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Total Synthesis and Study of 6-deoxyerythronolide B *via* Late-stage C—H Oxidation

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Abstract

Among the frontier challenges in chemistry in the 21st century are the interconnected goals of increasing synthetic efficiency and diversity in the construction of complex molecules. C—H Oxidation reactions, particularly when applied at late-stages of complex molecule syntheses, hold special promise for achieving both these goals. Here we report a late-stage C—H oxidation strategy in the total synthesis of 6-deoxyerythronolide B (6-dEB), the aglycone precursor to the erythromycin antibiotics. An advanced intermediate is cyclized to the 14-membered macrocyclic core of 6-dEB using a late-stage (step 19 of 22) C—H oxidative macrolactonization reaction that proceeds with high regio-, chemo-, and diastereoselectivity (>40:1). A chelate-controlled model for macrolactonization predicted the stereochemical outcome of C—O bond formation and guided the discovery of conditions for synthesizing the first diastereomeric 13-epi-6-dEB precursor. Overall, this C—H oxidation strategy affords a highly efficient and stereochemically versatile synthesis of the erythromycin core.

The concept of late-stage C—H oxidation (the introduction of oxidized functionality late in a synthetic sequence) is emerging as a powerful strategy for streamlining synthesis¹ and diversifying molecules.^{2–4} Highly selective C—H oxidation reactions^{2–9} allow reactive functional groups to be masked as inert C—H bonds, only to be unveiled as oxidized functionality in the final stages of a synthesis or derivatization. However, applications of C—H oxidation reactions at late stages in target-oriented synthesis^{7–9} are scarce due to the requirement that oxidation occur at one C—H bond amid scores of others, with predictably high levels of regio-, chemo- and stereoselectivity. Approaches for predicting and influencing the stereochemical course of C—H oxidations, in particular, are not well developed.

The polyketide macrolide antibiotics have inspired tremendous conceptual advances in total synthesis, including novel strategies for acyclic stereocontrol and macrocyclization methodologies.^{10–14} 6-Deoxyerythronolide B^{15–18} (6-dEB, Fig. 1) serves as the archetypical core of the polyketide macrolides¹⁹, sharing a striking stereochemical homology with most macrolide aglycones at all comparable stereocenters (Celmer's Rules).²⁰ Synthetic studies of erythromycin, spanning more than a quarter of a century, have relied on internal esterification of a stereochemically defined linear hydroxyacid for macrocycle construction (Fig. 1a).¹² We questioned whether this same core structure could be accessed through a late-stage C—H oxidative macrolactonization reaction where oxygen is installed directly

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into the hydrocarbon framework late in the synthesis. This C—H oxidation strategy offers several potential advantages. First, the amount of reactive oxygen functionality, *i.e.* the “oxygen load”, is minimized, thereby reducing side reactions that erode synthetic yields over the course of multi-step sequences (Fig. 1b).²¹ Second, this strategy can furnish diastereomeric macrolactones at the site of oxidation from a stereochemically versatile oxidation precursor.

Our retrosynthetic approach to 6-dEB focused on C13 oxidation/macrocyclization to forge the macrolide core, which when fully saturated, presents a formidable chemoselectivity challenge. We therefore envisioned selective oxidation at C13, in preference to six tertiary and five ethereal C—H bonds, through use of a C14—C15 vinyl moiety (Fig. 1). Towards this goal, we recently developed a palladium(II)/bis-sulfoxide (**3**) catalyzed allylic C—H macrolactonization reaction that converts simple linear alkenoic acids directly into 14- to 19-membered macrolactones with excellent levels of chemo- and regioselectivity.²² However, strategic application of this reaction at a late stage of a target-oriented synthesis hinges on a stereochemically predictive model for C—O bond formation during a global topological change (*i.e.* macrocyclization). Elegant examples of diastereoselective C—H oxidations in complex molecular settings have relied on the local topology of rigid, cyclic frameworks to predict and control diastereomeric outcomes.^{5,6} Albeit effective in these contexts, this conceptual framework cannot be used for predicting stereochemical outcomes with flexible, acyclic compounds, thus necessitating an alternative approach.

