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# Total Synthesis of Etnangien

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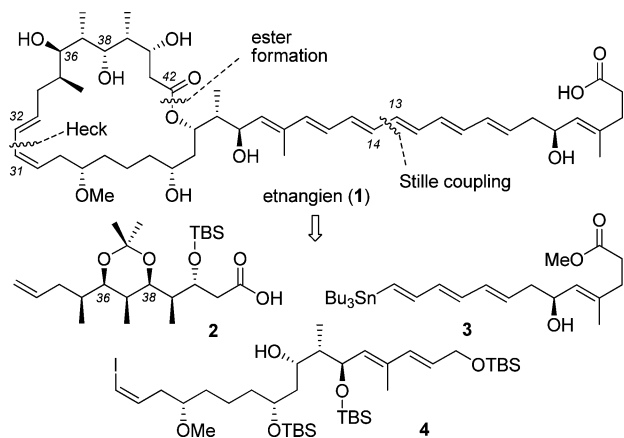
## Total Synthesis of Etnangien

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Etnangien presents a labile polyketide macrolide isolated by the group of Höfle from the myxobacterium *Sorangium cellulosum*.<sup>1</sup> It displays potent antibiotic activity against a range of Gram-positive bacteria, by inhibition of RNA-polymerase,<sup>2</sup> *in vitro* and *in vivo*. Importantly, it shows no cross-resistance to rifampicine, the only clinically used RNA-polymerase inhibitor so far. Furthermore, it also retains activity against retroviral DNA polymerase and shows only low cytotoxicity against mammalian cell cultures, which adds to its attractiveness for further development. This is however severely hampered by its notorious instability.<sup>1,3</sup> The unique structure of etnangien comprises a 22-membered macrolactone with a polyunsaturated side chain and includes 12 stereogenic centers. Recently, we proposed a full stereochemical assignment, as indicated in **1** for etnangien (Scheme 1), by extensive high-field NMR experiments, molecular modeling, chemical derivatization, and bioinformatics analysis.<sup>3</sup> Herein, we disclose the first total synthesis of etnangien and establish unequivocally its relative and absolute configuration.

## Scheme 1. Retrosynthetic Analysis of Etnangien

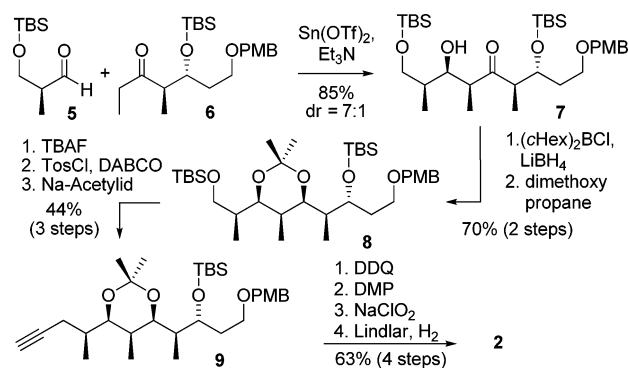


As outlined retrosynthetically in Scheme 1, our synthetic approach was based on a late-stage introduction of the side chain **3** by a cross-coupling strategy. The macrocyclic core, in turn, was envisioned to arise from building blocks **2** and **4**, which should be forged by an esterification and a Heck coupling to deliver the 30*Z*,32*E*-diene. In principle, both methodologies may be employed for ring closure, thus offering considerable flexibility in the synthesis. Notably, an acetonide protective group was chosen for OH-36 and -38 to induce a conformational bias for macrocyclization by mimicking the solution conformation of etnangien.<sup>3</sup> Importantly, the modular synthetic approach employed is flexible, highly

convergent, and stereocontrolled and thus offers the potential to provide a range of structural derivatives for SAR studies to further explore the biological potential of this promising macrolide antibiotic.

