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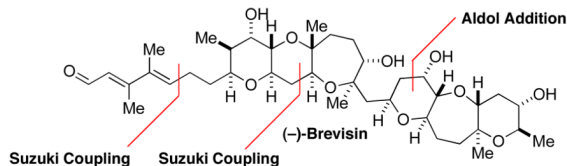
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## Total Synthesis of (–)-Brevisin: A Concise Synthesis of a New Marine Polycyclic Ether

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### Abstract



The first and highly efficient total synthesis of (–)-brevisin has been achieved. The title compound was synthesized in only 29 steps (longest linear sequence) from commercially available starting materials. The synthesis provided over 70 mg of marine polycyclic ether compound.

The polycyclic ether (–)-brevisin<sup>1</sup> (**1**; Figure 1) was isolated from the red tide dinoflagellate *Karenia brevis*, which produces a variety of polycyclic ethers such as the brevetoxins,<sup>2</sup> brevenal,<sup>3</sup> and the monocyclic ether amide brevisamide.<sup>4</sup> Brevisin's unique structure consists of two fused tricyclic ether ring assemblies bridged by a methylene carbon and a conjugated aldehyde side chain, which is similar to the side chain in brevenal and bevisamide. Interestingly, despite **1** has a unique structure, which is divided into two tricyclic ether units by the methylene, **1** inhibits the binding of tritiated 42-dihydrobrevetoxin B (PbTx-3) to the voltage sensitive sodium channels (VSSC).<sup>1a</sup> However, as with the other marine polycyclic ethers, the biological activities of **1** have not been fully investigated due to the extremely small supply from natural sources. In order to elucidate its interaction with a target protein and test other biological activities, such as mouse lethality and cytotoxicity, the chemical synthesis for supplying materials was essential. Here we report the first and highly efficient total synthesis of **1** using Suzuki–Miyaura cross coupling and an aldol addition as the key steps.

Our synthetic strategy to **1** is summarized in Scheme 1. The side chain fragment **2**<sup>4c,5</sup> and iodide fragment **3** would be connected by means of Suzuki–Miyaura cross coupling. The polycyclic ether core would be synthesized from the ABC-ring methyl ketone **4** and the EF-ring aldehyde **5** by an aldol addition and subsequent construction of the D-ring. Tricyclic

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**Supporting Information Available:** Detailed experimental procedures, characterizations, and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

ether **4** would be synthesized from the A-ring exocyclic enol ether **6**<sup>6</sup> and the C-ring ketene acetal phosphate **7** by our Suzuki–Miyaura cross coupling-based strategy.<sup>7</sup>

The A-ring fragment **6** was connected by Suzuki–Miyaura cross coupling to the C-ring ketene acetal phosphate **7**, which was prepared in 8 steps<sup>1c,8</sup> from commercially available 2-deoxy-D-ribose. Namely hydroboration of **6** with 9-BBN generated corresponding alkylborane, which was reacted in situ with **7** in the presence of aqueous Cs<sub>2</sub>CO<sub>3</sub> and a catalytic amount of PdCl<sub>2</sub>(dppf) giving rise to a cross-coupled product **8** in 86% yield. Successive hydroboration/oxidation of **8** with BH<sub>3</sub>·SMe<sub>2</sub> followed by regioselective DIBALH reduction<sup>9</sup> gave diol **9**. The primary alcohol of diol **9** was selectively protected with a TIPS group, and then the secondary alcohol was oxidized to the ketone **10** using TPAP–NMO.<sup>10</sup> Treatment of **10** with Zn(OTf)<sub>2</sub> in the presence of EtSH accomplished the deprotection of the TES groups and mixed thioacetal formation, and subsequent benzylation of the hydroxy group at C-10 afforded mixed thioacetal **11**. Mixed thioacetal **11** was oxidized to the corresponding sulfone, which was treated with AlMe<sub>3</sub> in one-pot manner<sup>11</sup> to introduce the C-15 methyl group. Then, subsequent deprotection of the TIPS group gave the alcohol **12**. Triflation of **12** followed by cyanidation with NaCN led to the corresponding nitrile, which was treated with MeLi to afford the methyl ketone **4** in 68% yield from **12** (Scheme 2).