Oxidative C—H macrolactonization is thought to proceed *via* a Pd^{II}/sulfoxide promoted allylic C—H cleavage to generate rapidly interconverting π -allylPd(carboxylate) intermediates (see deuterium isomerization studies in Supporting Information, SI), followed by a stereodetermining C—O bond forming event within the coordination sphere of the metal (Fig. 1c). We hypothesized that such palladium chelation would lead to transition structures with product-like transannular character, allowing the stereochemical outcome of macrolactonization to be predicted using the relative ground state product energies. Based on molecular modeling studies in which macrolide **1** was found to be 3 kcal/mol more stable than **epi-1** (MMFF94 force fields, see SI) due to a pseudo-equatorial disposed exocyclic vinyl moiety, we anticipated that chelate-controlled C—H macrolactonization would strongly favor formation of the natural epimer (Fig. 1d). Furthermore, disrupting the chelation event could provide a different stereochemical outcome by generating an earlier transition state with very little transannular character.

Results

Our study commenced with construction of a versatile, linear C—H oxidation precursor (**2**) using a series of powerful polyketide synthase (PKS)-inspired, stereoselective aldol- and alkylation reactions in a linear, iterative fashion (Fig. 2). Towards the goal of minimizing the “oxygen load”, a relatively inert allyl moiety, acting as a latent allylic alcohol, was installed during the first step of the synthetic route *via* Myers’ diastereoselective alkylation²³ (>20:1 d.r.), and carried through the entire linear polypropionate synthesis without manipulation (*vide infra*). Two highly selective (>20:1 d.r.) *syn* Evans’ aldol reactions²⁴ secured **8** as a single diastereomer. Ketalization²⁵ (>20:1 d.r.), followed by a Myers’ alkylation-reduction-oxidation sequence, provided **9** as the sole diastereomer. At this juncture, a β -keto imide (**10**) would provide the dipropionate unit needed to complete the alkenoic acid (**2**) synthesis.¹⁷ Standard generation of a titanium(IV) enolate using TiCl₄ led to modest yields and selectivities (49%, 7:1 d.r.), along with competitive removal of the *p*-methoxybenzyl-acetal (PMB-acetal). Gratifyingly, we found that Ti(O*i*-Pr)Cl₃, thought to generate a more nucleophilic enolate,²⁶ provided the necessary *syn-syn* aldol adduct **11** in good yield (88%) and selectivity (95:5 d.r.). This is a notable example of a β -keto imide-based aldol on a

stereochemically complex aldehyde. Chelate-controlled reduction with $\text{Zn}(\text{BH}_4)_2$ (>20:1 d.r.), followed by ketalization and chiral auxiliary hydrolysis, completed the synthesis of alkenoic acid **2** in only 18 steps, 18% overall yield, and with exquisite stereoselectivity (Fig. 2).

With the linear oxidation precursor in hand, we were poised to investigate whether late-stage C—H macrolactonization would proceed with the predicted levels of selectivity. Initial macrolactonization attempts with Pd(II)/bis-sulfoxide catalyst **3** led to sluggish conversion with only trace product formation. After increasing the catalyst loading (10 to 30 mol %) and concentration (0.01 M to 0.02 M), the 14-membered macrolide **1** was isolated in 34% yield (45% r.s.m., Fig. 3). Consistent with predictions made using the chelate-controlled model, only the desired C13 diastereomer was detectable by ^1H nuclear magnetic resonance (^1H NMR) of the crude reaction mixture (>20:1 d.r.). The mass balance of this reaction indicates that the reaction is highly selective for C13 oxidation. By recycling this valuable starting material through the reaction twice, we obtained diastereomerically pure macrolide **1** in 56% isolated yield (8% r.s.m.). The macrocyclization event presented here constitutes a rare example of a highly regio-, chemo-, and stereoselective C—H oxidation at a late-stage of a complex molecule synthesis.

