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Direct Entry to Erythronolides via a Cyclic Bis[Allene]

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Supporting Information

ABSTRACT: The complexity and low tractability of antibiotic macrolides pose serious challenges to addressing the problem of resistance through semi- or total synthesis. Here we describe a new strategy involving the preparation of a complex yet tractable macrocycle and the transformation of this macrocycle into a range of erythronolide congeners. These compounds represent valuable sectors of erythromycinoid structure space and constitute intermediates with the potential to provide further purchase in this space. The routes are short. The erythronolides were prepared in three or fewer steps from the macrocycle, which was prepared in a longest linear sequence of 11 steps.

Erythromycin is the archetypal macrolide and represents an important class of antibiotics.[1] Despite their structural complexity, erythromycin and its congeners have been used as frontline treatments for human infections, particularly of the respiratory tract. The erythromycin antibiotics are thought to exercise their protective properties primarily by blocking the elongation tunnel of domain V of the large ribosomal particle in bacteria.[2] Other functions include selective uptake by macrophages, extracellular kinase activity, and perhaps antiasthmatic function at low doses, among others.[3] Many insights have been derived from structural studies[2] and efforts to manipulate the polyketide synthase machinery.[4] The largest contributions have come from the chemical synthesis of macrolides derived from erythromycin itself.[5] The known structure−activity profile represents a herculean effort because of the intransigence of this natural product toward selective modification. Despite the considerable strides made in this area, the erythromycin structure has not been evaluated fully, and the typical modes of drug resistance continue to compromise effectiveness. Thus, the central problem remains: limited access to erythromycinoid structure space severely retards the search for effective macrolide antibiotics.

Although unconventional for macrolides, we envisioned that multiple targets could be derived from a common, advanced macrocyclic intermediate (Figure 1, top). Previous syntheses of erythromycin aimed to demonstrate new methods or superior strategies to secure the natural product.[6] As they were focused on this single polyketide target, these routes are not necessarily relevant to the discovery of new antibiotic leads. Nevertheless, de novo synthesis represents a means by which to gain unrestricted access to erythromycinoid structure space. Only recently has total synthesis produced a new erythromycinoid antibiotic candidate, namely, a desmethyl analogue that is thought to have the potential to address resistance.[7] The motif redundancy in erythromycin at C4−C6 and C10−C12 led us to consider allenic

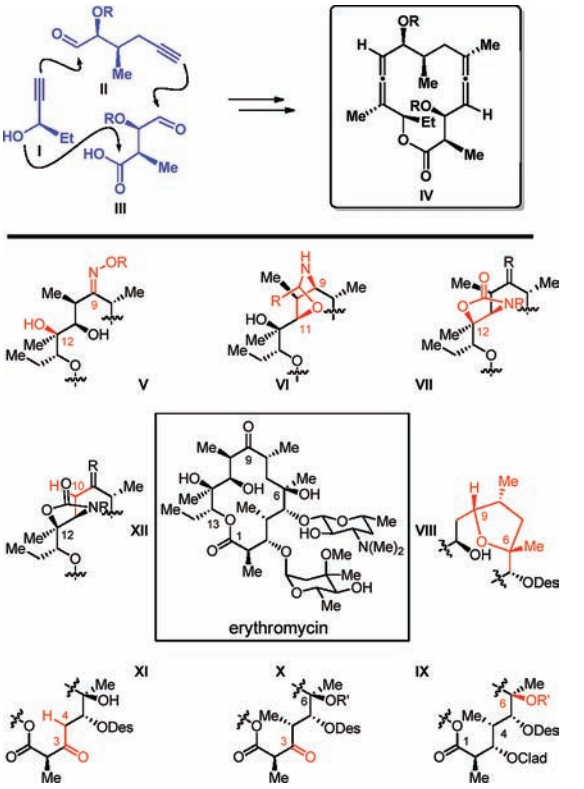

Figure 1. (top) Recursive assembly of a macrocyclic bis[allene] and (bottom) functional macrolide motifs.