The synthesis of the EF-ring fragment **5** started from the known hydroxy epoxide **13**.<sup>12</sup> A one-pot oxidation/Wittig reaction<sup>13</sup> of the **13** followed by the deprotection of the TBS group led to α,β-unsaturated ester **14**. Treatment of **14** with a catalytic amount of PPTS induced 6-*endo* cyclization<sup>12</sup> to afford the pyran **15**, and subsequent hydrogenation of **15** led to ester **16**. Methyl acetal formation of **16** with γ-methoxyallylstannane **17**<sup>14</sup> provided mixed methyl acetal **18** as a mixture of the diastereomers. This mixture was treated with HMDS and TMSI to afford allylstannane **19**. Reduction of the ester to the corresponding aldehyde by DIBALH and treatment with BF<sub>3</sub>·OEt<sub>2</sub> accomplished intramolecular allylation<sup>15</sup> to give the oxepane **20**. The relative configuration of **20** was confirmed by observed nOe correlations between H-24/H-29, H-29/H-31, and H<sub>3</sub>-39/H-32 and by the large proton coupling constant (8.8 Hz) between H-31 and H-32. The regioselective DIBALH reduction of **20** led to diol **21**. The primary alcohol of diol **21** was selectively tosylated, and then the secondary alcohol was protected by a TES group to afford tosylate **22**. The tosylate **22** was reduced by LiAlH<sub>4</sub> to afford the EF-ring compound **23**. Finally, ozonolysis of **23** provided the aldehyde **5** (Scheme 3).

Connection of **4** and **5** by aldol addition and construction of the polycyclic ether core were accomplished as shown in Scheme 4. Treatment of the lithium enolate derived from **4** with aldehyde **5** furnished a separable 2.8:1 mixture of C-23 diastereomers **24a**<sup>16</sup> and **24b**.<sup>17</sup> Treatment of **24a** with Et<sub>3</sub>SiH in the presence of TMSOTf<sup>18</sup> led to deprotection of TES ether with concomitant stereoselective reduction to cyclized product **25** in 98% yield. The unprecedented polycyclic ether core of **1** could be constructed in only 2 steps from the key fragments **4** and **5**. Removal of all benzyl groups of **25** followed by the reprotection with TES group afforded pentakis TES ether **26**. At this stage, in order to convert **26** to iodide **3**, only primary TES ether had to be selectively removed in the presence of four secondary TES ethers.

Recently we reported the highly selective deprotection of mono- and bis-silyl ethers by DIBALH.<sup>19</sup> This method was also applicable to the selective deprotection of a primary TES ether in the presence of two secondary TES ethers. Tris-TES ethers **27** and **28** were converted to the corresponding primary alcohols **29** and **30** in excellent yields (Scheme 5).

The completion of the total synthesis of **1** is illustrated in Scheme 6. Application of the above selective deprotection on pentakis-TES ether **26** gave primary alcohol **31** in 88% yield. Perhaps the neighboring ether oxygen atom of the A ring accelerated the deprotection and generated its high selectivity (Scheme 7). The primary alcohol **31** was converted to iodide **3** with I<sub>2</sub>, PPh<sub>3</sub>, and imidazole. Finally, connection of the fragments **2** and **3** by means of a Suzuki–Miyaura cross coupling<sup>20</sup> followed by the deprotection of all silyl groups and chemoselective oxidation of the allylic alcohol at C-1 gave rise to **1** in 75% yield for the three steps. The optical rotation and the other spectroscopic data of synthetic **1** were identical with those of natural **1**.

