

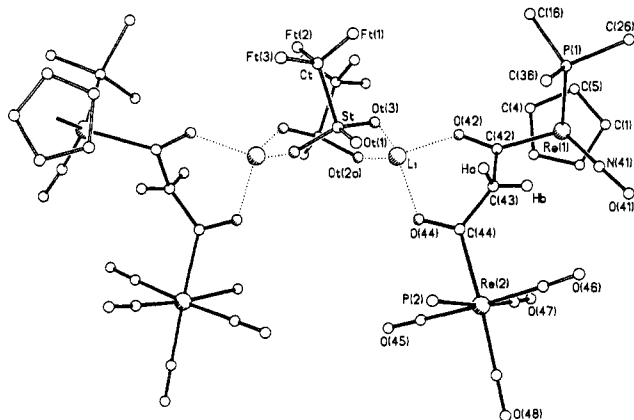
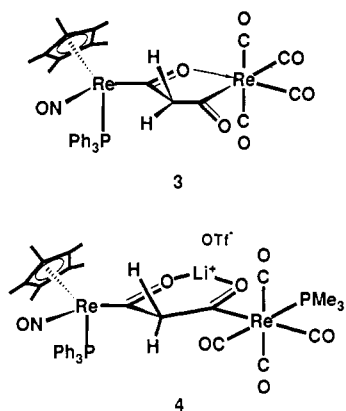


Figure 1. Molecular structure of **4** showing orientation of CF_3SO_3^- and Li^+ ions in relation to the dirhenium backbone. Bond distances (Å) and angles (deg) are as follows: $\text{Re}(1)\text{--C}(42)$ 2.069 (9), $\text{Re}(2)\text{--P}(2)$ 2.453 (5), $\text{Re}(2)\text{--C}(44)$ 2.194 (11), $\text{C}(42)\text{--C}(43)$ 1.563 (16), $\text{C}(43)\text{--C}(44)$ 1.516 (16), $\text{C}(42)\text{--O}(42)$ 1.228 (12), $\text{C}(44)\text{--O}(44)$ 1.254 (13), $\text{C}(43)\text{--H(a)}$ 0.935 (98), $\text{C}(43)\text{--H(b)}$ 0.939 (148); $\text{C}(42)\text{--C}(43)\text{--C}(44)$ 116.5 (9), $\text{Re}(1)\text{--C}(42)\text{--C}(43)$ 120.5 (7), $\text{Re}(2)\text{--C}(44)\text{--C}(43)$ 123.6 (7), $\text{Re}(1)\text{--C}(42)\text{--O}(42)$ 124.9 (8), $\text{Re}(2)\text{--C}(44)\text{--O}(44)$ 119.9 (8), $\text{C}(43)\text{--C}(42)\text{--O}(42)$ 114.6 (8), $\text{C}(43)\text{--C}(44)\text{--O}(44)$ 116.4 (9), $\text{C}(42)\text{--Re}(1)\text{--P}(2)$ 86.6 (3), $\text{C}(44)\text{--Re}(2)\text{--P}(2)$ 84.3 (3), $\text{Li--O}(42)$ 1.940, $\text{Li--O}(44)$ 1.908, $\text{Li--O}(3)$ 1.922, $\text{Li--O}(2a)$ 1.902 Å; the average O--Li--O angle is 109.1.

Chart I



spectrum of **4** are indicative of a favored nonplanar conformational preference in the malonyl ligand. Application of differential $^2J_{\text{CH}}$ coupling to malonyl or acyl ligand conformation awaits detailed spectroscopic and structural studies on a series of complexes related to **3** and **4**.

In an effort to clarify the question of malonyl ligand conformation, the unusual spectroscopic data, and the mode of lithium cation interaction with the transition metal ligands, an X-ray diffraction study was performed on **4**.⁴ Figure 1 shows the orientation of the CF_3SO_3^- and Li^+ ions in relation to the dirhenium backbone of the molecule. The arrangement of oxygen atoms around the Li^+ ion is tetrahedral, with two oxygen atoms provided by the malonyl ligand, and two triflate ions each providing one oxygen atom. The $\text{Li--O}(42)\text{--C}(42)\text{--C}(43)\text{--C}(44)$ and $\text{O}(44)$

