

# Total synthesis and study of 6-deoxyerythronolide B by late-stage C–H oxidation

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**Among the frontier challenges in chemistry in the twenty-first century are the interconnected goals of increasing synthetic efficiency and diversity in the construction of complex molecules. Oxidation reactions of C–H bonds, 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 give 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 synthesis<sup>1</sup> and diversifying molecules<sup>2–5</sup>. Highly selective C–H oxidation reactions<sup>2–9</sup> allow reactive functional groups to be masked as inert C–H bonds, only to be unveiled as an 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<sup>6–9</sup> are scarce because of the requirement for oxidation to occur at one C–H bond amid scores of others, with predictably high levels of regio-, chemo- and stereoselectivity. Approaches to predict and influence 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<sup>10–14</sup>. 6-dEB (Fig. 1)<sup>15–18</sup> serves as the archetypical core of the polyketide macrolides<sup>19</sup>, and shares a striking stereochemical homology with most macrolide aglycones at all comparable stereocentres (Celmer's rules)<sup>20</sup>. Synthetic studies of erythromycin, which span more than a quarter of a century, have relied on internal esterification of a stereochemically defined linear hydroxyacid for macrocycle construction (Fig. 1a)<sup>12</sup>. We questioned whether this same core structure could be accessed through a late-stage C–H oxidative macrolactonization reaction in which oxygen is installed directly into the hydrocarbon framework late in the synthesis. This C–H oxidation strategy offers several potential advantages. First, the amount of reactive oxygen functionality (that is, the 'oxygen load') is minimized, and thereby reduces side reactions that erode synthetic yields over the course of multistep sequences (Fig. 1b)<sup>21</sup>. Second, this strategy can furnish diastereomeric macrolactones at the site of oxidation from a stereochemically versatile oxidation precursor.

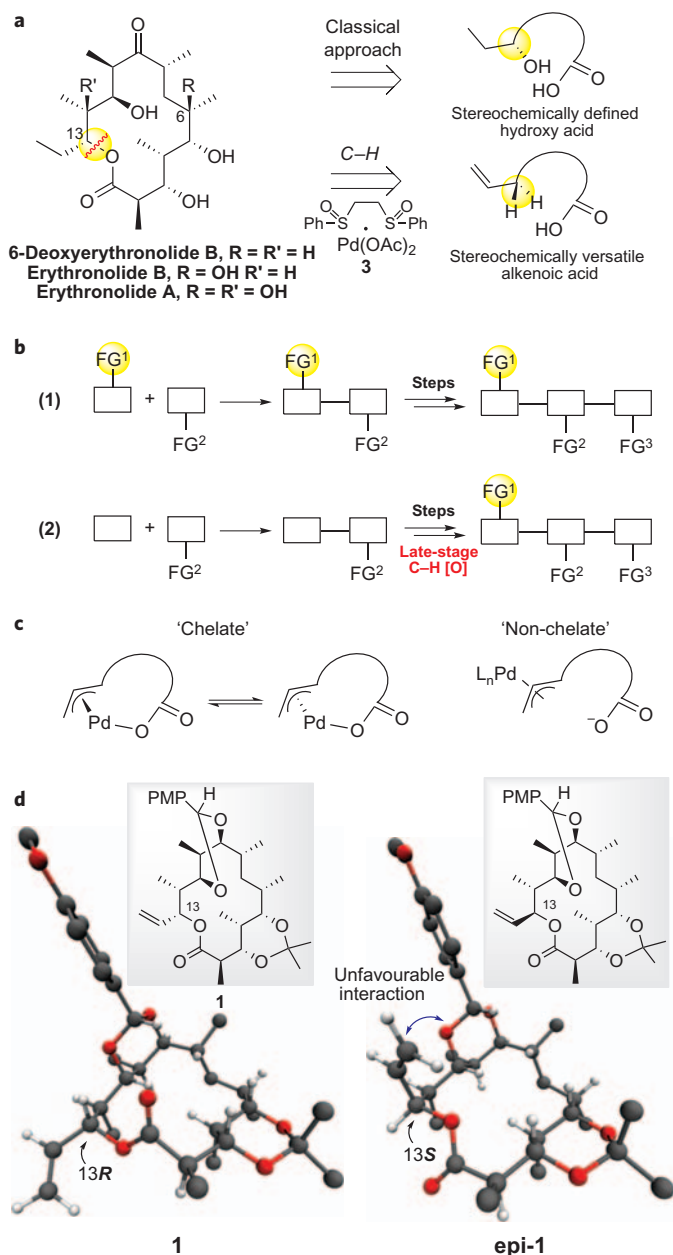
Our retrosynthetic approach to 6-dEB focused on C13 oxidation and macrocyclization to forge the macrolide core, which, when fully saturated, presents a formidable chemoselectivity challenge. We therefore envisioned selective oxidation at C13, in preference to six tertiary and five ethereal C–H bonds, through use of a C14–C15 vinyl moiety (Fig. 1). Towards this goal, we recently

