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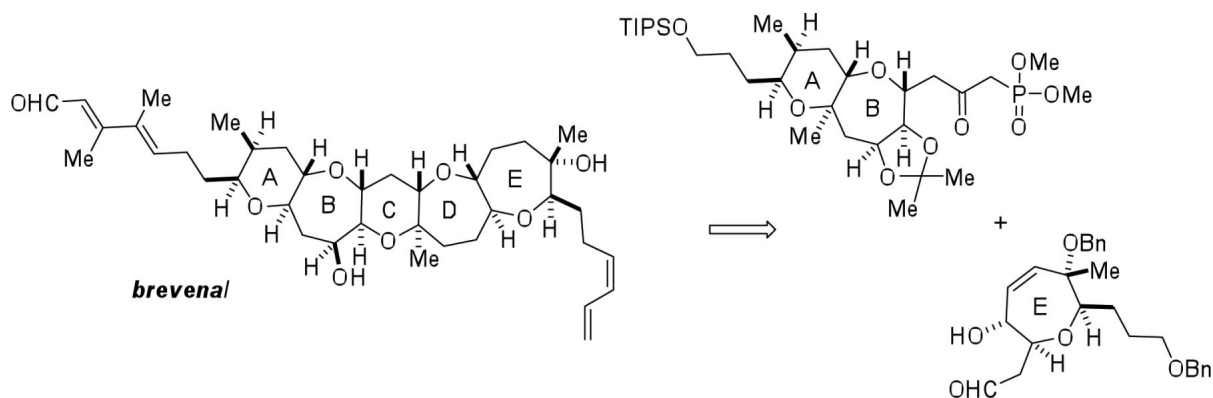
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A Highly Convergent Approach toward (-)-Brevenal

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Abstract



Progress toward a highly convergent, asymmetric synthesis of brevenal is reported. Construction of the AB-ring and E-ring cyclic ether fragments was achieved through asymmetric alkylation/ring-closing metathesis strategies. A Horner-Wadsworth-Emmons olefination was used in a key bond-forming step to couple the advanced cyclic fragments and enable rapid access to the AB-E ring system.

Marine polycyclic ether natural products have received much attention over the years due to their unique and highly complex molecular architecture, in addition to their diverse and potent biological activities.¹ A number of bioactive polyether natural products have been isolated from the marine dinoflagellate *Karenia brevis*, the organism responsible for toxic red tides along Florida's Gulf Coast. The most well-known compounds isolated from *K. brevis* are a family of neurotoxins called the brevetoxins. The brevetoxins are responsible for massive kills of fish and marine animals and can also adversely affect humans; inhaled brevetoxins cause respiratory irritation and breathing difficulties in sensitive populations.² At high concentrations, ingested brevetoxins lead to a collection of symptoms commonly referred to as neurotoxic shellfish poisoning (NSP).³ Brevenal (**1**) was isolated in 2004 from *K. brevis* and has been shown to counteract the toxic effects of the brevetoxins.⁴ Specifically, brevenal has been shown to competitively displace titrated dihydrobrevetoxin-B from voltage sensitive sodium channels in rat brain synaptosomes in a dose-dependent manner, alleviating the toxic effects of the brevetoxins *in vivo*.⁵ More importantly, picomolar concentrations of brevenal were found to increase tracheal mucus velocity to the same degree as that observed with millimolar concentrations of a sodium channel blocker, amiloride, which is used in the

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Supporting Information Available: Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

treatment of the debilitating lung disorder cystic fibrosis.⁶ As such, brevenal represents a potential lead for the development of novel therapeutic agents for the treatment of mucociliary dysfunction associated with cystic fibrosis and other lung disorders. To date, two syntheses of brevenal have been reported by the laboratories of Sasaki⁷ and Yamamoto.⁸

Our retrosynthetic analysis of brevenal includes the installation of the unsaturated side chains at both ends of the molecule late in the synthesis (Scheme 1). The pentacyclic polyether core was envisioned to arise from advanced enone **3** via an acid-catalyzed cyclodehydration to form the D-ring (**2**) followed by cyclization to afford the C-ring. Enone **3** would be made available through a Horner-Wadsworth-Emmons coupling between AB-ring β -ketophosphonate **4** and E-ring aldehyde **5**.