In conclusion, we have accomplished the first total synthesis of (–)-brevisin (**1**). The polycyclic ether core was constructed by means of a Suzuki–Miyaura cross coupling reaction and aldol addition as the key steps. It is noteworthy that the synthesis was accomplished in only 29 longest linear steps from commercially available 2-deoxy-D-ribose. Furthermore, based on our highly efficient synthetic strategy, we could synthesize over 70 mg of **1**. The present synthesis is one of the successful example of practical supplying marine polycyclic ether compound and will be important for the elucidation of brevisin's biological activity.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

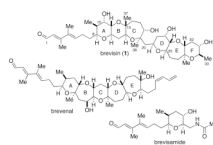
## Acknowledgments

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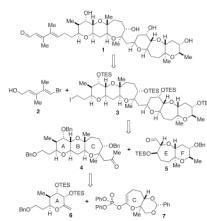
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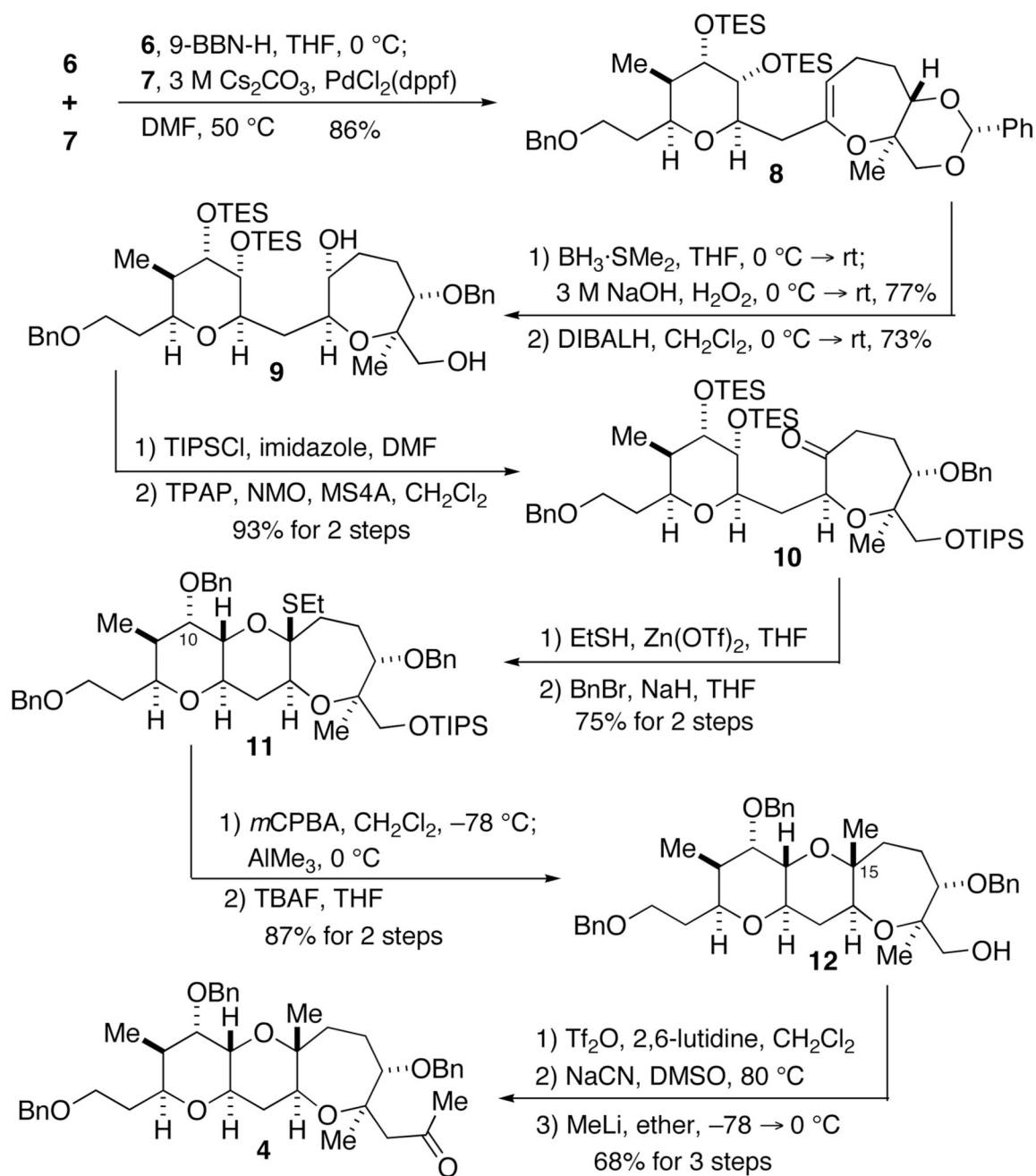
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16. The stereochemistry of the newly generated hydroxy group at the C-23 of **24a** was assigned after construction of the D ring. The coupling constant (3 Hz) between H-23 and H-24 in **25** indicated the axial orientation of the hydroxy group at the C-23.
17. The minor undesired C-23 diastereomer **24b** could also be converted to **25** by additional 3 steps and the details are described in the supporting information.
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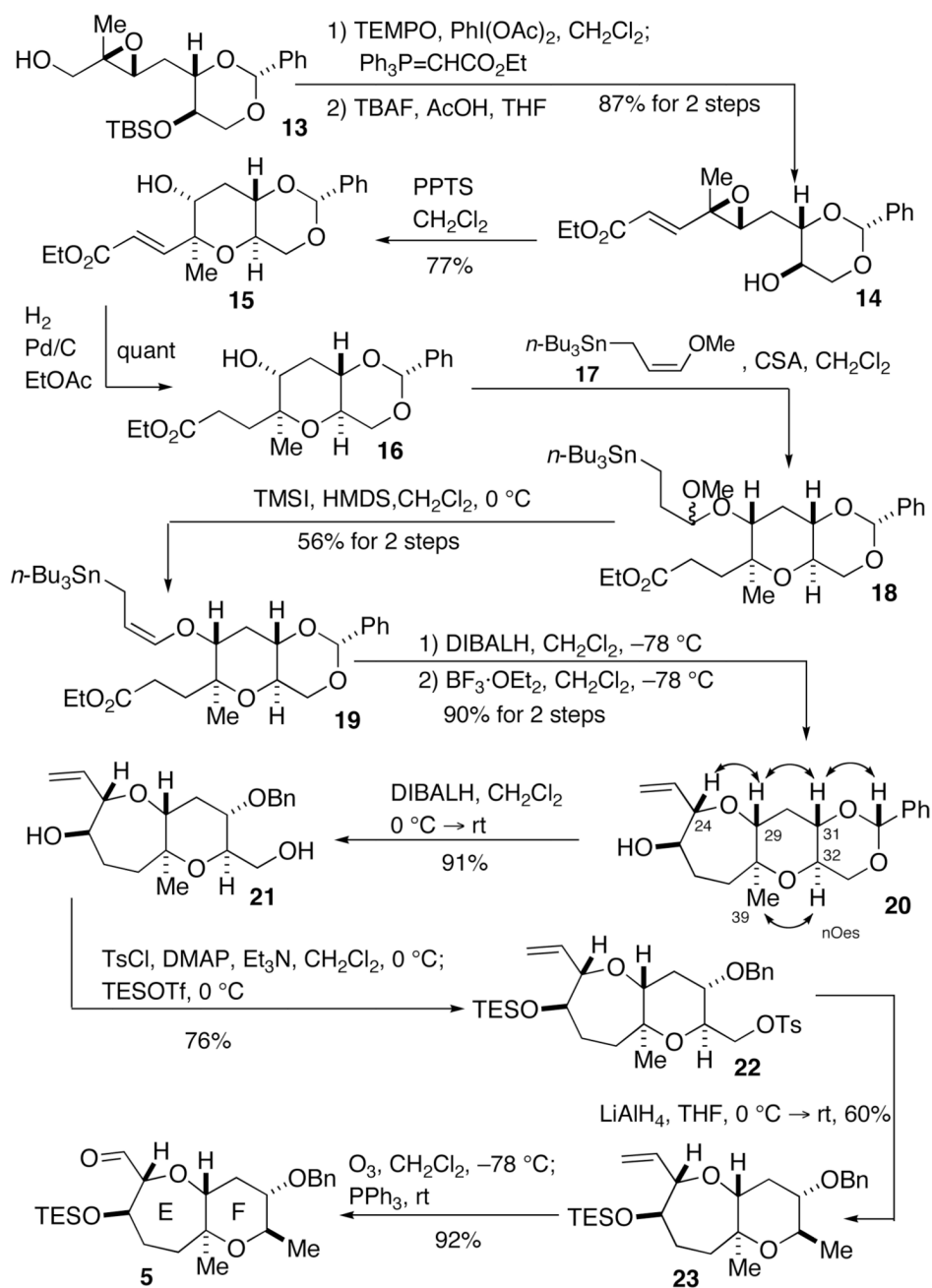
**Figure 1.**  
Structures of brevisin (**1**), brevenal, and brevisamide