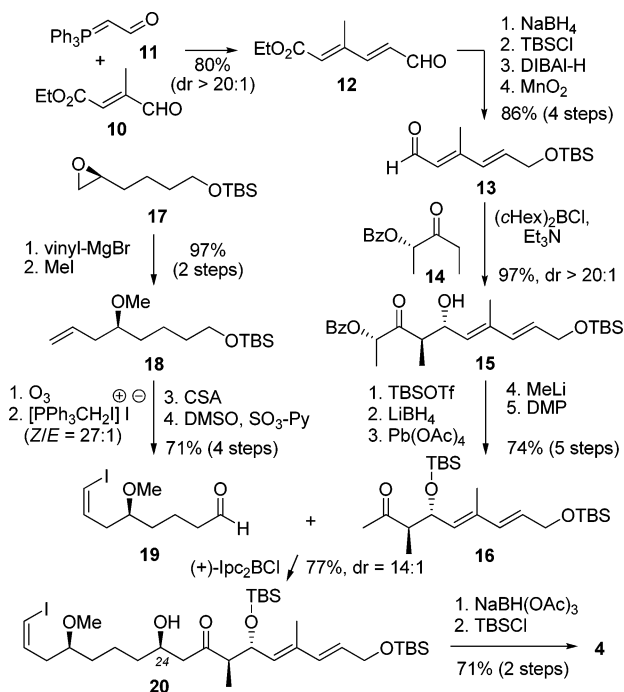
As shown in Scheme 2, our synthesis of C32–C42 subunit **2** utilizes a tin-mediated aldol reaction<sup>4</sup> of ethyl ketone **6**<sup>5</sup> with Roche ester derived aldehyde **5**, to give the expected (1,4)-*syn*-product **7** with high levels of stereocontrol and yield. Subsequent (1,3)-*syn* reduction of the hindered  $\beta$ -hydroxyketone **7** was efficiently accomplished after chelation [(*c*Hex)<sub>2</sub>BCl/LiBH<sub>4</sub>] (dr > 20:1). After acetonide protection of the derived diol and selective removal of the primary TBS group (TBAF), the required C2 homologation to **9** was enabled by nucleophilic substitution of the derived tosylate with sodium acetylide. Completion of the synthesis of **2** proceeded smoothly by PMB deprotection, oxidation to the acid, and Lindlar reduction of the alkyne.

## Scheme 2. Synthesis of the C32–C42 Subunit 2

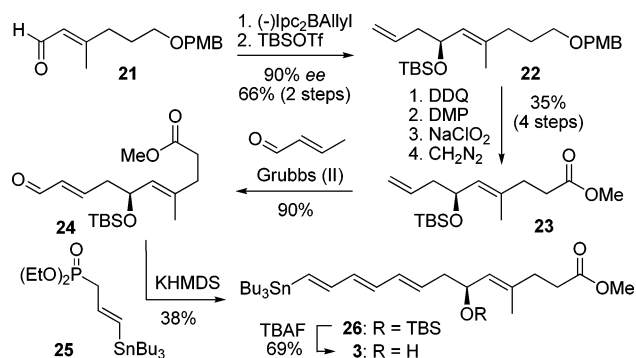


As shown in Scheme 3, construction of the C15–C31 subunit **4** commenced with known diene **12**, prepared by an optimized route from **10** and **11**.<sup>6</sup> The derived aldehyde **13** was homologated to antialdol **15** with high diastereoselectivity (dr > 20:1) and yield (97%) by a boron-mediated Paterson aldol reaction<sup>7</sup> with lactate derived ethyl-ketone **14**. For conversion to methyl ketone **16** (5 steps, 74%) use of Pb(OAc)<sub>4</sub> for diol cleavage was critical to avoid deprotection of the primary TBS group. The aldehyde coupling partner **19** was obtained in six steps (69%) from epoxide **17**, readily available by Jacobsen HKR methodology.<sup>8</sup> Introduction of the required terminal *Z*-vinyl iodide proceeded with excellent selectivity (dr = 27:1) optimizing a general Wittig–Stork–Zhao olefination protocol.<sup>9</sup> Finally, the pivotal aldol coupling of **16** with **19** to install the center at C24 with the desired configuration proceeded with high diastereoselectivity and yield (dr 14:1, 77%) by an Ipc-boron mediated aldol coupling. Subsequent 1,3-*anti* reduction of the derived hydroxyl ketone **20** with the Evans–Carreira protocol<sup>10</sup> and protection of the less hindered 24-OH gave building block **4** in good yields (71%).

