Supplementary Material Available: Spectral data for norcaradienes **4a–4e** and X-ray crystallographic data for **4a** including tables of fractional atomic coordinates, bond distances, and bond angles (9 pages); listing of observed and calculated structure factor amplitudes (10 pages). Ordering information is given on any current masthead page.

Novel Macrolactonization Strategy for the Synthesis of Erythromycin Antibiotics

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Erythromycins B (**1**) and A (**2**) (Scheme I) are the archetypal representatives of the clinically important family of 14-membered, macrolide antibiotics.[1,2] Owing to the challenges posed by their densely functionalized and stereochemically complex architecture, these compounds have elicited intense interest, and a number of elegant syntheses of derivatives of the aglycons of **1** and **2** and their respective seco acids, as well as of the natural antibiotic **2** itself, have been recorded.[3] In this context, we recently reported a facile, asymmetric synthesis of the erythronolide B seco-acid derivative **5** and have extended that work to the preparation of the related erythronolide A analogue **6**,[4] but the significant challenge of elaborating **5** and **6** into the corresponding natural antibiotics **1** and **2** remained. After consideration of a number of potential options, we were particularly intrigued by one exciting, albeit speculative, strategy for the end game of the syntheses of **1** and **2** that had not been previously explored. Namely, we envisaged that macrolactonization of glycosylated seco-acid derivatives related to **3** and **4**, which should be accessible from **5** and **6**, might serve as a key step in a novel and concise route to **1** and **2** and biologically interesting analogues thereof. However, prior to embarking upon a venture to convert synthetic **5** and **6** into intermediates analogous to **3** and **4**, it seemed prudent to establish first that such glycosylated seco acids would undergo macrolactonization; there was no precedent for such a cyclization.[5]

In previous formulations of strategies for the synthesis of erythromycin antibiotics, macrocyclization of a seco-acid derivative of the aglycon has been generally perceived as the primary subgoal. Significantly, the subsequent glycosylation of the hydroxyl groups at C(3) and C(5) of an intermediate macrolide leading eventually to a natural target has only been achieved in Woodward's seminal total synthesis of **2**.[3e] Critical to the success of the macrolactonization step in all cases thus far reported is the reduction of conformational space available to the seco-acid backbone, typically in two different regions. Rigidification of the segment between C(2) and C(6) has been most commonly achieved by formation of a cyclic protecting group involving the hydroxyl groups at C(3) and C(5). Conformational restriction of a second segment of the carbon framework has been most frequently accomplished by construction of a cyclic, six-membered protecting group array incorporating the functionality at C(9) and C(11).[3e-i,m-r] Other useful devices to rigidify the backbone include insertion of a double bond at strategic sites such as between C(10) and C(11)[3a-c] or between C(8) and C(9)[3s] or by incorporation of a conjugated enone between C(7) and C(5) in tandem with a double bond between C(11) and C(12).[3k]

The preceding investigations delineated some of the key structural features that must be embodied within the seco-acid matrix in order to optimize the prospects for successful macrolactonization. After careful consideration of these factors, we concluded that the critical question of whether glycosylated seco-acid derivatives of the erythromycins might be induced to undergo macrolactonization could be most expeditiously resolved by using conformationally constrained substances related to **3** and **4**. We reasoned that rigidity could be imparted to the C(9)–C(13) segment of the framework in a conventional manner by forming a cyclic derivative between the C(11) and C(9) hydroxyl groups. We further anticipated that the steric buttressing interactions between the two carbohydrate residues at C(3) and C(5) of **3** and **4** would advantageously reduce conformational mobility along the C(1)–C(8) subunit to facilitate cyclization. However, since one might also envision that unfavorable steric interactions between the two sugar residues could dramatically disfavor those conformers of **3** and **4** that were capable of undergoing cyclization, we undertook exploratory experiments to establish the viability of effecting macrolactonization of a fully glycosylated derivative of erythromycin B. We now report the details of some of those investigations.

In the first phase of these feasibility studies, erythromycin B (**1**) was converted into **9** according to Scheme II.[6] Transformation of **1** into **7** proceeded in 53% overall yield according to modifications of known procedures for N-demethylation, carbonyl reduction, and acetal formation in the erythromycin area.[7] Although the stereochemistry at the acetal carbon in **7** could not be unambiguously established, the equatorial orientation of the