In attempts to alter the stereochemical outcome of C—H macrolactonization, we aimed to disrupt the palladium chelation event responsible for the diastereoselectivity.²⁷ Addition of fluoride anion to π -allylPd complexes has been shown to enhance the rate of π - σ - π isomerization, presumably by interacting with a coordination site on palladium.²⁸ We anticipated that such an additive would disrupt the π -allylPd(carboxylate) chelate to favor an outer-sphere C—O bond forming event. Consistent with this hypothesis, the addition of tetra-*n*-butylammonium fluoride (TBAF) to the oxidative C—H macrolactonization reaction dramatically altered the stereoselectivity to furnish a separable mixture of C13 diastereomers in useful quantities (20% + 75% r.s.m.; 44% + 36% r.s.m., recycled 2X, 1.3:1 d.r. (**1**:**epi-1**), Fig. 3). Although the diastereoselectivity was not overturned, we were able to obviate the 3 kcal/mol energy preference for the natural epimer by switching the functionalization mechanism. Despite the potential for stereochemical analogues of erythromycin to display novel chemical and antibacterial properties, this is the first time that a stereochemical modification at the critical macrolide linkage has been reported.

In order to probe the loss of stereocontrol upon addition of fluoride, we aimed to determine the intrinsic diastereoselectivity of C—H oxidation near the allyl moiety in the absence of transannular interactions. Performing our intermolecular (non-chelated) allylic C—H esterification reaction on imide **11q** provided C13 *p*-nitrobenzoates in 73% yield as a 1:1 separable mixture of diastereomers (Fig. 3). Notably, in the absence of transannular effects, no diastereoselectivity resulted from the chiral information found in the polypropionate backbone. This result supports our hypothesis that C—O bond formation in the fluoride-controlled C—H macrolactonization protocol occurs through a non-chelated process.

To further probe the origin of diastereoselectivity in the chelate-controlled C—H macrolactonization, we attempted to synthesize **1** and **epi-1** through a classical acylation-based (Yamaguchi) macrolactonization,^{17,29} that, like the chelate-controlled C—H macrolactonization, is thought to proceed *via* a product-like transition state (Fig. 3). Toward this end, late-stage intermolecular C—H oxidation (*vide supra*) was critical for circumventing lengthy parallel *de novo* syntheses of each epimeric seco acid. As anticipated, Yamaguchi macrolactonization of hydroxyacid **12** led to an 87% yield of the natural epimer (macrolide **1**). In contrast, attempted cyclization of **epi-12** yielded oligomer as the exclusive reaction product (Fig. 3). These empirical cyclization results support our hypothesis that the origin of diastereoselectivity in the chelate-controlled C—H macrolactonization derives

from product-like transition states where a greater kinetic barrier of cyclization prevents formation of the less stable epimer.

With the C13 stereocenter in place, concurrent hydrogenation of the PMB-acetal and α -olefin with Pearlman's catalyst $[\text{Pd}(\text{OH})_2/\text{C}]$, site-selective oxidation of the C9 alcohol, and acetonide removal completed the synthesis of 6-deoxyerythronolide B (Fig. 4). Following peracetylation of 6-dEB, X-ray quality crystals were obtained of triacetate **13**, confirming the relative stereochemical assignments. In total, 6-dEB was synthesized in 22 steps and 7.8% overall yield, representing the most efficient route to this classic target to date. This efficiency can be attributed, at least in part, to a C—H oxidative macrolactonization strategy that minimizes the number of reactive functional groups carried through the synthetic sequence.

Discussion

Importantly, efforts to convert **epi-1** into 13-*epi*-6-deoxyerythronolide B following the same protocol used to construct 6-dEB failed due to decomposition during the acetonide removal step. Interestingly, while the uniform arrangement of catalytic domains in the polyketide synthases (PKSs) accounts for the substitution patterns found in the macrolide antibiotics, the evolutionary basis for “Celmer's Rules” has not yet been elucidated.^{30,31} While it is generally considered that evolution of the structure of erythromycin was driven by its shape complementarity to the ribosome³², the results presented here, along with the accepted low energy conformational models (*i.e.* “diamond-lattice”) for the erythromycin aglycones,²⁰ raise the interesting question of a contributing chemical basis for the observed stereochemistry that is conserved throughout the polyketide macrolides.

