cassal, J. M.; Fürst, A.; Meier, W. *Helv. Chim. Acta* **1977**, *60*, 2747.

(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; (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*-$NO_2C_6H_4SeCN$, $P(n\text{-}Bu)_3$, 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**).

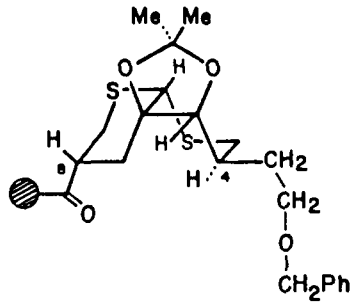
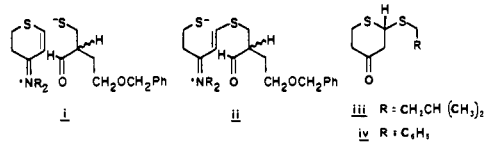


Figure 1.

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 $(i\text{-}Pr)_2NLi$ 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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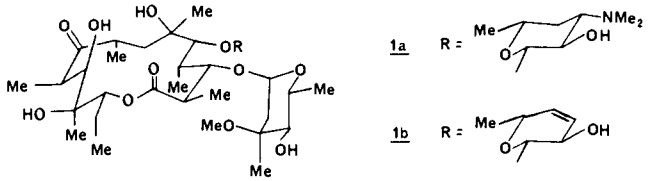
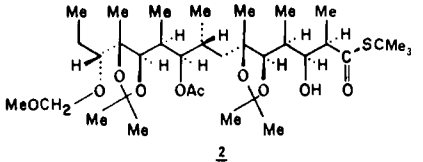
In reporting a total synthesis of erythromycin (**1a**) we described in the preceding paper[1] the synthesis of the erythronolide A seco acid derivative **2** in optically active form. In this paper we wish to report a successful transformation of **2** to **12** (synthetically equivalent to erythronolide A) via lactonization and also demonstrate that the proper functionalization of a substrate is critical for the successful lactonization.



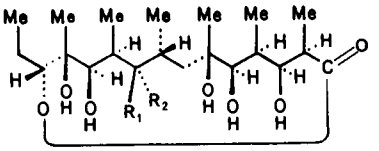
1a R =

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]

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(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.

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