developed an allylic C–H macrolactonization reaction catalysed by Pd(II)/bis-sulfoxide (**3**) that converts simple linear alkenoic acids directly into 14- to 19-membered macrolactones, with excellent levels of chemo- and regioselectivity<sup>22</sup>. However, the 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 (macrocyclization). Elegant examples of diastereoselective C–H oxidations in complex molecular settings have relied on the local topology of rigid, cyclic architectures to predict and control diastereomeric outcomes<sup>6,7</sup>. Albeit effective in these contexts, this conceptual framework cannot be used to predict stereochemical outcomes with flexible, acyclic compounds, and so an alternative approach is required.

Oxidative C–H macrolactonization is thought to proceed by an allylic C–H cleavage promoted by Pd(II)-sulfoxide to generate rapidly interconverting  $\pi$ -allyl-Pd(carboxylate) intermediates (see deuterium isomerization studies in the Supplementary Information), 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, and thus the stereochemical outcome of macrolactonization could be predicted using the relative ground-state product energies. Based on molecular modelling studies, macrolide **1** was found to be 3 kcal mol<sup>–1</sup> more stable than **epi-1** (MMFF94 force fields, see Supplementary Information) because of a pseudoequatorially disposed exocyclic vinyl moiety. We anticipated that chelate-controlled C–H macrolactonization would therefore strongly favour 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

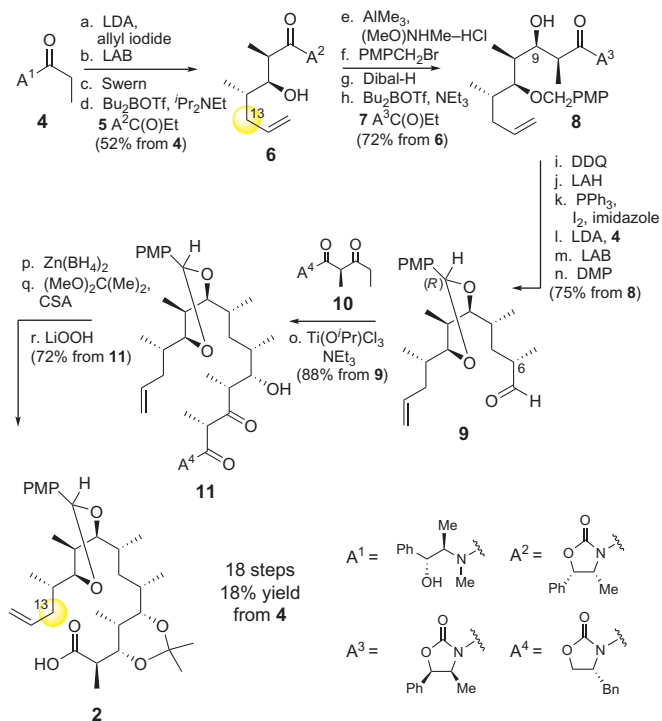
Our study commenced with the construction of a versatile, linear C–H oxidation precursor (**2**) using a series of powerful polyketide synthase (PKS)-inspired, stereoselective aldol and alkylation reactions in a linear, iterative fashion (Fig. 2). Towards the goal of minimizing the 'oxygen load', a relatively inert allyl moiety, acting as a



**Figure 1** | Macrocyclization approaches to macrolide antibiotics.

**a**, Structures and approaches towards the erythronolides. **b**, A general strategy to reduce the 'oxygen load' in a linear sequence through the use of late-stage C-H oxidation. **c**, Possible  $\pi$ -allyl-Pd(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; L = ligand,  $n = 1, 2$ ; PMP = *p*-methoxyphenyl.

