X-ray diffractometer and computing system was purchased with funds provided by the National Science Foundation (CHE 810 3011). We are grateful to Prof. O. P. Anderson and C. Schauer for performing the X-ray studies.

Supplementary Material Available: Physical data, experimental details, and X-ray data for **3** and **4** (R = Me) (21 pages). Ordering information is given on any current masthead page.

Macrocyclic Stereocontrol. Total Synthesis of (±)-3-Deoxyrosaranolide

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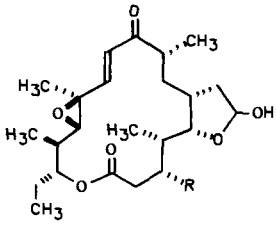
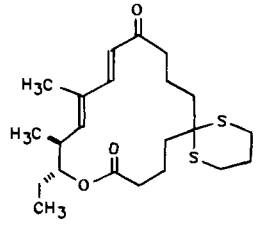
The conformational structure of medium- and large-ring molecules provides an effective medium through which asymmetric centers may efficiently control the stereochemical outcome of remote chemical reactions. To investigate the potential of this approach to stereocontrol in complex synthesis, we have undertaken an extensive application of the methodology[1] to a derivative of the macrolide antibiotic rosaramicin[2] (aglycon **1a**). Starting from the simple macrocycle **2**, we synthesized the racemic 3-deoxy



1a. R = OH
1b. R = H



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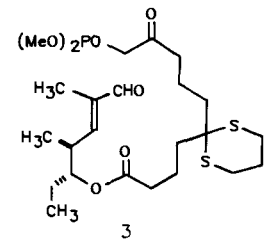
aglycon **1b** using the two adjacent asymmetric centers at C11 and C12 to efficiently control the six others spanning C4–C10.

The starting ketomacrolide **2** was readily prepared from acyclic ester **3**[3] by Horner–Emmons cyclization[4] (K_2CO_3, 18-crown-6, 0.01 M in toluene, 75 °C; 76%). On deprotonation with KN(Me_3Si)$_2$ and alkylation with CH_3I (THF, −78 → 20 °C), a single C8-methylated material was produced in 70% yield and with diastereoselection 20:1.[5] Deprotection (HgO, HBF_4/THF; >95%)[6] and X-ray crystallographic analysis[3] of the product **4** showed the natural 8-α configuration. Regio- and stereoselective introduction of the second side chain was accomplished (73%) with >20:1 regioselection for C6 and 6–10:1[7] α stereoselection by using LiN(Me_3Si)$_2$ and CH_3I. The identity of the product as **5a** (R = CH_3) was shown by X-ray crystallography.[3] An analogous alkylation using $BrCH_2COO$-*t*-Bu proceeded with the same regio- and stereoselection to yield **5b** (R = CH_2COO-*t*-Bu) (73%) as



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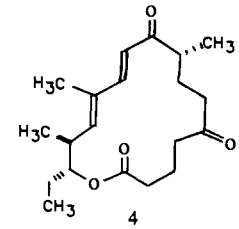

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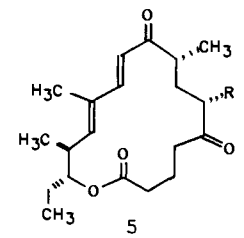

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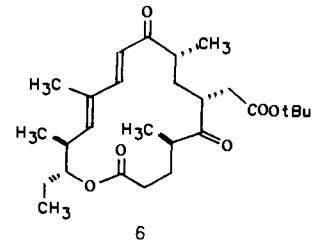

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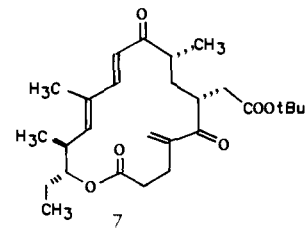
shown by spectral comparison with **5a** and by further conversions. Highly stereoselective (>40:1) introduction of the C4 methyl followed (LiN(Me_3Si)$_2$, THF, CH_3I; 71%) but led to the unnatural 4-β isomer **6**.[5]

Assuming that the desired 4-α stereochemistry could be obtained by a stereoanalogous enolate protonation, the C4 lithium enolate was treated with gaseous HCHO to give a single 4-hydroxymethyl ketone (62%), which was eliminated via the mesylate to the methylene ketone **7** (90%). Addition of thiophenol