functionality in these regions (**IV**). The remaining C2−C3 and C8−C9 partners would originate from opposite enantiomers of the same precursor. Thus, an alkynol (**I**), an alkynal (**II**), and an aldehyde (**III**) would enable a convergent, recursive alkynylation sequence, coordinated allene installation, and then lactone formation. A model study suggested that a macrocycle with two allenyl groups positioned in this way would potentially undergo stereo- and site-selective modification.[8]

Our strategy was driven in part by the key features of the erythromycin structure−activity profile (Figure 1, bottom).[5] In brief, prior studies suggest the following: (a) portions of the glycans, especially the amino sugar, are critical, and both the hydrophilic character of the β-face and the hydrophobic character of the α-face of the macrolide contribute to binding (center structure);[5i] (b) C9 amine or oxime functionality suppresses

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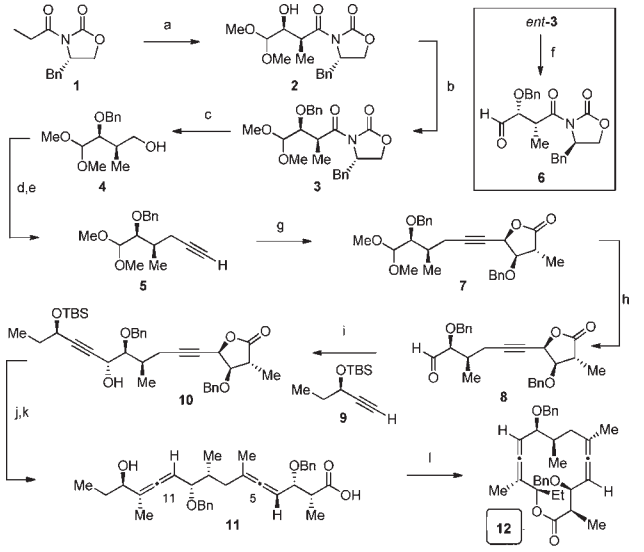
Scheme 1. Synthesis of 12[a]

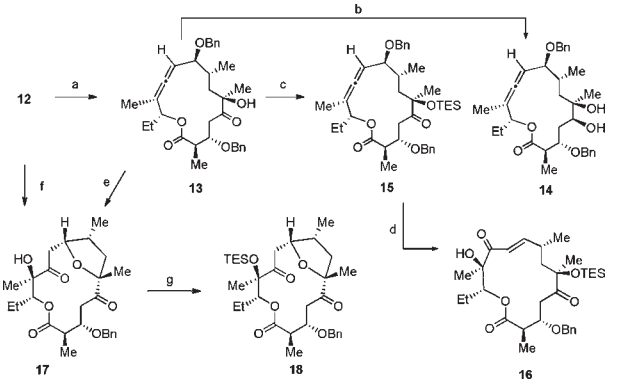


[a] Conditions: (a) *n*-Bu_2BOTf, NEt_3, DCM, −78 °C, then $(MeO)_2$-CHCHO, warm to 0 °C, 90%. (b) BnBr, Ag_2O, DCM, rt, 95%. (c) $LiBH_4$, Et_2O, 0 °C, 95%. (d) DABCO, TsCl, DCM, 0 °C. (e) Lithium acetylide ethylenediamine complex, DMSO, 15 °C, 82% (two steps). (f) HOAc, H_2O, CF_3CO_2H, rt, 95%. (g) *n*-BuLi, $ZnBr_2$, Et_2O, −78 to 0 °C, then **6**, 64%, 8:1 dr. (h) HOAc, H_2O, CF_3CO_2H, rt, 90%. (i) **9**, MeLi, $Ti(OiPr)_3Cl$, THF, −78 °C, then **8**, −78 to −40 °C, 89%, 6:1 dr. (j) MsCl, NEt_3, Et_2O, rt, cool to −20 °C, MeCuCNLi, −20 °C to rt. (k) HOAc, H_2O, CF_3CO_2H, rt, 88% (two steps). (l) 2,4,6-Trichlorobenzoyl chloride, NEt_3, DMAP, tol, 80 °C, 64%.

