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Direct Entry to 4,10-Didesmethyl (9*S*)-Dihydroerythronolide A via Catalytic Allene Osmylation

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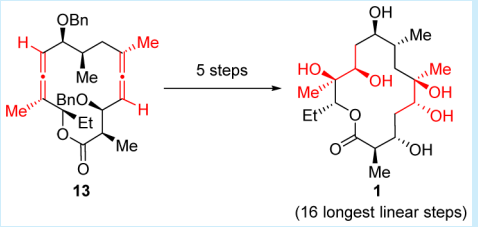
Supporting Information

ABSTRACT: Desmethyl erythronolides have emerged as macrolide targets that may prove effective against resistant bacteria. A five-step sequence to 4,10-didesmethyl (9*S*)-dihydroerythronolide A (**1**) from known cyclic bis[allene] **13** is reported. Key structural and mechanistic aspects of the synthesis are discussed along with catalytic allene osmylation. An improved route to **13** is also described.



Pathogenic bacteria resistant to standard and last-resort therapies have prompted an intense search for novel antibiotics.[1] The complex macrolide erythromycin A (Figure 1)

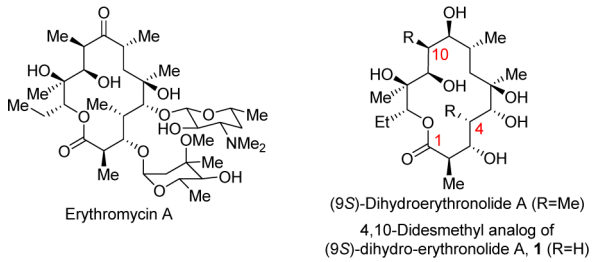


Figure 1. Erythromycin A, (9*S*)-dihydroerythronolide A, **1**.

and its analogues have been used widely as first-line antibacterial agents.[2] However, resistance mechanisms in growing populations compromise their effectiveness. For example, the ribosomal A2058G mutation appears to render this binding site incompatible with the methyl substitution pattern of the macrolide.[3] In principle, semisynthesis, total synthesis, and bioengineering methods would enable removal of certain combinations of methyl groups, but the task is not trivial. The complexity of erythromycin A limits direct access to these and related targets. The pressing importance of this problem prompted Andrade et al., in a tour de force, to evaluate desmethyl combinations through total syntheses.[4] These highly refined syntheses required more than 25 linear steps each. We have demonstrated the benefits of an alternative strategy that uses an advanced, structurally complex macrocyclic bis[allene] to generate diverse 14-membered polyketides. In one to three steps we have been able to gain entry to diverse erythromycin A-related targets from this intermediate.[5] This approach deliberately incorporates sites of unsaturation into the scaffold for late-stage oxidation and diversification. Although our strategy deviates from some notions of synthetic ideality,[6] it offers a much-improved cumulative step economy. In this report we demonstrate the superiority of this strategy with a concise synthesis of **1**, the 4,10-didesmethyl variant of (9*S*)-dihydroerythronolide A: compound **1** is prepared in five steps from **13**, our advanced intermediate, and in 16 linear steps overall; **13** is prepared by an improved and convenient route; a new procedure for catalytic osmium tetroxide oxidation of allenes is also described.

Schemes 1 and 2 summarize the synthesis of **1**. In our first-generation synthesis[5b] certain intermediates proved either reluctant to react or sensitive to storage. Accordingly, intermediates **3**–**8** were modified, and the sequence was improved for operational convenience and scale and to ensure that key compounds could be readily stockpiled. As before, we lactonized prior to allene elaboration, since macrolide cyclization efficiency is notoriously sensitive to the functionality and stereochemistry of the seco acid. We eliminated the use of dimethoxy acetaldehyde as an aldol partner and adopted the use of acrolien, to which the chiral anion of **2** added smoothly, as reported.[7] The resultant alcohol was readily masked as the benzyl ether (**3** → **4**).[8] Hydride reduction provided primary alcohol **5**, which was converted to the corresponding tosylate and then displaced with acetylide (→ **7**). Aldehyde **6** was prepared from the antipode of **4** (*ent*-**4**) using Lemieux–Johnson conditions.[9,10] Zinc bromide mediated addition of alkyne **7** to aldehyde **6**, as before,[5b] afforded alkyne **8** with concomitant lactonization.[11] Oxidative cleavage of the terminal