Initial efforts toward the total synthesis of brevenal focused on the construction of AB-ring β -ketophosphonate **4**. The retrosynthesis of **4** is centered on a glycolate alkylation/ring-closing metathesis approach, developed in our laboratory, for the enantioselective construction of medium-ring ethers (Scheme 2).⁹ It was envisioned that the β -ketophosphonate functionality would be installed in three steps from nitrile **6**. Access to the 6,7-fused system would hinge on closure of the medium-ring ether via a ring-closing metathesis reaction of diene **7**. Stereoselective alkylation of glycolate **8** followed by conversion of the oxazolidinone to the olefin would afford advanced diene **7**. The precursor to glycolate **8**, enol ether **9**, would be accessed from **10** via a cyclodehydration reaction. A Horner-Wadsworth-Emmons coupling of aldehyde **11** and β -ketophosphonate **12** would give rise to **10**.

The synthesis commenced with a monobenylation of commercially available 1,4-butanediol¹⁰ (**13**) followed by a Jones' oxidation¹¹ to afford carboxylic acid **14** (Scheme 3). Conversion to the methyl ester under acidic conditions followed by displacement with lithiodimethyl methylphosphonate¹² then furnished β -ketophosphonate **12** in excellent yield over the four steps. The preparation of aldehyde **11** began with a highly diastereoselective "Evans" *syn* propionate aldol addition¹³ between phenylalanine-derived *N*-propionylthiazolidinethione **15** and aldehyde **16**. The resultant aldol adduct **17** was protected as the trimethylsilyl (TMS) ether, and reductive removal of the auxiliary furnished the desired aldehyde **11**.

With both aldehyde **11** and β -ketophosphonate **12** prepared, efforts were directed toward the completion of the AB-ring fragment. Enone **10** was prepared in 90% yield under mild reaction conditions using a modified Horner-Wadsworth-Emmons olefination.¹⁴ 1,4-reduction of **10**¹⁵ followed by deprotection of the TMS group generated hydroxy ketone **18**. After screening a variety of cyclodehydration conditions, it was discovered that camphorsulfonic acid (CSA) in the presence of molecular sieves afforded enol ether **9** in excellent yield. Enol ether **9** was then transformed to thioacetal **19** via an epoxide intermediate,¹⁶ and the resulting hydroxyl group was protected as the triethylsilyl (TES) ether. The thioethyl group was converted to a methyl group in one pot, using Sasaki's protocol, to give pyran **20**.¹⁷ It was found that protection of the hydroxyl group was necessary for this reaction to proceed in high yield.

With the necessary A-ring functionality in place, construction of the B-ring then ensued. The benzyl group was cleaved in the presence of sodium naphthalenide¹⁸ to generate alcohol **21**. Swern oxidation¹⁹ of the resultant hydroxyl group, followed by a methylene Wittig reaction,²⁰ afforded olefin **22**. The TES ether was then cleaved with CSA and ethanol to give alcohol **23**. At this point, our glycolate alkylation/ring-closing metathesis strategy was applied to construct the seven-membered B-ring. Alcohol **23** was transformed to the glycolic acid in the presence of sodium hydride and bromoacetic acid. In one pot, the resultant acid was converted to the mixed pivalic anhydride and treated in situ with the lithium salt of (*R*)-4-isopropyl-2-oxazolidinone to produce acyl oxazolidinone **8**. Treatment of the sodium enolate of **8** with

