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Novel Transannular Rearrangements of Azalide Iminoethers

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Abstract: The transannular reactions between the aglycone hydroxyl groups and the iminoether and lactone groups of the 9a- and 8a-azalide iminoethers **4** and **5** were investigated under a variety of conditions. Translactonization by the 11-hydroxyl groups of **4** and **5** were found to give the corresponding 13-membered iminoethers **21** and **9**. The thermal rearrangement of **4** produced an epimeric mixture of the 9,11-iminoethers **15** and **16**. Further elaboration of isomer **16** produced 8-*epi* azithromycin **20**. Finally, we have proposed an alternative structure, the amino γ-lactone **25**, for one of the reported products (**14**) from the Beckmann rearrangement of erythromycin A (*9E*)-oxime **13**. An authentic sample of 9a-aza-9a-homoerythromycin A **14** was prepared in three steps from iminoether **4**.
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INTRODUCTION

Transannular rearrangements involving the 6-, 11- and 12-hydroxyl groups of erythromycin A and related macrolide antibiotics have played a pivotal role in the chemistry of these compounds.[1a-f] For example, erythromycin A (**1**) undergoes an acid-catalyzed cascade of transformations involving the transannular addition of the 6-hydroxyl group to the ketone, followed by elimination of water to give anhydroerythromycin A (**2**) and subsequent formation of a 6,9-9,12-spiroketal.[1a] The acid degradation of erythromycin has been associated with unpredictable oral absorption and gastrointestinal intolerance of erythromycin A in the clinic, and has inspired the preparation of erythromycin derivatives with improved acid stabilities, namely, clarithromycin,[2a,b] dirithromycin,[2a,c] roxithromycin[2a,d] and azithromycin.[3b] Anhydroerythromycin **2** can undergo another transformation, that is, a translactonization by the 11-hydroxyl group to give the 12-membered macrolide **3**.[1a] This equilibration process has been observed under acidic, basic or thermal reaction conditions and provides a separable mixture of **2** and **3**. The observation that **2** undergoes a translactonization while a variety of monocyclic macrolides do not, provides evidence that the bridged dihydrofuran ring imparts a macrocyclic conformation to **2** which is suitable for translactonization by the 11-hydroxyl group.

Recent studies involving the Beckmann rearrangements of the (*9E*)- and (*9Z*)-oximes of erythromycin A have led to the syntheses of two series of ring expanded, 15-membered, nitrogen containing macrolides collectively known as the azalides.[3a,b] In the Beckmann rearrangement of the (*9E*)-oxime, the transannular addition of the 6-hydroxyl to the intermediate nitrilium species results in the formation of the 9a-aza-6,9-iminoether **4**. Similarly, the Beckmann rearrangement of the (*9Z*)-oxime produces the 8a-aza-6,9-iminoether **5**. These structures bear a striking similarity to anhydroerythromycin A (**2**) and might be expected to undergo an intramolecular translactonization to give novel 13-membered azalides. In addition, the iminoether groups of **4** and **5** might undergo internal transformations by the neighboring ring hydroxyl groups with the formation of new bicyclic iminoethers.

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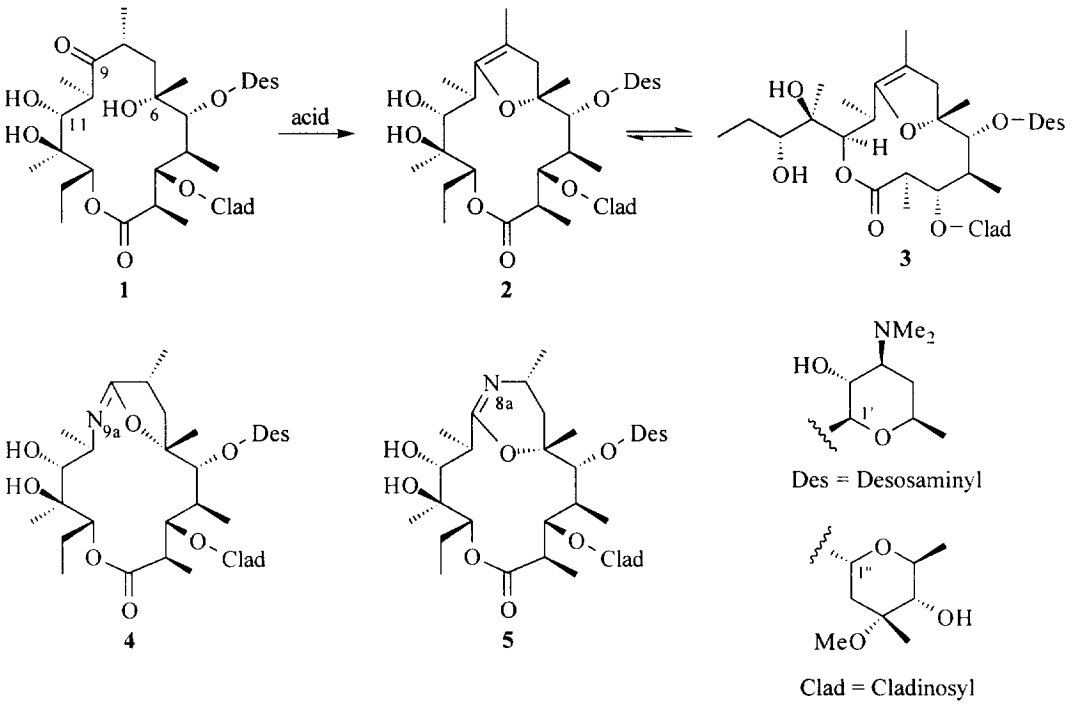
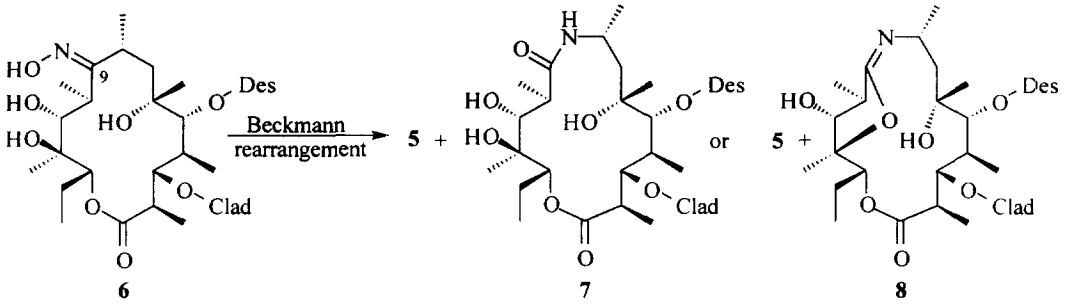
In this paper we describe the transannular reactions of the iminoether and lactone groups of **4** and **5**, and related azalides, by the aglycone hydroxyl groups. Elaboration of these transformed products leads to the synthesis of several novel macrocyclic platforms. Furthermore, we provide spectroscopic and chemical evidence supporting an alternative structural assignment for one of the products derived from the Beckmann rearrangement of (9*E*)-erythromycin A oxime.



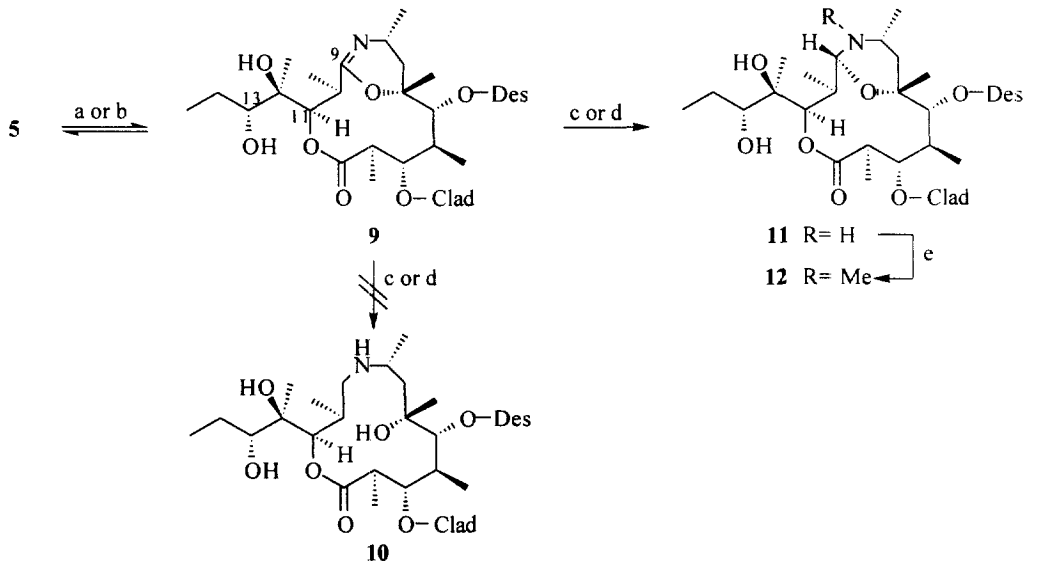
RESULTS AND DISCUSSION

The Beckmann rearrangement of (9*Z*)-erythromycin A oxime **6** produced mixtures of the 6,9-iminoether **5** and the lactam **7** when performed under aqueous conditions, or the 6,9-iminoether **5** and the 9,12-iminoether **8** when performed under anhydrous conditions.[3a] The transannular rearrangement of **5** was attempted under a variety of reaction conditions with the following results: heating in nitromethane for 18 hours at 100°C led to the recovery of **5**; heating in pyridine for 18 hours at 100°C led to the recovery of **5** and a trace amount of the translactone **9**; heating in a methanolic suspension of potassium carbonate[4] for 7.5 hours at 55°C produced a 2:1 mixture of **5** and **9**; and either reacting with an ethanolic solution of lithium hydroxide monohydrate for 8 hours at room temperature or heating in glacial acetic acid for 16 hours at 70°C produced a 1:1 mixture of **5** and **9**. While the translactonization in acetic acid provided the same ratio of **5** and **9** as the lithium hydroxide mediated transformation, the latter method provided the cleanest conversion to the translactone **9**. The structural identification of **9** was based primarily upon the downfield shift of H-11 from 3.48 ppm in **5** to 5.25 ppm in **9**, and the corresponding upfield shift of H-13 from 4.89 ppm in **5** to 2.92 ppm in **9**.[5] The reversibility of the translactonization was demonstrated by re-equilibrating **9** in a solution of lithium hydroxide in ethanol for 8 hours to give a 1:1 mixture of **5** and **9**. The translactone **9** was found to be stable towards isomerization as a solid or in $CDCl_3$ solution at room temperature.



We have observed that bridged, 15-membered macrolides whose cyclic iminoethers contain an exocyclic double bond differ from those with an endocyclic double bond in three respects. First, 2-iminotetrahydrofurans such as **4** and **8** are readily reduced with sodium borohydride in methanol. In contrast, the dihydrooxazine **5** is not reduced under these conditions and is only slowly reduced with sodium borohydride in ethylene glycol.[6] Secondly, the exocyclic 2-iminotetrahydrofurans **4** and **8** have infrared absorptions at higher frequency, 1705 cm^{-1} and 1695 cm^{-1} respectively, than the endocyclic dihydrooxazine **5**, 1665 cm^{-1}. Finally, as will be later demonstrated with compound **4**, the iminoethers with endocyclic double bonds are thermodynamically preferred over their exocyclic counterparts. The observation that the 6,9-iminoether **5** was not transformed into the 9,12-iminoether **8** upon heating in nitromethane is consistent with **5** being the thermodynamically more stable iminoether isomer.[7]

Reduction of the translactone **9** using sodium borohydride in ethylene glycol produced the tetrahydrooxazine **11**, instead of the expected azalide **10**. The reduction of **9** under more forcing conditions (Pt, HOAc, 1000 psi H_2, 18 hours) also gave **11** as the predominant product. The formation of a stable tetrahydrooxazine product was unexpected and was not observed in the analogous reduction of the parent 15-membered azalide **5**.



(a) LiOH, EtOH; (b) HOAc 70°C; (c) $NaBH_4$, ethylene glycol; (d) H_2, PtO_2, HOAc; (e) HCHO, HCO_2H

The nitrogen of the tetrahydrooxazine **11** was methylated under Eschweiler-Clarke conditions to give derivative **12**. The stereochemistry at the 9-position of **11** and **12** was determined by a combination of NOESY and NOE difference ^{1}H NMR experiments. Strong NOE's between H-9 in **11** and H-8, H-10, the 6-methyl protons and the 10-methyl protons indicated that the newly created stereocenter at C-9 has the (*R*)-configuration.[8] In contrast, the (*S*)-isomer would be expected to produce a strong NOE between H-9 and the 8-methyl protons. Similarly, H-9 in **12** produced strong NOE's with H-8, H-10, and the 6-methyl, 10-methyl and 8a-methyl groups. A modeled, representative conformation of structure **12** that is consistent with the NOE interactions is depicted in Figure 1.

Confirmation of the bridging atom as the 6-oxygen, and not the 12- or 13-oxygens, was determined from a detailed NMR analysis of **12**. The appearance of the 13-hydroxyl proton, identified by its coupling with the H-13, eliminated the possibility of a 13-oxygen bridged structure. Likewise, the appearance of a 12-hydroxyl proton, identified by a 4-bond coupling with the 12-methyl, eliminated the possibility of a 12-oxygen bridged structure. In addition, a long-range COSY correlation between H-9 and the 6-methyl protons was observed which is consistent with the 6,9-bridged structure **12** and not the alternative 12- or 13-oxygen bridged structures.