atoms form a six-membered ring which exists in a boat conformation with H_a axial and H_b equatorial. The $\text{Li--O}(42)$ and $\text{Li--O}(44)$ distances are 1.940 and 1.908 Å, respectively. These distances indicate a significant lithium–oxygen interaction, similar to that observed in the solid-state structure of 2,4-pentandionatolothium (Li--O distances: 1.941 and 1.923 Å).⁵ Two oxygen atoms of each CF_3SO_3^- ion bridge two lithium atoms with $\text{O}(3)\text{--Li}$ and $\text{O}(2a)\text{--Li}$ distances of 1.922 and 1.902 Å, respectively. Octahedral coordination exists at both rhenium atoms with only small deviations (angles range from 84.3 to 95.2° and from 173.8 to 176.8°). The $\text{ON--Re}(1)\text{--C}(42)\text{--O}(42)$ torsion angle (θ) is 178.5°, which places $\text{O}(42)$ anti to the NO ligand. The $\text{Re}(1)\text{--C}(42)$ distance of 2.069 Å is significantly shorter than the 2.194 (11) Å $\text{Re}(2)\text{--C}(44)$ distance, indicative of a greater degree of carbene character in the former bond. The bridging methylene hydrogens, H_a and H_b , were located on a difference map and refined. H_a is at a 2.88 Å nonbonded distance from both $\text{C}(35)$ and $\text{C}(36)$ of a phenyl ring on phosphorus and is 2.78 Å from the centroid of that phenyl ring. This nonbonded interaction between H_a and the phenyl rings is consistent with the unusual upfield shift (δ 1.48) of one methylene hydrogen in the ^1H NMR solution spectrum of **4**.⁶ Studies are currently underway to determine the influence of metal ion chelation on the conformation, stability, and reactivity of **4** and related acyl compounds.

Acknowledgment. Partial support from the National Science Foundation (CHE-8721344) is gratefully acknowledged.

Supplementary Material Available: Tables of fractional coordinates, bond distances, bond angles, hydrogen atom coordinates, and thermal parameters and spectral (^1H NMR, $^{13}\text{C}\{^1\text{H}\}$, ^{13}C NMR, and IR) and analytical (elemental analysis) data for **4** and **4**- ^{13}CO (6 pages); table of observed and calculated structure factors (28 pages). Ordering information is given on any current masthead page.

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A Concise Asymmetric Synthesis of the Seco Acid of Erythronolide B

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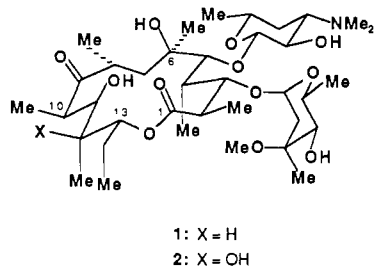
The erythromycins **B** (**1**) and **A** (**2**), which are broad spectrum anti-infectives originally isolated from *Streptomyces erythraeus*, are perhaps the best known members of the family of macrolide antibiotics.^{2,3} These substances, which possess a molecular architecture richly endowed with stereochemical and functional complexities, have served admirably as a forum for the invention and development of new methods for asymmetric synthesis. Consequent to these efforts, a number of elegant achievements, including the total syntheses of the aglycons of **1** and **2** as well as of **2** itself, have already been recorded.⁴ Despite these notable

(4) X-ray data for **4**, $[\text{C}_{38}\text{H}_{41}\text{NO}_5\text{P}_2\text{Re}_2\text{Li}]^+[\text{CF}_3\text{SO}_3]^-$: monoclinic, $\text{C}2/c$, $a = 18.269$ (3) Å, $b = 22.622$ (3) Å, $c = 22.903$ (4) Å, $\beta = 100.01$ (1)°, $V = 9322$ (3) Å³, $Z = 8$, $\mu = 56.6$ cm⁻¹, $D_{\text{calc}} = 1.73$ g cm⁻³, $T = 296$ K, Nicolet R3m/μ diffractometer with graphite monochromator and Mo Kα radiation ($\lambda = 0.71073$ Å). Two octants of data were collected (7436 reflections) of which 7043 were independent ($R_{\text{int}} = 2.44\%$) and 4697 were observed with $F_o \geq 5\sigma$. Solution by Patterson map located the Re atoms, blocked-cascade refinement, non-hydrogen atoms anisotropic, phenyl rings constrained to rigid hexagons, hydrogen atoms isotropic (fixed and idealized positions) except for the bridging methylene hydrogen atoms of the malonyl ligand which were located on a difference map and refined: $R_F = 4.53\%$, $R_{wF} = 4.92\%$, data/parameter = 9.3, GOF = 1.027, highest peak = 3.27 e⁻ Å⁻³ (1.00 Å from $\text{Re}(2)$).