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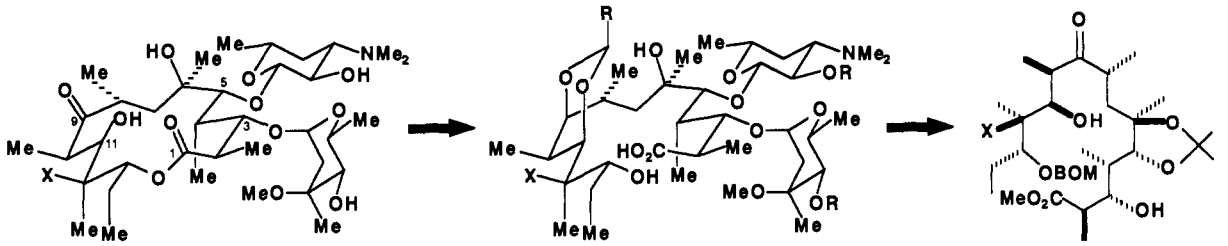
Scheme I

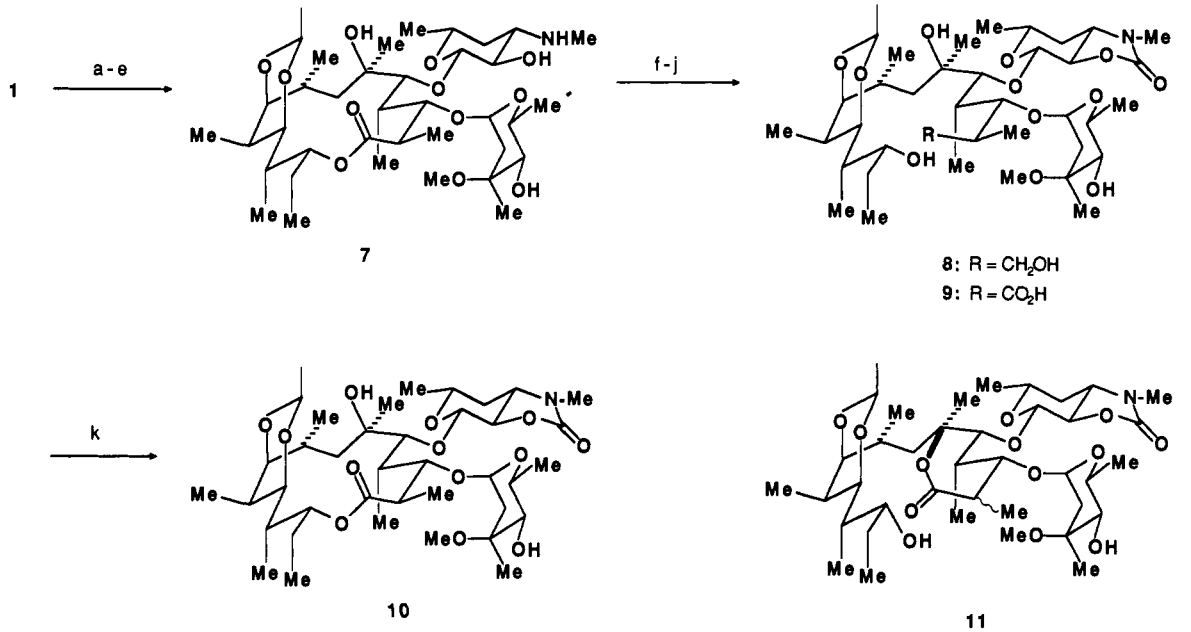


1: X = H
2: X = OH

3: X = H
4: X = OBOM

5: X = H
6: X = OBOM

Scheme II[a]