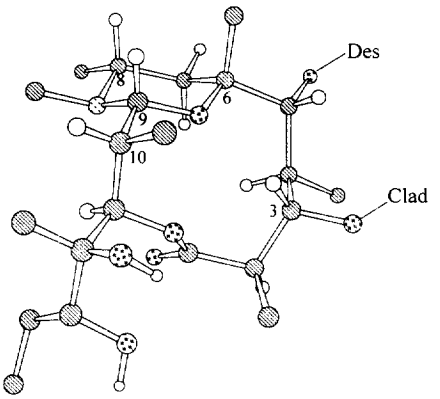


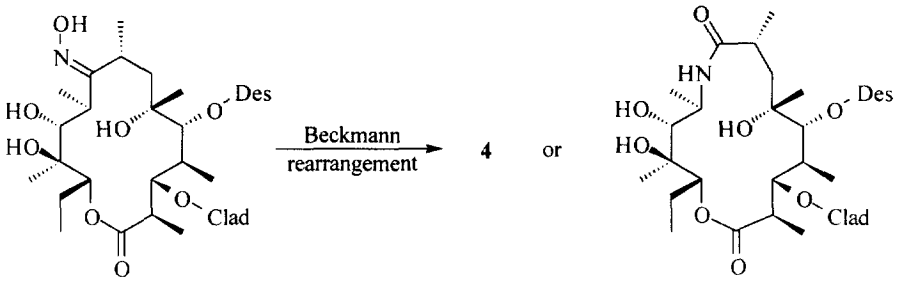
Figure 1. Modeled, representative conformation of structure **12** derived from the NOE data. The aglycone and hydroxyl protons are shown as unshaded circles.

It is interesting to note that the tetrahydrooxazine **11** does not undergo a retro-translactonization to the 15-membered isomer in the presence of an ethanolic solution of lithium hydroxide, as did its precursor **9**. Examination of the modeled conformation of structure **12**, the *N*-methyl derivative of **11**, shows that the lactone carbonyl and the 13-hydroxyl group are in reasonable proximity for translactonization to occur. The absence of a translactonization product suggests that structure **11** is the thermodynamically preferred isomer.

Next, the transannular rearrangements of the products derived from the Beckmann rearrangement of (9*E*)-erythromycin A oxime **13**, namely the 6,9-iminoether **4** and the lactam **14** [3b], were investigated. The thermal equilibration of the 6,9-iminoether **4** in xylenes (1.5 hours at 120°C) produced a mixture of **4** and two isomeric iminoethers. When **4** was heated in nitromethane at 100°C for 1 hour, a 16:56:28 ratio of **4** and the same two isomeric iminoethers resulted. The thermal rearrangement in nitromethane provided the major isomer of the iminoethers mixture as a crystalline precipitate upon cooling. The second isomer could be isolated by the silica gel chromatography of the mother liquors.

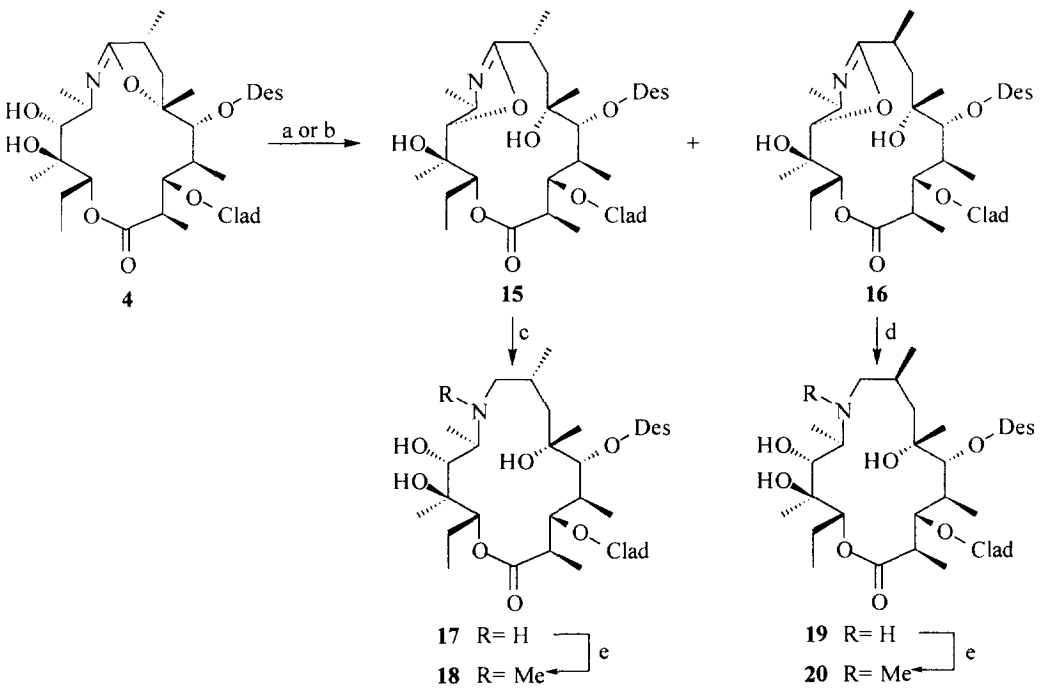
The formation of two new iminoethers from a macrolide which contains two aglycone hydroxyl groups led us to believe that we had isolated the isomeric 9,11- and 9,12-iminoethers. The identification of the crystalline precipitate from nitromethane as the 9,11-iminoether **15** was supported by 1) the shift of the infrared absorption of the 2-iminotetrahydrofuran **4** (1705 cm^{-1}) to that of an oxazoline (1650 cm^{-1}), 2)

sodium borohydride reduction in ethylene glycol of **15** to the amine **17**, and 3) the assignment of the 6- and 12-hydroxyl protons in the ^{1}H NMR spectra of **15** at 3.70 and 3.65 ppm. Confirmation of this structure[9] was provided by an X-ray analysis of a poly-solvated crystal grown in nitromethane.



13 **14**

The identification of the second isomer was more problematic. Tentative assignment of the second iminoether as the 9,12-iminoether was supported by an infrared absorption at 1650 cm^{-1} and by the identification of a 6-hydroxyl proton (3.34 ppm) in its ^{1}H NMR spectrum. However, catalytic reduction of the second isomer failed to produce the amine **17**, as would be expected of the 9,12-iminoether, but resulted in the formation of product which was isomeric with **17**. This led us to conclude that the second iminoether isomer was not the 9,12-iminoether, but the 8-epi-9,11-iminoether **16**. We had previously observed a similar



4 **15** **16**

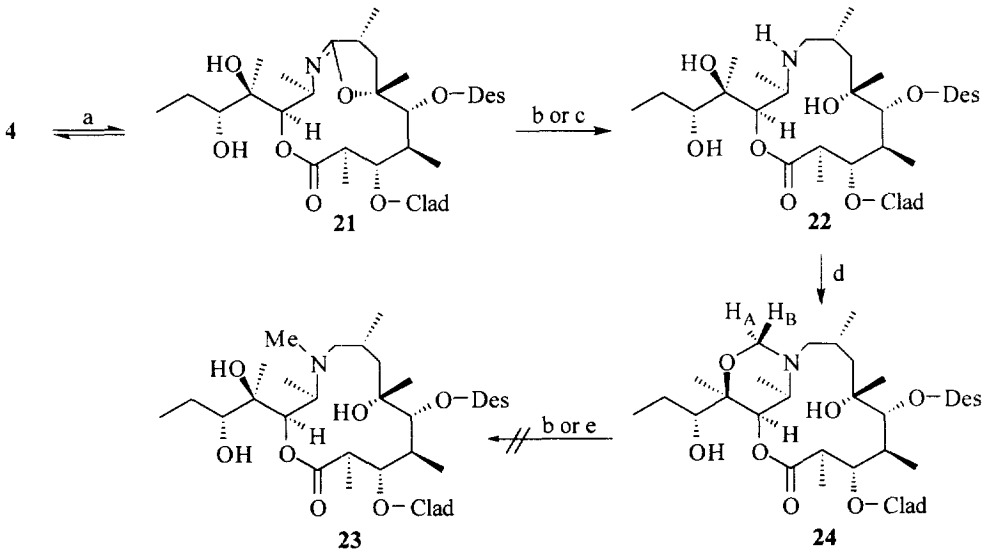
(a) xylenes, 120°C, 1.5 hours; (b) $MeNO_2$, 100°C, 1 hour; (c) $NaBH_4$, ethylene glycol; (d) H_2, PtO_2, HOAc, 1000 psi; (e) HCHO, HCO_2H.

epimerization at the 10-position of the 9,12-iminoether **8**.[3a,10] The epimerization of the 9,12-iminoether **8** proceeded through a 9,10-didehydro enamine tautomer and resulted in the incorporation of deuterium at the 10-position when conducted in the presence of deuteriomethanol. In the present case, the epimerization at the 8-position would be expected to proceed through an 8,9-didehydro enamine with incorporation of deuterium at the 8-position.[11] Heating a solution of **4** in deuteriomethanol provided a mixture of iminoethers, similar to the mixture obtained from the nitromethane reaction, from which 8-deuterio-8-epi-9,11-iminoether was isolated. The location of the 8-deuterio atom was evident by the disappearance of the H-8 signal at 2.75 ppm in **16**, the collapse of the H-7a triplet to a doublet at 2.29 ppm and the collapse of the 8-Me doublet to a singlet at 1.19 ppm in the ^{1}H NMR spectrum.

Structural confirmation of **16** as a 9,11-iminoether and not a 9,12-iminoether was achieved by a deuterium isotope shift study. Two ^{13}C NMR spectra were recorded in $CDCl_3$ under identical conditions except for the addition of either H_2O or D_2O. Four carbons showed 0.12-0.13 ppm upfield shifts in the D_2O sample which were ascribable to a two-bond deuterium isotope effect. This indicated the attachment of a free hydroxyl group to these carbons. The four carbons were unambiguously identified as C-4", C-2', C-6 and C-12, thereby confirming the 11-oxygen as the bridging atom in the iminoether.

The identification of the iminoether **16** as an 8-epi isomer lead to the conclusion that its reduction product was the 8-epi azalide **19**. Eschweiler-Clarke methylation of **19** provided 8-epi-azithromycin **20**. A comparison of the ^{1}H NMR data for **20** with that of azithromycin[12] **18** showed a close similarity between the chemical shifts and coupling constants of these two isomers. This suggested that 8-epi azithromycin and azithromycin exist in similar conformations in $CDCl_3$ solution.

The base mediated translactonization of the 6,9-iminoether **4** using either lithium hydroxide monohydrate in ethanol or heating in a suspension of potassium carbonate in methanol, gave an approximately 2:1 mixture of **4** and the 11-translactone **21**. The conversion was best accomplished with lithium hydroxide in ethanol, as the latter procedure produced small amounts (ca. 10%) of the thermal rearrangement products **15** and **16**. The structural identification of the 11-translactone **21** was based primarily on a downfield shift of H-11 from 3.60 ppm in **4** to 5.16 ppm in **21** and an upfield shift of H-13 from 4.89 ppm in **4** to 3.00 ppm in **21**.



(a) LiOH, EtOH; (b) H_2, PtO_2, 1000 psi; (c) $NaBH_4$, ethylene glycol; (d) HCHO, HCO_2H; (e) $NaCNBH_3$, MeOH.

The infrared absorption of the translactone **21** at 1705 cm^{-1} was identical with that of its 2-iminotetrahydrofuran precursor **4**. Attempted translactonization of **4** in acetic acid, under the conditions used for the translactonization of **5**, resulted in the formation of a complex mixture of products which contained trace quantities of **21**.

In contrast to the facile sodium borohydride reduction of the iminoether **4**, the iminoether **21** was found to be unreactive towards sodium borohydride in methanol. Reduction of **21** with a large excess of sodium borohydride in ethylene glycol produced a mixture of **21**, **22**, and 9-deoxo-9a-aza-homoerythromycin **17**. The formation of **17** resulted from the retro-translactonization of **21** to give **4**, followed by reduction with sodium borohydride. The identification of the amine **22** was not obvious. The ^1H NMR of **22** in $CDCl_3$ contained broadened resonances and did not show a discernible H-11 proton at 25°C. Upon heating to 55°C, however, H-11 appeared as a broad singlet at 5.04 ppm. This indicated that the 13-membered azalide existed in a number of slowly interconverting conformations at 25°C.

High pressure hydrogenation of **21** in acetic acid, using reagent quantities of platinum oxide, gave a clean conversion to the reduction product **22** without the formation of **17**. Methylation of the amine **22** under Eschweiler-Clarke conditions produced a surprising result. The adduct **24** was found to be unexpectedly stable and reduction to the expected azalide **23** was not achieved. The tetrahydrooxazine **24** was isolated and subjected to more forcing reduction conditions, including those of Eschweiler-Clarke methylation with a large excess of formic acid, reduction with sodium cyanoborohydride in methanol, and high pressure hydrogenation with reagent quantities of platinum oxide in acetic acid. All of these reaction conditions resulted in the recovery of **24**. As expected, the addition of formaldehyde to a solution of **22** readily produced the tetrahydrooxazine **24**.

The propensity for 13-membered azalides to form stable aminal rings, i.e. **11** and **24**, most likely results from the stabilizing effect of locking the otherwise conformationally mobile 13-membered rings into rigid bicyclic systems. This was reflected in the sharp, well defined ^1H NMR spectra of **24**, which is in contrast to the poorly resolved spectra of its precursor **22**. The identification of the 12-oxygen, and not the 6- or 13-oxygens, as the bridging atom in the formaldehyde adduct **24** was based on a NOESY ^1H NMR experiment. Interactions of H_A of the aminal methylene group with H-9a and the 10- and 12-methyl protons, and of H_B of the aminal methylene group with H-8, are consistent with the structure **24** as shown in Figure 2. Alternative conformations of the tetrahydrooxazine ring or alternative bridged structures involving either the 6-oxygen or 13-oxygen would not allow for the observed NOESY interactions. The presence of a hydrogen bond between the 6-hydroxyl group and the ring nitrogen (dashed bond in Figure 2) was inferred from the NOESY interactions between the hydroxyl proton and H-3, (H-4 or H-8), H-10, H-7b and H_B of the aminal methylene group.