**Scheme 1.**  
Synthetic Plan of **1**

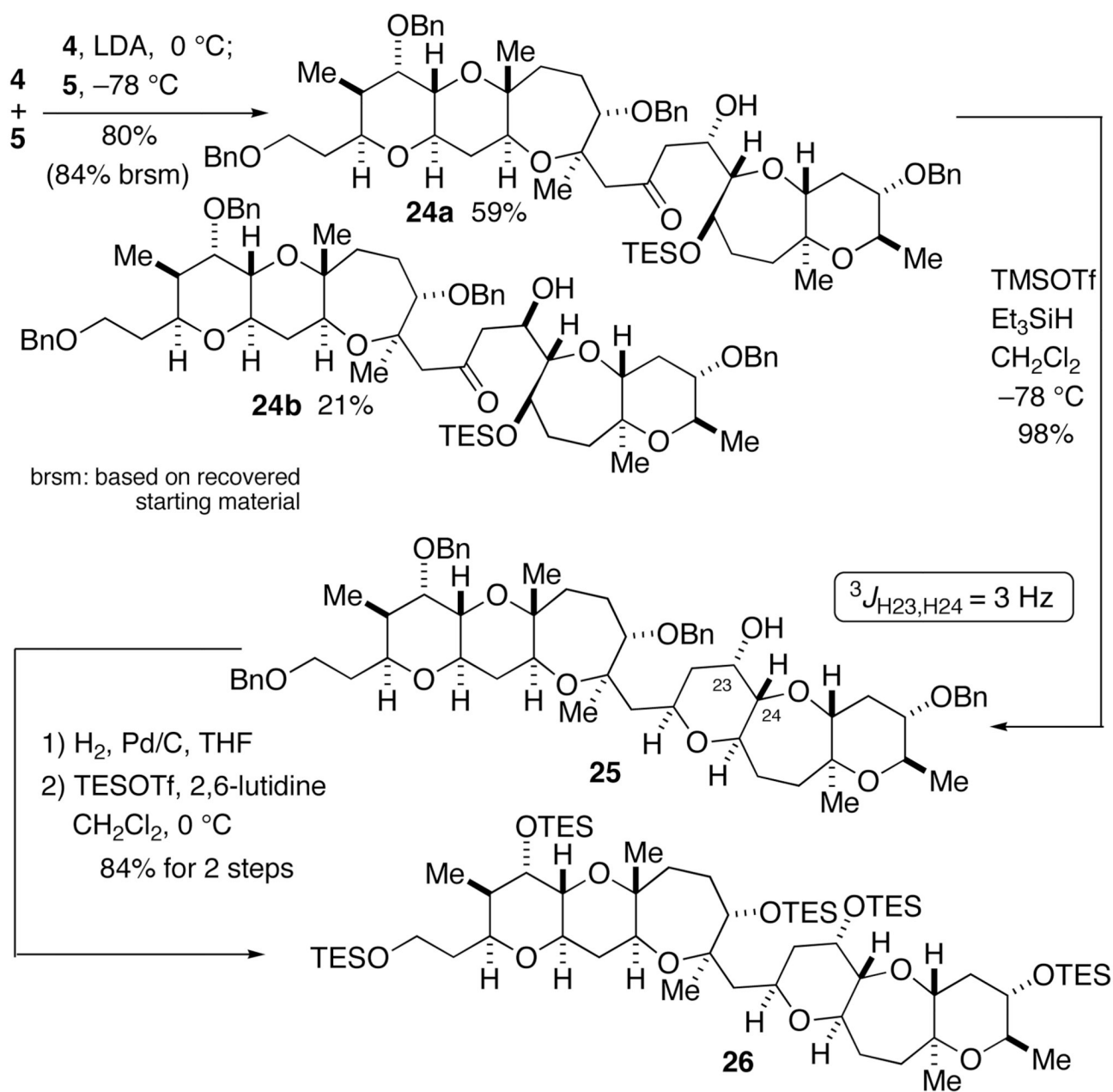


**Scheme 2.**  
Synthesis of the ABC ring fragment

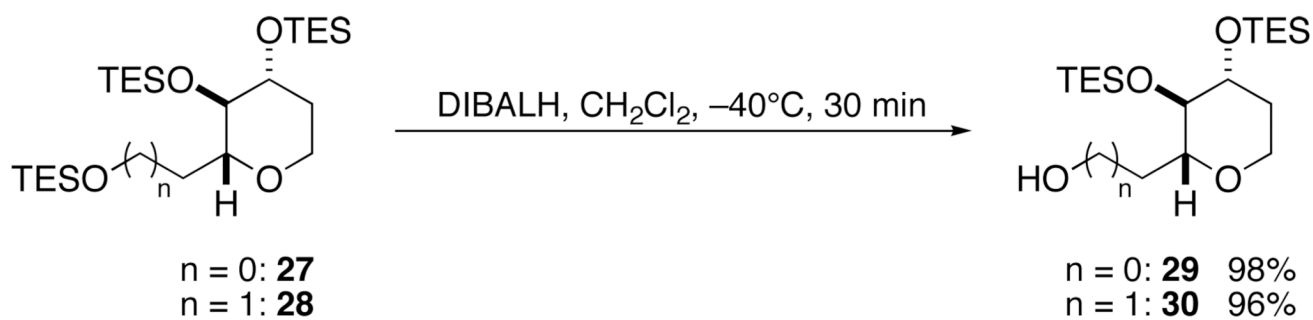


