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.

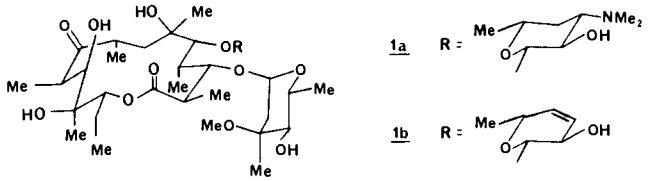
Asymmetric Total Synthesis of Erythromycin. 2. Synthesis of an Erythronolide A Lactone System

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

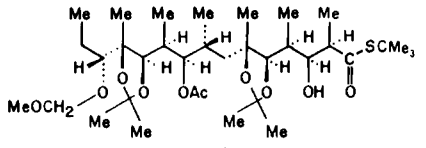
Received February 23, 1981

In 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.



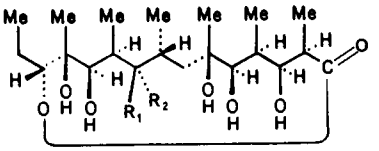
1a R =

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.

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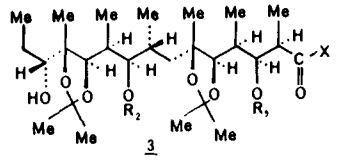
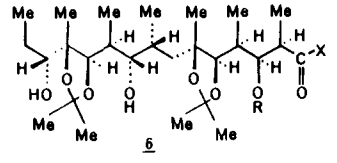
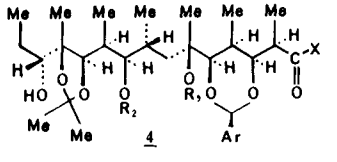
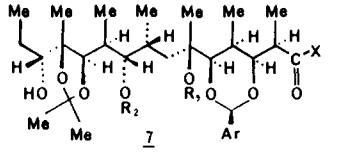
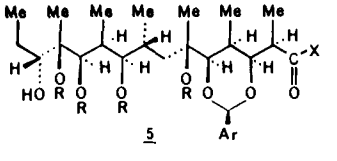
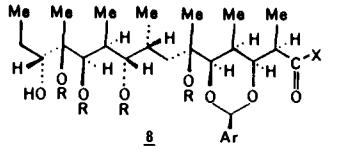
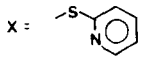
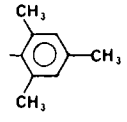
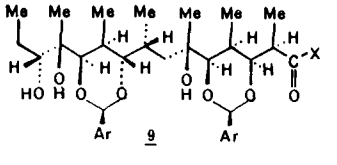
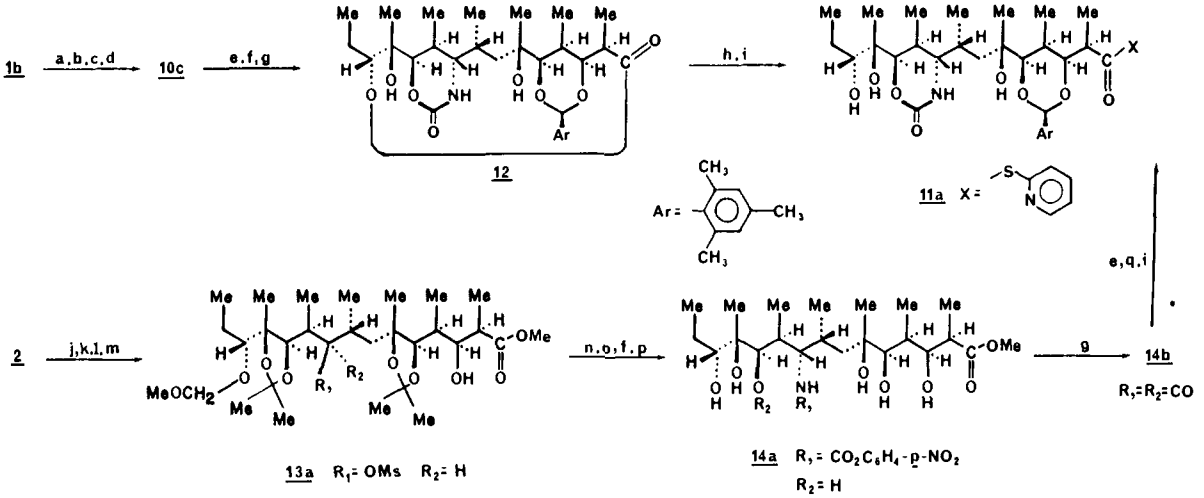
Table I. Results of Lactonization Study

9R substrates	lactone, %	9S 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.

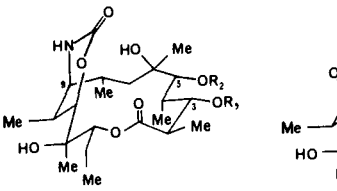
Asymmetric Total Synthesis of Erythromycin. 3. Total Synthesis of Erythromycin

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

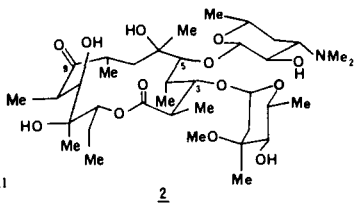
Received February 23, 1981

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

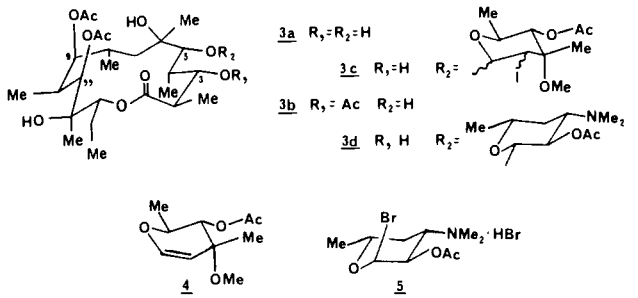


2

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.

§ 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) 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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