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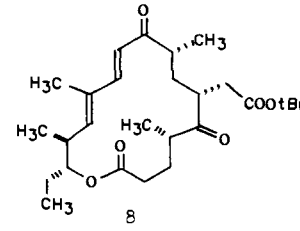

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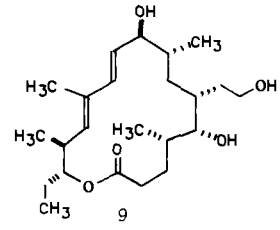

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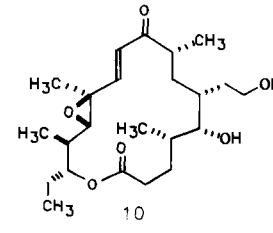

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(catalytic Et_3N; 71%) and Raney nickel desulfurization (W2 Ra Ni, EtOH; 62%) then gave the required 4-α **8** with >25:1 stereoselection. Alternatively, catalytic reduction with H_2/(Ph_3P)$_3$RhCl (C_6H_6) gave 9:1 **8**:**6** (75%).

Final conversions to **1b** included stereoselective reduction and epoxidation. While the 5-β alcohol was formed with >20:1 stereoselection by direct $NaBH_4$–$CeCl_3$[8] reduction, the 5-α alcohol **9** could be prepared with 5:1 stereoselection at C5 by reduction ($NaBH_4$, CH_2Cl_2/*i*-PrOH) of the mixed anhydride prepared by *tert*-butyl ester hydrolysis (CF_3COOH) and acylation (Et_3N, ClCOOEt) (50% overall). Oxidation (MnO_2; 75%) and epoxidation (MCPBA, Na_2CO_3, CH_2Cl_2; 88%) then led to diastereomer **10** (>15:1), which was further oxidized to **1b** with (Ph_3P)$_3RuCl_2$[9] in 47% yield at 56% conversion. Racemic **10** thus prepared was indistinguishable from naturally derived material[3] by ^{13}C NMR, 270-MHz ^1H NMR, IR, and MS.

In all, 11 kinetic reactions were used in various conversions that establish stereochemistry in the 16-membered macrolide described above. Among these reactions, conditions were readily found that gave eight of the reactions at least 15:1 stereoselection and the

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(3) Supplementary material.

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(5) Equilibration with base gave ca. 1:1 diastereomeric mixture at the newly established center only.

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(7) Ratio by isolation (6:1) and by calibrated HPLC (10:1).

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remainder 5-10:1 stereoselection. Desired stereoisomers at C4-C10 were prepared selectively in every case. These and previous results provide firm evidence that macrocyclic stereocontrol is a general and effective strategy that can be of significant value in complex synthesis. While one may argue that the approach lacks convergency since it postpones certain construction steps until after the coupling of major fragments, the objection is not a serious one: only those few reactions that set stereochemistry need be postponed.

The high stereoselection commonly produced in the kinetic reactions of macrocycles is related to the conformational preferences of the reaction transition states; however, the details of such preferences in complex structures like those described above are as yet unclear. Our next goal is to find a reliable way to predict macrocyclic diasteroselection so that macrocyclic stereocontrol strategies may be used rationally in complex synthesis and so that the mechanism of the stereoselection may be elucidated.[10]

Acknowledgment. We are grateful to Dr. A. K. Ganguly of Schering Corp. for a generous supply of rosaramicin and to Diana Burman for assisting in the preparation of early intermediates.

Supplementary Material Available: Outlines of preparations of **3** and naturally derived **1b**, ORTEP crystal structures for **4** and **5a**, and full spectral data for **1b-10** (13 pages). Ordering information is given on any current masthead page.

(10) This work was supported by grants from the National Science Foundation and the National Institutes of Health.