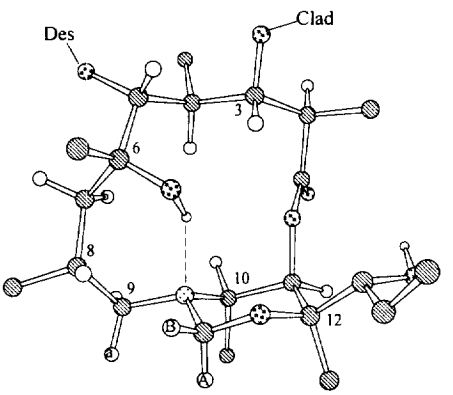
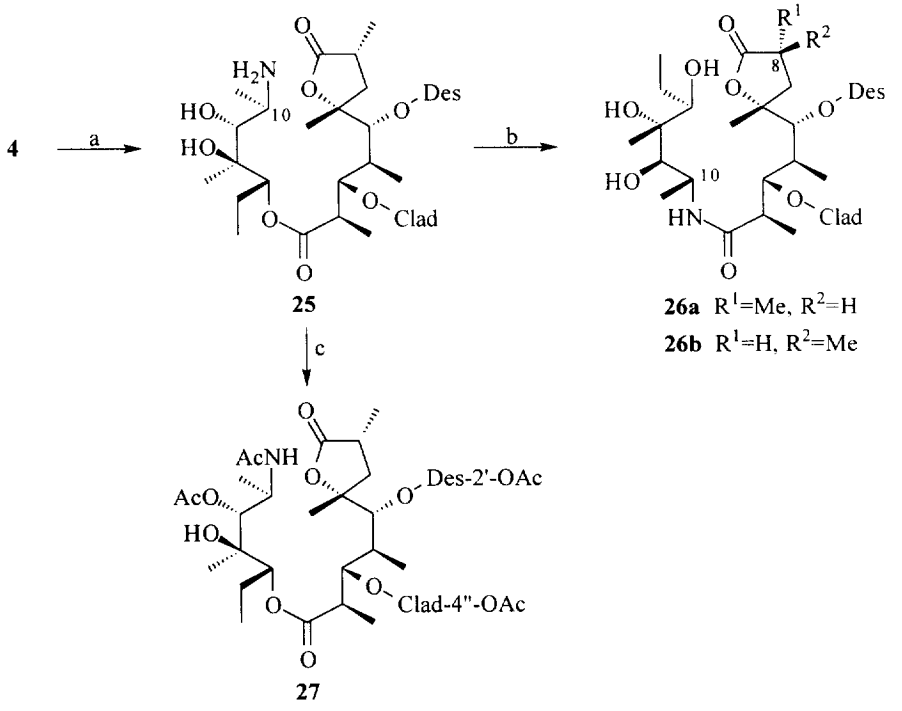


Figure 2. Modeled, representative conformation of structure **24** derived from the NOE data. The aglycone and hydroxyl protons are shown as unshaded circles.

Impetus for examining possible transannular reactions of the lactam **14** was based primarily on its reported[3b] infrared amide absorption of 1760 cm^{-1}. This high frequency absorption is comparable to that observed in ring-strained, beta-lactam derivatives and suggested that the macrocyclic conformation had produced a torsionally strained, non-planar amide. It was interesting to see if this unusual conformation might also be suitable for the transannular reactions between the 6-, 11-, or 12-hydroxyl groups and the lactam or lactone groups.

The synthesis of the lactam **14** proved difficult in our hands. The Beckmann rearrangement of the (9*E*)-oxime **13** is reported[3b] to give the lactam **14** when a pyridine solution of **13** is treated with an ether solution of *p*-toluenesulfonyl chloride, whereas the 6,9-iminoether **4** is produced when an aqueous acetone solution of **13** and sodium bicarbonate is treated with *p*-toluenesulfonyl chloride. Our attempts to replicate the synthesis of the lactam using the TsCl/pyridine conditions led to the formation of only the 6,9-iminoether **4**. Surprisingly, a product that was consistent with the data reported for the lactam was isolated in less than 5% yield from the Beckmann rearrangement in aqueous acetone. This material was employed in our initial translactonization attempts with unexpected results.

Addition of lithium hydroxide monohydrate to an ethanolic solution of the "lactam" produced two isomeric products **26a** and **26b** in which the macrocyclic lactone (ν_{max} 1725 cm^{-1}) had been converted into an amide group (ν_{max} 1660 cm^{-1}). Repeating this reaction in CD_3OD in the presence of NaOD resulted in the incorporation of deuterium at the C-8 position of **26a** and **26b** which suggested that the products were epimeric at that position. The rearrangement of the "lactam" was also observed in $CDCl_3$ solution and proceeded with retention of configuration at the C-8 position to give **26a**. Since these observations were inconsistent with the reported lactam structure **14**, the data supporting that structure was reexamined.



(a) HOAc, H_2O; (b) LiOH, EtOH; (c) Ac_2O, C_5H_5N.

The tetra-acetate derivative of the "lactam" was prepared by the literature procedure[3b] and its physical data, like that of the precursor "lactam", were found to be in excellent agreement with the reported values. However, we have concluded that this data is more consistent with the structure **27** for the tetraacetate derivative, and the amino γ-lactone **25** as its "lactam" precursor. The 1760 cm^{-1} infrared absorption was reinterpreted as that of a γ-lactone and not a lactam. The rearrangement[13] of **25** in $CDCl_3$, therefore, produces the amide **26a** which, under basic conditions, epimerizes at the 8-position to give the isomer **26b**.

The complete ^1H and ^{13}C NMR assignments for structures **25**, **26a** and **27** have been determined by a combination of COSY, TOCSY, HMQC, HMQC-TOCSY and HMBC techniques. The downfield shift of H-10 from 3.09 ppm in **25** to 4.37 ppm in **27** is consistent with the acylation of the primary amine. Furthermore, the amide proton of **27** at 7.40 ppm correlates with H-10 in the COSY spectrum and shows correlations with the H-10, H-11 and the 10-methyl in the TOCSY spectrum. Also, the infrared spectrum of **27** shows an amide absorption at 1660 cm^{-1} while retaining the 1760 cm^{-1} absorption of the γ-lactone. Similarly, the rearrangement product **26a** shows a downfield shift of the H-10 resonance signal to 4.11 ppm and its infrared spectrum shows an amide band at 1660 cm^{-1} and a γ-lactone absorption at 1760 cm^{-1}.

The identification of the amino γ-lactone **25** led to the conclusion that the 6,9-iminoether **4** was the only product that was directly formed in the Beckmann rearrangement of (9*E*)-erythromycin A oxime **13** at ice bath temperatures.[9] The amino γ-lactone **25** was presumably formed by the hydrolysis of **4**, possibly during a prolonged acidic work-up of a Beckmann rearrangement reaction. This suspicion was supported by the observation that the 6,9-iminoether **4** was readily hydrolyzed to **25** in dilute aqueous acetic acid.

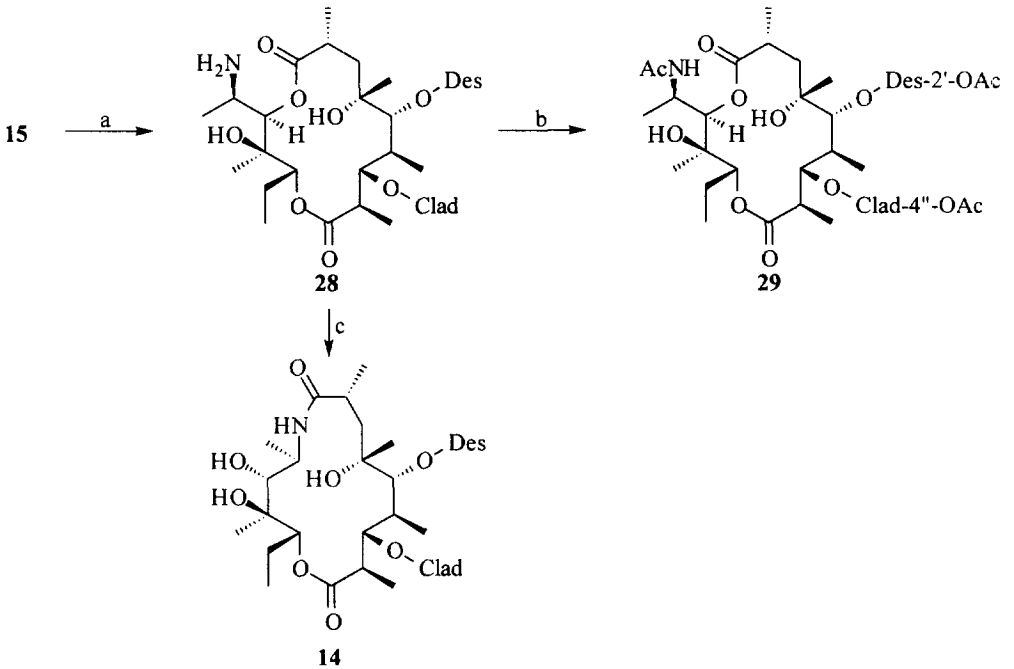
The hydrolysis of the 6,9-iminoether **4** to the amino γ-lactone **25** suggested that hydrolysis of the 9,11-iminoether **15** would provide the amino dilactone **28**, which could then be cyclized to form the authentic lactam **14**. The aqueous acetic acid hydrolysis of **15** indeed provided the amino dilactone **28** in good yield.[14] This unusual structure was fully characterized by a variety of NMR techniques and was derivatized as the triacetyl analog **29**. An extensive set of one-bond, relayed, and long range ^1H-^{13}C connectivities, established by HMQC, HMQC-TOCSY, and HMBC experiments, respectively, allowed unambiguous assignments for all ^1H and ^{13}C resonances of structure **28**. Particularly noteworthy was the HMBC spectrum which yielded over 80 two- and three-bond, proton-carbon correlations. For example, the two very similar lactone carbons could be clearly distinquished as C-1 (176.4 ppm) correlated with H-2, H-3, H-13 and the 2-methyl, whereas C-9 (176.6 ppm) correlated with H-7, H-8, H-11 and the 8-methyl.

The thermal rearrangement of **28** to the lactam **14** was not as facile as expected. The unexpected stability of **28** toward lactamization is presumably due to an internal network of hydrogen bonds involving the primary amine and the 6- and 12-hydroxyl groups which effectively removes the amine from proximity to the lactone carbonyl. The presence of a strong hydrogen bond involving the 6-hydroxyl proton was manifested as a concentration independent singlet at 3.9 ppm in the ^1H NMR of **28.** The aminodilactone **28** did, however, rearrange slowly in methanol at 60°C to give the lactam **14** and a minor amount of the γ-lactone **25**. Evidently, the protic solvent disrupts the internal hydrogen bonds and allows the amine, or the 6-hydroxyl group, to react with the lactone.

Complete ^1H and ^{13}C NMR signal assignments of the lactam **14** were established by COSY, TOCSY, LR-COSY, one-bond ^1H-^{13}C correlation (HETCOR) and long-range ^1H-^{13}C correlation (LR-HETCOR) spectra. The location of the nitrogen atom in the macrolide ring was evident on the basis of ^1H-^1H correlations in the TOCSY spectrum between the NH and H-10, H-11 and the 10-methyl protons. Similar conclusions were derived from the observed long-range ^1H-^{13}C correlations between the lactam carbonyl and the H-7 and 8-methyl protons. Further evidence for the location of the nitrogen atom could be inferred from the chemical shift values of H-8 (2.20 ppm) and H-10 (4.11 ppm). Confirmation of the lactam structure **14** was provided by an X-ray analysis of the crystalline hydrochloride salt. A 3-D representation of the X-ray structure is shown in Figure 3.

The synthesis of authentic **14** provided a means to re-examine the crude products of the Beckmann rearrangement of the (9*E*)-oxime of erythromycin A **13** by ^1H NMR spectroscopy. This study revealed that

if **14** is formed during the Beckmann rearrangement, it is present in an amount which is below the detection limits of the 500 MHz ^{1}H NMR. The unlikely possibility that the lactam **14** is formed during the Beckmann rearrangement and subsequently dehydrated to the 6,9-iminoether **4** was also investigated. The lactam **14** was subjected to the Beckmann rearrangement conditions, namely, reaction with *p*-toluenesulfonyl chloride in pyridine or with *p*-toluenesulfonyl chloride in a mixture of aqueous sodium bicarbonate and acetone. In each case, the recovery of **14** was strong evidence that the 6,9-iminoether **4** was not formed from the lactam **14** during the Beckmann rearrangement of **13**.



(a) HOAc, H_2O; (b) Ac_2O, C_5H_5N; (c) MeOH, 60°C.

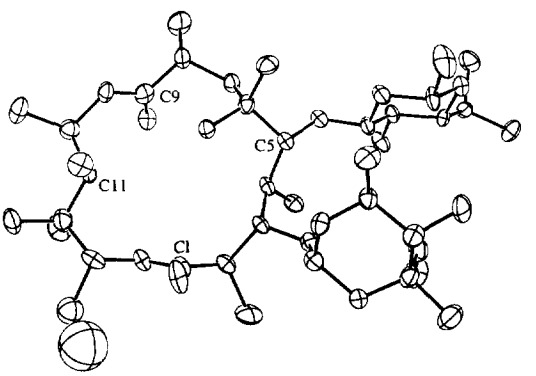


Figure 3. ORTEP drawing of the lactam **14** as viewed from above the lactone carbonyl group.

The antibacterial activities of derivatives **9**, **11**, **12**, **14**, **15**, **16**, **18**, **19**, **20**, **21**, **22**, **24**, **25** and **28** were determined against a panel of gram-negative and gram-positive bacteria. All the derivatives were found to be weakly active relative to the standards, 9-deoxo-8a-aza-8a-methyl-homoerythromycin A[3a] and 9-deoxo-9a-aza-9a-methyl-homoerythromycin A (azithromycin)[3b] **18**. Surprisingly, 9a-aza-9a-homoerythromycin **14** was found to be almost inactive. This is in contrast with the isomeric 8a-aza-8a-homoerythromycin **7** which displayed gram-positive activities comparable with that of erythromycin A, but is consistent with the poor activities observed for a related 9a-aza-11-deoxy 14-membered lactam.[15]

EXPERIMENTAL SECTION

General procedures. The 6,9-iminoethers **4** and **5** were prepared by their reported procedures.[3a,b] Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were determined on Varian XL-400, Unity-400 and Unity-500 spectrometers. Chemical shifts are reported in ppm and are referenced to chloroform (7.24 ppm for ^{1}H and 77.0 ppm for ^{13}C). The infrared spectra were run in $CHCl_3$ solution on a model 1420 Perkin-Elmer ratio recording infrared spectrophotometer. Mass spectra were measured on a Finnigan MAT90. Thin layer chromatography was performed on Analtech silica gel GF plates and column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Unless otherwise indicated, a 90:10:1 mixture of methylene chloride: methanol: concentrated ammonium hydroxide was used to both develop the TLC plates and to pack, load and elute the silica columns. Microanalyses were carried out by Robertson Laboratory Inc., Madison, NJ.