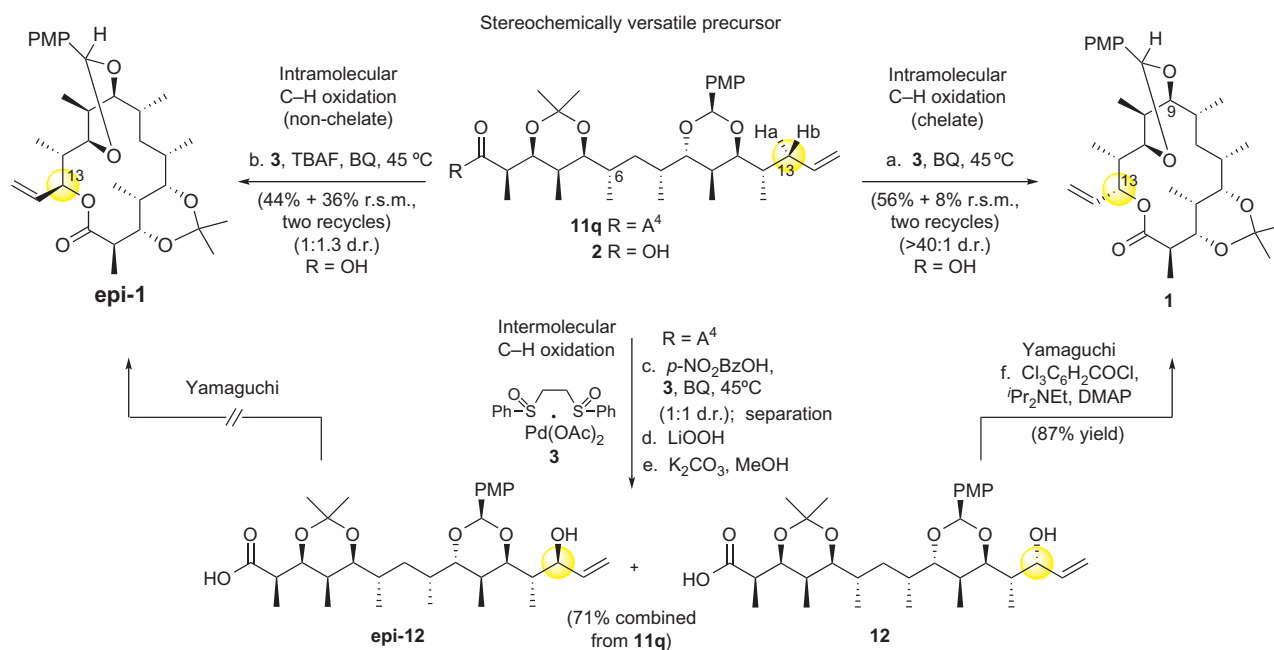
latent allylic alcohol, was installed during the first step of the synthetic route using Myers' diastereoselective alkylation<sup>23</sup> (>20:1 diastereomer ratio (d.r.)), and carried through the entire linear polypropionate synthesis without manipulation (see below). Two highly selective (>20:1 d.r.) *syn* Evans' aldol reactions<sup>24</sup> secured **8** as a single diastereomer. Ketalization<sup>25</sup> (>20:1 d.r.), followed by a Myers' alkylation-reduction-oxidation sequence, provided **9** as the sole diastereomer. At this juncture, a  $\beta$ -keto imide (**10**) would provide the dipropionate unit needed to complete the alkenoic acid (**2**) synthesis<sup>17</sup>. Standard generation of a titanium(IV) enolate using  $\text{TiCl}_4$  led to modest yields and selectivities (49%, 7:1 d.r.),