(1) Recipient of a PHS Postdoctoral Fellowship (HL07571), 1987–1989.
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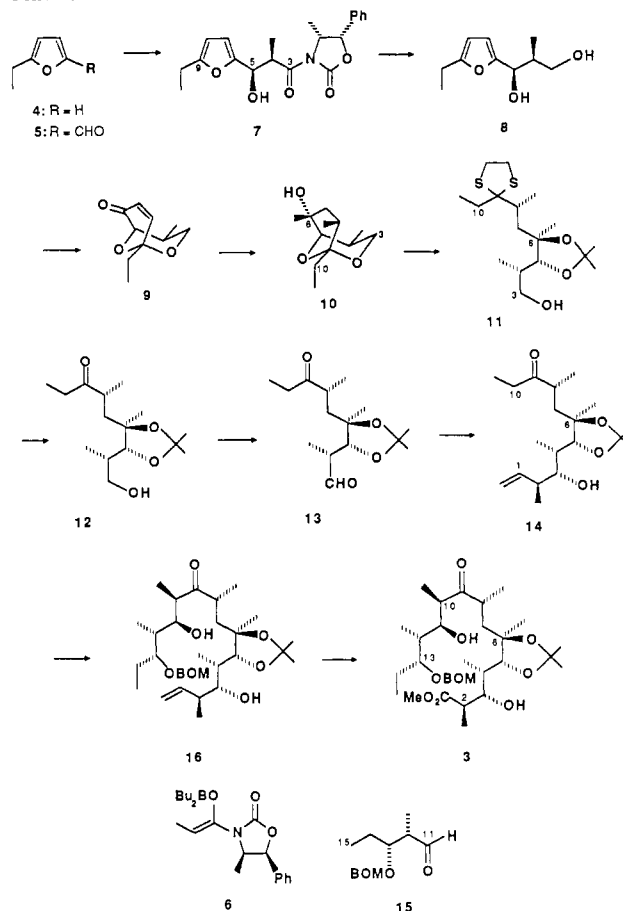
accomplishments, there remains the exciting challenge of designing even more concise and efficient strategies and tactics to elaborate the ten asymmetric centers and the attendant functionality that punctuate the structural matrices of **1** and **2**.



As part of our interest in developing general strategies for the asymmetric synthesis of complex natural products, we initiated an investigation directed toward the stereoselective construction of the polyoxygenated array **3**, which constitutes the intact framework of the seco acid of erythronolide B in protected form. To achieve maximal efficiency, the minimization of unproductive protection/deprotection sequences was imposed as a limiting constraint during formulation of the synthetic plan. The mainstay of the strategy that eventuated for the synthesis of **3** entailed the stereoselective elaboration of dihydropyranones that are readily available via the oxidative processing of enantiomerically pure furfuryl carbinols.⁵ Specifically, we envisioned that the alcohol **7** could be rapidly transformed into **10**, which comprises the C(3)–C(10) subunit common to the erythromycin antibiotics. Subsequent conversion of **10** into **14** followed by the union of **14** with **15**, a subunit that corresponds to the C(11)–C(15) segment of **1**, via diastereoselective aldol reaction^{4d,j} and oxidative scission of the terminal olefin would deliver **3**. The successful reduction of this strategy to practice constitutes the subject of the present report.

The task of constructing the ketone **14**, which incorporates the C(1)–C(10) skeletal subunit of the erythromycins, was engaged as the first subgoal of the overall synthetic plan (Scheme I).^{6,7} Toward this objective, Vilsmeier–Haack formylation (DMF; POCl₃; 0 °C → room temperature; 1.5 h; 90%) of commercially available 2-ethylfuran (**4**) gave aldehyde **5** which underwent Evans

Scheme I



aldol condensation⁸ with boron enolate **6** (CH₂Cl₂; –78 → 0 °C; 1.5 h; 81%) to generate the syn adduct **7**. Hydride reduction⁹ of **7** (LiBH₄; THF; –30 → 0 °C; 2.5 h; 90%) effected removal of the chiral auxiliary with concomitant reduction of the C(3) carbonyl group to give the syn diol **8**. When **8** was treated with bromine in 15% aqueous acetonitrile (–20 °C; 0.5 h; room temperature; 0.5 h; 63%), smooth conversion to the bicyclic enone **9** occurred by an intriguing process involving sequential oxidation of the furan ring and acid-catalyzed bicyclopentamerization of an intermediate dihydroxy enedione.^{5a} The bicyclic enone **9** embraces two significant design features. Namely, ketal formation between the two hydroxyls at C(3) and C(5) and the ketone at C(9) provides *internal protection for these functionalities while simultaneously establishing a conformationally biased skeletal framework* that enforces successive transformations to proceed with high levels of diastereoselectivity. Thus, 1,4-addition of a methyl group to **9** (LiCuMe₂; Et₂O; –78 → –10 °C; 2 h; 90%) proceeded exclusively from the more accessible exo face of the bicyclic array, and the subsequent 1,2-addition of a second methyl group (MeLi–CeCl₃; THF; –78 °C; 1.5 h; 94%) also occurred with a high degree of diastereoselectivity (>20:1) to afford the tertiary alcohol **10**. At this juncture, C(3)–C(10) of the erythromycin backbone were secured.