Two-dimensional NMR methods. Proton-proton scalar coupling correlations spectra (COSY) were obtained using the standard 90-t1-90-t2 pulse sequence[16] and its variant, referred to as long-range (LR) COSY, 90-t1-tau-90-tau-t2 using tau delays of 0.25 sec.[16] Relayed ^{1}H-^{1}H correlations were obtained using the TOCSY experiment[17] employing FLOPSY[18] as mixing scheme with a mixing time of 0.04-0.08 sec. One-bond ^{1}H-^{13}C correlations were obtained by the HMQC pulse sequence[19] using a BIRD null delay of 0.3 sec. Long-range ^{1}H-^{13}C experiments were obtained using the HMBC pulse sequence[20] with a delay optimized for ca. 5 Hz ^{1}H-^{13}C coupling. Relayed ^{1}H-^{13}C correlations were recorded using the HMQC-TOCSY technique[21] using the same mixing time as TOCSY. Inverse detection techniques (HMQC, HMBC and HMQC-TOCSY) were used for all compounds except for the ^{1}H-^{13}C correlation data for compound **14** which were obtained on an older Varian XL-400 spectrometer using the HETCOR[22] and LR-HETCOR[23] pulse sequences. NOE data were obtained by means of the NOESY pulse sequence[24] using a mixing time of 0.3 sec. One-dimensional NOE difference spectra were also utilized to resolve certain NOE assignments ambiguities.

Molecular modeling of structures 12 and 24. Conformations of structures **12** and **24** were generated using a subset of the NOE's described herein as constraints in our proprietary distance geometry algorithm. Two hundred conformations of each structure were generated and then energy minimized using MMFF94(s)[25] with a distance dependent dielectric of 2r. The resultant energy minimized conformations were then filtered for compliance to the original constraints; the lowest energy conformations which match the constraints for each structure are represented in figures 1 and 2. Additionally, coupling constants predicted[26] on the basis of the models generated were found to compare well with those experimentally determined, which were not incorporated as constraints in either the generation or filtering of the conformations.

In developing the NOE constraints, "dummy" atoms representing the center of mass for methylene and methyl hydrogens were employed to avoid uncertainty regarding assignment of a particular hydrogen as well as unnecessary loss of conformations due to simple rotation of hydrogens about the methyl group. The particular NOE's employed for structures **12** and **24** are listed below with their relative strengths. The constraints for very strong (vs) signals was 2-3Å, for vs when using a dummy atom was 2-4Å, for strong (s)

was 2-4Å, and for medium (m) was 2-6Å. The distance range for the energy minimized conformations which matched all of the constraints upon filtering are listed in parentheses adjacent to the respective constraint.

For structure **12**, the constraints used were: (2.2-2.3Å) H-3,H-1"(vs); (2.1-2.2Å) H-4,H-7 (s); (2.2-3.6Å) H-5,H-1'(s); (2.9-3.8Å) 4-Me,H-1'(s); (2.8-2.9Å) H-9,6-Me (vs), (2.6-3.9Å) H-11,12-Me (s); (2.6-3.9Å) H-10,12-Me (s); (3.0-3.1Å) H-2,4-Me (s); (2.9-3.0Å) H-9,10-Me (s); (3.3-3.6Å) OMe,3"-Me (vs); (2.6-2.9Å) 2-Me,H-1" (vs); (2.3-3.6A) H-5,H-5" (s); (2.9-3.8Å) 4-Me,H-1' (s); (2.1-5.9Å) H-1',H-5" (m); (3.4-3.8Å) H-3,10-Me (m); (2.9-3.9Å) H-13,15-Me (m); (3.2-3.6Å) H-11,8a-Me (s). Coupling constants (Hz) predicted for structure **12** as shown in Figure 1 compared to those experimentally determined (in parentheses) are: $J_{2,3}$ 10.1 (10.4), $J_{3,4}$ 0.9 (~0), $J_{4,5}$ 10.2 (9.2), $J_{9,10}$ 2.7 (2.3), $J_{10,11}$ 0.7 (~0), $J_{13,14a}$ 10.9 (9.2), $J_{13,14b}$ 1.3 (~1).

For structure **24**, the constraints used were: (2.9-3.3Å) H-2,4-Me (s); (2.2-3.1Å) H-3,H-1" (s); (2.2-3.6Å) H-5,H-5" (s); (2.1-3.7Å) H-5,H-1' (s); (2.9-3.0Å) H-5,6-Me (s); (2.6-3.0Å) 2-Me,H-1" (s); (2.1-3.1Å) H-3,6-OH (m); (2.5-2.7Å) H-10,H-11 (s); (2.5-2.9Å) H-3,H-5 (m); (2.6-5.3Å) NCH_AH_BO,6-OH (m); (2.7-3.0Å) NCH_AH_BO,12-Me (s); (2.8-3.9Å) H-13,H-15 (m); (2.3-5.5Å) H-1',H-5" (m); (2.9-4.5Å) 4-Me,H-1' (m); (2.3-3.9Å) H-4,6-OH (s); (2.2-3.2Å) H-8,6-OH (s); (2.2-3.6Å) H-4,H-10 (m). Coupling constants (Hz) predicted for structure **24** as shown in Figure 2 compared to those experimentally determined (in parentheses) are: $J_{2,3}$ 10.2 (11), $J_{3,4}$ 0.7 (~1), $J_{4,5}$ 9.1 (9), $J_{7a,8}$ 1.2 (~1), $J_{7b,8}$ 8.7 (7), $J_{8,9a}$ 2.3 (~1), $J_{8,9b}$ 11.5 (11), $J_{10,11}$ 1.6 (3), $J_{13,14a}$ 1.2 (3), $J_{13,14b}$ 10.7 (11).

9-Deoxo-6-deoxy-8a,9-didehydro-6,9-epoxy-11-((2*S*,3*S*)-2,3-dihydroxy-2-pentyl)-8a-aza-8a-homo-12,13-bisnor-erythromycin A (9). A stirred solution of **5** (500 mg, 0.685 mmol) in glacial acetic acid (5 mL) was heated in a 70°C oil bath for 16 hours and was then cooled to room temperature. After stirring an additional 64 hours at room temperature, the acetic acid was evaporated under vacuum and the resulting oil was partitioned between methylene chloride (6 mL) and water (6 mL). The mixture was stirred rapidly while the pH was adjusted from 4 to 5 with 5N sodium hydroxide. The methylene chloride layer was removed, the aqueous layer was washed with methylene chloride (6 mL) and the methylene chloride washes were discarded. Methylene chloride (6 mL) was added to the aqueous layer and the mixture was stirred rapidly while the pH was adjusted to 10 with 5N sodium hydroxide. The methylene chloride layer was removed, the aqueous layer was re-extracted with more methylene chloride (2 x 6 mL) and the combined pH 10 methylene chloride extracts were dried with anhydrous magnesium sulfate, filtered and evaporated to a foam (318 mg). Examination of the crude foam by ^{1}H NMR revealed a 55:45 mixture of **5**:**9**. The foam was initially purified by silica chromatography (2 x 24 cm column) collecting 8 mL fractions. Fractions 23-30 were combined and evaporated to a foam (148 mg). The foam was dissolved in 2.5% methanol in methylene chloride (1 mL), loaded onto a Brockmann I basic alumina column (2.5 x 2 7.5 cm, wet packed with 2.5% methanol in methylene chloride) and was eluted with 2.5% methanol in methylene chloride, collecting 4 mL fractions. Fractions 51-62 were combined and evaporated to afford **9** as a foam (110 mg, 22%): ^{1}H NMR ($CDCl_3$) δ 5.25 (br s, H-11), 4.88 (d, H-1"), 4.33 (d, H-1'), 4.15 (d, H-3), 4.00 (dq, H-5"), 3.67 (d, H-5), 3.46 (ddq, H-5'), 3.35 (m, H-8), 3.27 (s, OMe), 3.18 (dd, H-2'), 3.01 (dd, H-4"), 2.92 (br d, H-13), 2.78 (d, 13-OH), 2.78 (m, H-10), 2.78 (m, H-2), 2.43 (ddd, H-3'), 2.36 (d, H-2"eq), 2.32 (br d, 4"-OH), 2.26 (s, NMe_2), 1.90 (m, H-4), 1.89 (m, H-7a), 1.73 (br s, 12-OH), 1.64 (m, H-4'eq), 1.64 (m, H-14a), 1.55 (dd, H-2"ax), 1.43 (s, 6-Me), 1.36 (m, H-14b), 1.30 (d, 5"-Me), 1.26 (d, 2-Me and 10-Me), 1.23 (m, H-4'ax), 1.23 (m, H-7b), 1.20 (d, 5'-Me), 1.16 (d, 8-Me), 1.15 (s, 12-Me), 1.06 (d, 4-Me), 0.97 (t, H-15). ^{13}C NMR ($CDCl_3$) δ 175.1, 159.5 103.9, 97.3, 82.1, 79.8, 79.6, 78.0, 77.3, 76.9, 75.8, 72.4, 70.8, 69.2, 65.4, 49.4, 47.1, 44.6, 42.4, 40.3, 37.6, 34.9, 32.2, 28.5, 24.3, 23.1, 22.9, 21.5, 21.2, 18.3, 17.8, 14.8, 11.8, 11.4, 9.45. IR ($CHCl_3$) 3540, 2970, 2940, 2880, 2835, 2785, 1720, 1660, 1455, 1375, 1320, 1250, 1160, 1110, 1085, 1065, 1050, 1030, 1010 cm^{-1}. FAB-MS (Li spike) m/z 737 (M+Li), 731 (M+1), 573 (M+1–(desosamine)), 398 (M–(desosamine)–(O-cladinose)), 158 (desosamine). Elemental analysis: calculated for $C_{37}H_{66}N_2O_{12}$: C, 60.80: H, 9.10: N, 3.84%; found: C, 60.66: H, 9.04: N, 3.72%.

Alternate synthesis of 9-deoxo-6-deoxy-8a,9-didehydro-6,9-epoxy-11-((2*S*,3*S*)-2,3-dihydroxy-2-pentyl)-8a-aza-8a-homo-12,13-bisnor-erythromycin A (9). A solution of **5** (100 mg, 0.137 mmol) in ethanol (1 mL) was treated with lithium hydroxide monohydrate (11.5 mg, 0.274 mmol), the suspension was sonicated briefly and was stirred at room temperature for 8 hours. Methylene chloride (6 mL) and water (6 mL) were added, the methylene chloride layer was removed and the aqueous layer was re-extracted with more methylene chloride (2 x 4 mL). The combined extracts were dried with magnesium sulfate, filtered and evaporated to a foam (100 mg). Examination of the foam by ^{1}H NMR showed an approximately 1:1 mixture of **5** and **9** The foam was purified by silica chromatography (2.5 x 23 cm), collecting 8 mL fractions. Fractions 10-13 were observed by TLC to contain **5** and fractions 14-20 were combined and evaporated to a foam (41 mg). The foam was dissolved in acetonitrile and after 18 hours the suspended solid was filtered to give **9** as a crystalline solid (20 mg, 20%). mp 181-182°C.

Equilibration of 9-deoxo-6-deoxy-8a,9-didehydro-6,9-epoxy-11-((2*S*,3*S*)-2,3-dihydroxy-2-pentyl)-8a-aza-8a-homo-12,13-bisnor-erythromycin A (9). A solution of **9** (12 mg, 0.016 mmol) and lithium hydroxide monohydrate (1.2 mg, 0.029 mmol) in ethanol (0.2 mL) was stirred at room temperature for 8 hours. The reaction was worked up as described in the previous example to give a foam (10 mg). Examination of the foam by ^{1}H NMR revealed a 1:1 mixture of **5** and **9**, as in the above reaction, and demonstrated that the reaction had reached equilibrium.