Isolation and X-ray Crystal Structure of the Cuprate Complex $[Li_2Cu_3Ph_6]_2[Li_4Cl_2(Et_2O)_{10}]$: The First X-ray Structural Characterization of an Anionic Organocopper-Lithium Cluster

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The widespread use of lithium organocuprates as reagents in organic synthesis has led to considerble interest in their structures.[1] Solution ^1H NMR and molecular weight determinations have indicated that, depending on how the cuprate is prepared, species such as $LiCuR_2$, $LiCu_2R_3$, Li_2CuR_3, or $Li_2Cu_3R_5$ are present.[2] However, none of these interesting aggregates has been isolated where R is a simple alkyl or aryl group. The most relevant published work has concerned the dimeric species $[Li_2Cu_2Ar_4]$[3] involving the chelating group $2\text{-}Me_2NCH_2C_6H_4^-$. However, the nitrogen donors undoubtedly play a significant role in the structure and a direct structural comparison to complexes involving methyl or unsubstituted phenyl groups is open to question. The only X-ray structural characterizations of cuprate complexes involve the species $[Cu(Mes)_2][Cu(dppe)_2]$[4] (Mes = mesityl), in which two aryl groups are σ-bound to a linear copper(I) and the cluster $[Li(THF)_4][Cu_5Ph_6]$.[5] The former was obtained by the disproportionation of [Cu(Mes)] with dppe and does not contain lithium while the latter, although isolated from a lithium cuprate solution, has a Li:Cu ratio of 1:5 rather than the usual 1:1 ratio.

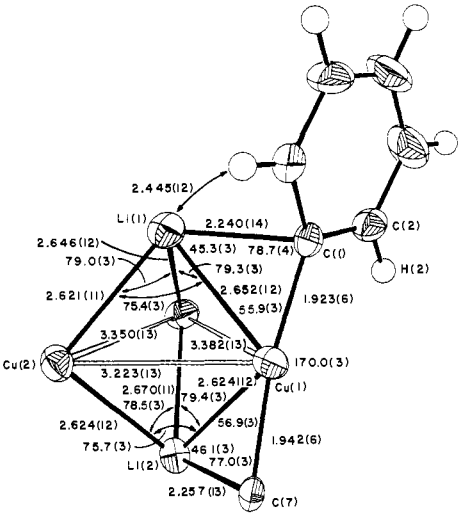

Figure 1. Thermal ellipsoid plot of the anion of **1**. Five of the phenyl groups have been omitted for clarity.

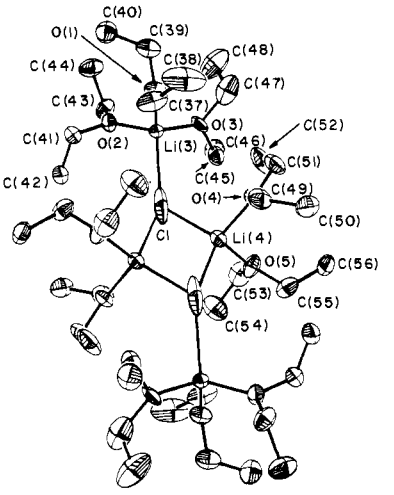

Figure 2. Thermal ellipsoid plot of the cation of **1**. Hydrogen atoms have been omitted for clarity.

In this paper we report the first X-ray crystal structure of a cluster involving a framework of both lithium and copper atoms, prepared in a fortuitous manner. We were examining crystalline products from cuprate solutions, derived from CuCN[6] and 2 equiv of LiPh in ether, with the object of explaining their high reactivity toward various organic substrates.[7] These solutions invariably afforded a mixture of yellow and colorless crystals after filtration and cooling to -20 °C. The X-ray data[8] for the yellow crystals revealed that the compound crystallizes as $[Li_2Cu_3Ph_6]_2$-$[Li_4Cl_2(Et_2O)_{10}]$ (**1**) (Figures 1 and 2). The presence of chloride

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(8) A yellow crystal of **1** of dimensions 0.40 × 0.40 × 0.37 mm was mounted on a Syntex $P2_1$ diffractometer equipped with a graphite monochromator. With Mo Kα (λ = 0.71069 Å) and the crystal cooled to 140 K, crystal data were as follows: monoclinic $P2_1/n$; a = 13.214 (8) Å, b = 18.20 (1) Å, c = 24.42 (2) Å, β = 97.17 (5)°; Z = 2; μ = 11.75 cm^{-1}. Data were collected to $2\theta_{max}$ of 47° with an ω scan technique. A total of 8618 unique data were collected of which 5287 had $I > 2\sigma(I)$. Scattering factors and corrections for anomalous scattering were from Vol. IV of the International Tables. The structure was solved by direct methods. Computer programs are those of SHELXTL, Version 3, July 1981 package. The absorption correction was applied. The non-hydrogen atoms were anisotropically refined (652 parameters) and the final R factors are R = 0.0632 and R_w = 0.0487.

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