The next stage involved unraveling the bicyclic ketal and addition of the C(1)–C(2) subunit. Unfortunately, numerous attempts to induce ketal exchange to access **12** directly from **10** under a variety of conditions were unavailing, and a reliable, albeit three step, procedure was implemented. Subjection of **10** to a Lewis acid-catalyzed thioketal–ketal exchange reaction

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(6) The structure assigned to each compound was in full accord with its spectral (¹H and ¹³C NMR, IR, and MS) characteristics. Analytical samples of all new compounds were obtained by distillation, recrystallization, or preparative HPLC or TLC and gave satisfactory combustion analysis (C, H) and/or identification by high-resolution mass spectrometry. All yields are based on isolated, purified materials.

(7) Abbreviations: BOM = PhCH₂OCH₂–; CSA = camphorsulfonic acid; DMAP = 4-(dimethylamino)pyridine; DMF = N,N-dimethylformamide; LHMDs = LiN(SiMe₃)₂; NBS = N-bromosuccinimide; Tf = trifluoromethanesulfonyl; THF = tetrahydrofuran.

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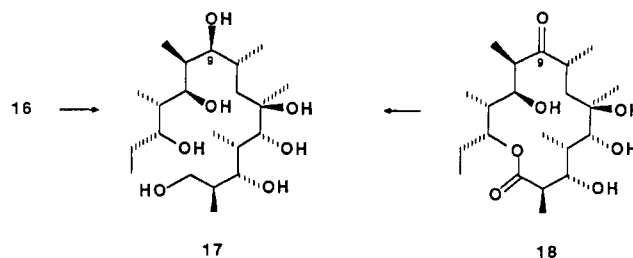
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(Me₃SiSCH₂CH₂SSiMe₃;¹¹ TiCl₄; CH₂Cl₂; -78 °C; 0.5 h; room temperature; 2 h) followed by thermodynamically-controlled formation¹² [CSA; (CH₃)₂CO/CH₂Cl₂ (1:1), room temperature; 2 h; 60% overall from **10**] of a 1,2-acetonide from the C(5) and C(6) hydroxyls of the intermediate triol furnished **11**. Subsequent removal [NBS; (CH₃)₂CO/H₂O (9:1); 0 °C; 0.25 h; 75%] of the dithiolane-protecting group then gave keto alcohol **12**. Swern oxidation [(COCl)₂; Me₂SO; Et₃N; CH₂Cl₂; -60 °C → room temperature; 0.5 h; 90%] of the primary alcohol function present in **12** produced **13**. Introduction of the C(1)-C(2) unit was then conveniently achieved by the chemoselective, Lewis acid-mediated reaction of tri-*n*-butylcrotylstannane^{13,14} with the aldehyde function of **13** (CH₃CH=CHCH₂SnBu₃; BF₃·OEt₂; CH₂Cl₂; -90 °C; 0.5 h; 82% combined) to deliver a mixture (ca. 4:1) of the desired homoallylic alcohol **14**, surprisingly contaminated with the anti adduct that was *epimeric* at C(2); both structures were confirmed by single-crystal X-ray analyses.¹⁵ Thus, construction of the intact C(1)-C(10) intermediate **14** was achieved by an efficient process wherein the resident chirality at C(4) and C(5), which was established at the outset by a diastereoselective aldol reaction, determined the sense of emerging chirality at the four remaining stereogenic centers of this fragment.

Completion of the synthesis of the erythronolide B seco acid derivative **3** was realized by coupling the C(1)-C(10) ketone **14** with the C(11)-C(15) aldehyde **15** and subsequent unmasking of the C(1) carboxyl group by oxidative processing of the terminal olefin. Thus, chelation controlled aldol condensation of **15**¹⁶ with the (*Z*)-enolate of **14** [LHMDS (3.0 equiv); THF, -78 °C; 3 h; 72% total (88% based on recovered **14**)] furnished a mixture (ca. 6:1) of diastereomeric syn adducts with the requisite **16** in predominance.¹⁷ Oxidative cleavage¹⁸ of the terminal double bond present in **16** [(a) O₃; MeOH; Sudan III; -95 °C; (b) Et₃N; Ac₂O; CH₂Cl₂; 0 °C → room temperature; 45 min; 61% overall] produced the methyl ester **3**.