7

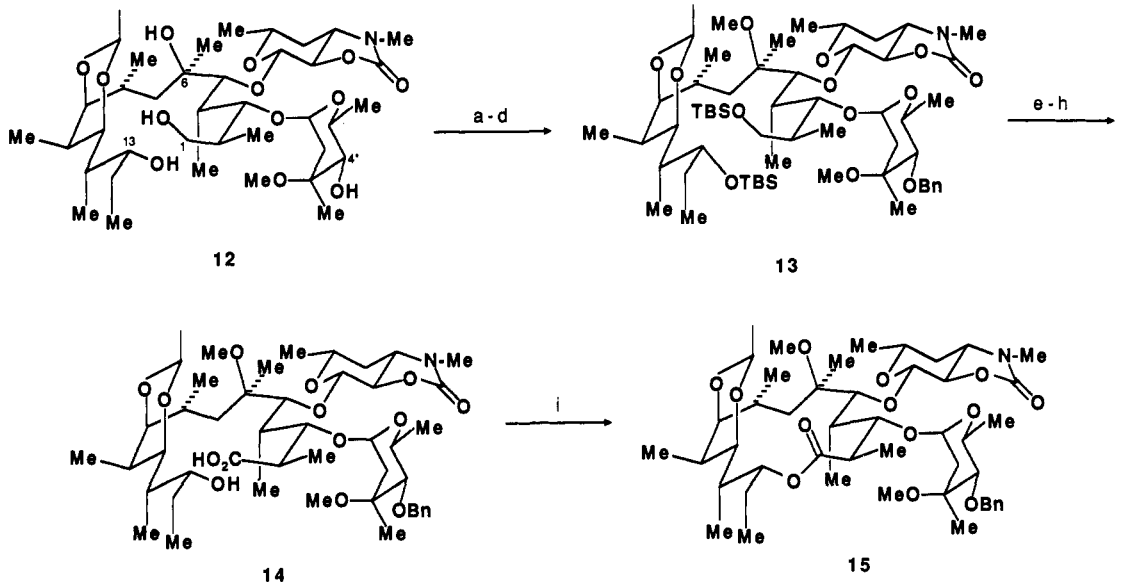
8: R = CH_2OH
9: R = CO_2H

10

11

[a](a) I_2/MeOH/$h\nu$; (b) Cbz-Cl/DMAP; (c) $NaBH_4$; (d) $CH_3CH(OEt)_2/H^+$; (e) 5% Pd–C/H_2/EtOH; (f) $LiAlH_4$; (g) *p*-$O_2NC_6H_4OCOCl$/DMAP; (h) NaH; (i) TEMPO (cat.)/NaOCl; (j) $NaClO_2$/aqueous Bu^tOH/2-methyl-2-butene; (k) 2,4,6-$Cl_3C_6H_2COCl/Et_3N$/THF; DMAP/PhMe/Δ.

Scheme III[a]



12

13

14

15

[a](a) TBS-Cl/DMAP; (b) NaH/Bu_4NI/BnBr; (c) TBS-OTf/NEt_3; (d) KH/MeI/18-C-6; (e) Bu_4NF/THF/room temperature; (f) PDC/CH_2Cl_2; (g) $NaClO_2$/aqueous Bu^tOH/2-methyl-2-butene; (h) Bu_4NF/HMPA/80 °C; (i) 2,4,6-$Cl_3C_6H_2COCl/Et_3N$/THF; DMAP/PhMe/Δ.

methyl group has been assigned on the basis of thermodynamic considerations and literature precedent.[7e] Somewhat surprisingly, we found that the lactone function in 7 stubbornly resisted cleavage under a wide variety of acidic and basic reaction conditions, and degradation pathways preempted simple hydrolysis. However, hydride reduction of the lactone group followed by formation of

a cyclic carbamate moiety on the pendant desosamine residue delivered the tetraol **8** in 53% yield. Selective oxidation[8] of the primary hydroxyl gave the requisite seco-acid **9** in 78% yield, thereby setting the stage to test the crucial macrocyclization step.[9]

In the event, subjection of **9** to the highly effective Yamaguchi macrolactonization protocol[9h,j] afforded a separable mixture (1:2.4:1; 96% combined yield) of the desired 14-membered lactone **10** together with two isomeric lactones. On the basis of spectral evidence, these two substances have been tentatively identified as the C(2)-epimeric seven-membered lactones **11**; however, these structural assignments must be confirmed. Cyclization of **9** could also be effected via its 2-pyridyl thioester,[9c] but lactonization under these conditions was considerably less efficient and provided primarily a mixture of the two lactones **11** together with only a small amount of **10** (49% combined yield). An authentic sample of **10** for purposes of comparison was prepared directly from **7** [$COIm_2$ (5 equiv), toluene, reflux, 20 h; 10% aqueous Na_2CO_3, room temperature, 16 h; 71%]. The formation of a seven-membered lactone as **11** from **9** was surprising, since there have been a number of reports of successful cyclizations of erythronolide seco-acid derivatives bearing unprotected hydroxyl groups at C(6) and C(12) to provide 14-membered lactones as the exclusive products.[10] Inasmuch as there were preliminary indications that **10** and **11** might interconvert under certain conditions, we were also concerned that the 14-membered lactone might arise from translactonization of the seven-membered lactone intermediate rather than by direct cyclization.[11]

In order to improve the efficiency of the macrolactonization and to circumvent the possibility of translactonization processes, the fully protected seco-acid derivative **14** was prepared in eight steps (27% overall yield) from **12**, which was an intermediate in the previous synthesis of **9** (Scheme III). The success of this sequence lay in the significant difference in the chemical reactivity of the four hydroxyl groups, which followed the order C(1) ≫ C(4″) > C(13) ≫ C(6), thereby allowing selective protection and manipulation of each hydroxyl function. When **14** was subjected to the conditions of the Yamaguchi lactonization protocol,[9h] the protected derivative of erythromycin B (**15**) was obtained in 53% yield. An authentic sample of **15** for comparison was prepared independently from erythromycin B (**1**) in eight steps,[12] and the two compounds thus obtained were identical by ^1H and ^{13}C NMR. Several preliminary attempts to effect the cyclization of **14** under conditions previously defined by Corey[9c] or Keck[9i] did not afford detectable amounts of the desired lactone **15**.