bromoacetonitrile resulted in a highly diastereo-selective glycolate alkylation²¹ to furnish the nitrile. The modest yield associated with this reaction is attributed to the formation of an unidentifiable byproduct formed during the enolization process. All attempts to optimize this reaction, however, were unsuccessful. The oxazolidinone was then reductively cleaved to reveal alcohol **25**. Oxidation of **25** to the aldehyde under Swern conditions occurred in high yield. Initially, the resulting aldehyde was subjected to a methylene Wittig reaction using an ylide generated in situ from potassium *t*-butoxide and methyltriphenylphosphonium bromide. The presence of the nitrile, however, facilitated an elimination reaction under these rather basic conditions, thus regenerating alcohol **23**. To circumvent this undesired elimination, the methylenation reaction was performed using crystallized, salt-free methylene triphenylphosphorane, thereby giving rise to the desired diene **7**.²² B-Ring formation was achieved upon exposure of **7** to Grubbs' second generation catalyst,²³ affording bicycle **26** in 94%. Dihydroxylation of the resultant olefin occurred readily to furnish the desired diol as a single diastereomer. Subsequent protection of the diol afforded advanced acetone **6**. Diisobutylaluminum hydride easily reduced the nitrile to the aldehyde. In two steps, **6** was converted to β -ketophosphonate **4** to complete the AB-ring fragment with 27 steps in the longest linear sequence. The stereochemistry was confirmed by nOESY analysis.

With the AB-ring β -ketophosphonate in hand, efforts then focused on the synthesis of the E-ring aldehyde (**5**, Scheme 4). An asymmetric aldol addition, originally reported by Kobayashi and coworkers,²⁴ between oxazolidinone **27** and aldehyde **28** was used to prepare aldol adduct **29**. The auxiliary was converted to the methyl ester and the free hydroxyl group was protected as the TES ether to give ester **30**. Conversion of **30** to aldehyde **31** was carried out using a two step reduction-oxidation sequence. After generation of a terminal olefin from the aldehyde functionality through a Wittig reaction, the TES group was removed to furnish alcohol **32**. Alkylation of **32** with bromoacetic acid followed by coupling with a valine-derived oxazolidinone enabled isolation of glycoyl oxazolidinone **34**. Generation of the sodium enolate of **34** followed by alkylation with bromoacetonitrile introduced the third stereogenic center with excellent diastereoselectivity (95:5 *dr*). Reductive removal of the auxiliary then furnished alcohol **35**, and the resultant hydroxyl group was easily oxidized to aldehyde **36** under Swern conditions. Treatment of **36** with divinyl zinc installed the second olefin as a mixture of diastereomers (**37**). Exposure of this diastereomeric mixture to Grubbs' second generation catalyst enabled the isolation of cyclic ethers **38** and **39**. The undesired diastereomer **38** could be converted to **39** via a two step oxidation/reduction sequence. Protection of **39** as a TES ether and reduction of the nitrile generated E-ring aldehyde **5** in 16 steps from **27**.

With both the AB-ring β -ketophosphonate and E-ring aldehyde prepared, attention was directed toward coupling of the fragments and completing brevenal (Scheme 5). β -Ketophosphonate **4** and aldehyde **5** were joined through a barium hydroxide-mediated Horner-Wadsworth-Emmons reaction to provide advanced enone **3** in excellent yield. In order to complete the total synthesis of brevenal, we envision the closure of the D-ring via an acid-catalyzed cyclodehydration. Manipulation of the resulting enol ether (**2**) to give ketone **40** followed by formation of the C-ring via acetalization will give the pentacyclic polyether core (**41**). Installation of the left- and right-hand side chains will then furnish brevenal (**1**).

In summary, a highly convergent approach toward the total synthesis of brevenal has been reported. Two key cyclic ether fragments have been constructed utilizing our asymmetric glycolate alkylation/ring-closing metathesis approach. Fragment coupling has been carried out in excellent yield and efforts to complete the carbon framework and elaborate the side chains are ongoing.