9-Deoxo-11-((2*S*,3*S*)-2,3-dihydroxy-2-pentyl)-8a-dehydro-6,9-epoxy-8a-aza-8a-homo-12,13-bisnor-erythromycin A (11). A viscous solution of **9** (60 mg, 0.08 mmol) in ethylene glycol (1 mL) was cooled in an ice bath under a nitrogen atmosphere. Sodium borohydride (12 mg, 0.32 mmol) was added and the solution was allowed to slowly warm to room temperature over several hours. After stirring for 18 hours, the mixture was partitioned between water (6 mL) and methylene chloride (6 mL), the methylene chloride was removed, and the aqueous layer was re-extracted with additional methylene chloride (2 x 4 mL). The combined methylene chloride extracts were dried with magnesium sulfate, filtered and evaporated under vacuum to a foam (55 mg), shown to be a 30:70 mixture of **9** and **11** by ^{1}H NMR. The foam was subsequently dissolved in a mixture of tetrahydrofuran (0.5 mL) and ethylene glycol (1.5 mL). The solution was cooled in an ice bath and treated with sodium borohydride (40 mg, 1.06 mmol). After slowly warming to room temperature, the reaction was stirred for 18 hours and was worked up as described above to give substantially pure **11** (52 mg, 86%): ^{1}H NMR ($CDCl_3$) δ 5.33 (s, H-11), 4.84 (d, H-1"), 4.40 (d, H-1'), 4.28 (d, H-9), 4.17 (d, H-3), 4.00 (dq, H-5"), 3.55 (d, H-5), 3.52 (ddq, H-5'), 3.30 (s, OMe), 3.29 (dd, H-2'), 3.03 (m, H-8/ H-13/ H-4"), 2.78 (ddd, H-3'), 2.73 (m, H-2), 2.48 (s, NMe_2), 2.47 (br s, 4"-OH), 2.37 (d, H-2"eq), 2.20 (m, H-10/ H-4), 1.90 (m, H-4'eq), 1.82 (br s, 12-OH), 1.69 (m, H-14a), 1.57 (dd, H-2"ax), 1.48 (s, 6-Me), 1.46 (m, H-7a), 1.38 (m, H-14b), 1.31 (d, 5"-Me), 1.31 (m, H-4'ax), 1.26 (two d's, 2-Me and 5'-Me), 1.26 (s, 3"-Me), 1.24 (d, 10-Me), 1.20 (m, H-7b), 1.15 (s, 12-Me), 1.14 (d, 8-Me), 1.07 (d, 4-Me) and 1.01 (t, H-15). ^{13}C NMR ($CDCl_3$) δ 175.7, 103.7, 97.2, 85.4, 82.5, 79.2, 78.3, 78.1, 77.2, 76.9, 72.4, 70.9, 70.3, 69.1, 67.9, 65.3, 65.2, 49.4, 47.1, 47.0, 40.3, 37.8, 37.5, 36.2, 34.9, 28.6, 23.0, 22.8, 21.6, 21.2, 20.7, 18.2, 17.7, 14.4, 12.8, 11.9, 9.5. IR ($CHCl_3$) 3530, 2970, 2940, 2880, 2835, 2785, 1710, 1455, 1375, 1315, 1260, 1160, 1105, 1085, 1065, 1045, 1030, 1010 cm^{-1}. FAB-MS m/z 734.2 (M+1), 576.1 (M+1–(desosamine)), 158 (desosamine). Elemental analysis: calculated for $C_{37}H_{68}N_2O_{12}$: C, 60.62: H, 9.36: N, 3.82%; found: C, 60.33: H, 9.22: N, 3.69%.

9-Deoxo-11-((2*S*,3*S*)-2,3-dihydroxy-2-pentyl)-8a-dehydro-6,9-epoxy-8a-aza-8a-methyl-8a-homo-12,13-bisnor-erythromycin A (12). A solution of **11** (30 mg, 0.04 mmol) in $CHCl_3$ (0.5 mL) was treated with 37% formaldehyde (0.04 mL, 0.05 mmol) and 98% formic acid (0.04 mL, 0.10 mmol) and was stirred for 19 hours in a 60°C oil bath. After cooling to room temperature, methylene chloride (3 mL) and water (1 mL) were added, the pH of the rapidly stirred mixture was adjusted to 10 with 1N sodium hydroxide, the methylene chloride layer was removed, dried with magnesium sulfate, filtered and evaporated to a foam (29 mg). The

foam was purified by silica chromatography (2.5 x 18 cm column) collecting 3 mL fractions. Fractions 29-34 were combined and evaporated to give **12** (10 mg, 33%). ^{1}H NMR ($CDCl_3$) δ 5.60 (s, H-11), 4.88 (d, H-1"), 4.39 (d, H-1'), 4.18 (d, H-3), 4.00 (dq, H-5"), 3.69 (br s, 13-OH), 3.60 (d, H-9), 3.55 (d, H-5), 3.49 (ddq, H-5'), 3.30 (s, OMe), 3.26 (dd, H-2'), 3.03 (br d, H-4"), 2.94 (br d, H-13), 2.77 (dq, H-2), 2.62 (ddd, H-3'), 2.40 (br s, 4"-OH), 2.39 (s, NMe_2), 2.39 (m, H-8/ H-10), 2.37 (d, H-2"eq), 2.18 (m, H-4), 2.06 (s, NMe), 1.79 (br d, H-4'eq), 1.69 (m, H-14a), 1.57 (br s, 12-OH), 1.54 (dd, H-2"ax), 1.45 (m, H-7a), 1.43 (s, 6-Me), 1.38 (m, H-14b), 1.31 (d, 5"-Me), 1.27 (m, H-4'ax), 1.26 (two d's, 2-Me and 5'-Me), 1.25 (s, 3"-Me), 1.20 (m, H-7b), 1.14 (s, 12-Me), 1.07 (2d, 4- and 8-Me), 1.00 (t, H-15). ^{13}C ($CDCl_3$) δ 176.3 (C-1), 103.6 (C-1'), 97.0 (C-1"), 91.8 (C-9), 82.7 (C-5), 79.3 (C-3), 78.0 (C-4"), 77.4 (C-12), 77.0 (C-6), 76.0 (C-13), 72.6 (C-11), 72.4 (C-3"), 70.9 (C-2'), 68.9 (C-5'), 65.3 (C-3'), 65.2 (C-5"), 53.0 (C-8), 49.4 (OMe), 47.1 (C-2), 40.2 (NMe_2), 36.8 (C-4), 35.8 (C-7), 35.8 (8a-Me), 34.9 (C-2"), 33.7 (C-10), 28.9 (C-4'), 22.6 (C-14), 21.5 (C-8 + C-3"), 21.2 (5'-Me), 19.8 (6-Me), 18.2 (5"-Me), 17.2 (12-Me), 14.7 (2-Me), 12.3 (10-Me), 11.9 (C-15), 9.3 (4-Me). IR ($CHCl_3$) 3530, 2980, 2940, 2880, 2840, 1715, 1455, 1375, 1315, 1260, 1160, 1105, 1085, 1065, 1050, 1030, 1010 cm^{-1}. FAB-MS m/z 747.5 (M+1), 589.3 (M+1–(desosamine)). Elemental analysis: calculated for $C_{38}H_{70}N_2O_{12}$: C, 61.09: H, 9.45: N, 3.75%; found: C, 61.19: H, 9.30: N, 3.76%.

9a-Aza-9a-homoerythromycin A (14). A solution of the amino dilactone **28** (1.0 g, 1.34 mmol) in methanol (5 mL) was heated in a 60°C oil bath for 16 hours. The methanol was evaporated under vacuum and the residue was dissolved in hot nitromethane (5 mL). After stirring for 18 hours at room temperature, the suspension was filtered. The solid was washed with nitromethane (1 mL) and dried under a stream of nitrogen to give **14** (0.55 g, 55%) as a white crystalline solid. mp 162-163°C. ^{1}H NMR ($CDCl_3$) δ 6.11 (d, NH), 4.95 (d, H-1"), 4.75 (dd, H-13), 4.29 (d, H-1'), 4.14 (d, H-3), 4.11 (dq, H-10), 3.99 (dq, H-5"), 3.47 (s, H-11), 3.39 (ddq, H-5'), 3.35 (d, H-5), 3.23 (s, OMe), 3.17 (dd, H-2'), 2.93 (dd, H-4"), 2.69 (m, H-2), 2.45 (ddd, H-3'), 2.27 (s, NMe_2), 2.26 (d, 4"-OH), 2.24 (d, H-2"eq), 2.20 (m, H-8), 2.10 (dd, H-7a), 1.91 (dq, H-4), 1.73 (m, H-14a), 1.64 (m, H-4'eq), 1.45 (dd, H-2"ax), 1.40 (m, H-14b), 1.29 (s, 6-Me), 1.21 (d, 5"-Me), 1.16 (m, H-4'ax), 1.15 (m, H-7b), 1.15 (s, 3"-Me), 1.12 (d, 5'-Me), 1.10 (s, 12-Me), 1.09 (d, 2-Me), 1.07 (d, 10-Me), 1.01 (d, 8-Me), 0.93 (d, 4-Me), 0.76 (t, H-15). ^{13}C NMR ($CDCl_3$) δ 179.6 (C-1), 177.8 (C-9), 103.0 (C-1'), 94.5 (C-1"), 83.5 (C-5), 77.9 (C-4"), 77.4 (C-13), 77.3 (C-3), 74.8 (C-6), 74.6 (C-12), 72.7 (C-3"), 71.6 (C-11), 70.8 (C-2'), 68.6 (C-5'), 65.5 (C-5"), 65.3 (C-3'), 49.4 (OMe), 45.7 (C-10), 45.2 (C-2), 42.2 (C-4), 40.4 (NMe_2), 38.7 (C-7), 36.5 (C-8), 34.5 (C-2"), 29.4 (C-4'), 27.8 (6-Me), 21.4 (3"-Me), 21.2 (5'-Me), 21.1 (C-14), 19.9 (8-Me), 18.1 (5"-Me), 16.4 (12-Me), 14.7 (2-Me), 13.3 (10-Me), 11.0 (C-15), 9.2 (4-Me). IR ($CHCl_3$) 3540, 3440, 2975, 2940, 2880, 2840, 2790, 1715, 1660, 1500, 1455, 1450, 1375, 1325, 1280, 1180, 1160, 1105, 1085, 1065, 1045, 1010 cm^{-1}. FAB-MS (Li spike) m/z 756.6 (M+Li), 750.4 (M+1), 592.1 (M+1–(desosamine)), 158 (desosamine). Elemental analysis: calculated for $C_{37}H_{68}N_2O_{13}$: C, 59.32: H, 9.16: N, 3.74%; found: C, 59.10: H, 9.21: N, 3.71%.

X-Ray crystal Structure of 14. Compound **14** was crystallized as a hydrochloride salt from acetonitrile $C_{37}H_{70}ClN_2O_{13}$, M_r = 786.429, orthorhombic, $P2_12_12_1$, a = 20.719(5), b = 22.575(3), c = 10.416(2) Å, V = 4872(3) Å^3, Z = 4, D_x = 1.072 g cm^{-3}, monochromatized radiation λ(Cu K_α) = 1.541838 Å, μ =1.13 mm^{-1}, F(000) = 1708, T = 294 K. Data were collected on a Rigaku AFC5 diffractometer to a θ limit of 72.5° which yielded 3671 unique reflections. Of these 2590 were considered observed ($I \geq 3\sigma(I)$. The structure was solved by direct methods (SHELXS-86)[27] and refined using full-matrix least-squares on F (SDP-PLUS).[28] All atoms of the compound were located and two molecules of acetonitrile were included. It appears that more solvent molecules may be in the lattice but these seem to be disordered and were not included in the model. The final model was refined using 463 parameters and the observed data. Most non-hydrogen atoms, excepting C6, C51, C52 and those atoms of the solvent molecules, were refined with anisotropic thermal displacements and H-atoms were included at their calculated positions. The final agreement statistics are: R = 0.098, wR = 0.109, S = 8.11 with $(\Delta/\sigma)_{max}$ = 0.25. The least-squares weights were defined using $1/\sigma^2(F)$. The maximum peak

height in a final difference Fourier map is 0.55(8) eÅ^{-3} and this peak is located in the area of possible disordered solvent. The atomic coordinates for this structure will be deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

9-Deoxo-9,11-epoxy-9,9a-didehydro-9a-aza-9a-homoerythromycin A. (15). A solution of 6,9-iminoether **4** (280 mg, 0.38 mmol) in xylenes (3 mL) was heated in a 120°C oil bath for 1.5 hours. The solvent was evaporated and the resulting oil was dissolved in dichloromethane and applied to three 20 x 20 x 0.1 cm. basic alumina, preparative-layer plates . The plates were developed with 2.5% methanol in methylene chloride and the product was visualized by staining the edge of the plates with iodine. The product band was removed, eluted with 20% methanol in methylene chloride, and the solvents were evaporated under vacuum to give **15** (130 mg, 46%) as a foam. ^{1}H NMR ($CDCl_3$) δ 5.07 (br s, H-3), 4.85 (dd, H-13), 4.64 (d, H-1'), 4.54 (d, H-1"), 4.42 (d, H-11), 4.18 (dq, H-10), 3.98 (dq, H-5"), 3.72 (d, H-5), 3.70 (s, 6-OH), 3.65 (br s, 12-OH), 3.57 (ddq, H-5'), 3.34 (s, OMe), 3.28 (dd, H-2'), 3.03 (dd, H-4"), 2.72 (m, H-8), 2.58 (dq, H-2), 2.51 (ddd, H-3'), 2.35 (d, H-2"eq), 2.29 (s, NMe_2), 2.21 (d, 4"-OH), 2.18 (dd, H-7a), 2.02 (m, H-4), 1.67 (m, H-4'eq), 1.62 (m, H-14a), 1.57 (dd, H-2"ax), 1.51 (m, H-7b), 1.49 (m, H-14b), 1.41 (d, 8-Me), 1.31 (s, 12-Me), 1.29 (d, 10-Me), 1.25 (s, 6-Me), 1.24 (d, 5"-Me), 1.23 (d, 2-Me), 1.22 (m, H-4'ax), 1.22 (d, 5'-Me), 1.21 (s, 3"-Me), 1.17 (d, 4-Me), 0.91 (t, H-15). ^{13}C NMR ($CDCl_3$) δ 176.2 (C-1), 170.0 (C-9), 102.1 (C-1'), 95.3 (C-1"), 82.9 (C-13), 82.2 (C-11), 81.0 (C-5), 77.6 (C-4"), 76.3 (C-3), 75.1 (C-6), 73.2 (C-12), 72.6 (C-3"), 70.6 (C-2'), 69.4 (C-5'), 65.8 (C-5"), 65.1 (C-3'), 63.4 (C-10), 49.2 (OMe), 43.4 (C-2), 43.4 (C-4), 40.2 (NMe_2), 39.5 (C-7), 34.5 (C-2"), 29.7 (C-8), 28.5 (C-4'), 25.0 (6-Me), 24.1 (C-14), 21.6 (3"-Me), 21.6 (12-Me), 21.0 (5'-Me), 19.2 (8-Me), 18.0 (5"-Me), 17.3 (10-Me), 11.3 (C-15), 10.8 (2-Me), 10.8 (4-Me). IR ($CHCl_3$) 3460, 2975, 2940, 2880, 2840, 2790, 1725, 1680, 1650, 1560, 1455, 1375, 1360, 1325, 1305, 1280, 1260, 1190, 1160, 1120, 1105, 1085, 1075, 1045, 1010 cm^{-1}. FAB-MS m/z 731 (M+1), 573 (M+1–(desosamine)), 398 (M+1–(desosamine)–(O-cladinose)), 158 (desosamine).