unwanted side effects (**V**);[5c,f] (c) C9−C11 or C11−C12 heteroannulation can improve binding and appears to represent opportunities to overcome resistance (**VI**, **VII**);[5b] (d) C6−C9 heterocyclization leads to interesting (albeit nonantibiotic) activity (**VIII**);[5e] and (e) retention of the C6 and C12 heteroatom connectivity is desirable, and ether formation at C6 may improve the antibiotic activity and suppress other activity (**V**, **IX**).[5g] C3 ketone derivatives[5b] (**X**) and alterations to the hydrophobic face of the macrocycle (e.g., at C4, C8, and C10; **XI** and **XII**) may overcome resistance.[2b,7] Hence, modification of the C3−C6 and C9−C12 regions offers opportunities to improve drug properties and avoid bacterial resistance.

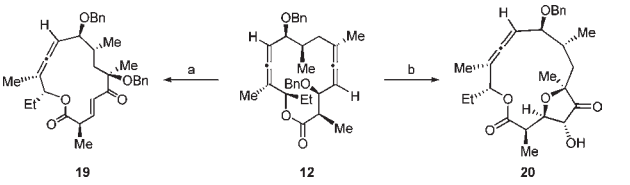
Three components were prepared and joined to provide macrocycle **12** (Scheme 1). Addition of the enolate derived from oxazolidinone **1** to commercially available dimethoxyacetaldehyde afforded the expected aldol product as a single isomer (**2**, 90%).[9] Subsequent benzyl ether formation to give **3** (95%) followed by hydride reduction provided the desired primary alcohol **4** (95%). A tosylate was derived from this alcohol and then without purification was subjected to lithium acetylide to give component **5** (82% over two steps). The antipode of **3** was exposed to mild acid and thereby furnished component **6** (95%; see inset). The alkynylide derived from **5** was then combined with **6** in the presence of zinc bromide.[10] The addition products spontaneously lactonized under the reaction conditions, and the major product (**7**) was taken forward (64%, 8:1 dr). Mild acid treatment of acetal **7** gave aldehyde **8** (90%). The alkynylide derived from component **9** was combined with **8** in the presence of chlorotriisopropoxytitanium,[11] and the major product (**10**) was taken forward (89%, 6:1 dr). A single-flask procedure

Scheme 2. Erythronolides via Osmylation[a]



[a] Conditions: (a) OsO_4, *t*-BuOH, H_2O, rt, 83%. (b) $Zn(BH_4)_2$, Et_2O, 0 °C, 68%. (c) TESOTf, 2,6-lutidine, DCM, rt, 83%. (d) OsO_4, *t*-BuOH, H_2O, rt, 32%. (e) OsO_4, *t*-BuOH, H_2O, rt, 50%. (f) OsO_4, *t*-BuOH, H_2O, rt, 46%. (g) TESOTf, 2,6-lutidine, DCM, rt, 78%.

Scheme 3. Erythronolides via Epoxidation[a]



[a] Conditions: (a) DMDO, CH_3OH, −50 to −15 °C, 81%. (b) DMDO, $CHCl_3$, −40 to −15 °C, then MeCuCNLi, 2-methyl-THF, −15 °C, 64%.

effected the conversion of the diyne to the corresponding bis[allene];[12] the crude material was then treated with mild acid to furnish **11** (88% over two steps). The seco acid smoothly lactonized, forming **12** (64%).[8,13]

Osmium tetroxide selectively converted the C4−C6 allenyl group of **12** into the hydroxyketone (**13**, 83% yield; Scheme 2). Reduction of the ketone cleanly gave **14** (68%).[14] Triacetoxyborohydride[15] reduction of the ketone gave the C5 epimer, and sodium borohydride gave a 1:1 mixture of these products (data not shown). Silylation of **13** to give **15** (83%) and then brief osmylation resulted in the formation of **16** (32%), a C9−C12 hydroxyenone. In contrast, osmylation of **13**, which contains a hydroxyl, produced bicycle **17** (50%). Similarly, double osmylation of **12** gave **17** directly (46%). Silylation of **17** gave **18** as a crystalline solid (78%; see the Supporting Information for the X-ray crystal structure).