In conclusion, C—H oxidative macrolactonization is demonstrated to be a novel approach for complex macrolide synthesis, as well as a rapid means of achieving stereochemical diversity at the key lactone position. Predictably high levels of substrate-based diastereocontrol are possible from advanced linear intermediates under reaction conditions that proceed *via* chelate-controlled cyclization. Moreover, conditions that break chelation remove this element of stereocontrol and enable access to an alternative diastereomer. This work highlights that predictably selective C—H oxidation methods can be strategically utilized at late-stages to increase the overall efficiency of target-oriented synthesis. Additionally, methods subject to reagent modulation can rapidly generate stereochemical divergency and may find use in diversity-oriented synthesis.^{33–35}

Methods

Preparation of Palladium Catalyst (3)

A dry 1 dram borosilicate vial was charged sequentially with recrystallized $\text{Pd}(\text{OAc})_2$ (2.9 mg, 0.0127 mmol, 0.3 equiv), *meso*-1,2-bis(phenylsulfinyl)ethane (3.6 mg, 0.0127 mmol, 0.3 equiv), CH_2Cl_2 (142 μL), and a teflon stir bar. The reaction was then stirred for 12 hours in 40°C bath, resulting in a bright red solution. For more information see SI.

Synthesis of macrolide 1

Freshly prepared catalyst (**3**) solution in a 1 dram vial was charged with 1,4-benzoquinone (BQ, 9.2 mg, 0.0852 mmol, 2.0 equiv) and alkenoic acid **2** (23.3 mg, 0.0426 mmol, 1.0 equiv) in CH_2Cl_2 (1.99 mL). The reaction was capped and stirred in a 45°C bath for 72 hrs. The resulting dark green reaction was cooled to r.t. and quenched with saturated ammonium chloride (NH_4Cl , 5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were then dried over magnesium sulfate (MgSO_4), filtered, and concentrated *in vacuo* to afford a clear oil. HPLC analysis of

the crude product showed a d.r. >40:1. Purification by flash chromatography (10% EtOAc/hexanes to 25% EtOAc/hexanes + 1% AcOH) furnished macrolide **1** as a clear oil (7.8 mg, 0.0143 mmol, 34%) and recovered alkenoic acid **2** (10.5 mg, 0.0192 mmol, 45%). Recycling experiments were performed twice, using the above procedure, to yield macrolide **1** in 56% overall yield along with 8% recovered alkenoic acid **2**. For more information see SI.

¹H NMR (500 MHz, CDCl₃) δ 7.51 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.03 (m, 1H), 5.78 (ddd, *J* = 17.0, 10.8, 4.5 Hz, 1H), 5.73 (s, 1H), 5.21 (dt, *J* = 17.0, 1.5 Hz, 1H), 5.17 (dt, *J* = 10.5, 1.5 Hz, 1H), 3.97 (d, *J* = 6.5 Hz, 1H), 3.84 (d, *J* = 10.5 Hz, 1H), 3.80 (s, 3H), 3.70 (d, *J* = 9.0 Hz, 1H), 3.41 (d, *J* = 10.5 Hz, 1H), 2.82 (dq, *J* = 11.0, 6.5 Hz, 1H), 2.38 (m, 1H), 2.21 (m, 1H), 1.93 (q, *J* = 6.5 Hz, 1H), 1.74–1.82 (m, 2H), 1.49 (s, 3H), 1.47 (s, 3H), 1.40 (app t, *J* = 13.3 Hz, 2H), 1.22 (d, *J* = 6.5 Hz, 3H), 1.20 (d, *J* = 6.5 Hz, 3H), 1.07 (d, *J* = 6.0 Hz, 3H), 1.05 (d, *J* = 6.0 Hz, 3H), 1.01 (d, *J* = 7.0, 3H), 0.87 (d, *J* = 7.0, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 175.2, 159.9, 135.5, 131.6, 127.5, 115.8, 113.6, 100.6, 95.2, 85.5, 77.6, 74.8, 73.5 (2 peaks), 55.3, 41.6, 39.6, 35.9, 32.6, 31.9, 29.7, 28.3, 26.8, 20.1, 16.3, 16.0, 13.5, 12.3, 8.0, 7.4; IR (film, cm⁻¹): 2961, 2937, 2856, 1729, 1616, 1517, 1456, 1382; HRMS (ESI) *m/z* calc'd for C₃₂H₄₉O₇ [M + H]⁺: 545.3478, found 545.3500; [α]_D²³ = -6.4° (c = 0.34, CH₂Cl₂).