Alternate synthesis of 15. A solution of **4** (4.0 g, 5.48 mmol) in nitromethane (15 mL) was refluxed for one hour under a nitrogen atmosphere. The stirred solution was cooled to room temperature, seeded and stirred overnight. The suspension was filtered and dried under a stream of nitrogen to give **15** as a white, polysolvated crystalline solid (2.16 g, 54%). mp 204-207°C. Elemental analysis: (dried at 120°C for 3 hours): calculated for $C_{37}H_{66}N_2O_{12}$: C, 60.80: H, 9.10: N, 3.84%; found: C, 60.56: H, 8.90: N, 4.24%.

9-Deoxo-9,11-epoxy-8-epi-9,9a-didehydro-9a-aza-9a-homoerythromycin A. (16). A solution of **4** (2.0 g, 2.74 mmol) in nitromethane (20 mL) was heated in a 100°C oil bath for 2 hours. The solvent was evaporated under vacuum and the resulting foam was examined by ^{1}H NMR which showed a 0.3:2:1 ratio of **4**, **15** and **16**. The foam was purified by silica chromatography (4 x 35.5 cm column), collecting 25 mL fractions. Fractions 37-45 were combined and evaporated to give **16** as a foam (0.42 g, 21%). ^{1}H NMR ($CDCl_3$) δ 5.05 (dd, H-13), 4.80 (d, H-3), 4.75 (d, H-1"), 4.25 (d, H-1'), 4.08 (d, H-11), 3.98 (dq, H-10), 3.97 (dq, H-5"), 3.49 (ddq, H-5'), 3.45 (d, H-5), 3.34 (s, 6-OH), 3.28 (dd, H-2'), 3.20 (s, OMe), 2.97 (t, H-4"), 2.75 (m, H-8), 2.73 (m, H-2), 2.69 (ddd, H-3'), 2.39 (s, NMe_2), 2.29 (d, H-2"eq), 2.29 (t, H-7a), 2.25 (d, 4"-OH), 1.83 (m, H-14a), 1.75 (m, H-4'eq), 1.52 (dd, H-2"ax), 1.48 (dq, H-4), 1.45 (m, H-14b), 1.31 (d, 5"-Me), 1.25 (m, H-7b), 1.24 (m, H-4'ax), 1.20 (d, 5'-Me), 1.20 (d, 2-Me), 1.19 (d, 8-Me), 1.19 (s, 12-Me), 1.07 (d, 10-Me), 1.06 (d, 4-Me), 0.88 (t, H-15). ^{13}C NMR ($CDCl_3$) δ 174.1 (C-1), 172.7 (C-9), 103.5 (C-1'), 99.1(br) (C-1"), 83.1 (C-3, C-11), 79.9 (br, C-5), 77.6 (C-4"), 77.2 (C-13), 75.9 (C-6) , 73.1 (C-12), 72.3 (C-3"), 71.9 (C-2'), 69.2 (C-5'), 65.9 (C-5"), 63.6 (C-3'), 61.1 (C-10), 49.2 (OMe), 43.8 (C-2), 41.3 (C-7), 40.6 (NMe_2 + C-4), 35.3 (C-2"), 31.7, 31.0 (br), 30.9, 22.7 (br), 21.8, 21.4, 21.2, 18.3, 17.4, 16.1, 15.8, 11.6, 10.7. IR ($CHCl_3$) 3440, 2970, 2935, 2880, 2825, 2780, 1730, 1650, 1455, 1450, 1375, 1350, 1325, 1280, 1160, 1110, 1075, 1050, 1010 cm^{-1}. FAB-MS m/z 731 (M+1), 573 (M+1–(desosamine)), 398 (M+1–(desosamine)–(O-cladinose)), 158

(desosamine).. Elemental analysis: calculated for $C_{37}H_{66}N_2O_{12}$: C, 60.80: H, 9.10: N, 3.83%; found: C, 60.53: H, 8.87: N, 3.75%.

9-Deoxo-9,11-epoxy-8-epi-8-deuterio-9,9a-didehydro-9a-aza-9a-homoerythromycin A (8-deuterio 16). A solution of **4** (200 mg, 0.274 mmol) in deuteriomethanol (2 mL) was heated in a 70°C oil bath for 28 hours. The solvent was evaporated and the foam was purified by silica chromatography (2 x 33 cm column), collecting 8 mL fractions. Fractions 48-58 were combined and evaporated to give the title compound as a glass (60 mg, 30%).

9-Deoxo-9a-aza-9a-homoerythromycin A (17). A viscous solution of **15** (200 mg, 0.27 mmol) in ethylene glycol (2 mL) was cooled in an ice bath under a nitrogen atmosphere. Sodium borohydride (12 mg, 0.32 mmol) was added and the solution was allowed to slowly warm to room temperature over several hours. After stirring for 5 hours, the mixture was partitioned between water (10 mL) and methylene chloride (5 mL), the methylene chloride was removed, dried with magnesium sulfate, filtered and evaporated under vacuum to a foam (180 mg, 59%). Examination of the foam by ^{1}H NMR revealed a 2:1 mixture of **17** and **15**.

9-Deoxo-8-epi-9a-aza-9a-homoerythromycin A (19). A solution of **16** (0.45 g, 0.62 mmol) in acetic acid (10 mL) was hydrogenated for 2 hours at 1000 psi in the presence of platinum oxide (0.1 g). The mixture was filtered through solka-floc, the filtrate was evaporated under vacuum, and the residue was partitioned between methylene chloride (100 mL) and aqueous potassium carbonate (100 mL). The aqueous layer was re-extracted with more methylene chloride (2 x 50 mL) and the combined methylene chloride extracts were dried with magnesium sulfate, filtered and evaporated to a foam. The foam was purified by silica chromatography (2 x 27 cm column), collecting 8 mL fractions. Fractions 43-51 were combined and evaporated to give **19** as a solid (0.3 g, 66%). ^{1}H NMR ($CDCl_3$) δ 4.93 (d, H-1"), 4.72 (dd, H-13), 4.32 (d, H-1'), 4.09 (d, H-3), 4.04 (dq, H-5"), 3.66 (d, H-11), 3.57 (d, H-5), 3.49 (ddq, H-5'), 3.31 (s, OMe), 3.27 (dd, H-2'), 3.01 (t, H-4"), 2.89 (m, H-2), 2.69 (dq, H-10), 2.50 (m, H-9a), 2.48 (ddd, H-3'), 2.38 (d, H-2"eq), 2.35 (s, NMe_2), 2.32 (d, 4"-OH), 2.02 (dq, H-4), 1.97 (m, H-8), 1.97 (m, H-9b), 1.88 (m, H-14a), 1.67 (m, H-4'eq), 1.57 (dd, H-2"ax), 1.52 (m, H-14b), 1.36 (m, H-7a + 7b), 1.29 (d, 5"-Me), 1.21 (d, 5'-Me), 1.21 (d, 2-Me), 1.20 (m, H-4'ax), 1.14 (d, 10-Me), 1.11 (d, 4-Me), 0.95 (d, 8-Me), 0.88 (t, H-15). ^{13}C NMR ($CDCl_3$) δ 177.1, 104.3, 97.3, 85.8, 78.2, 78.0, 74.5, 73.9, 72.8, 72.7, 70.7, 69.0, 65.5, 65.4, 54.1, 50.6, 49.3, 44.9, 42.1, 40.3, 35.3, 30.5, 28.7, 21.5, 21.2, 20.8, 20.7, 17.8, 15.9, 13.3, 11.0, 9.65. IR (film) 3480 2972, 2937, 1732, 1457, 1375, 1274, 1167, 1110, 1107, 1077, 1055, 1034, 1014 cm^{-1}. APCI-MS m/z 735.4 (M+1), 577.3 (M+1–(desosamine)). Elemental analysis: calculated for $C_{37}H_{70}N_2O_{12}$: C, 60.47: H, 9.60: N, 3.81%; found: C, 60.22: H, 9.45: N, 3.69%.

9-Deoxo-8-epi-9a-aza-9a-methyl-9a-homoerythromycin A (20). A mixture of **19** (0.1 g, 0.14 mmol), 37% aqueous formaldehyde (0.012 mL, 0.16 mmol) and formic acid (0.013 mL, 0.34 mmol) in $CHCl_3$ (3 mL) was heated in a 70°C oil bath for 1.5 hours. The mixture was cooled to room temperature and was partitioned between methylene chloride (10 mL) and aqueous potassium carbonate (10 mL). The aqueous layer was re-extracted with methylene chloride (2 x 10 mL) and the combined extracts were dried with magnesium sulfate, filtered and evaporated to give **20** as a foam (0.1 g, 98%). ^{1}H NMR ($CDCl_3$, 55°C) δ 5.00 (d, H-1"), 4.70 (dd, H-13), 4.47 (d, H-1'), 4.18 (d, H-3), 4.09 (dq, H-5"), 3.56 (d, H-11), 3.56 (ddq, H-5'), 3.55 (d, H-5), 3.34 (s, OMe), 3.30 (dd, H-2'), 3.04 (dd, H-4"), 2.89 (dq, H-10), 2.83 (m, H-2), 2.47 (ddd, H-3'), 2.34 (d, H-2"eq), 2.34 (m, H-9a), 2.30 (s, NMe_2), 2.29 (s, NMe), 2.00 (m, H-9b), 1.89 (m, H-14a), 1.79 (dq, H-4), 1.77 (m, H-8), 1.66 (m, H-4'eq), 1.59 (dd, H-2"ax), 1.55 (m, H-14b), 1.52 (m, H-7a), 1.31 (d, 5"-Me), 1.30 (m, H-7b), 1.24 (m, H-4'ax), 1.23 (d, 5'-Me), 1.21 (d, 2-Me), 1.09 (d, 4-Me), 1.01 (d, 8-Me), 0.95 (d, 10-Me), 0.88 (t, H-15). ^{13}C NMR ($CDCl_3$, 55°C) δ 179.3, 103.3, 86.3, 78.4, 77.9, 77.5, 76.4, 75.4, 75.2, 72.9, 70.8, 69.3, 65.9, 65.6, 49.3, 45.0, 42.9, 40.5, 40.3, 34.9, 29.0, 21.5, 21.2, 21.1, 20.9, 17.6, 16.1, 15.0, 10.9, 9.11, 6.12. IR (film) 3496 2972, 2938, 1710, 1456, 1381, 1275, 1187, 1167, 1110, 1085, 1053, 1028, 1002 cm^{-1}. ESI-MS m/z

749.5 (M+1), 591.3 (M+1–(desosamine)). Elemental analysis: calculated for $C_{38}H_{72}N_2O_{12}$: C, 60.94: H, 9.69: N, 3.74%; found: C, 61.19: H, 9.52: N, 3.46%.

9-Deoxo-6-deoxy-9a,9-didehydro-6,9-epoxy-11-((2*S*,3*S*)-2,3-dihydroxy-2-pentyl)-9a-aza-9a-homo-12,13-bisnor-erythromycin A (21). A solution of **4** (2.0 g, 2.74 mmol) in ethanol (12 mL) was treated with lithium hydroxide monohydrate (230 mg, 5.48 mmol). The suspension was sonicated briefly then stirred at room temperature for 4 hours. Methylene chloride (30 mL) and water (30 mL) were added, the methylene chloride layer was removed and the aqueous layer was re-extracted with more methylene chloride (2 x 20 mL). The combined extracts were dried with magnesium sulfate, filtered and evaporated to a foam (1.85 g). Examination of the foam by ^{1}H NMR showed a 2:1 mixture of **4** and **21**. The foam was initially purified by silica chromatography (20 x 5 cm column), collecting 20 mL fractions. Fractions 22-28 were combined and evaporated to a foam (540 mg). The foam was re-chromatographed on a 1.5 x 30 cm silica column collecting 8 mL fractions. Fractions 18-22 were combined and evaporated to a foam (0.4 g, 20%). A portion of the foam (115 mg) was dissolved in nitromethane (0.3 mL) and, after 3 days, the precipitated solid was filtered and dried under a stream of nitrogen to give 40 mg of **21**. mp 149-150°C. ^{1}H NMR ($CDCl_3$) δ 5.16 (br s, H-11), 4.84 (d, H-1"), 4.30 (d, H-1'), 4.08 (d, H-3), 3.99 (dq, H-5"), 3.93 (m, H-10), 3.70 (d, H-5), 3.44 (ddq, H-5'), 3.25 (s, OMe), 3.16 (dd, H-2'), 3.00 (dd, H-4"), 3.00 (br d, H-13), 2.80 (m, H-2), 2.64 (m, H-8), 2.48 (d, 13-OH), 2.42 (ddd, H-3'), 2.36 (d, H-2"eq), 2.22 (d, 4"-OH), 2.24 (s, NMe_2), 1.96 (m, H-7a), 1.75 (m, H-4), 1.64 (m, H-14a), 1.64 (m, H-14b), 1.53 (m, H-4'eq), 1.46 (dd, H-2"ax), 1.44 (d, 10-Me), 1.32 (m, H-7b), 1.27 (d, 5"-Me), 1.25 (d, 2-Me), 1.19 (m, H-4'ax), 1.19 (d, 5'-Me), 1.12 (d, 8-Me), 1.07 (d, 4-Me), 0.95 (t, H-15). ^{13}C NMR ($CDCl_3$) 175.0, 166.4, 104.1, 97.4, 87.9, 81.9, 79.1, 78.0, 76.9, 76.6, 72.4, 70.7, 69.2, 65.4, 65.3, 53.3, 49.4, 46.9, 40.2, 38.6, 37.9, 34.9, 34.7, 28.5, 25.3, 23.0, 21.5, 21.2, 18.5, 18.3, 18.0, 15.6, 14.6, 11.6, 9.22. IR ($CHCl_3$) 3540, 2970, 2935, 2880, 2835, 2785, 1720, 1705, 1455, 1450, 1375, 1320, 1295, 1260, 1245, 1160, 1110, 1085, 1050, 1010 cm^{-1}. FAB-MS m/z 731 (M+1), 573 (M+1–(desosamine)), 398 (M–(desosamine)–(O-cladinose)), 158 (desosamine). Elemental analysis: calculated for $C_{37}H_{66}N_2O_{12}$: C, 60.80: H, 9.10: N, 3.83%; found: C, 60.70: H, 9.02: N, 3.72%.

