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Synthesis of the all-*syn* C_{35}–C_{39} stereopentad of etnangien by the γ-hydroxybutenolide approach

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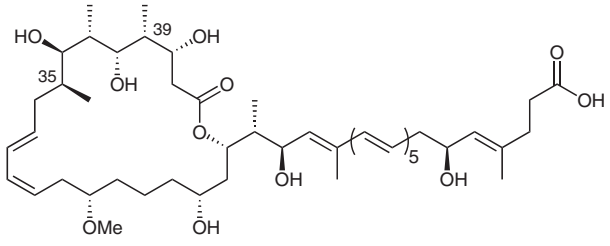
ABSTRACT

The synthesis of the all-*syn* C_{35}–C_{39} stereopentad of etnangien has been achieved using the asymmetric aldol reaction of a γ-hydroxybutenolide (5-hydroxy-4-methylfuran-2(5*H*)-one) as the key step in the five-step synthesis. The reaction of the titanium enolate of (*S*)-4-isopropyl-3-propionyl-2-oxazolidinone with 5-hydroxy-4-methylfuran-2(5*H*)-one gave good yields and diastereoselectivity of corresponding lactone, which was converted into a lactone with an all-*syn* stereotriad.

Etnangien is a polyketide macrolide isolated from two strains of myxobacterium *Sorangium cellulosum*, So ce750 and So ce1045 (Fig. 1).[1,2] It is a powerful antibiotic that acts against a broad range of Gram-positive bacteria in both in vitro and in vivo assays.[1] Etnangien and its corresponding methyl ester join the rifamycins as inhibitors of bacterial RNA polymerase, a promising yet underutilized approach in antibiotic therapy.[3] The low mammalian cell cytotoxicity of etnangien has prompted a multi-faceted scientific investigation of etnangien's potential as a therapeutic agent.[1,2,4–9] The total synthesis of etnangien was accomplished by Menche in 2009.[6]

One of the biggest challenges in the synthesis of etnangien is the construction of the stereochemically-rich polypropionate fragment of the macrocyclic moiety.[4,10] Our retrosynthetic analysis of etnangien envisions an olefination reaction between C_{32} and C_{33}, a Mukaiyama aldol reaction to establish the stereochemistry at C_{40}, and a macrolactonization (Scheme 1). Lactone **1**, which has the imbedded all-*syn* C_{35}–C_{39} stereopentad, is potentially available by the substrate-controlled aldol reaction of γ-hydroxybutenolide **2**[11] with ethyl ketone **3**[12,13] and appropriate reduction reactions. The employment of γ-hydroxybutenolides as substrates in the asymmetric aldol reaction[14,15] has very little precedent, limited to Nagoa's seminal studies of the reaction of tin(II) enolates of 3-acetyl-4(*S*)-isopropyl-1,3-thiazolidine-2-thione with γ-hydroxybutenolides.[14a] Herein, we report the successful development of



etnangien

Figure 1. Structure of etnangien.

the asymmetric aldol reaction employing γ-hydroxybutenolide **2** and its application to the synthesis of lactone **1**.[16]

The previous studies in the reaction of the titanium enolate of **3**[13,17] with aldehydes were the starting point for our own studies. Since γ-hydroxybutenolides are inherently acidic, the key to the successful asymmetric aldol reaction between the titanium enolate of **3** with γ-hydroxybutenolide **2** was in generating the appropriate conjugate base of **2**. Unlike Nagoa's studies of the tin enolates of 3-acetyl-4(*S*)-isopropyl-1,3-thiazolidine-2-thione,[14a] in which 1.5 equiv of the γ-hydroxybutenolide were used per equivalent of enolate, one equivalent of the titanium enolate of **3** fully consumed one equivalent of **2** in an acid/base reaction. The addition of 2–3 equiv of the titanium enolate of **3** per equivalent of **2** gave complex mixtures that contained an appreciable amount of the