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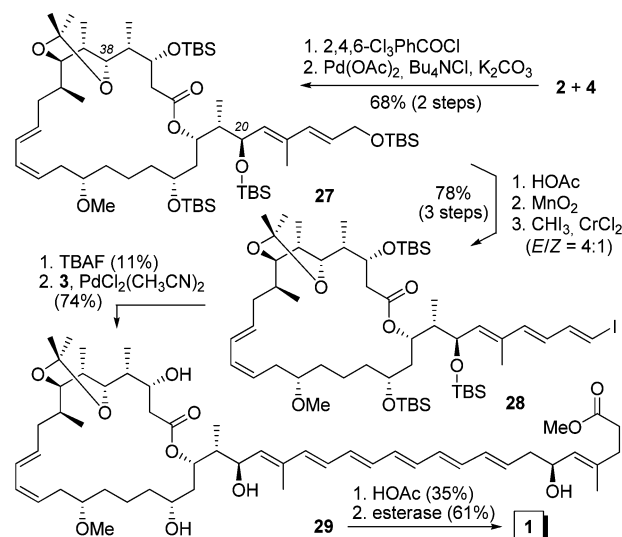
**Scheme 3.** Preparation of the C15–C31 Subunit 4

As shown in Scheme 4, our synthesis of the side chain fragment **3** was based on a Brown allylation of readily available aldehyde **21** to give after TBS protection homoallylether **22**. After conversion to methylester **23**, homologation to enal **24** proceeded smoothly by cross metathesis in the presence of Grubbs(II) catalyst. Finally, the required stannane was introduced by HWE reaction with **25**<sup>11</sup> to give after deprotection the desired building block **3**.

**Scheme 4.** Assembly of the C1–C13 Subunit 3

To install the labile side chain in a late stage of the synthesis, our strategy for fragment union relied on first closing the macrocyclic core (Scheme 5). After esterification of **2** and **4** by means of the Yamaguchi protocol (97%), Heck macrocyclization proceeded with excellent yield and diastereoselectivity (70%, *E/Z* > 20:1) validating our protective group strategy.<sup>12</sup> After selective removal of the primary TBS group (HOAc) and allylic oxidation, the required *E*-vinyl iodide was introduced by a Takai reaction (92%, *E/Z* = 4:1). Global deprotection of the macrocyclic core proved challenging, due to a pronounced and unexpected<sup>1,3</sup> tendency for trans-lactonization,  $\delta$ -lactone formation with the 38-OH, steric hindrance of the 20-OTBS, and general base and acid sensitivity of the substrate. Finally, the strategy involved first removing all TBS groups (TBAF), attachment of the side chain by Stille coupling, and subsequent acetone cleavage under only mildly acidic condi-

tions (65% HOAc). At last, enzyme catalyzed ester cleavage<sup>3</sup> gave etnangien (**1**) which was identical to an authentic sample (<sup>1</sup>H, <sup>13</sup>C NMR, optical rotation),<sup>1</sup> thus allowing confident assignment of the relative and absolute configuration and validating our earlier proposal.<sup>3</sup>

**Scheme 5.** Completion of the Synthesis

In conclusion, this first total synthesis of etnangien proceeds in 23 steps (longest linear sequence) and 0.25% yield and establishes unequivocally the relative and absolute configuration. Notable features include highly stereoselective aldol reactions, an efficient conformation controlled Heck macrocyclization, and a late-stage introduction of the labile side chain. Importantly, the modular synthesis should be amenable to designed analogues of this novel RNA-polymerase inhibitor, thus enabling further exploration of the promising biological potential of this macrolide antibiotic.

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**Supporting Information Available:** Experimental procedures, characterization data and <sup>1</sup>H and <sup>13</sup>C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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