9-Deoxo-11-((2*S*,3*S*)-2,3-dihydroxy-2-pentyl)-9a-aza-9a-homo-12,13-bisnor-erythromycin A (22). A solution of **21** (100 mg, 0.137 mmol) in acetic acid (2 mL) was hydrogenated for 24 hours at 1500 psi in the presence of platinum oxide (100 mg). The acetic acid was decanted and evaporated under vacuum. The residue was diluted with methylene chloride (5 mL) and water (5 mL) and the mixture stirred rapidly while the pH was adjusted to 11. The methylene chloride layer was removed and the aqueous layer was reextracted with more methylene chloride (2 x 5 mL). The combined extracts were dried with magnesium sulfate, filtered and evaporated to a foam (93 mg). A portion of the foam (40 mg) was purified on two 20 x 20 x 0.05 cm alumina plates, using 5% methanol in methylene chloride as both the developing and eluting solvents, to give **22** as a foam (20 mg, 20%). ^{1}H NMR ($CDCl_3$, 55°C) δ 5.04 (br s, H-11), 4.82 (d, H-1"), 4.81 (d, H-3), 4.35 (d, H-1'), 4.04 (dq, H-5"), 3.61 (d, H-5), 3.46 (ddq, H-5'), 3.27 (s, OMe), 3.18 (dd, H-2'), 3.11 (m, H-10), 3.08 (br d, H-13), 3.00 (dd, H-4"), 2.91 (m, H-2), 2.82 (br d, H-9a), 2.47 (ddd, H-3'), 2.32 (d, H-2"eq), 2.28 (d, 4"-OH), 2.27 (s, NMe_2), 2.11 (m, H-4), 2.00 (m, H-9b), 1.89 (m, H-8), 1.67 (m, H-14a), 1.63 (m, H-4'eq), 1.53 (dd, H-2"ax), 1.50 (m, H-7a), 1.42 (m, H-14b), 1.32 (m, H-7b), 1.32 (d, 5"-Me), 1.29 (d, 10-Me), 1.24 (d, 2-Me), 1.20 (d, 5'-Me), 1.20 (m, H-4'ax), 1.16 (d, 4-Me), 0.98 (t, H-15), 0.95 (d, 8-Me). ^{13}C NMR ($CDCl_3$, 55°C) 174.3, 103.9, 98.1, 82.9, 80.9, 78.3, 78.2, 78.1, 76.8, 75.1, 72.6, 71.1, 69.0, 65.9, 65.7, 49.4, 46.7, 41.4, 40.4, 40.3, 39.2, 35.5, 29.6, 29.2, 27.5, 23.5, 22.0, 21.5, 21.2, 18.5, 15.8, 15.5, 11.6, 9.78. IR ($CHCl_3$) 3540, 3470, 2960, 2930, 2890, 2830, 2780, 1720, 1455, 1450, 1375, 1315, 1250, 1160, 1100, 1085, 1060, 1045, 1030, 1005 cm^{-1} FAB-MS m/z 735.7 (M+1), 577.7 (M+1–(desosamine)), 402 (M–(desosamine)–(O-cladinose)), 158 (desosamine). Elemental analysis: calculated for $C_{37}H_{70}N_2O_{12}$: C, 60.47: H, 9.60: N, 3.81%; found: C, 60.31: H, 9.68: N, 3.63%.

9-Deoxo-9a,12-methylene-11-((2*S*,3*S*)-2,3-dihydroxy-2-pentyl)-9a-aza-9a-homo-12,13-bisnor-erythromycin A (24). A solution of **22** (14 mg, 0.02 mmol) in $CHCl_3$ (0.5 mL) was treated with 37% formaldehyde (0.002 mL, 0.03 mmol) and 98% formic acid (0.002 mL, 0.06 mmol), and was stirred for 30 hours in a 60°C oil bath. After cooling to room temperature, methylene chloride (3 mL) and water (1 mL) were added, the pH of the rapidly stirred mixture was adjusted to 11 with 1N sodium hydroxide, the methylene chloride layer was removed, dried with magnesium sulfate, filtered and evaporated to give **24** as a foam (15 mg, 100%). ^{1}H NMR ($CDCl_3$) δ 6.45 (br s, 6-OH), 4.90 (d, H-1"), 4.53 (d, H-3), 4.50 (d, H-11), 4.33 (d, H-1'), 4.20 (d, NCH_AH_BO), 4.08 (d, NCH_AH_BO), 4.01(dq, H-5"), 3.65 (d, H-5), 3.61 (br d, H-13), 3.43 (ddq, H-5'), 3.27 (s, OMe), 3.23 (m, H-10), 3.20 (dd, H-2'), 2.98 (dd, H-4"), 2.82 (m, H-2), 2.49 (ddd, H-3'), 2.31 (d, H-2"eq), 2.30 (s, NMe_2), 2.22 (d, 4"-OH), 2.17 (br d, H-9a), 1.86 (m, H-4), 1.86 (m, H-8), 1.84 (dd, H-9b), 1.64 (br d, H-4'eq), 1.70 (d, H-7a), 1.60 (m, H-14a), 1.54 (dd, H-2"ax), 1.42 (m, H-7b), 1.31 (d, 5"-Me), 1.29 (d, 2-Me), 1.22 (m, H-4'ax), 1.21 (s, 12-Me), 1.21 (d, 5'-Me), 1.19 (d, 10-Me), 1.15 (m, H-14b), 1.10 (d, 4-Me or 8-Me), 0.93 (t, H-15), 0.87 (d, 4-Me or 8-Me). ^{13}C NMR ($CDCl_3$, 55°C) 173.7, 115.6, 103.5, 97.0, 83.4, 80.7, 78.0, 76.8, 75.6, 74.0, 73.5, 72.6, 71.1, 70.98, 68.8, 65.5, 59.1, 57.5, 49.5, 46.9, 42.6, 40.3, 38.7, 35.4, 29.0, 26.6, 25.5, 22.8, 21.5(2), 21.4, 18.7, 16.5, 10.9, 9.54. IR ($CHCl_3$) 2965, 2935, 2875, 2835, 2780, 1720, 1455, 1375, 1315, 1250, 1160, 1100, 1085, 1060, 1045, 1005 cm^{-1} FAB-MS m/z 747.7 (M+1), 589.7 (M+1–(desosamine)), 414 (M–(desosamine)–(O-cladinose)), 158 (desosamine). Elemental analysis: calculated for $C_{38}H_{70}N_2O_{12}$: C, 61.1: H, 9.45: N, 3.75%; found: C, 60.92: H, 9.30: N, 3.75%.

Amino-γ-lactone 25 The pH of a suspension of 6,9-iminoether **4** (2.0 g, 2.74 mmol) in water (6 mL) was adjusted to 4 with acetic acid and the resulting solution was stirred for 22 hours at room temperature. Methylene chloride (6 mL) was added and the pH of the mixture was adjusted to 7.4 with the addition of sodium bicarbonate. The methylene chloride layer was removed and more methylene chloride (6 mL) was added to the aqueous layer. The pH was adjusted to 9.5 with 2N sodium hydroxide, the methylene chloride layer was removed and the aqueous layer was re-extracted with more methylene chloride (2 x 4 mL). The combined pH 9.5 extracts were dried with magnesium sulfate, filtered and evaporated under vacuum to afford **25** (1.3 g, 63%) as a foam. mp 78-83°C. ^{1}H NMR ($CDCl_3$) δ 4.94 (dd, H-13), 4.71 (d, H-1"), 4.34 (d, H-1'), 4.13 (d, H-3), 3.95 (dq, H-5"), 3.69 (d, H-5), 3.47 (ddq, H-5'), 3.28 (d, H-11), 3.24 (s, OMe), 3.16 (dd, H-2'), 3.09 (m, H-10), 2.95 (d, H-4"), 2.71(m, H-8), 2.69 (m, H-2), 2.45 (ddd, H-3'), 2.29 (d, H-2"eq), 2.24 (s, NMe_2), 2.21 (t, H-7a), 2.04 (m, H-7b), 1.95 (dq, H-4), 1.85 (m, H-14a), 1.63 (m, H-4'eq), 1.49 (s, 6-Me), 1.50 (m, H-14b), 1.47 (dd, H-2"ax), 1.21 (d, 8-Me), 1.20 (d, 5"-Me), 1.17 (s, 3"-Me), 1.17 (d, 5'-Me), 1.16 (m, H-4'ax), 1.13 (s, 12-Me), 1.13 (d, 2-Me), 1.12 (d, 4-Me), 1.09 (d, 10-Me), 0.83 (t, H-15). ^{13}C NMR ($CDCl_3$) δ 179.4 (C-1), 175.9 (C-9), 103.7 (C-1'), 95.5 (C-1"), 86.0 (C-6), 81.0 (C-5), 78.6 (C-13), 77.8 (C-3), 77.8 (C-4"), 75.7 (C-11), 74.4 (C-12), 72.6 (C-3"), 70.6 (C-2'), 69.1 (C-5'), 65.1 (C-5"), 65.4 (C-3'), 49.3 (OMe), 47.8 (C-10), 43.0 (C-2), 40.3 (NMe_2), 39.6 (C-4), 37.9 (C-7), 35.0 (C-2"), 34.0 (C-8), 29.0 (C-4'), 25.0 (6-Me), 22.1 (C-14), 21.5 (12-Me), 21.1 (5'-Me), 18.9 (10-Me), 18.2 (3"-Me), 17.9 (5"-Me), 15.0 (8-Me), 12.2 (2-Me), 11.0 (C-15), 10.8 (4-Me). IR ($CHCl_3$) 3540, 3460, 2980, 2940, 2880, 2840, 2790, 1760, 1725, 1455, 1380, 1160, 1105, 1085, 1050, 1000 cm^{-1}. FAB-MS m/z 749 (M+1), 591 (M+1–(desosamine)), 158 (desosamine). Elemental analysis: calculated for $C_{37}H_{68}N_2O_{13}$: C, 59.34: H, 9.15: N, 3.74%; found: C, 59.05: H, 9.09: N, 3.53%.

Rearranged amino-γ-lactones 26a and 26b. Lithium hydroxide monohydrate (12 mg, 0.29 mmol) was added to a rapidly stirred solution of **25** (100 mg, 0.134 mmol) in ethanol (1 mL). After 1 hour at room temperature, methylene chloride (5 mL) and water (5 mL) were added. The methylene chloride layer was removed, dried with magnesium sulfate, filtered and evaporated to a foam (90 mg). The foam was purified by silica chromatography (2.5 x 23 cm column), collecting 4 mL fractions. Fractions 24-28 were combined and evaporated to give **26a** (40 mg) as a foam. Fractions 37-41 were combined and evaporated to give **26b** (17 mg) as a foam. Data for **26a**: ^{1}H NMR ($CDCl_3$) δ (7.40 (d, NH), 4.90 (d, H-1"), 4.31 (d, H-1'), 4.17 (d, H-3),

4.11 (dq, H-10), 3.98 (dq, H-5"), 3.74 (d, H-11), 3.61 (d, H-5), 3.55 (ddq, H-5'), 3.26 (dd, H-2'), 3.26 (s, OMe), 3.15 (br d, H-13), 2.89 (dd, H-4"), 2.77 (m, H-8), 2.56 (ddd, H-3'), 2.45 (m, H-2), 2.31 (d, H-2"eq), 2.28 (s, NMe_2), 2.17 (t, H-7a), 1.95 (dq, H-4), 1.92 (m, H-7b), 1.65 (m, H-4'eq), 1.52 (m, H-14a), 1.54 (s, 6-Me), 1.41 (dd, H-2"ax), 1.35 (m, H-14b), 1.19 (m, H-4'ax), 1.24 (d, 8-Me), 1.24 (d, 10-Me), 1.23 (d, 5'-Me), 1.22 (d, 5"-Me), 1.17 (s, 3"-Me), 1.12 (s, 12-Me), 1.09 (d, 2-Me), 1.07 (d, 4-Me), 1.02 (t, H-15). ^{13}C NMR ($CDCl_3$) δ 179.2 (C-9), 174.5 (C-1), 105.6 (C-1'), 95.9 (C-1"), 86.6 (C-5), 86.3 (C-6), 83.7 (C-13), 78.9 (C-3), 77.8 (C-4"), 75.3 (C-11), 74.9 (C-12), 72.6 (C-3"), 70.7 (C-2'), 69.7 (C-5'), 65.5 (C-5"), 65.0 (C-3'), 49.4 (OMe), 49.1 (C-10), 42.7 (C-2), 39.8 (NMe_2), 39.1 (C-7), 38.7 (C-4), 34.9 (C-2"), 34.1 (C-8), 28.2 (C-4'), 25.1 (C-14), 23.8 (6-Me), 21.5 (12-Me), 21.5 (3"-Me), 21.2 (5'-Me), 17.8 (5"-Me), 15.7 (10-Me), 14.9 (8-Me), 11.6 (C-15), 11.0 (4-Me), 9.60 (2-Me). IR ($CHCl_3$) 3460, 2980, 2940, 2880, 2840, 2795, 1760, 1660, 1460, 1455, 1360, 1345, 1295, 1160, 1110, 1085, 1065, 1050, 1000 cm^{-1}. FAB-MS m/z 749 (M+1), 591 (M–(desosamine)), 158 (desosamine). Data for **26b**: ^1H NMR ($CDCl_3$) δ 7.05 (d, NH), 4.84 (d, H-1"), 4.38 (d, H-1'), 4.15 (d, H-3), 4.14 (dq, H-10), 3.95 (dq, H-5"), 3.81 (d, H-11), 3.65 (d, H-5), 3.58 (ddq, H-5'), 3.31 (dd, H-2'), 3.26 (s, OMe), 3.23 (br d, H-13), 2.95 (dd, H-4"), 2.93 (m, H-8), 2.89 (t, H-7a), 2.82 (ddd, H-3'), 2.56 (m, H-2), 2.46 (s, NMe_2), 2.32 (d, H-2"eq), 2.11 (dq, H-4), 1.85 (m, H-4'eq), 1.59 (m, H-14a), 1.55 (m, H-7b), 1.45 (dd, H-2"ax), 1.34 (m, H-14b), 1.29 (m, H-4'ax), 1.24 (d, 5'-Me), 1.24 (d, 10-Me), 1.23 (d, 8-Me), 1.20 (d, 5"-Me), 1.11 (d, 4-Me), 1.09 (d, 2-Me), 1.00 (t, H-15). ^{13}C NMR ($CDCl_3$) δ 181.1, 174.6, 103.9, 95.9, 87.0, 84.5, 82.3, 78.7, 77.8, 75.1, 74.7, 72.7, 70.3, 69.2, 65.7, 65.5, 49.5, 48.0, 42.9, 41.7, 40.2, 38.8, 35.9, 35.1, 29.4, 26.9, 24.8, 21.6, 21.1, 20.6, 18.0, 17.3, 15.0, 12.1, 11.6, 11.0. IR ($CHCl_3$) 3480, 2980, 2940, 2880, 2840, 2795, 1760, 1660, 1460, 1455, 1380, 1160, 1105, 1085, 1065, 1050, 1000 cm^{-1}. FAB-MS m/z 749 (M+1), 591 (M+1–(desosamine)), 158 (desosamine).