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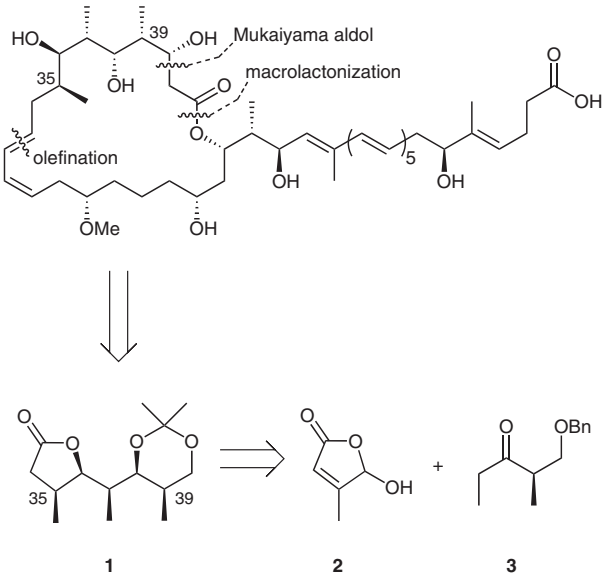
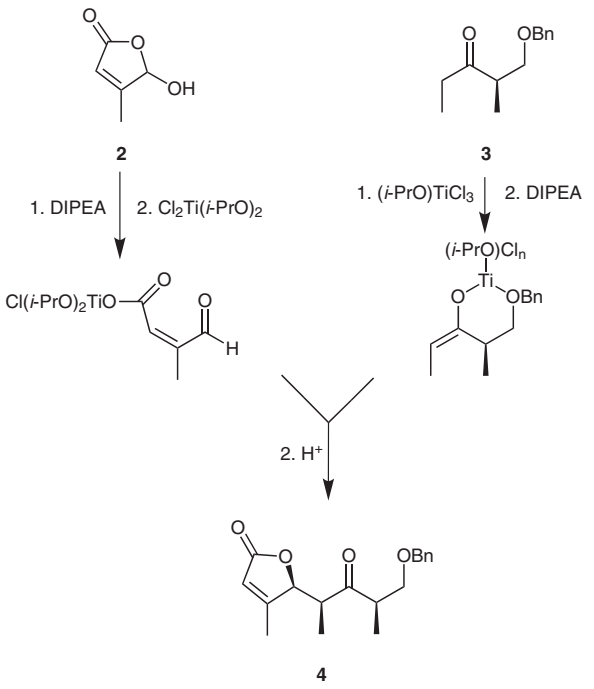
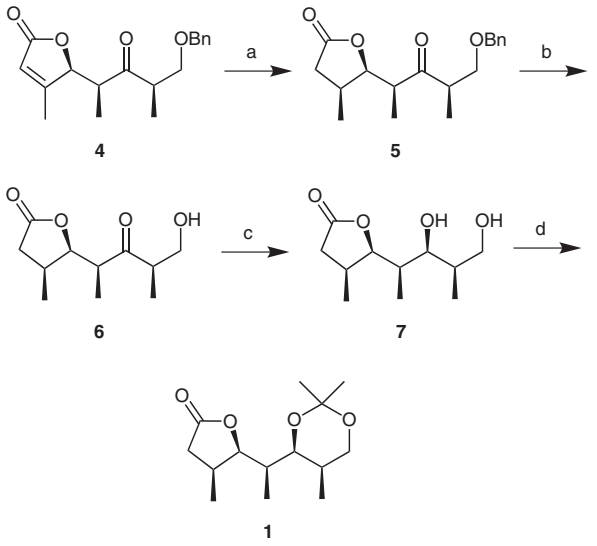


Scheme 1. Retrosynthetic analysis of etnangien.



Scheme 2. Reaction of titanium enolate of **3** with **2** to give **4** (81% yield based on recovered **3**; 94:6 dr).