**Figure 2** | Synthesis of C-H macrolactonization precursor **2**. Reaction conditions: a, LDA (2.1 equiv.), LiCl (6.0 equiv.), allyl iodide (1.5 equiv.),  $-78^\circ\text{C}$ , >20:1 d.r., 96%; b,  $\text{NH}_3\text{BH}_3$  (4.0 equiv.), LDA (4.0 equiv.),  $0^\circ\text{C}$ , 98%; c, Swern (oxalyl chloride (1.3 equiv.),  $\text{NEt}_3$  (5.0 equiv.), DMSO (1.6 equiv.),  $-78^\circ\text{C}$ ); d, **5** (1.0 equiv.),  $\text{Bu}_2\text{BOTf}$  (1.2 equiv.),  $^i\text{Pr}_2\text{NEt}$  (1.4 equiv.),  $-78^\circ\text{C}$ , >20:1 d.r., 55% (two steps); e,  $\text{AlMe}_3$  (5.0 equiv.),  $(\text{MeO})\text{NHMe-HCl}$  (5.0 equiv.),  $-10^\circ\text{C}$ , 86%; f,  $\text{PMPCH}_2\text{Br}$  (1.8 equiv.), NaH (1.8 equiv.),  $0^\circ\text{C}$ , 96%; g, Dibal-H (2.0 equiv.),  $-78^\circ\text{C}$ , 91%; h, **7** (1.0 equiv.),  $\text{Bu}_2\text{BOTf}$  (1.2 equiv.),  $\text{NEt}_3$  (1.2 equiv.),  $-78^\circ\text{C}$ , >20:1 d.r., 96%; i, DDQ (1.2 equiv.),  $\text{MgSO}_4$  (14.0 equiv.), >20:1 d.r., 93%; j, LAH (3.0 equiv.),  $-78^\circ\text{C}$ , 96%; k,  $\text{PPh}_3$  (1.2 equiv.),  $\text{I}_2$  (1.4 equiv.), imidazole (1.5 equiv.), 94%; l, **4** (2.1 equiv.), LDA (4.0 equiv.), LiCl (12.7 equiv.),  $0^\circ\text{C}$ , >20:1 d.r., 94%; m,  $\text{NH}_3\text{BH}_3$  (4.0 equiv.), LDA (4.0 equiv.),  $0^\circ\text{C}$ , 99%; n, DMP (1.6 equiv.), 96%; o, **10** (1.5 equiv.),  $\text{TiCl}_4$  (1.2 equiv.),  $\text{Ti}(\text{O}^i\text{Pr})_4$  (0.4 equiv.),  $\text{NEt}_3$  (1.6 equiv.),  $-78^\circ\text{C}$ , 95:5 d.r., 88%; p,  $\text{Zn}(\text{BH}_4)_2$  (1.6 equiv.),  $-78^\circ\text{C}$ , >20:1 d.r., 75–86%; q, CSA (catalyst), 2,2-dimethoxypropane (9.8 equiv.), 84%; r,  $\text{LiOOH}_{\text{aq}}$  (2.0 equiv.),  $0^\circ\text{C}$ , 99%.  $\text{Bu}_2\text{BOTf}$  = dibutylboron trifluoromethanesulfonate, CSA = camphorsulfonic acid, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMP = Dess-Martin periodinane, DMSO = dimethylsulfoxide,  $^i\text{Pr}_2\text{NEt}$  = diisopropylethylamine, LAB = lithium amidotrihydroborate, LAH = lithium aluminium hydride, LDA = lithium diisopropylamide,  $\text{Ti}(\text{O}^i\text{Pr})_4$  = titanium tetraisopropoxide.

along with competitive removal of the *p*-methoxybenzylidene acetal (PMB acetal). Gratifyingly, we found that  $\text{Ti}(\text{O}^i\text{Pr})\text{Cl}_3$ , thought to generate a more nucleophilic enolate<sup>26</sup>, 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  $\beta$ -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, with an 18% overall yield and 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 the Pd(II)/bis-sulfoxide catalyst **3** led to sluggish conversion with only trace product formation. After increasing



**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., recycled twice); 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., recycled twice); c, **3** (0.1 equiv.), BQ (2.0 equiv.), *p*-NO<sub>2</sub>BzOH (1.5 equiv.), 45 °C, 72 h, 1:1 d.r., 73% (combined); d, LiOOH<sub>aq</sub> (2.0 equiv.); e, K<sub>2</sub>CO<sub>3</sub> (3.0 equiv.), MeOH, 97% (two steps); f, Cl<sub>3</sub>C<sub>6</sub>H<sub>2</sub>COCl (15.0 equiv.), <sup>i</sup>Pr<sub>2</sub>NEt (20.0 equiv.), DMAP (40.0 equiv.), benzene, 87%. BQ = 1,4-benzoquinone, DMAP = *N,N*-4-dimethylaminopyridine, *p*-NO<sub>2</sub>BzOH = *p*-nitrobenzoic acid.