Supplementary Material

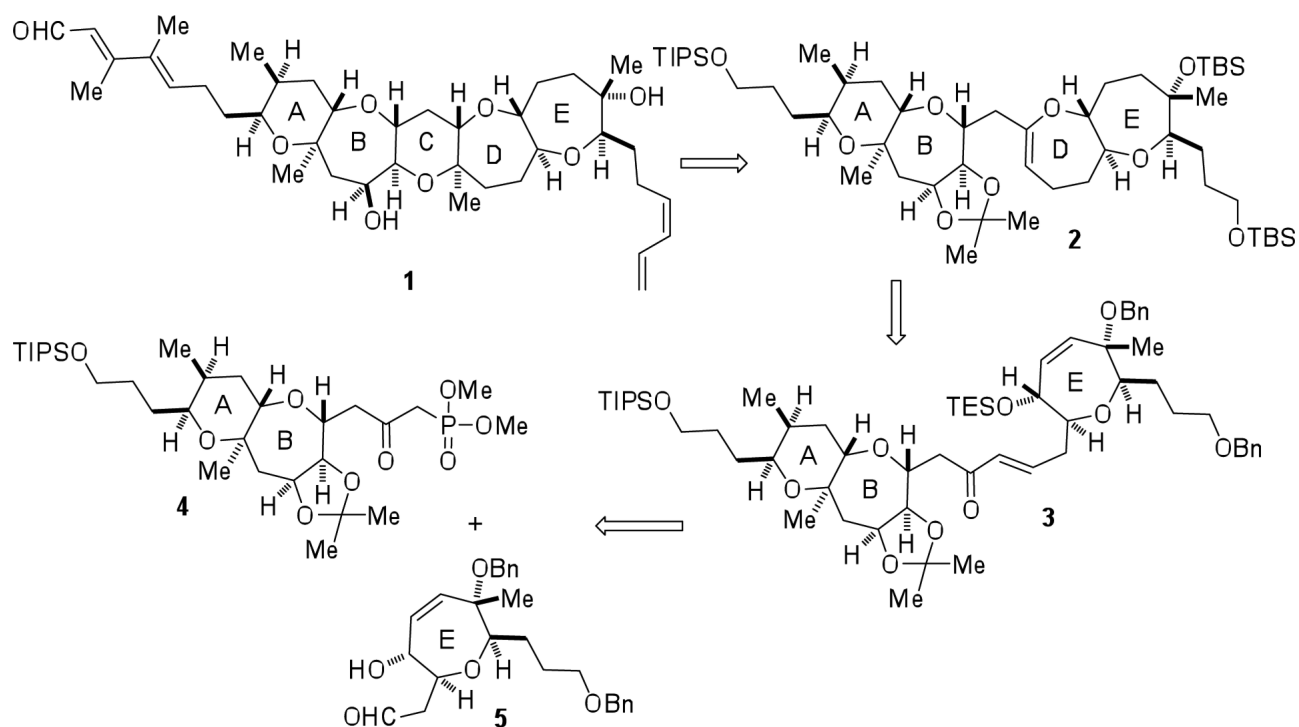
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Acknowledgments