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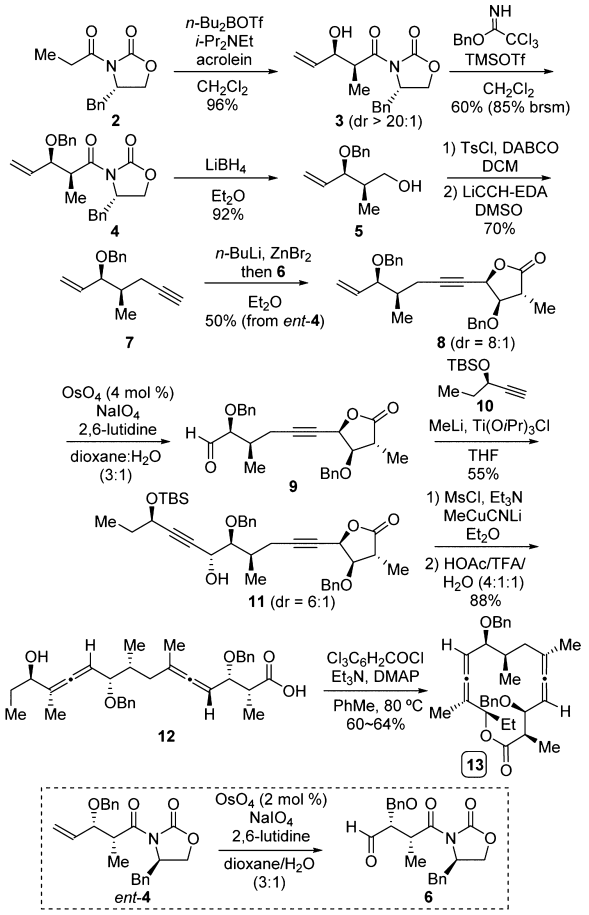
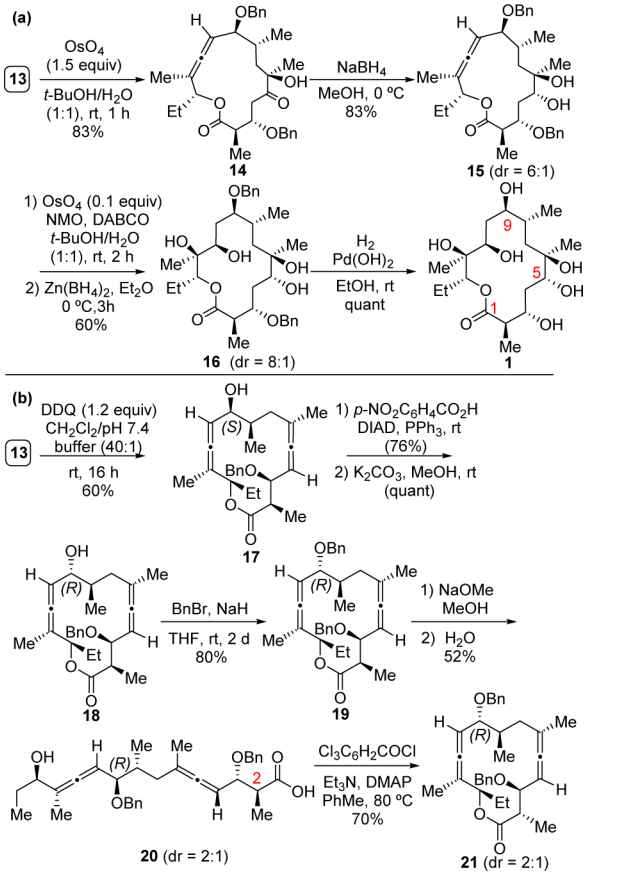
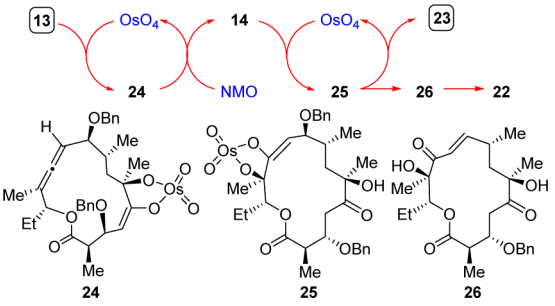
Scheme 1. Synthesis of 13