Synthesis of macrolide **2**

The above procedure for the synthesis of macrolide **1** was followed except for the addition of solid tetrabutyl ammonium fluoride trihydrate (TBAF, 7.34 mg, 0.0233 mmol, 0.30 equiv). ¹H NMR analysis of the crude product showed a d.r. 1.3:1 (**1:epi-1**). Purification by flash chromatography described above furnished a 1.3:1 mixture of macrolide **1:epi-1** as a clear oil (8.3 mg, 0.0152 mmol, 20%) and recovered alkenoic acid **2** (32.0 mg, 0.0585 mmol, 75%). Recycling experiments were performed twice, using the above procedure, to yield macrolide **2** in 44% overall yield, as a 1.3:1 diastereomeric mixture, along with 36% recovered alkenoic acid **2**. For more information see SI.

¹H NMR (500 MHz, CDCl₃) δ 7.43 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 5.95 (ddd, *J* = 17.0, 11.0, 6.5 Hz, 1H), 5.73 (s, 1H), 5.52 (br s, 1H), 5.19 (d, *J* = 17.0 Hz, 1H), 5.07 (d, *J* = 10.5 Hz, 1H), 4.27 (d, *J* = 8.0 Hz, 1H), 4.09 (d, *J* = 5.5 Hz, 1H), 3.90 (d, *J* = 10.0 Hz, 1H), 3.81 (s, 3H), 3.36 (d, *J* = 11.0 Hz, 1H), 2.66 (dq, *J* = 9.5, 7.0 Hz, 1H), 2.53 (m, 1H), 2.15–2.21 (m, 2H), 1.80 (m, 2H), 1.51 (s, 3H), 1.46 (s, 3H), 1.38 (m, 1H), 1.31 (d, *J* = 6.5 Hz, 3H), 1.30–1.38 (m, 1H), 1.26 (d, *J* = 7.0 Hz, 3H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.01 (d, *J* = 7.5 Hz, 3H), 0.97 (d, *J* = 7.0, 3H), 0.96 (d, *J* = 7.0, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 172.9, 159.8, 136.9, 131.7, 127.2, 114.5 (broad), 113.6, 99.6, 94.6, 85.2, 77.5, 76.2, 72.9, 72.6, 55.3, 43.8, 40.3, 36.3, 33.0, 31.9, 29.9, 28.9, 27.1, 19.8, 16.5, 16.4, 15.8, 13.8, 7.8, 5.0; IR (film, cm⁻¹): 3071.5, 2969, 2938, 2889, 1736, 1616, 1516, 1461, 1381, 1248; HRMS (ESI) *m/z* calc'd for C₃₂H₄₉O₇ [M + H]⁺: 545.3478, found 545.3495; [α]_D²³ = -15.7° (c = 1.30, CH₂Cl₂).

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Figure 1. Macrocyclization approaches to macrolide antibiotics

a, Structures and approaches towards the erythronolides. **b,** A general strategy for reducing the "oxygen load" in a linear sequence through the use of late-stage C—H oxidation. **c,** Possible π -allylPd(carboxylate) intermediates for C—H macrolactonization. **d,** Energy minimized structures of macrolides **1** and **epi-1** using MMFF94s force field implemented in Molecular Operating Environment (MOE). FG, functional group; PMP, *p*-methoxyphenyl.