Scheme 3 shows products derived from allene epoxidation.[16] Exposure of **12** to dimethyldioxirane (DMDO) in methanol smoothly delivered the C3−C6 alkoxyenone **19** (81%). Epoxidation with DMDO in chloroform[17] followed by treatment with Lewis acid,[12] however, delivered the C3−C6 furanone **20**. Remarkably, lithium methylcyanocuprate promoted the formation of **20** in good yield (64%).[8,17f]

Sequential allene osmylation and allene halohydration[18] is shown in Scheme 4. Following osmylation of **12**, C4−C6 ketoalcohol **13** was transformed by *N*-bromosuccinimide (NBS)/water in MeCN into the C11 bromo/C12 hydroxyl compound **21**, which upon ketone reduction gave **22**

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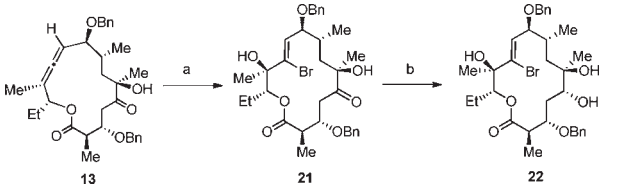
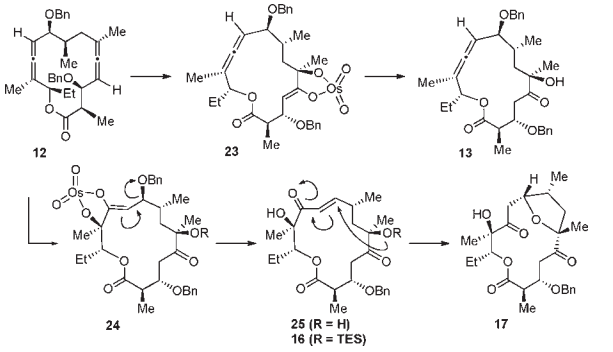
Scheme 4. Erythronolides via Combined Methods[a]



[a] Conditions: (a) NBS/H_2O, MeCN, rt, 99%. (b) $Zn(BH_4)_2$, Et_2O, 0 °C, 98%.

Scheme 5. Mechanistic Rationale for Osmylation of 12

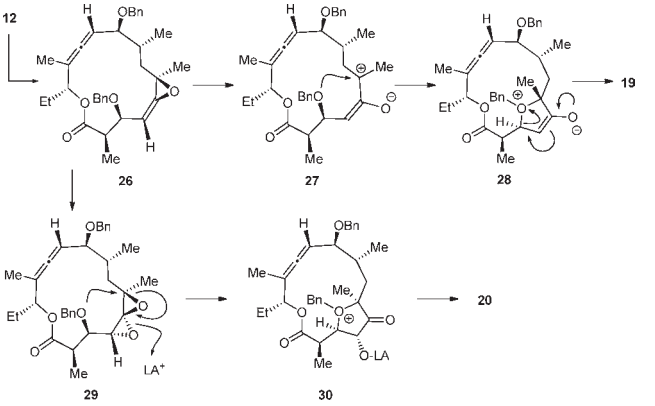


(Scheme 4).[14] Both of these reactions proceeded in excellent yield (>95%).