Scheme 2. Synthesis of 1 and Cyclization of 20



Scheme 3. Proposed Catalytic Cycle



alkene revealed aldehyde **9**,[12] which was joined with **10** and advanced to **13** as reported.

A five-step sequence from **13** to **1** is shown in Scheme 2a along with catalytic osmylation studies in Scheme 3 and Table 1. Owing to the need to effect divergent stereochemical outcomes for the hydroxyls at C5 and C11 (*vide infra*), we used a two-stage oxidation procedure. Treatment of **13** with osmium tetroxide gave hydroxy ketone **14** in excellent yield, regioselectivity, and stereoselectivity. Reduction with sodium borohydride afforded diol **15** (dr = 6:1). Catalytic osmylation of **15** was also highly efficient and selective. Reduction of the resultant ketone with zinc borohydride provided tetraol **16** (dr = 8:1), and hydrogenolysis cleanly furnished didesmethyl target **1**.

Lactonization, osmylation, and reduction of the C5 and C11 keto functionalities were examined in detail.[13] The landmark total synthesis of erythromycin[14] showed that successful macrolactonization of this target can be problematic. Cyclic motifs spanning C3−C5 and C9−C11 as well as the *S* configuration of the C9 combine to enable lactonization (Figure 1). These design principles have been followed in virtually all syntheses of the erythronolides.[15] Although we opted to prepare the 9*S* configuration of **12**, we could not be certain that this feature and the allenic moieties spanning C4−C6 and C10−C12 would facilitate cyclization. In the event, **12** readily cyclized (Scheme 1). Still, we doubted that the configuration at C9 was essential for the success of this strategy and were anxious to test this hypothesis. Compound **20**, the C9 epimer of **12**, was prepared from **13** (Scheme 2b).

The action of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) on **13** selectively cleaved the C9 benzyl ether in 60% yield.[16] Mitsunobu conditions[17] were successfully applied to afford, subsequent to methanolysis, **18**. After the matter of benzyl group reinstallation, lactone **19** was opened to give **20**, the 9*R* variant of **12**, and was then smoothly closed again (**20** → **21**). Although the somewhat stringent conditions required to open **19** also promoted epimerization at C2 (dr = 2:1),[18] the mixture was taken on and efficiently cyclized in 70% overall yield (dr = 2:1).[19] Indeed, this strategy is compatible with either configuration at C9.

Efficient catalytic allene oxidation with osmium tetroxide transforms each allenic moiety of substrate **13** to the corresponding hydroxy ketone with no evidence of regioisomeric or stereoisomeric products (Table 1). Excess osmium tetroxide (2.5 equiv) gave bicycle **22** (Table 1, entry 1). Inclusion of a tertiary amine greatly accelerated the reaction and gave **23** as the major product (Table 1, entry 2). DABCO