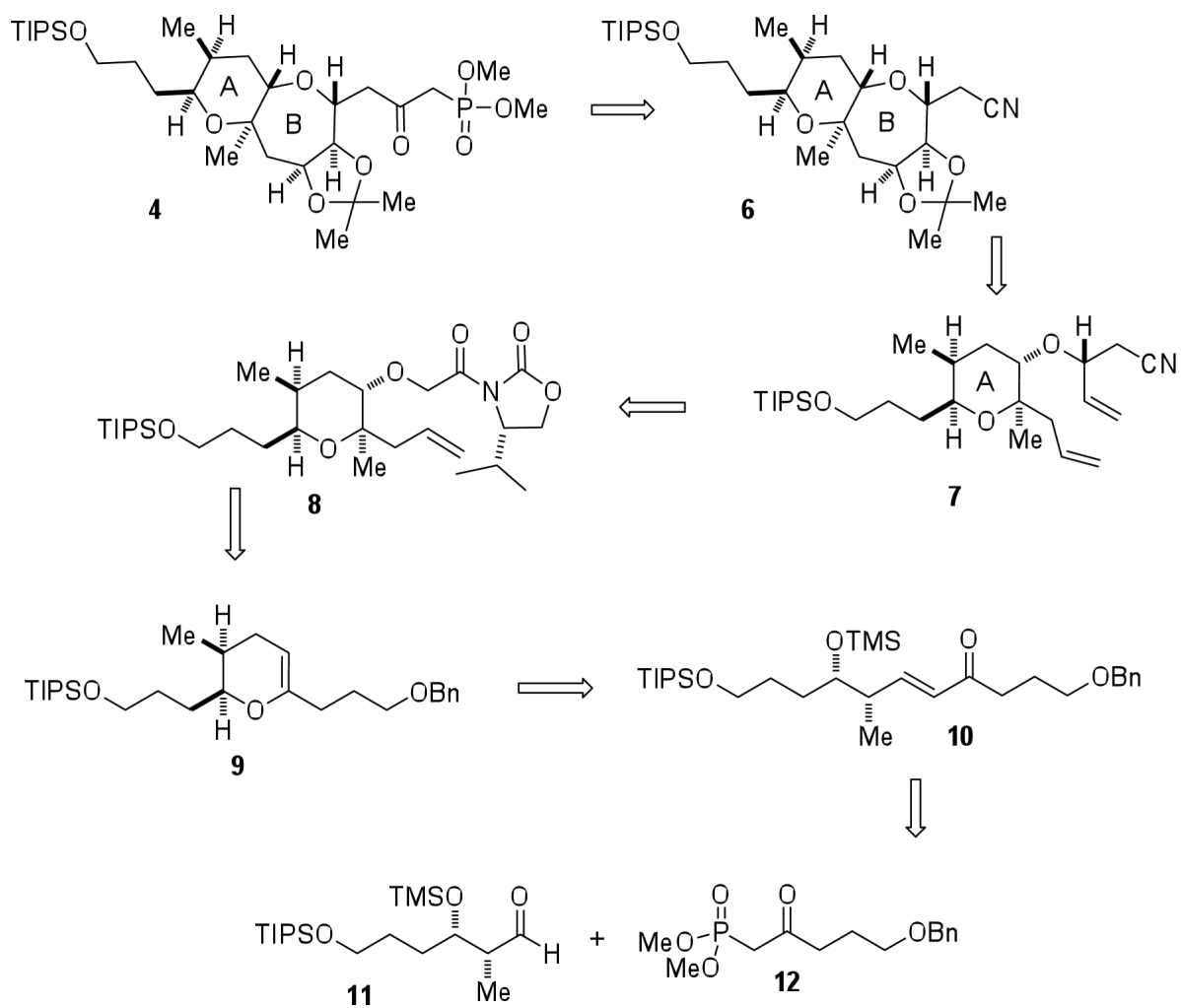
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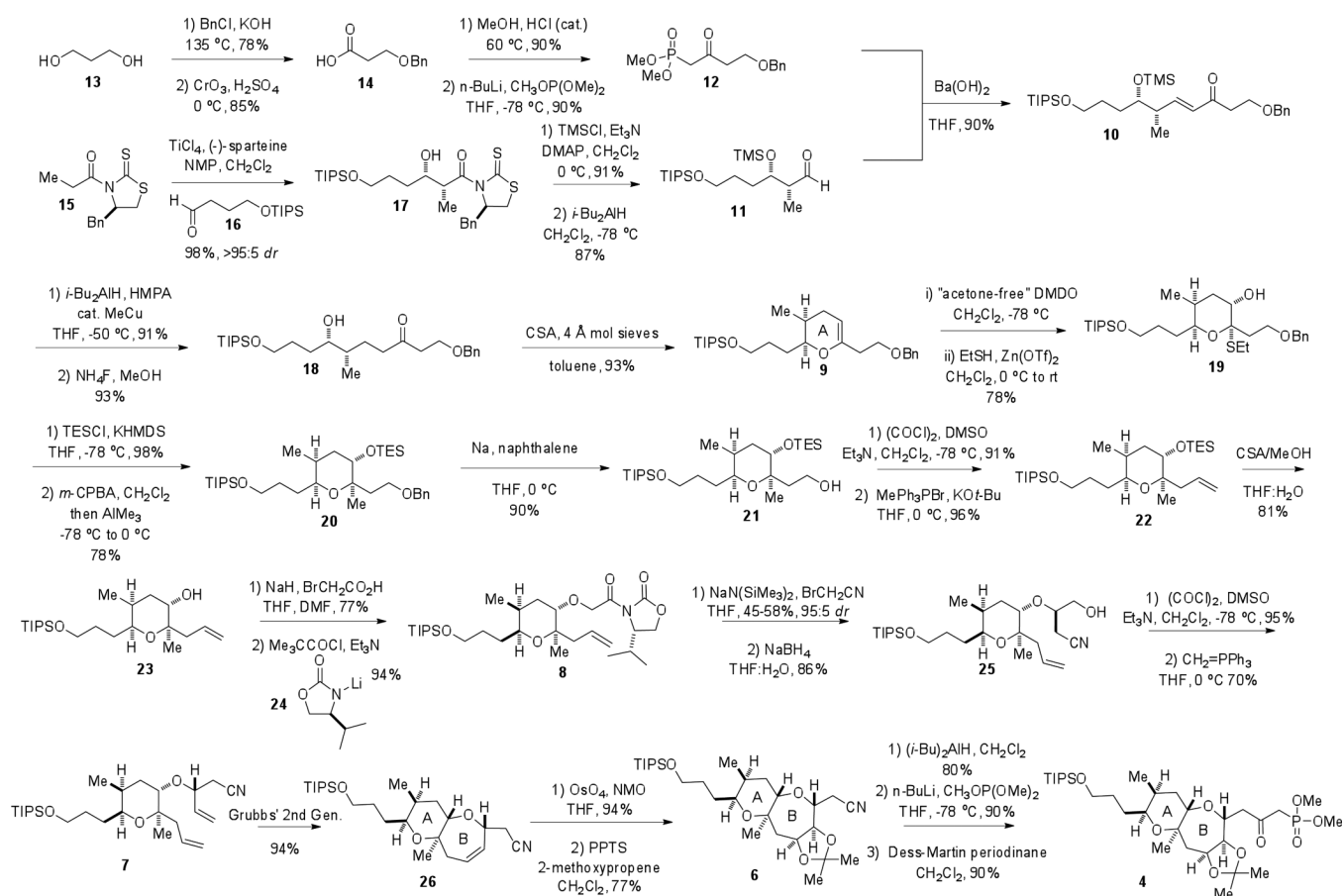