Allenes are central to this strategy. The coordinated synthesis of both allenes from **10** allowed the concurrent installation of the C12 and C6 methyl groups to give **11** (Scheme 1). However, the C6 allenyl group formed slowly in comparison with the C12 allenyl group, suggesting that the substituents need not be identical. The extended conformational constraints imposed by allenyl groups relative to alkynyl and alkenyl functionality and the presence of two such groups in seco acid **11** probably facilitate the macrocyclization.[6j] The four sites of unsaturation housed within **12** were transformed with apparently complete selectivity (Schemes 2−4). The observed order of reactivity is C5−C6 > C4−C5 > C11−C12 > C10−C11. The C5−C6 π bond was expected to be most reactive because of the high substitution and the fact that the reactivity of the C11−C12 π bond is attenuated by the C13 ester. After oxygen delivery to C5−C6 via epoxidation or osmylation, the C4−C5 π bond is the most highly reactive nucleophilic site of unsaturation remaining.[8] The allenyl groups also provide a topological bias. In all of the allene reactions shown, the products were isolated as single isomers. The outcomes reflect the cooperative effects of intrinsic allene stereoselectivity, macrocyclic stereocontrol,[19] and (for the intramolecular transformations) proximity of the reacting partners. Although late-stage modification of isolated π bonds is a known strategy in terpene syntheses,[20] it is rare in macrolide synthesis,[6g] and the use of cyclic bis[allenes] in synthesis is rarer still.[21]

Allene oxidation methods are underutilized. For example, a disproportionately small number of reports on allene osmylation[22] appear in the literature in comparison with alkene osmylation.[23] Although allene osmylation is not well studied, it is clear that the osmium adducts formed and hydrolyzed (e.g., **23** → **13**, **24** → **25**; Scheme 5). Unlike simple alkene-derived osmate

Scheme 6. Mechanistic Rationale for Epoxidation of 12



esters, these intermediates are also enolates.[24] β-Elimination and subsequent intramolecular conjugate addition is reasonable. Interestingly, the C3 benzyloxy group is retained, whereas the C9 group is lost. These phenomena are most likely traceable to the stereoelectronics of the osmate ester intermediates.[25]

We suggest that the formation of **19** and **20** is closely related and involves opening of the allene oxide (**26** → **27**) or spirodiepoxide (**29** → **30**) and capture of the C3 benzyloxy group (Scheme 6). The transfer of benzyloxy from C3 to C6 may well be promoted by 3,4-elimination in the case of **19**. The analogous spirodiepoxide pathway is interrupted and the benzyl group lost under conditions that lead to **20**. Interestingly, the configuration at C6 in **19** is opposite that in **20**. This may reflect the comparatively high stability of oxyallyl zwitterion **27**, which could explain benzyloxy capture with overall retention of configuration at C6. In the case of **29**, the comparatively low stability of a cation derived from the spirodiepoxide combined with the proximity of the C3 OBn to C6 could lead to **30** directly with inversion at C6. This mechanistic framework is also consistent with the reaction conditions used for these transformations. We favor this rationale, but further studies are needed to evaluate these hypotheses.

The face selectivity of the allene halohydration differs from that of the allene oxidation reactions. Nevertheless, the (*Z*)-bromo/β-C12 hydroxyl of **22** was expected. Whereas oxidation occurs from the more accessible face of the reacting allenyl double bond, bromination occurs from the less accessible face and water adds to the more accessible face (mechanism not shown). Although these reactions have not been studied in complex allenes, this sort of selectivity is well-known for acyclic systems.[18]

The strategy presented herein focuses on substances that can be called upon to react along differing pathways.[26] The longest linear sequence to **12** is 11 steps, and compounds **13**−**22** were prepared from this intermediate in three or fewer steps; this compares well to previous work in the area.[6,7] Compound **12** is a processable intermediate that integrates the routes to targets that occupy underexplored erythromycinoid structure space, including valuable desmethyl, cyclic, and other functionalized variants. Taken together, the convergent assembly of **5**, **6**, and **9**, the conversion of **10** to **11**, and the reactions summarized in Schemes 2−4 suggest a realistic route by which to effect extensive and expeditious changes to the macrolide scaffold represented by erythromycin.

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■ ASSOCIATED CONTENT

Supporting Information. Synthetic methods, detailed spectroscopic characterization data (HMBC, NOESY, etc.), crystallographic data (CIF), and complete refs 6i–6k. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) The scope of allene osmylation and conformational, computational, and additional synthetic details will be disclosed separately.

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