The structure of the aldol adduct **16** was unambiguously verified by its conversion into polyol **17**. In the event, hydride reduction of **16** with Me₄NBH(OAc)₃¹⁹ proceeded with high stereoselectivity to give the 9(*S*)-alcohol as the major product (75%), and subsequent refunctionalization of the carboxyl terminus [(a) O₃; EtOAc; Sudan III; (b) LiAlH₄] followed by removal of the hydroxyl-protecting groups (NH₂OH·HCl; KH₂PO₄; H₂O-MeOH/Δ; 4 h) gave **17**. An authentic sample of **17** was prepared from naturally derived erythronolide B (**18**)²⁰ by sequential hydride reduction [(a) NaBH₄; PhMe/*t*-BuOH (5:1); (b) LiAlH₄; THF]. The two samples of **17** thus independently obtained were identical by ¹³C NMR and TLC. It is noteworthy that reduction of the ketone function at C(9) of **16** gave predominantly the 9(*S*)-stereochemistry since this configuration will be required for

eventual preparation of intermediates that will be suitably constituted for macrolactonization.^{4c}



In summary, the concise synthesis of **3**, a protected derivative of the seco acid of erythronolide B, has been achieved by a convergent approach wherein the longest linear sequence employs only 14 chemical operations with the total number of steps being 18 including the transformations necessary to prepare the aldehydic partner **15** employed in the final carbon-carbon bond construction. The approach is efficient, and substantial quantities of material may be prepared so that the conversion of **3** into the natural antibiotic **1** constitutes a viable objective for future efforts.

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Splitting of a Two-Electron Cyclic Voltammetric Wave into Its One-Electron Components: The (η-C₆Me₆)₂Ru^{2+/+/0} Couples[†]

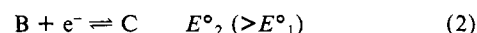
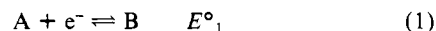
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We report results on the redox couple (η-C₆Me₆)₂Ru^{2+/0} which show, apparently for the first time, definitive evidence that cyclic voltammetric (CV) scan rate changes can allow visual discrimination between the two one-electron components of a two-electron electrochemical wave. Applied to the reduction of the bis-arene complex, this approach resulted in the separation of one wave into two at high scan rates and quantitative agreement between theory and experiment over a range of observation times. The results offer hope in deciphering the relative timing of charge transfer and conformational changes in multiple electron-transfer reactions.

Although there is evidence that some two-electron transfers proceed without one-electron intermediates,^{1,2} it is usually thought that the reaction A + 2e⁻ ⇌ C progresses in a sequence of two discrete one-electron steps,³ each with its own E° value (eq 1 and 2).⁴⁻⁶ A cyclic voltammetric wave with the characteristics of a



[†] This may be considered as Part 20 of the series Structural Consequences of Electron-Transfer Reactions. Part 19: Merkert, J.; Nielson, R. M.; Weaver, M. J.; Geiger, W. E. *J. Am. Chem. Soc.*, in press.

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(16) The aldehyde **15** was prepared according to the following procedure: (1) (a) (4*S*)-4-(2-methylethyl)-3-(1-oxopropyl)-2-oxazolidinone; *n*-Bu₂BOTf; Et₃N; -78 °C; 0.5 h; -78 → 0 °C; 1 h;⁸ (b) EtCHO; -78 °C; 0.5 h; -78 → 0 °C; 1 h; 80%. (2) PhCH₂OCH₂Cl; *i*-Pr₂NEt; CH₂Cl₂; room temperature; 45 h; 91%. (3) LiAlH₄; 0 °C; 45 min; 74%. (4) (COCl)₂; Me₂SO; *N*-methylmorpholine; CH₂Cl₂; -60 °C → room temperature; 0.5 h; 88%.

(17) The coupling constants, J_{H(10)-H(11)} = 2.0 Hz and J_{H(11)-H(12)} = 9.9 Hz, observed for **16** were in excellent agreement with values (J_{H(10)-H(11)} = 2 Hz and J_{H(11)-H(12)} = 10 Hz) reported previously. See ref 4d,j.

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