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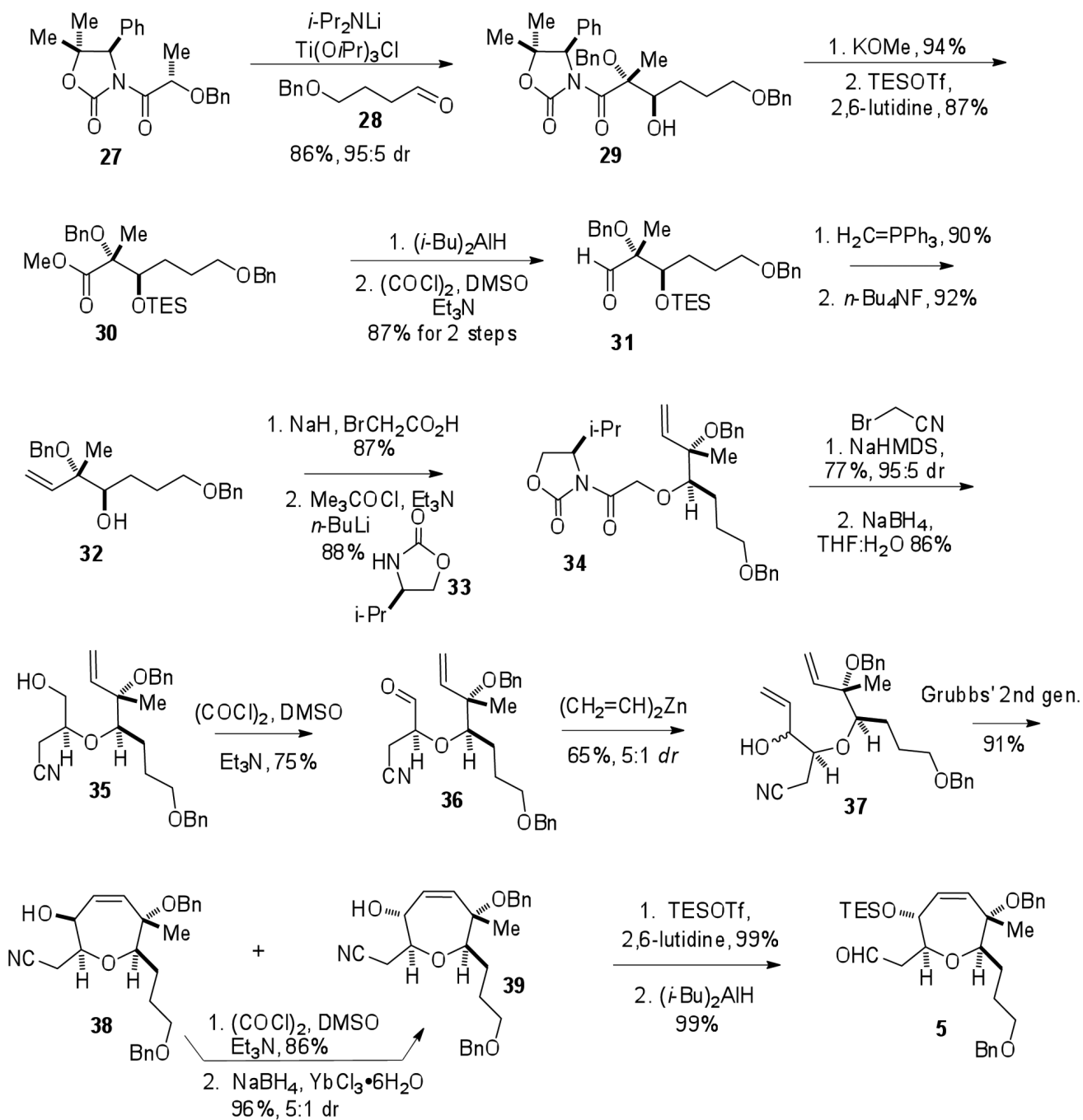
Scheme 1.
Retrosynthetic analysis.