Figure 2. Synthesis of C—H macrolactonization precursor 2

(a) LDA (2.1 equiv), LiCl (6.0 equiv), allyl iodide (1.5 equiv), -78°C , >20:1 d.r., 96% (b) NH_3BH_3 (4.0 equiv), LDA (4.0 equiv), 0°C , 98% (c) oxalyl chloride (1.3 equiv), NEt_3 (5.0 equiv), DMSO (1.6 equiv), -78°C (d) **5** (1.0 equiv), Bu₂BOTf (1.2 equiv), *i*-Pr₂NEt (1.4 equiv), -78°C , >20:1 d.r., 55% (2-steps) (e) AlMe₃ (5.0 equiv), (MeO)NHMe-HCl (5.0 equiv), -10°C , 86% (f) PMBBBr (1.8 equiv), NaH (1.8 equiv), 0°C , 96% (g) Dibal-H (2.0 equiv), -78°C , 91% (h) **7** (1.0 equiv), Bu₂BOTf (1.2 equiv), NEt₃ (1.2 equiv), -78°C , >20:1 d.r., 96% (i) DDQ (1.2 equiv), MgSO₄ (14.0 equiv), >20:1 d.r., 93% (j) LAH (3.0 equiv), -78°C , 96% (k) PPh₃ (1.2 equiv), I₂ (1.4 equiv), imidazole (1.5 equiv), 94% (l) **4** (2.1 equiv), LDA (4.0 equiv), LiCl (12.7 equiv), 0°C , >20:1 d.r., 94% (m) NH_3BH_3 (4.0 equiv), LDA (4.0 equiv), 0°C , 99% (n) DMP (1.6 equiv), 96% (o) **10** (1.5 equiv), TiCl₄ (1.2 equiv), Ti(O*i*-Pr)₄ (0.4 equiv), NEt₃ (1.6 equiv), -78°C , 95:5 d.r., 88% (p) Zn(BH₄)₂ (1.6 equiv), -78°C , >20:1 d.r., 75–86% (q) CSA (cat.), 2,2-dimethoxypropane (9.8 equiv), 84% (r) LiOOH_(aq) (2.0 equiv), 0°C , 99%. A¹, auxiliary number one; PMB, *p*-methoxybenzyl; LDA, lithium diisopropylamide; LAB, lithium amidotrihydroborate; DMSO, dimethylsulfoxide; OTf, trifluoromethanesulfonate; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; LAH, lithium aluminum hydride; DMP, Dess-Martin periodinane; CSA, camphorsulfonic acid.

Figure 3. Synthesis of macrolides 1 and epi-1

Reaction conditions: (a) **3** (0.3 equiv), BQ (2.0 equiv), 45°C, 72 h, >40:1 d.r., 34% + 45% r.s.m. (56% + 8% r.s.m., 2x recycle) (b) **3** (0.3 equiv), BQ (2.0 equiv), TBAF (0.3 equiv), 45°C, 72 h, 1:1.3 d.r., 20% + 75% r.s.m. (44% + 36% r.s.m., 2x recycle) (c) **3** (0.1 equiv), BQ (2.0 equiv), *p*-NO₂BzOH (1.5 equiv), 45°C, 72 h, 1:1 d.r., 73% (combined) (d) LiOOH_(aq) (2.0 equiv) (e) K₂CO₃ (3.0 equiv), MeOH, 97% (2-steps) (f) Cl₃C₆H₂COCl (15.0 equiv), *i*-Pr₂NEt (20.0 equiv), DMAP (40.0 equiv), Benzene, 87%. BQ, 1,4-benzoquinone; r.s.m., recovered starting material; TBAF, tetra-*n*-butylammonium fluoride; *p*-NO₂BzOH, *p*-nitrobenzoic acid; DMAP, *N,N*-4-dimethylaminopyridine.

Figure 4. Synthesis of 6-deoxyerythronolide B

Reaction conditions for completing the synthesis of 6-dEB and its triacetate derivative **13** (X-ray crystallographic analysis shown): (a) $\text{Pd(OH)}_2/\text{C}$ (cat.), H_2 (1 atm), *i*-PrOH, 96% (b) TPAP (cat.), NMO (5.0 equiv), 0°C , 84% (c) 1M $\text{HCl}_{(\text{aq})}$ (11 equiv), 98% (d) Ac_2O (93.0 equiv), DMAP (cat.), Pyridine, 96%. TPAP, tetra-*n*-propylammonium perruthenate; NMO, *N*-methylmorpholine oxide.