the catalyst loading (from 10 to 30 mol%) and concentration (from 0.01 to 0.02 M), the 14-membered macrolide **1** was isolated in 34% yield (45% recovered starting material (r.s.m.)), Fig. 3). Consistent with predictions made using the chelate-controlled model, only the desired C13 diastereomer was detectable by <sup>1</sup>H nuclear magnetic resonance (<sup>1</sup>H NMR) spectroscopy of the crude reaction mixture (>40:1 d.r., liquid chromatographic analysis). 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.

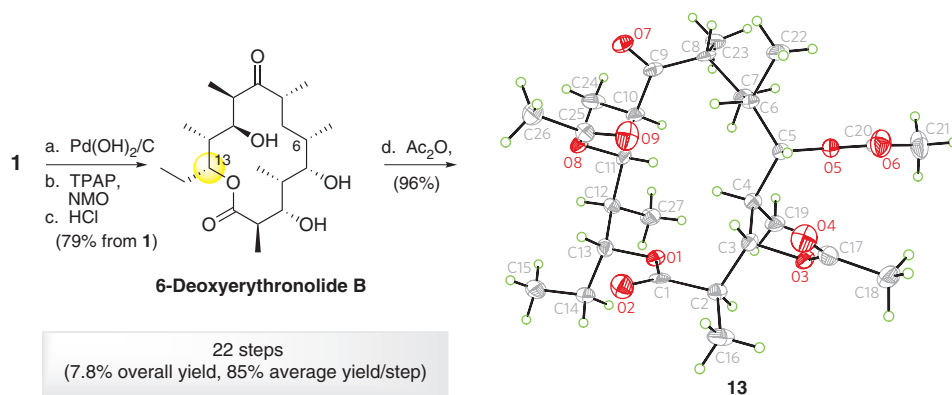
In attempts to alter the stereochemical outcome of C–H macrolactonization, we aimed to disrupt the palladium chelation event responsible for the diastereoselectivity<sup>27</sup>. Addition of fluoride anion to  $\pi$ -allyl-Pd complexes has been shown to enhance the rate of  $\pi$ - $\sigma$ - $\pi$  isomerization, presumably by interacting with a coordination site on palladium<sup>28</sup>. We anticipated that such an additive would disrupt the  $\pi$ -allyl-Pd(carboxylate) chelate to favour 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 twice, 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<sup>-1</sup> 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.

To probe the loss of stereocontrol with the 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 classic acylation-based (Yamaguchi) macrolactonization<sup>17,29</sup> that, like the chelate-controlled C–H macrolactonization, is thought to proceed through a product-like transition state (Fig. 3). Towards this end, late-stage intermolecular C–H oxidation (see above) was critical to circumvent lengthy *de novo* syntheses of each epimeric seco acid. As anticipated, Yamaguchi macrolactonization of the hydroxyacid **12** led to the natural epimer (macrolide **1**, 87% yield). 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 in which a greater kinetic barrier of cyclization prevents the formation of the less stable epimer.

With the C13 stereocentre in place, concurrent hydrogenation of the PMB acetal and  $\alpha$ -olefin with Pearlman's catalyst (Pd(OH)<sub>2</sub>/C), site-selective oxidation of the C9 alcohol and acetonide removal completed the synthesis of 6-dEB (Fig. 4). Following peracetylation of 6-dEB, X-ray-quality crystals of triacetate **13** were obtained, which confirmed the relative stereochemical assignments. In total, 6-dEB was synthesized in 22 steps with 7.8% overall yield, which represents 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.



**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, Pd(OH)<sub>2</sub>/C (catalyst), H<sub>2</sub> (1 atm), <sup>i</sup>PrOH, 96%; b, TPAP (catalyst), NMO (5.0 equiv.), 0 °C, 84%; c, 1M HCl<sub>aq</sub> (11 equiv.), 98%; d, Ac<sub>2</sub>O (93.0 equiv.), DMAP (catalyst), pyridine, 96%. NMO = *N*-methylmorpholine oxide, TPAP = tetra-*n*-propylammonium perruthenate.