The novel macrolactonizations of **9** and **14** establish for the first time that carbohydrate residues on the hydroxyl functions at C(3) and C(5) provide sufficient restriction of rotational freedom along the C(1)–C(8) segment of the erythromycin seco-acid backbone for macrolactonization to occur. This exciting discovery should greatly simplify the synthesis of the natural antibiotics themselves and allow facile accessibility to unusual analogues. Indeed, application of this tactical device to a practical total synthesis of erythromycin B is the subject of current investigation, the results of which will be reported in due course.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra of intermediates in Schemes II and III and footnote 12 and of authentic samples of **10** and **15** (55 pages). Ordering information is given on any current masthead page.

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(10) See refs 3b,e,h,n–p,r,s, and 9j.

(11) More recent experiments have cast doubt on at least some aspects of this hypothesis. For example, when **10** was subjected to several conditions known to effect translactonization, there was no evidence for the formation of compounds **11**; decomposition pathway seemed dominant. However, we have not determined whether **11** might be transformed into **10**, since it is difficult to isolate either diastereoisomer in pure form.

(12) The sequence of reactions and the unoptimized yields for each step were as follows: (a) I_2, MeOH, *hν* (96%). (b) Cbz-Cl, DMAP (95%). (c) MeI, KOH, DME-DMSO (75%).[13] (d) $NaBH_4$, MeOH, 0 °C (71%). (e) $MeCH(OEt)_2$, PPTS, CH_2Cl_2 (62%). (f) H_2, 10% Pd–C, aqueous EtOH–acetate buffer (pH = 4.8) (85%). (g) $COIm_2$, toluene, reflux; 10% aqueous Na_2CO_3–THF (94%). (h) BnBr, Bu_4NI, KH, 18-crown-6, THF (92%).

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Synthesis and Reactivity of $[Re(N\text{-}2,6\text{-}C_6H_3\text{-}i\text{-}Pr_2)_3]^-$ and the X-ray Structure of $Hg[Re(N\text{-}2,6\text{-}C_6H_3\text{-}i\text{-}Pr_2)_3]_2$

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Recently synthesized trigonal-planar $Os(NAr)_3$ (NAr = N-2,6-C_6H_3-*i*-Pr_2)[1] has been shown to have limited reactivity.[2] Since relatively labile and reactive rhenium(V) bisimido complexes have been prepared recently,[3] we became interested in preparing what we hoped to be relatively reactive $[Re(NAr)_3]^-$. We report here the synthesis and some reactions of this species along with an X-ray study of $Hg[Re(NAr)_3]_2$.

$Re(NAr)_3Cl$[4] is cleanly reduced by 2 equiv of sodium amalgam in THF to give $[Na(THF)_2][Re(NAr)_3]$ (**1a**). $[NEt_4][Re(NAr)_3]$ (**1b**) is formed if NEt_4Cl is present. Since **1a** is soluble in toluene, sodium may be bound to nitrogen (cf. lithium salts of anionic W(VI) and Mo(VI) imido complexes[5]) or directly to rhenium (cf. **4** below). **1b** is not soluble in toluene or ether. If only 1 equiv of sodium amalgam is employed, the pentane-soluble product has the formula $Hg[Re(NAr)_3]_2$ (**1c**). We speculate that reduction to give $Re(NAr)_3$ radicals occurs first and that two of these then attack Hg to give **1c**. The structure of **1c**, as determined in an X-ray study, is shown in Figure 1.[6] The Hg–Re distance [2.621 (1) Å] is consistent with its being a single bond. The linear imido ligands (Re=N—C 173 (1)°) are arranged in a "propellar" fashion, and the two ends are staggered with respect to each other (S_6 symmetry). The Re=N bonds [1.76 (1) Å] are longer than the Os=N bonds (1.737 Å average) found in $Os(NAr)_3$. The

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(2) Schofield, M. H.; Kee, T. P.; Anhaus, J. T.; Schrock, R. R.; Johnson, K. H.; Davis, W. M. *Inorg. Chem.*, in press.

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(6) Crystals were mounted on glass fibers in air. Data were collected on a Rigaku AFC6R diffractometer at room temperature using Mo Kα radiation (space group $Pa\bar{3}$ with a = 19.548 (6) Å, Z = 4, FW = 1624.64, and ρ = 1.444 g cm^{-3}). A total of 4214 reflections were collected in the range $3° < 2\theta < 55°$ with 638 having $I > 3.00\sigma(I)$ being used in the structure refinement by full-matrix least-squares techniques (123 variables) using the TEXSAN crystallographic software package from Molecular Structure Corporation; final R_1 = 0.034, R_2 = 0.036. Full details can be found in the supplementary material.

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