**Scheme 3.**  
Synthesis of the EF ring fragment

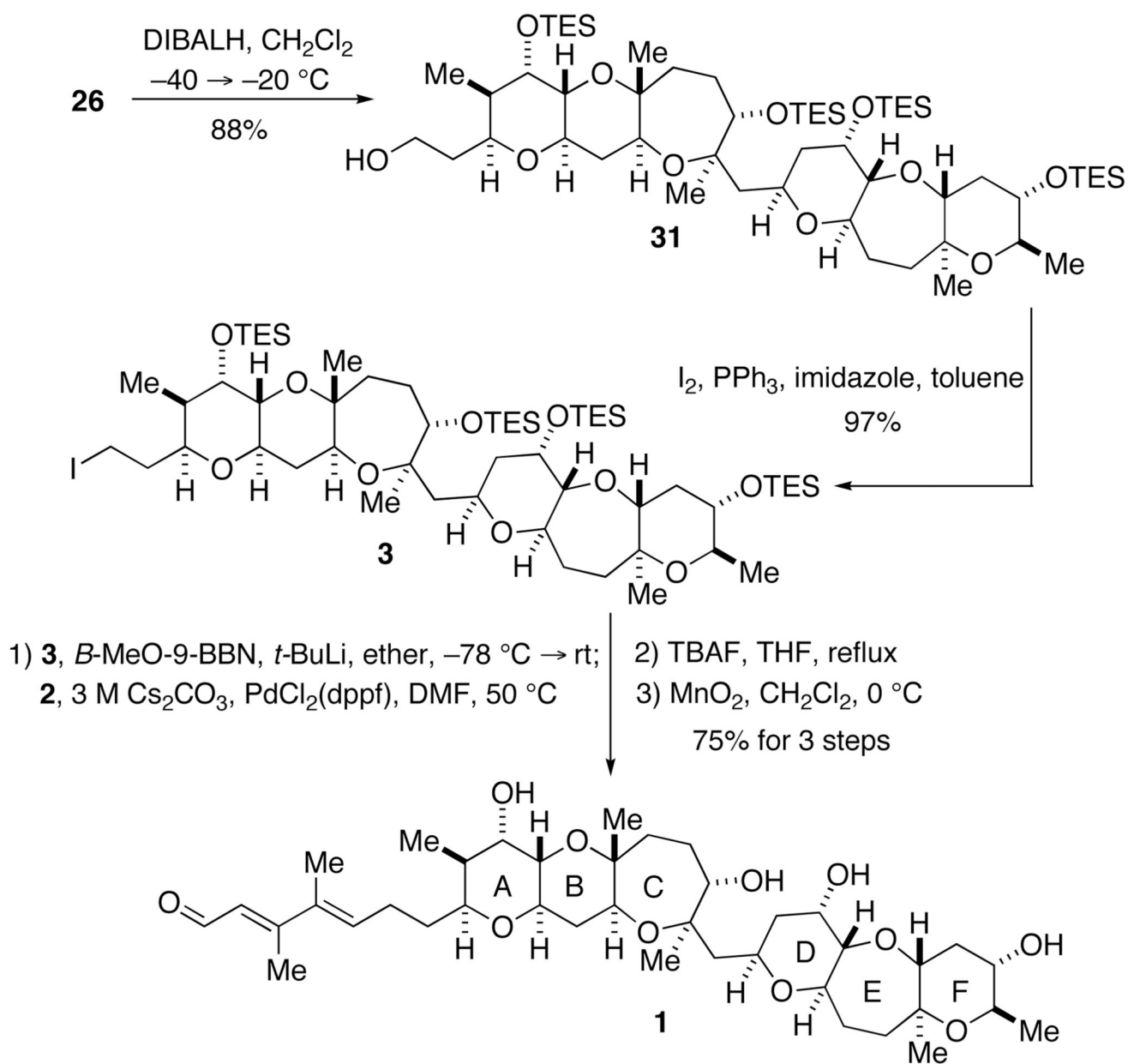




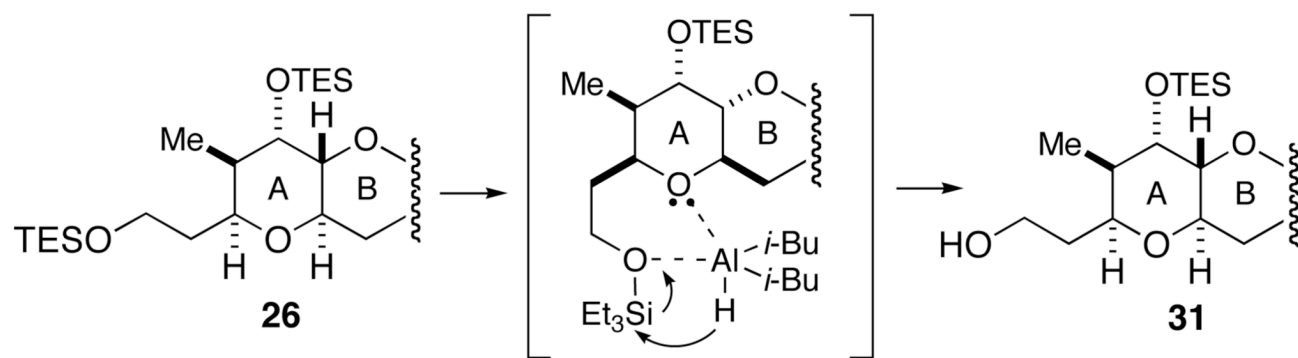
**Scheme 4.**  
 Synthesis of the ABC/DEF ring compound **26**



**Scheme 5.**  
Treatment of tris-TES ethers with DIBALH



**Scheme 6.**  
Completion of the total synthesis



**Scheme 7.**  
Selective deprotection of **26**