## Discussion

Importantly, efforts to convert **epi-1** into 13-*epi*-6-deoxyerythronolide B using the same protocol as that to construct 6-dEB failed because of decomposition during the acetonide removal step. Interestingly, although the uniform arrangement of catalytic domains in the PKS accounts for the substitution patterns found in the macrolide antibiotics, the evolutionary basis for ‘Celmer’s rules’ has not yet been elucidated<sup>30,31</sup>. Although it is generally considered that evolution of the structure of erythromycin was driven by its shape complementarity to the ribosome<sup>32</sup>, the results presented here, along with the accepted low-energy conformational models (that is, ‘diamond lattice’) for the erythromycin aglycones<sup>20</sup>, raise the interesting possibility 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 through 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 used strategically at late stages to increase the overall efficiency of target-oriented syntheses. Additionally, methods subject to reagent modulation can rapidly generate stereochemical divergency and may find use in diversity-oriented syntheses<sup>33–35</sup>.

## Methods

**Preparation of palladium catalyst (3).** A dry 1 dram (4 ml) borosilicate vial was charged sequentially with recrystallized Pd(OAc)<sub>2</sub> (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<sub>2</sub>Cl<sub>2</sub> (142 μl), and a Teflon stir bar. The reaction mixture was then stirred for 12 hours in a 40 °C bath, which resulted in a bright red solution. (For more details see Supplementary Information.)

**Synthesis of macrolide 1.** Freshly prepared catalyst (**3**) solution in a 1 dram (4 ml) 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<sub>2</sub>Cl<sub>2</sub> (1.99 ml). The reaction mixture was capped and stirred in a 45 °C bath for 72 hours. The resulting dark green solution was cooled to room temperature and quenched with saturated ammonium chloride (5 ml). The layers were separated and the aqueous layer extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 ml). The combined organic layers were then dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford a clear oil. High-performance liquid chromatography 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 details see Supplementary Information.)

<sup>1</sup>H NMR spectra (500 MHz, CDCl<sub>3</sub>) 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). <sup>13</sup>C NMR spectra (125 MHz, CDCl<sub>3</sub>) 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 (two 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. Infrared (film, cm<sup>-1</sup>) 2961, 2937, 2856, 1729, 1616, 1517, 1456, 1382. High-resolution mass spectroscopy (HRMS) (electrospray ionization (ESI)) *m/z* calculated for C<sub>32</sub>H<sub>49</sub>O<sub>7</sub> (M + H)<sup>+</sup> 545.3478; found 545.3500. (α)<sub>D</sub><sup>23</sup> = -6.4° (*c* = 0.34, CH<sub>2</sub>Cl<sub>2</sub>).

**Synthesis of macrolide 2.** The above procedure for the synthesis of macrolide **1** was followed except for the addition of solid TBAF (7.34 mg, 0.0233 mmol, 0.30 equiv.). Analysis of the <sup>1</sup>H NMR spectra 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 details see Supplementary Information.)

<sup>1</sup>H NMR spectra (500 MHz, CDCl<sub>3</sub>) 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). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) 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. Infrared (film, cm<sup>-1</sup>) 3071.5, 2969, 2938, 2889, 1736, 1616, 1516, 1461, 1381, 1248. HRMS (ESI) *m/z* calculated for C<sub>32</sub>H<sub>49</sub>O<sub>7</sub> (M + H)<sup>+</sup> 545.3478; found 545.3495. (α)<sub>D</sub><sup>23</sup> = -15.7° (*c* = 1.30, CH<sub>2</sub>Cl<sub>2</sub>).

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### Author contributions

E.M.S. and M.C.W. conceived and designed the experiments, E.M.S. performed the experiments and E.M.S. and M.C.W. co-wrote the paper.

### Additional information

Supplementary information and chemical compound information accompany this paper at [www.nature.com/naturechemistry](http://www.nature.com/naturechemistry). Reprints and permission information is available online at <http://npg.nature.com/reprintsandpermissions/>. Correspondence and requests for materials should be addressed to M.C.W.