Rearranged 8-deuterio-amino-γ-lactones 26a and 26b. A solution of **25** (50 mg, 0.07 mmol) in deuteriomethanol (0.5 mL) was treated with a drop of 40% NaOD in D_2O and the solution was stirred at room temperature for 3.5 hours. Methylene chloride (4 mL) and water (4 mL) were added and the mixture was stirred rapidly while the pH was adjusted to 10 with 2N HCl. The methylene chloride layer was removed, dried with magnesium sulfate, filtered and evaporated to a foam (34 mg, 68%). Examination of the foam by ^1H NMR revealed a mixture of **26a** and **26b** whose 8-protons had been exchanged with deuterium atoms. This was evident by the collapse of both the H-7a and H-7b dd's to a set of doublets at 2.17 and 1.92 ppm for **26a** and 2.89 and 1.55 ppm for **26b**.

(2'-*O*,4"-*O*,11-*O*,10-*N*)-Tetraacetyl-amino-γ-lactone 27. A solution of acetic anhydride (1 mL, 10.6 mmol) and **25** (300 mg, 0.4 mmol) in pyridine (4 mL) was stirred at room temperature for 3 days. The mixture was poured onto ice-water (20 mL), the pH was adjusted from 5.2 to 8.5 with 2N sodium hydroxide and the aqueous layer was extracted with chloroform (30 mL). The chloroform was washed with water (20 mL), dried with magnesium sulfate, filtered and evaporated to a foam (370 mg). The foam was purified on a silica column (2.5 x 24 cm), collecting 8 mL fractions. Fractions 12-18 were combined and evaporated to give **27** (221 mg, 60%) as a foam. mp 98-103°C. ^1H NMR ($CDCl_3$) δ 6.41 (d, NH), 4.91 (br d, H-13), 4.69 (d, H-1"), 4.69 (dd, H-2'), 4.58 (d, H-4"), 4.56 (d, H-11), 4.53(d, H-1'), 4.37 (dq, H-10), 4.25 (dq, H-5"), 4.04 (d, H-3), 3.64 (d, H-5), 3.62 (ddq, H-5'), 3.22 (s, OMe), 2.63 (m, H-8), 2.66 (ddd, H-3'), 2.55 (m, H-2), 2.30 (d, H-2"eq), 2.18 (s, NMe_2), 2.05 (s, 11-OAc), 2.02 (s, 4"-OAc), 1.99 (dd, H-7a), 1.96 (s, 2'-OAc), 1.85 (s, NHAc), 1.86 (m, H-7b), 1.80 (dq, H-4), 1.75 (m, H-14a), 1.65 (m, H-4'eq), 1.52 (dd, H-2"ax), 1.49 (m, H-14b), 1.38 (s, 6-Me), 1.23 (m, H-4'ax), 1.19 (s, 12-Me), 1.15 (d, 8-Me), 1.12 (d, 5'-Me), 1.07 (d, 2-Me), 1.02 (s, 3"-Me), 1.00 (d, 10-Me), 1.00 (d, 5"-Me), 0.91 (d, 4-Me), 0.77 (t, H-15). ^{13}C NMR ($CDCl_3$) δ 179.3 (C-9), 174.8 (C-1), 171.8 (11-OAc), 170.5 (4"-OAc), 169.9 (2'-OAc), 169.1 (10-NHAc), 100.2 (C-1'), 94.7 (C-1"), 85.4 (C-6), 79.8 (C-5), 78.5 (C-11 and C-4"), 77.2 (C-13), 76.9 (C-3), 75.1 (C-12), 72.9 (C-3"), 71.4 (C-2'), 68.0 (C-5'), 63.0 (C-3'), 62.7 (C-5"), 49.3 (OMe), 45.4 (C-10), 42.4 (C-2), 40.5 (NMe_2), 39.3 (C-4), 36.9 (C-7), 35.1 (C-2"), 34.0 (C-8), 30.9 (C-4'), 24.9 (6-Me), 23.3 (10-NHAc), 22.1 (C-14), 21.3, 20.8, and 20.8 (2'-, 4"-, and 11-

OAc), 20.8 (5'-Me), 19.1 (12-Me), 17.4 (5"-Me), 16.6 (10-Me), 15.1 (8-Me), 11.6 (2-Me), 10.8 (C-15), 10.5 (4-Me), IR ($CHCl_3$) 3420, 2980, 2940, 2880, 2835, 2780, 1760 (sh), 1735, 1660, 1515, 1450, 1370, 1240, 1160, 1120, 1105, 1080, 1050, 1000 cm^{-1}. FAB-MS (Li spike) m/z 923 (M+Li), 917 (M+1), 717 (M+1–(2'-OAc-desosamine)), 200 (2'-OAc-desosamine).

Amino-dilactone 28. To a suspension of 9,11-iminoether **15** (730 mg, 1.0 mmol) in water (2 mL) was added acetic acid (0.25 mL) and the resulting solution was stirred for 5 hours at room temperature. Methylene chloride (10 mL) was added and the pH was adjusted to 11 with 2N sodium hydroxide. The methylene chloride layer was removed and the aqueous layer was re-extracted with more methylene chloride (2 x 4 mL). The combined extracts were dried with magnesium sulfate, filtered and evaporated under vacuum to a foam (650 mg). The foam was dissolved in diethyl ether (8 mL) and, after stirring for 20 minutes at room temperature, was filtered to give **28** as a crystalline solid (600 mg, 80%). mp 165.5-166°C. ^1H NMR ($CDCl_3$) δ 5.12 (dd, H-13), 4.80 (d, H-11), 4.66 (d, H-1"), 4.64 (d, H-1'), 4.27 (d, H-3), 3.95 (s, 6-OH), 3.92 (dq, H-5"), 3.90 (s, 6-OH), 3.84 (d, H-5), 3.56 (ddq, H-5'), 3.34 (s, OMe), 3.28 (dd, H-2'), 3.22 (dq, H-10), 2.97 (d, H-4"), 2.90 (m, H-8), 2.46 (ddd, H-3'), 2.61 (m, H-2), 2.42 (d, H-2"eq), 2.27 (s, NMe_2), 1.95 (m, H-14a), 1.84 (m, H-7a), 1.84 (dq, H-4), 1.63 (m, H-7b), 1.65 (m, H-4'eq), 1.55 (dd, H-2"ax), 1.47 (m, H-14b), 1.40 (d, 8-Me), 1.23 (m, H-4'ax), 1.22 (s, 3"-Me), 1.17 (d, 5'-Me), 1.17 (d, 2-Me), 1.17 (d, 5"-Me), 1.11 (s, 6-Me), 1.09 (s, 12-Me), 1.09 (d, 4-Me), 1.02 (d, 10-Me), 0.80 (t, H-15). ^{13}C NMR ($CDCl_3$) δ 176.6 (C-9), 176.4 (C-1), 101.7 (C-1'), 94.8 (C-1"), 80.2 (C-5), 79.2 (C-11), 77.9 (C-13 and C-4"), 75.0 (C-3), 74.7 (C-6), 74.3 (C-12), 72.7 (C-3"), 70.6 (C-2'), 69.4 (C-5'), 65.8 (C-5"), 65.2 (C-3'), 49.2 (OMe), 46.9 (C-10), 44.1 (C-4), 43.4 (C-2), 40.3 (NMe_2), 40.1 (C-7), 35.8 (C-8), 34.7 (C-2"), 28.6 (C-4'), 23.8 (6-Me), 22.7 (C-14 and 10-Me), 21.7(3"-Me), 21.1 (5'-Me), 19.6 (12-Me), 17.9 (5"-Me), 17.6 (8-Me), 12.2 (2-Me), 10.8 (C-15), 9.8 (4-Me). IR ($CHCl_3$) 3460, 2980, 2940, 2880, 2840, 2790, 1760, 1725, 1455, 1380, 1340, 1325, 1300, 1290, 1160, 1120, 1110, 1105, 1085, 1050, 1000 cm^{-1}. FAB-MS (Li spike) m/z 756.2 (M + Li), 750.1 (M+1), 591.9 (M+1–(desosamine)), 158 (desosamine). Elemental analysis: calculated for $C_{37}H_{68}N_2O_{13}$: C, 59.34: H, 9.15: N, 3.74%; found: C, 59.28: H, 9.31: N, 3.58%.

(2'-*O*,4"-*O*,*N*)-Triacetyl-amino-dilactone 29. A solution of acetic anhydride (0.37 mL, 3.90 mmol) and **28** (110 mg, 0.15 mmol) in pyridine (1.5 mL) was stirred at room temperature for 3 days. The mixture was partitioned between methylene chloride (8 mL) and water (8 mL) and the pH was adjusted to 10 with 2N sodium hydroxide. The aqueous layer was separated and extracted with more methylene chloride (2 x 5 mL). The combined methylene chloride was dried with magnesium sulfate, filtered and evaporated to give **29** (120 mg, 94%) as a foam. ^1H NMR ($CDCl_3$, 55°C) δ 5.36 (br s, NH), 5.27 (br d, H-11), 4.99 (dd, H-13), 4.93 (m, H-1' and H-2'), 4.74 (d, H-4"), 4.57 (d, H-1"), 4.37 (d, H-3), 4.34 (dq, H-5" and H-10), 3.97 (ddq, H-5'), 3.80 (d, H-5), 3.37 (s, OMe), 2.95 (ddd, H-3'), 2.90 (m, H-8), 2.48 (m, H-2), 2.39 (d, H-2"eq), 2.37 (s, NMe_2), 2.08, 2.05, and 1.89 (three s's, Ac), 1.80 (m, H-7a), 1.78 (m, H-4), 1.72 (m, H-14a), 1.65 (dd, H-2"ax), 1.63 (m, H-14b), 1.55 (d, 8-Me), 1.42 (m, H-4'eq), 1.26 (d, 2-Me), 1.24 (two d's, 10-Me and 5"-Me), 1.23 (m, H-4'ax), 1.23 (d, 5'-Me), 1.12 (m, H-7b), 1.00 (d, 4-Me), 0.83 (t, H-15). ^{13}C NMR ($CDCl_3$) δ 176.7, 175.7, 170.1, 169.7, 169.4, 98.8, 93.3, 84.5 br, 80.7, 77.9, 74.7, 73.6, 72.8, 72.4 br, 71.6, 67.9, 63.6, 62.6, 48.8, 46.5, 42.6, 42.5, 40.7, 38.4, 35.7, 34.5, 31.7, 23.9, 23.2, 23.1, 23.1, 21.5, 21.4, 21.1, 20.7, 17.7, 15.0, 11.5, 11.2, 10.1. IR ($CHCl_3$) 3520, 2450, 3020, 2980, 2940, 2880, 2840, 2780, 1735, 1675, 1505, 1455, 1370, 1240, 1160, 1120, 1080, 1040, 1000 cm^{-1}. FAB-MS (Li spike) m/z 882.0 (M+Li), 199.8 (2'-OAc-desosamine). Elemental analysis: calculated for $C_{43}H_{74}N_2O_{16}$: C, 59.02: H, 8.52: N, 3.20%; found: C, 58.93: H, 8.44: N, 3.05%.

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4. Similar treatment of anhydroerythromycin **2** with potassium carbonate in refluxing methanol provides a 1 : 6 ratio of **2** : **3**, see ref. 1a.
5. For clarity, the erythromycin numbering system is retained in all rearrangement products.
6. The ethylene glycol serves the dual purpose of activating the borohydride reducing agent and simplifying the workup by eliminating the borate complexes.
7. Attempted thermal equilibration of iminoether **8** results in the elimination of water to give the corresponding 10,11-anhydro derivative. This compound also forms on treatment of **8** with acetic acid, see ref. 10.
8. It is not clear from molecular models whether compound **11** results from a stereospecific reduction of the imino group from the β-face or whether reduction occurs from the α-face followed by rapid equilibration to a thermodynamically preferred form.
9. After we concluded our work on the transannular rearrangements of the 6,9-iminoether **4**, a communication describing the formation of the 9,11-iminoether **15** by the low temperature Beckmann rearrangement of the (9*E*)-oxime of erythromycin A was published. Unassigned ^{1}H NMR data and an X-ray structure were presented. Yang, B. V.; Goldsmith, M.; Rizzi, J. P. *Tetrahedron Lett.* **1994**, *35*, 3025.
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