Scheme 3. Reagents and conditions: (a) H_2, Rh/alumina; (b) H_2, Pearlman's catalyst, 59%, 98:2 dr (two steps); (c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, IPA/H_2O, 79%, 93:7 dr; (d) $(CH_3)_2C(OCH_3)_2$, H^+, 74%.

desired lactone **4**. The addition of the titanium enolate of **3** to the sodium or lithium salt of **2** or the conjugate base of **2** generated by the addition of DIPEA led to mostly recovered starting materials. These results suggested a strategy of generating the conjugate base of **2** from $(i\text{-PrO})_{4-x}TiCl_x$, with amines serving as a base. Attempts to generate the conjugate base of **2** employing $TiCl_4$ led to a significant isomerization of **2** to give the corresponding *E*-acid of **2**. The reactions of the conjugate base of **2**, generated by the addition of DIPEA and $TiCl(i\text{-PrO})_3$, with the titanium enolate of **3** gave fair yields of **4** (50–55%) and good diastereoselectivity (>90:10 dr) but were plagued by the incomplete conversion of ketone **3**. The optimal conditions for generating the conjugate base of **2** employed DIPEA as the base followed by the addition of $TiCl_2(i\text{-PrO})_2$, with careful control of the temperature so as to insure complete formation of the conjugate base but with minimal isomerization (Scheme 2). When this conjugate base of **2** reacted with the titanium enolate of **3** generated from $TiCl_3(i\text{-PrO})$/DIPEA,[17] lactone **4** was obtained in 67% yield (81% yield based on recovered **3**) and greater than 94:6 dr with less than 10% recovered yield of **3**.[18]

Three reductions are necessary to secure the fourth and fifth stereogenic centers, and to deprotect the benzyl ether (Scheme 3). The reduction of the alkenyl moiety of the unsaturated lactone was complicated by the lack of diastereoselectivity in the reduction as well as reduction of the aromatic ring of the benzyl group by several catalyst systems. Of the catalysts screened, Rh/alumina in diethyl ether gave the best diastereoselectivity (~7:1, **5**:*trans*-**5**) with the least (<10%) hydrogenation of the benzyl group.[19] Hydrogenolysis (1 atm H_2, Pearlman's catalyst) of the benzyl ether of **5** gave alcohol **6** (59% yield, two steps). Unexpectedly, the conversion of **6** to **7** was relatively unselective under a variety of standard conditions known to effect the *syn*-reduction of β-hydroxyketones.[20] For example, the reduction of **6** with reagents such as $Zn(BH_4)$, catecholborane, $BH_3{\cdot}C_5H_5N/TiCl_4$, etc., gave good to excellent yields of the desired alcohol but in only 1:1 to 3:1 dr. The solution to this problem was the counterintuitive use of the Luche reduction ($NaBH_4/CeCl_3{\cdot}H_2O$),[21] which is not known to favor *syn*-reduction of β-hydroxyketones. The reduction proceeded with increasing selectivity with more bulky alcohol solvents (MeOH, EtOH, IPA; 3:1, 6:1, 13:1 dr), although the reaction rate slowed and conversion of the starting material suffered. The use of water as a co-solvent (5%) in IPA was advantageous for both insuring complete conversion of **6** to **7** and reproducible diastereoselectivity (79% yield, 13:1 dr). Diol **7** was readily converted into the acetonide **1** by the reaction with 2,2-dimethoxypropane using phosphomolybdic acid as a catalyst (74% yield).

We also examined an alternative approach to synthesizing *syn*-polypropionate fragments employing the well-known and extensively employed enolates of *N*-acyloxazolidinones.[22] We were able to achieve good yields and diastereoselectivity in the reaction of the titanium enolate of **8** with **2** by using either one as the limiting reagent (Scheme 4). The addition of three equivalents of the titanium enolate of **8** (LDA/$TiCl(i\text{-OPr})_3$; Thornton's conditions[23]) to **2** gave lactone **9** in 68% yield and 98:2 dr (dr of the crude product was 92:8).[24] As in the case for the reaction of the titanium enolate