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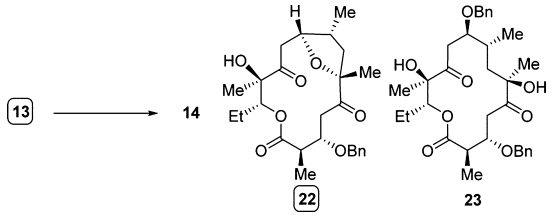
Table 1. Osmylation of Cyclic Bis[allene] 13



entry[a]	OsO_4 (equiv)	additive (equiv)	time (h)	yield (%) 14	22	23
1	2.5	none	4	0	46	0
2	2.5	DABCO (4)	20 min	0	20	44
3	0.3	DABCO (4)	40 min	0	20	60
4	0.1	DABCO (4)	2	0	15	60
5	0.1	DABCO (1)	2	0	15	77
6	0.02	DABCO (0.2)	20	0	15	75

[a]Reaction conditions: 0.02−0.04 mmol of **13** in 1:1 *t*-BuOH/H_2O (0.03 M), rt; under catalytic conditions (Table 1, entries 3−6): *N*-methylmorpholine-*N*-oxide (2 equiv) was used as terminal oxidant. Yields were determined after FCC purification. DABCO = 1,4-diazabicyclo[2.2.2]octane.

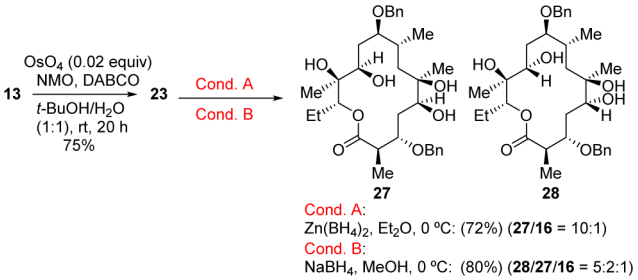
outperformed pyridine and quinuclidine in terms of both yield and rate enhancement.[20] Catalysis was achieved using *N*-methylmorpholine-*N*-oxide (NMO) as terminal oxidant (Table 1, entries 3−6). In Table 1, entry 6 demonstrates that these conditions support low catalyst loading (2 mol %) for overnight reactions with virtually no change in yield.

Allene oxidation with osmium tetroxide proceeds by way of the osmium(VI) enolate[21] (e.g., **13** → **24**). Scheme 3 outlines a mechanistic framework for the conversion of **13** to **23**. The osmium reagent approaches the most nucleophilic double bond (C5−C6) of **13** from the most accessible face to generate the *E*-enolate **24**, which hydrolyzes to give **14**. Similarly, **25** forms from approach of the oxidant to the most accessible face of the more substituted double bond (C11−C12) of the remaining allene to give the *E*-enolate. In our earlier work,[5b] stoichiometric osmylation of the C10−C12 allene was confounded by an unwanted elimination/addition sequence that gave **22** instead of the desired **23**. We posit that the persistent problem faced in previous allene osmylation reactions was the slow hydrolysis of the osmate ester and that DABCO, and other additives, accelerate this hydrolysis. In the present case, the ligand releases the macrolide from the osmium before this unwanted transformation can dominate. On the basis of these data, we conclude that the formation of **25** is effected by way of the osmium enolate or a close variant.

Catalytic allene oxidation enabled a two-step maneuver from allenic substrate **13** to macrolide analogues **27** and **28** (Scheme 4). Zinc borohydride reduction of **23** yielded 5β,11β-tetraol **27**, whereas sodium borohydride reduction yielded 5α,11α-tetraol **28**. These conditions furnished the products in excellent overall yield and complement the synthesis of 5α,11β-target **1**.[22]

We have reported a series of allene oxidation/elaboration methods in both simplified and complex settings.[23] Catalytic methods to effect allene oxidation are underexplored and hold considerable promise for concise, practical, and broadly useful routes to high-value molecular architectures.[24] The present disclosure describes an improved route to **13**, its subsequent conversion—in five or fewer steps—to erythronolides **1**, **27**, and **28**, and catalytic oxidation of the allenic moieties with

Scheme 4. Two-Step Synthesis of Macrolides from 13



osmium tetroxide that made direct access to these targets possible.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01151.

Procedures and additional data (PDF)

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Notes

The authors declare no competing financial interest.

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