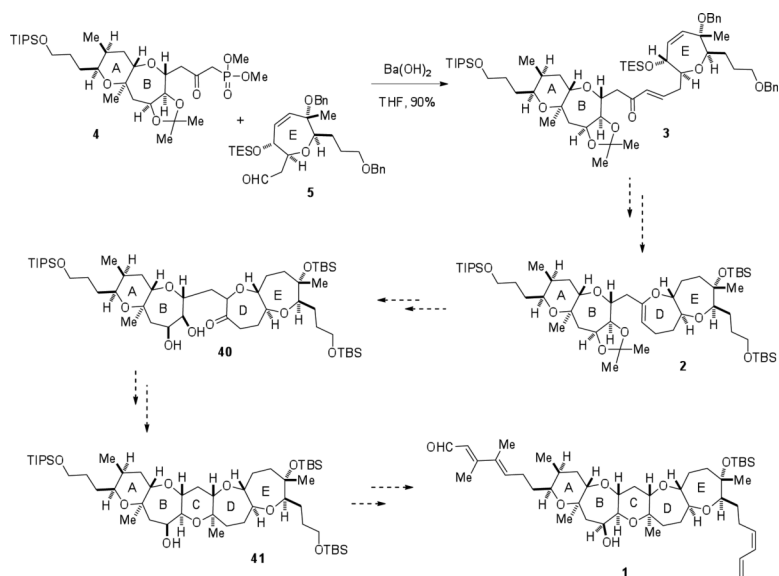
Scheme 2.
Retrosynthetic plan for β -ketophosphate **4**.



Scheme 3.
Synthesis of AB-ring β -ketophosphate 4.



Scheme 4.
Synthesis of aldehyde **5**.



Scheme 5.
Coupling of the fragments and proposed endgame.